Use and outcomes of contemporary combination antiretroviral therapy in people living with HIV

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Declaration

I, Lauren Greenberg, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

The introduction of antiretroviral therapy (ART) has transformed HIV from a fatal illness into a manageable, chronic condition. As there is currently no cure for HIV, ART, typically including three antiretroviral drugs (ARVs), is a lifelong commitment, and there are concerns around long-term toxicities. Integrase strand transfer inhibitors (INSTIs) are one of the latest ARV classes to be approved and treatment guidelines uniformly recommend them as first-line treatment for people living with HIV (PLWH). However, limited data exist on long-term clinical outcomes associated with contemporary ART, including INSTIs, and contemporary ART regimens, including two-drug regimens. In this thesis, I use data from the International Cohort Consortium of Infectious Diseases (RESPOND) to assess the use and outcomes of contemporary ART, with a focus on two-drug regimens and INSTIs, including the association between INSTI use and incident cancer. I also assess temporal trends in cancer incidence across different ART-eras. RESPOND is a collaboration of 17 cohort studies, including approximately 30,000 PLWH from across Europe and Australia.

I found that uptake of dolutegravir compared to cobicistat-boosted elvitegravir or raltegravir has increased over time. INSTI discontinuation was low overall and mainly due to toxicity in the first 6 months of use. Discontinuation was higher for raltegravir, primarily due to treatment simplification, whilst discontinuation due to nervous system toxicities was highest on dolutegravir.

Virological and immunological outcomes were similar between those on two-drug and three-drug regimens. Additionally, after accounting for baseline characteristics, there was a similar incidence of severe clinical events on both regimen types.

When assessing cancer trends from 2006-2019, I found that whilst the age-standardised incidence of AIDS-related and infection-related cancers has decreased over time, body mass index-related cancers have increased, whilst non-AIDS-related cancers and smoking-related cancers remained constant. Overall, there was no association between cancer risk and INSTI exposure.

Impact Statement

Since the start of the HIV pandemic, approximately 74.9 million people have acquired HIV and 32.0 million have died from AIDS-related illnesses, globally. Since 1986, there have been 34 ARVs approved by the European Medicines Agency for treatment of HIV and the use of these ARVs has transformed HIV from a fatal illness into a manageable, chronic condition, in settings where these treatments are readily available. With such a wide range of ARVs, it is now possible to take a more individual-centred approach when choosing treatment regimens for PLWH. However, to do this, long-term data on the safety and efficacy of contemporary ARVs is needed, and this was a primary motivation for this thesis.

There are many ways in which the findings from this thesis could impact PLWH and health-care professionals involved with HIV-care. Firstly, the thesis focuses specifically on the use and outcomes of INSTIs and two-drug regimens (2DRs). INSTIs are recommended as first-line and switch treatment in all international treatment guidelines and 2DRs are being increasingly widely used today. However systematic post-marketing assessment of long-term follow-up data on both of these is still lacking. The results presented in this thesis are in line with existing evidence that INSTIs and 2DRs are a relatively safe and effective option for PLWH. They can be used to help inform HIV treatment guidelines, provide reassuring evidence for clinicians and PLWH taking these treatments, for example that treatment discontinuation is relatively low, and inform caretakers about which groups of individuals may benefit from closer monitoring whilst on treatment. The data also suggests that clinicians use of INSTIs as a group should not be a safety concern for cancer risk.

Another focus of the PhD was comparing cancer trends across different ART-eras, with results showing that whilst AIDS-defining cancers and infection-related cancers were decreasing over time, BMI-related cancers were increasing, and non-AIDS defining cancers and smoking-related cancers remained constant. This data provides important insight for clinicians and HIV researchers into the types of cancers which

need closer monitoring amongst the population of PLWH. It also highlights the need for a closer focus on prevention strategies, for example for smoking.

Within academia, the results of this thesis highlight key future research areas regarding HIV treatment and adverse events associated with treatment. One example of this is that INSTI discontinuation was higher in specific subgroups of the population, such as females and those with hepatitis C coinfection, and it is important to understand the reason for this. It would also be beneficial to assess the use and outcomes of individual INSTIs, once there is sufficient follow-up.

Much of the research presented in this thesis has been disseminated via publication in peer-reviewed journals and via posters and presentations at international conferences; the details of these are provided at the end of each results chapter. Additionally, all conference presentations have been reported in the media, for example by the National AIDS Treatment Advocacy Project, ensuring the results reach a wider audience.

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Chapters

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Frequently used abbreviations

/b	Boosted with ritonavir or cobicistat
/c	Cobicistat boosted
/r	Ritonavir boosted
2DRs	Two-drug regimens
3DRs	Three-drug regimens
ADC	AIDS-defining cancer
ADE	AIDS-defining event
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
ARV	Antiretroviral
ATV	Atazanavir
BMI	Body mass index
cART	Combination antiretroviral therapy
CD4	Cluster of differentiation 4
CDC	Centres for Disease Control and Prevention
CHIP	Centre of Excellence for Health, Immunity and Infections
CI	Confidence interval
CKD	Chronic kidney disease
CNS	Central nervous system
cTO	Composite treatment outcome
CVD	Cardiovascular disease
D:A:D	Data Collection on Adverse Events of Anti-HIV Drugs
DHHS	Department of Health and Human Services
DRV	Darunavir
DTG	Dolutegravir
EACS	European AIDS Clinical Society
EFV	Efavirenz
EMA	European Medicines Agency
ESLD	End stage liver disease
ESRD	End stage renal disease
EVG	Elvitegravir
FDA	Food and Drug Administration

HBV	Hepatitis B
HCV	Hepatitis C
HICDEP	HIV Cohorts Data Exchange Protocol
HIV	Human immunodeficiency virus
HR	Hazard ratio
IAS	International AIDS Society
IDU	Injecting drug users
INSTI	Integrase strand transfer inhibitor
IQR	Interquartile range
IR	Incidence rate
IRR	Incidence rate ratio
IU	International units per litre
KM	Kaplan Meier
KS	Kaposi's sarcoma
LTFU	Lost to follow-up
MI	Myocardial infarction
MICE	Multivariate imputation by chained equations
MSM	Men who have sex with men
NADC	Non-AIDS-defining cancer
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleos(t)ide reverse transcriptase inhibitor
OR	Odds ratio
PI	Protease inhibitor
PLWH	People living with HIV
PYFU	Person years of follow up
RAL	Raltegravir
RCT	Randomised controlled trial
RESPOND	International Cohort Consortium of Infectious Diseases
RNA	Ribonucleic acid
RPV	Rilpivirine
RR	Relative risk
VL	Viral load
WHO	World Health Organisation

Chapter 1 Introduction

1.1 Introduction

This chapter provides an overview of human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), including the discovery of HIV and AIDS, the natural history of HIV, and the transmission of the virus. I also describe the pandemic to date. Much of this chapter and this thesis focus on the pandemic in Europe and Australia, however Chapter 1 also provides a short overview of the pandemic worldwide. Additionally, I provide an overview of available treatment for people living with HIV (PLWH), including the mechanisms of the different drug classes, the recommended treatment strategies, and potential limitations of treatment. The majority of the information provided in this chapter is based on literature up to 2018, which was the start of my PhD.

1.2 Discovery of HIV and AIDS

AIDS was first identified in 1981 when cases of pneumocystis jiroveci pneumonia (formerly known as pneumocystis carinii pneumonia, PCP), a severe pulmonary infection, and Kaposi's sarcoma (KS), a rare and aggressive cancer affecting both skin and internal organs, were reported amongst groups of seemingly healthy, homosexual men in Los Angeles and New York City (1–4). Although there are sporadically reported cases of AIDS as early as the 1920s in the Democratic Republic of the Congo in Africa, the 1981 outbreak is recognised as the start of the AIDS pandemic, as it spread to several continents around the world (5,6).

The number of cases of AIDS and AIDS-related deaths rapidly increased during the 1980s (7). By the end of 1981, there were approximately 270 individuals with AIDS in the United States of America (USA) and 121 reported AIDS-related deaths (7,8). By the end of 1983, this had risen to 3,064 cases of AIDS and 1,292 deaths. In the following years, AIDS spread across most continents, and in 1985, there were approximately 20,000 cases reported globally (7–10).

AIDS was originally thought to be exclusive to homosexual men and the virus was referred to as “gay-related immunodeficiency syndrome” or “GRID” in the press (11,12). This caused a considerable amount of stigma, and discrimination was evident in areas such as health insurance, jobs, and housing (13). In the months that followed, it became clear the virus affected other groups including haemophiliacs, injecting drug users (IDUs), Haitian immigrants, and women (14–18).

In 1982, the Centers for Disease Control and Prevention (CDC) officially defined AIDS as “a disease, at least moderately predictive of a defect in cell-mediated immunity, occurring in a person with no known cause for diminished resistance to that disease” (14). This included diseases such as PCP and KS.

The following year, two groups of researchers independently discovered the retrovirus believed to be the causative agent of AIDS. In France, Barré-Sinoussi et al. isolated a retrovirus they entitled lymphadenopathy associated virus (19,20) and in USA, Gallo et al. isolated a retrovirus which they named human T-lymphotropic retrovirus (21,22). These were later shown to be the same virus (23) and in 1986, were renamed HIV by a subcommittee of the International Committee on Taxonomy of Viruses (23,24).

Further research revealed another retrovirus, related to HIV, which was largely restricted to West Africa (25–27). This strain was subsequently named HIV-2, and the strain affecting people worldwide was called HIV-1. Individuals with HIV-2 have a lower viral load (VL), slower disease progression, and lower risk of transmission compared to those with HIV-1 (27,28).

1.3 Origin of the virus

HIV-1 and HIV-2 are types of lentiviruses (see Section 1.4) specific to primate populations, called simian immunodeficiency viruses (SIV) (29). HIV-1 originated from SIV in chimpanzees whilst HIV-2 originated from SIV in sooty mangabeys (25,27,30). The two strains arose from multiple cross-species transmissions from simians to humans in West Central Africa (29). It is believed that the first transmission of HIV-1

occurred around 1910-1930 in Kinshasa in West Africa, known then as Leopoldville (27). Cross-species SIV transmission occurred through exposure to infected blood and bodily fluid of primates, and this was likely caused by bushmeat hunting for food and trade, and from bites from primates kept as pets (27,29,31). Many factors contributed to an increased risk of human exposure to SIV including an increase in the bushmeat trade, socio-economic changes during colonial expansion, and urbanisation of countries in West Africa (31–34). HIV spread to other regions in Africa around 1950-1970 and this was facilitated by increased transport links, changing sexual behaviours, and the use of unsterilized needles for treatment and vaccination of other diseases (31–34). It is believed that HIV spread from Africa to Haiti in the 1960s after Haitian professionals returned from working in West Africa (27,32,35). From there, it spread to USA and then worldwide.

1.4 Life cycle of the virus

HIV is part of a subgroup of retroviruses known as lentiviruses. Retroviruses are a unique group of viruses which are composed of ribonucleic acid (RNA) rather than DNA, and contain the enzymes needed to convert the viral RNA into DNA (36). Lentiviruses are typically chronic, potentially fatal diseases with a long incubation period (37). The main way that HIV infects a host is by interacting with the host's immune system, in particular CD4 cells. CD4 cells are a subgroup of white blood cells involved in fighting infections by coordinating the immune response against foreign antigens (38,39). Also known as CD4 lymphocytes, T-cells or T-lymphocytes, CD4 cells are the primary target of HIV (37,40). Once the virus has infected the CD4 cells, it replicates within the host (36). There are several steps involved in the HIV replication cycle, as shown in Figure 1.1.

Initially, a viral glycoprotein, gp120, interacts with a CD4 protein in the host. Glycoproteins are found on the surface of the viral cell and play a major role in infection (41). This interaction causes a structural change in the virus which allows the gp120 to bind with a chemokine receptor on the CD4 cell surface, usually the C-C chemokine receptor type 5 (CCR5) or C-X-C chemokine receptor type 4 (CXCR4)

coreceptor (36,42). Another viral glycoprotein, gp41, then facilitates the fusion between the virus cell envelope, which contains the viral capsid, and the host cell membrane. Once this has taken place, the virus cell envelope opens to reveal the capsid, which is then released into the host cell cytoplasm, along with two copies of the viral RNA and the enzymes needed to facilitate viral replication. This process is known as uncoating (43).

After entry into the host cell membrane, the viral RNA is converted into a double stranded DNA using the enzyme reverse transcriptase (RT) (36). This is done by building a chain of nucleotides which are found in the host cell. Integrase enzymes are then used to trim each 3' end of the viral DNA and help splice it with the host cell DNA (44,45). The newly formed cell is called a "provirus".

Following integration with the host cell DNA, the viral DNA is converted back into messenger RNA using enzymes found in the host (44). Long chains of viral polyproteins are formed, and protease enzymes are used to cleave these chains into smaller, core viral proteins (46). A new viral capsid is then formed from two new strands of HIV RNA, along with the core viral proteins and other enzymes needed for replication. The capsid peels off the host cell and forms a new virus particle, which is able to infect other cells (46). This process is known as budding and after this takes place, the host CD4 cell dies.

Figure 1.1 HIV life cycle

Source: (47)

1.5 Natural History of HIV

The natural history of HIV refers to the course of the infection in the absence of treatment, and can be categorised into three stages: primary, asymptomatic, and symptomatic (48–51). Before the introduction of effective anti-HIV treatment, there was much research done to study the rate of HIV progression and factors that affect this. Other categorisations were also introduced by the CDC and World Health Organisation (WHO) to monitor the progression of HIV and this is discussed below in Section 1.5.4.

1.5.1 Primary stage

The primary stage of HIV refers to the initial period after an individual acquires HIV (51). During this stage, there is a high rate of viral replication, which results in a sharp, short-term rise in VL and, consequently, a decline in CD4 count (52). In some cases, the VL can reach over 1 million copies per millilitre (mL) (53). Viral RNA becomes detectable in the blood 7-10 days after infection, and during this time, approximately

25-65% of individuals experience mild symptoms, such as fever, skin rash, muscle pain, and swollen lymph nodes (51,54,55).

In the early stages of HIV infection, the body begins to produce antibodies (56–58). These usually become detectable between 4 weeks and 3 months after infection (48,58). At this point, seroconversion has taken place and the individual goes from being HIV-negative to HIV-positive.

1.5.2 Asymptomatic stage

After seroconversion, the asymptomatic stage begins. This lasts for an average of 10 years and individuals are usually free of symptoms during this time (51,59). HIV is still replicating in this period, however at a much slower rate. The creation of antibodies causes an immune response to HIV which reduces the VL in the blood, and in turn increases the CD4 count (50,51,59,60). The VL stabilises, and the level of VL at this point is called the VL set point (61).

For approximately 5% of individuals, the asymptomatic stage can last for 20-25 years. These individuals are known as long-term non-progressors (LTNP) (62–64). A small subset of LTNPs can remain virologically suppressed (defined as VL<50 copies/mL) without treatment, and are called elite controllers (62,63).

1.5.3 Symptomatic stage

For the majority of individuals with HIV, the immune response eventually fails in the absence of treatment, and this leads to the symptomatic stage of HIV (48,51). As the disease progresses, there is an increase in VL and a decrease in CD4 count (Figure 1.2) (65–67). CD4 cells decline at a rate of approximately 50 cells per year, however this rate varies depending on several factors including age, the rate of increase of VL, and VL set point (51,68–72).

As the CD4 count drops, the immune system becomes weakened and individuals are more vulnerable to serious opportunistic infections (OI), specific AIDS-defining cancers (ADC), and other serious conditions, as listed in Table 1.1 (48). Individuals are

generally symptom free as long as their CD4 count remains above 350 cells per cubic millimetre (mm^3) (48,61). HIV is said to have progressed to AIDS once an OI or ADC is diagnosed (51). The CDC definition of AIDS also includes a CD4 count below 200 cells/mm^3 (see below).

There are many factors which affect the rate of disease progression including age, gender, and ethnicity (73–76). The survival rate after being diagnosed with AIDS depends on the type of OI or ADC, and the treatment received (77). The median survival time after an AIDS diagnosis in 1985 was estimated to be 11.6 (interquartile range, IQR, 6.2-18.7) months (77). However, as more effective treatments have been introduced, the proportion of AIDS-related deaths has dramatically decreased and the term 'AIDS' is less commonly used in clinical practice (77–79). Results from the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study, including a cohort of almost 50,000 adults with HIV, showed that the percentage of deaths attributable to AIDS had decreased from 34% in 1999-2000 to 22% in 2009-2011 (80).

Figure 1.2 Changes in HIV-RNA and CD4 count in the absence of treatment over the course of HIV

Adapted from: (81)

Table 1.1 List of opportunistic infections and AIDS defining cancers

Bacterial infections, multiple or recurrent
Candidiasis of bronchi, trachea, oesophagus, or lungs
Cervical cancer, invasive
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (greater than one month's duration)
Cytomegalovirus diseases (other than liver, spleen, or nodes)
Encephalopathy attributed to HIV
Herpes simplex - chronic ulcers (greater than one month's duration); or bronchitis, pneumonitis, or esophagitis
Histoplasmosis, disseminator or extrapulmonary
Isosporiasis, chronic intestinal (greater than one month's duration)
Kaposi's sarcoma
Lymphoma – Burkitt's, immunoblastic, primary, or brain
Mycobacterium avium complex or Mycobacterium kansasii (disseminated or extrapulmonary) or Mycobacterium tuberculosis (pulmonary, disseminated or extrapulmonary) or other Mycobacterium (disseminated or extrapulmonary)
Pneumocystis jiroveci pneumonia
Pneumonia, recurrent
Progressive multifocal leukoencephalopathy
Salmonella septicaemia, recurrent
Toxoplasmosis of brain
Wasting syndrome attributed to HIV

Adapted from: (82,83)

1.5.4 CDC and WHO classification

Classifying HIV into clinical stages is a useful method for monitoring the HIV pandemic and guiding clinical care (84,85). The CDC and WHO have both published classification systems which can be used in different clinical settings (86,87).

The CDC defines three stages of HIV based on an individual's CD4 count or the diagnosis of an OI or ADC (86). Higher categories indicate a more severe disease and once an individual has moved into a higher category, it is not possible to move back to a lower category, regardless of whether their CD4 count or clinical symptoms improve. Whilst the stages are determined by CD4 count, if an OI or ADC is diagnosed, the individual is said to be in stage 3, irrespective of their CD4 count. Table 1.2 shows the CDC classification system.

Table 1.2 CDC clinical stages of HIV/AIDS for all individuals >6 years

Stage*	CD4 Count	
	Cells/μL	Percentage[1]
1	≥500	≥26
2	200-499	14-25
3	<200	<14

Source: (86)
*if CD4 count is unknown, the stage is set to unknown; if a stage-3-defining opportunistic infection has been diagnosed, then the stage is set to 3 regardless of CD4 count
[1]CD4 percentage is only used if CD4 count is missing

The WHO classify the stages of HIV based on the presence of clinical symptoms and conditions, as shown in Table 1.3. This classification was first published in 1990, and then updated in 2007 (87,88). It does not take into account the CD4 count, and is therefore more commonly used in resource limited settings where regular CD4 count testing is not feasible (87). There are 4 stages included, with stage 1 defined as early HIV infection and stage 4 as advanced HIV infection. As with the CDC classification, individuals cannot go back a stage and once diagnosed with a condition, they remain in that stage even after recovery.

Table 1.3 WHO clinical stages of HIV/AIDS for adults and adolescents with confirmed HIV

Clinical stage 1	
Asymptomatic	Persistent generalized lymphadenopathy
Clinical stage 2	
Moderate unexplained weight loss (<10% of presumed or measured body weight)	Recurrent respiratory tract infections sinusitis, tonsillitis, otitis media and pharyngitis)
Recurrent oral ulceration	Papular pruritic eruptions
Herpes zoster	Seborrhoeic dermatitis
Angular cheilitis	Fungal nail infections
Clinical stage 3	
Unexplained severe weight loss (>10% of presumed or measured body weight)	Pulmonary tuberculosis (current)
Unexplained chronic diarrhoea for longer than one month	Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis
Unexplained persistent fever (above 37.6°C intermittent or constant, for longer than one month)	Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, or bacteraemia)
Persistent oral candidiasis	Unexplained anaemia (haemoglobin <8 g/dL), neutropenia (neutrophils <500 cells/µL) or chronic thrombocytopaenia (platelets <50,000 cells/µL)
Oral hairy leukoplakia	
Clinical stage 4	
HIV wasting syndrome	Chronic isosporiasis
Pneumocystis pneumonia	Chronic cryptosporidiosis (with diarrhoea)
Recurrent severe bacterial pneumonia	Progressive multifocal leukoencephalopathy
Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site)	Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)	Disseminated non-tuberculous mycobacterial infection
Extrapulmonary tuberculosis	Atypical disseminated leishmaniasis

Kaposi's sarcoma	Invasive cervical carcinoma
Cytomegalovirus infection (retinitis or infection of other organs)	Lymphoma (cerebral or B-cell non-Hodgkin) or other solid HIV-associated tumours
Central nervous system toxoplasmosis	Recurrent non-typhoidal Salmonella bacteraemia
Extrapulmonary cryptococcosis including meningitis	Disseminated mycosis (coccidiomycosis or histoplasmosis)
HIV encephalopathy	

Source: (87)

1.6 Measuring HIV progression

The first diagnostic test for HIV was approved by the Food and Drug Administration (FDA) in 1992 (89). It took 10 minutes to perform and allowed clinicians to detect antibodies to HIV-1 by mixing a patient's serum or plasma with an antibody reagent. Many studies have shown that, once diagnosed with HIV, the natural progression of the virus can be effectively monitored by an individual's CD4 count and HIV VL (70,90–94).

1.6.1 CD4 count

The number of CD4 cells present in the blood for healthy individuals is approximately 800-1,200 cells/mm^3 of blood (or equivalently cells per microlitre, cells/µL) (44). However, this is extremely variable and fluctuates based on factors including ethnicity, stress, exercise, smoking, whether the individual had a recent illness, and the time of day the measurement was taken (95–100). Additionally, women tend to have higher CD4 counts than men (100,101) and children have higher counts than adults (102).

The number of CD4 cells in the blood or the percentage of white blood cells that are CD4 cells are often used as an indicator of the risk of infection and mortality for individuals with HIV (103). Additionally, CD4 count was previously used to determine when individuals with HIV should start treatment, although this is no longer the case (104). This is discussed further in Section 1.11.

In addition to CD4 count, the CD4:CD8 ratio is used in many clinical settings (84,85,105). CD8 cells are another subgroup of white blood cells. Whilst the level of CD4 cells in the blood are often depleted in individuals with HIV, levels of CD8 cells are often elevated (106). A low CD4:CD8 ratio could indicate an increased risk of HIV progression and mortality (105,106). Additionally, new data suggests that the CD4:CD8 ratio may be more accurate than CD4 counts alone for predicting the risk of non-AIDS events (107–110).

1.6.2 Viral load

The levels of HIV RNA present in the blood is quantified by the number of copies of HIV per mL of blood plasma. VL testing was first introduced in 1985 using the enzyme-linked immunosorbent assay (ELISA) test (111,112). There are now several different tests available, with varying levels of accuracy, cost, and ease (113–115). These tests include nucleic acid tests, measuring correlates of VL, for example the level of circulating p24 protein in the blood, and testing dried blood spots (116–119). Point-of-care based tests are a simplified type of test which are becoming increasingly available and provide a binary result of whether the VL is above or below a certain threshold (120,121). The level of detection of these tests has improved over time, although it differs between regions, and typically ranges from 30 copies/mL to 400 copies/mL (115,120).

1.6.3 CD4 count and viral load as surrogate markers in randomised controlled trials

Approvals for the first anti-HIV drugs by the FDA were given based primarily on data from randomised controlled trials (RCTs) using clinical endpoints, such as disease progression and mortality (122). The success of early HIV treatment resulted in a drastic reduction in the incidence of HIV-related illnesses (123,124). It quickly became impractical to assess clinical endpoints in RCTs as event rates were too low to accurately compare between treatment arms and would require an extremely large sample and long follow-up. Tests to detect changes in VL measurements and CD4 count became commercially available in 1995 and could therefore be routinely used

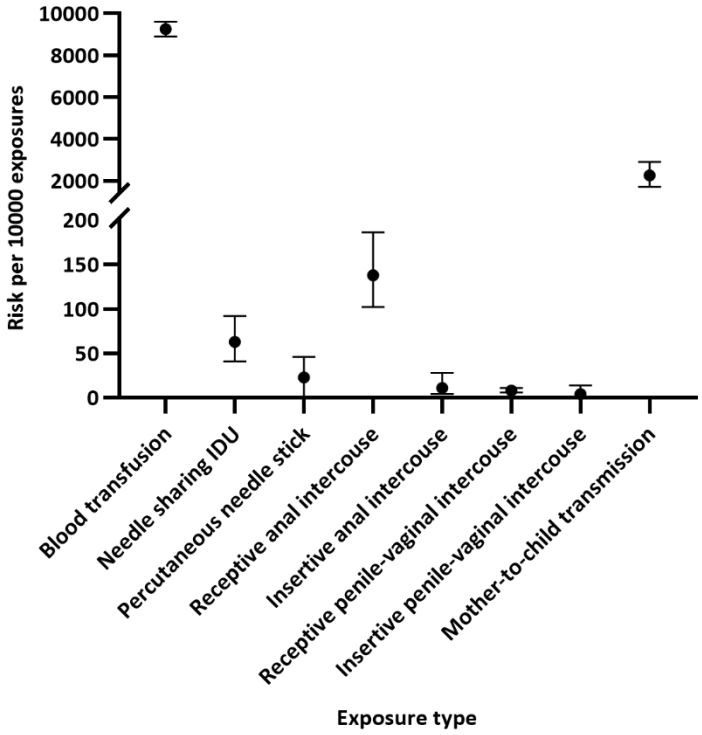
in clinical practice (111,112). Thus in 1997, the FDA recommended using changes in VL measurements and changes in CD4 count as surrogate markers to assess the efficacy of new anti-HIV drugs (122).

There are many advantages and disadvantages to this approach. As mentioned above, several studies have shown that changes in CD4 count and VL are strong predictors of disease progression and mortality (see Section 1.5 and Figure 1.2) (70,91–93,103,125–128). They are easy to quantify, and these outcomes occur more often than clinical outcomes allowing trials to recruit fewer participants and have a shorter follow-up. However, a difference in these surrogate markers between treatment groups may not translate directly into a clinical benefit. For example, several RCTs reported an improvement in CD4 count between treatment groups but no difference in the clinical endpoint of progression to AIDS or death (129). Additionally, it is possible for those with a high VL to develop an AIDS defining event (ADE), even with a high CD4 count (90). Quality controlled VL testing may not be possible in resource limited settings, such as some areas in sub-Saharan Africa, as testing requires good infrastructure, including continuous power, clean running water, and facilities to centrifuge samples (115,130). In these cases, using VL as a surrogate marker may not be possible.

1.7 Transmission of HIV

HIV is a communicable disease which can be transmitted via multiple routes including sexual transmission, vertical transmission from mother to child, and transmission through contact with infected blood (131). Each mode of transmission carries a different level of risk, as shown in Figure 1.3. The risk associated with all types of transmission can be reduced by taking antiretroviral therapy (ART), either to suppress the VL for those with HIV, to prevent HIV through pre-exposure prophylaxis (PrEP), or to prevent HIV through post-exposure prophylaxis (PEP).

Figure 1.3 Estimated risk of HIV transmission and 95% confidence intervals, by type of exposure route (132)



PrEP is advised in treatment guidelines for high risk adults, for example men who have sex with men (MSM) who do not consistently use condoms (84,85). Recommendations state that individuals should be tested for HIV before starting PrEP and every 3 months thereafter. PrEP is currently available as a once-daily combination pill containing emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF), which are both anti-HIV drugs, and has been shown to reduce the risk of transmission by up to 75% (133–139).

PEP is recommended to be taken as quickly as possible after exposure and rarely later than 72 hours after (136,140–144). Treatment should be continued for 28 days and HIV testing should be done at time of exposure, and at 1 and 3 months after exposure using an antibody test or an antigen/antibody combination test (84,85,145–147).

In 2016, a campaign was launched by the Prevention Access Campaign called “undetectable equals untransmittable” or “U=U”, which states that the risk of HIV

transmission from an individual with a suppressed VL (defined as < 200 copies/mL) to a sexual partner is negligible (148). This was based on evidence from many RCTs and observational studies (149–153). More recently, in 2019, the PARTNER2 study reported zero within-couple HIV transmissions from 972 homosexual, sero-discordant couples where the partner with HIV had a suppressed VL (154). Figure 1.4 shows the risk of transmission from heterosexual sex, according to the VL of the sexual partner with HIV. Whilst "U=U" mainly refers to sexual transmission of HIV, the risk of transmission via other routes is also substantially reduced if the individual with HIV has a suppressed VL. However, as there is limited data available, this is not formally recommended as a method of prevention for other forms of transmission (85,155).

Figure 1.4 Mean (+standard error) rate of heterosexual transmission of HIV-1 among 415 couples, according to the HIV RNA level of the HIV–positive partner

Source: (152)

1.7.1 Sexual transmission

The most common route of transmission of HIV is through sexual intercourse (131). Globally, heterosexual sex has the highest rate of transmission, accounting for approximately 80% of new infections, however in Central and Western Europe, the rate of transmission is higher in MSM (131). Several factors contribute to the risk of sexual transmission, including the type of sexual act performed, with receptive anal sex carrying the highest rate of transmission, the presence of a sexually transmitted infection (STI), and the VL of the sexual partner (44,156,157). The risk of receptive anal intercourse is estimated to be 138/10,000 exposures (95% confidence interval, CI: 102-186) and for receptive vaginal intercourse 8/10,000 exposures (95% CI: 6-11). These risks are lower for insertive anal and vaginal intercourse (132). The risk from oral sex is extremely low, however it is difficult to estimate as few studies report this as a single exposure (132,158)

Condom use is one of the main methods recommended to reduce the risk of sexual transmission, however, this is only effective if used consistently and correctly. Additionally, gender and social inequalities mean that it is not always possible to negotiate condom use with a partner (159–162). Male circumcision has also been shown to be an effective preventative measure for males, although there is little evidence showing that it affects male to female transmission (163–167). A preventative measure specifically for women is vaginal microbicides with studies showing that use of a dapivirine ring reduces the incidence of HIV transmission by approximately 30% (168,169). The dapivirine ring releases the drug over a 1-month period which has resulted in improved adherence. However, there are still problems with acceptability including difficulty inserting the ring, vaginal discomfort, cultural issues affecting a woman's willingness to use the ring, and interference with sexual intercourse (170,171).

1.7.2 Mother to child transmission

Mother to child transmission, also known as vertical transmission, can occur during pregnancy through the placenta, during birth when the foetus is exposed to cervical blood and secretions, or after birth through breastfeeding (172,173). The risk of vertical transmission has been estimated to be as high as 40% in breast feeding mothers in the absence of treatment, although it can vary based on factors, such as the VL and CD4 count of the mother (173–177). The highest risk of transmission is in late pregnancy or during birth (172). With effective treatment, the risk of mother to child transmission in Europe is now estimated to be less than 1% (178–180). However, rates of transmission differ across regions with higher rates reported in studies based in Africa and Asia compared to those in Europe and USA (181,182).

Strategies to reduce the risk of vertical transmission include HIV testing and treatment for pregnant women, providing information and support at antenatal visits, ensuring safe delivery of the baby, ensuring safe infant feeding, and providing 5 weeks of ART after birth as PEP (143,144,183).

1.7.3 Transmission via blood

Parenteral transmission occurs through injecting drug use, contaminated medical injections, accidental needlestick injuries, and blood transfusions (184). These types of exposures can carry a very high rate of transmission, with estimated risks of 0.2%-2.5% for IDUs, and 88%-100% for blood transfusions (184–187). In the 1970s and early 1980s, thousands of people in the UK suffering from haemophilia received treatment made from blood donations imported from USA which were contaminated with blood-borne viruses including HIV and hepatitis C (HCV) (188). Many subsequently became infected with these viruses. In 1985, many countries introduced routine screening of blood donations for HIV and since then, the risk of infection from blood transfusions has significantly reduced (189).

Factors which affect the risk of parenteral transmission include the type of injection equipment used, the volume of infected blood on the needle, the depth of the

needlestick injury, and the VL of the person from which the blood came (184). Methods such as offering opioid substitution therapy, clean needle exchanges, and disinfecting needles before use are all effective in reducing this risk (190). There is also an increased risk of parenteral transmission for health care workers, which is likely to further increase as the population living with HIV age and need more clinical procedures, although this risk is minimal if the source blood came from an individual with an undetectable VL (191). One study of 1,344 health care workers reported 179 percutaneous exposures to bodily fluids from individuals with HIV over a 6-month period (192). The risk of transmission after percutaneous exposure was estimated to be 0.3% (95% CI: 0.1%-0.7%) (192).

1.8 The HIV pandemic

1.8.1 Global

Since the start of the HIV pandemic, approximately 74.9 (95% CI: 58.3-98.1) million people have acquired HIV and 32.0 (23.6-43.8) million have died from AIDS-related illnesses (193). Figure 1.5 shows the global annual rate of new diagnoses of HIV since 1990, as well as the total number of PLWH, and the total number of deaths from AIDS-related illnesses (193). In 2019, there were approximately 38.0 (31.6-44.5) million PLWH, with more than 50% of those living in Eastern and Southern Africa (194). There were also 1.7 (1.2-2.2) million new diagnoses of HIV globally (193). Advances in HIV treatment and prevention have led to a decrease in the global rate of new HIV diagnoses, however this varies considerably across regions of the world and between transmission risk groups (79,194).

Figure 1.5 Global prevalence of HIV, new HIV diagnoses, and AIDS-related deaths from 1990-2017

Source: (193)
Number of people living with HIV reported in tens of millions.

1.8.2 Europe

In 2019, there were 24,801 individuals newly diagnosed with HIV in the Europe Union and European Economic Area (hereafter referred to as Europe); the majority of which were men (80%) (195). A further 111,648 individuals were newly diagnosed in the East of the WHO European Region, including 85,995 in the Russian Federation (195). Transmission via MSM accounted for approximately 39% of new diagnoses in Europe, which was higher than heterosexual sex (33%) and IDU (4%) (195).

Since 2013, the rate of new HIV diagnoses in Europe has declined overall from 6.6 cases to 5.4 cases per 100,000 population (195). However, this varies across countries and in some countries, mainly in Eastern Europe, the rate of new diagnoses has increased (79,195). Figure 1.6 shows the distribution of new HIV diagnoses across Europe in 2017.

The increase in new diagnoses seen in Eastern Europe is largely driven by IDUs, although the method of transmission is often underreported in this region (196).

There are approximately 2.9 million IDUs in Eastern Europe and Central Asia and the prevalence of HIV in this subpopulation, as well as the prevalence of other coinfections such as HCV, is higher in these regions than in the rest of the world (194). Whilst public health programs such as opioid substitution therapy are available in Eastern Europe, these are generally limited (197–200). Additionally, there is a lack of integration between health care services, such as treatment for drug use, HCV, and HIV, and this has been shown to lead to a lower use of health care services by IDUs (199–202). Social stigma in the region has also likely resulted in IDUs and individuals with HIV being less likely to seek treatment (198,199).

Figure 1.6 Distribution of new HIV diagnoses across the Europe Union and European Economic Area, and the Russian Federation in 2017

Source: (203)

1.8.3 90:90:90 targets

In 2014, the Joint United Nations Programme on HIV and AIDS (UNAIDS) published a set of targets aimed at eventually eradicating HIV. These are known as the "90:90:90 targets" (204). They stated that by 2020, 90% of individuals living with HIV should know their HIV status, 90% of those diagnosed with HIV should be on anti-HIV treatment, and 90% of those on treatment should have a suppressed VL. If these three targets are met, it would equate to 73% of individuals with HIV being virologically suppressed (204). By 2030, these targets would then need to be increased to 95:95:95. An update report in 2017 showed that there had been substantial improvements towards the goal globally, with an estimate of 70%, 77%, and 82% for the three targets, respectively (79). However, a special report published in 2020 during the coronavirus disease pandemic showed that, whilst the first target had continued to improve to 81%, the others had gone down to 67% and 59%, respectively (205). Additionally, there is a large amount of heterogeneity in these results across countries and across specific subgroups of the population, as discussed below (79,194). In 2020, UNAIDS published a new set of interim targets to reach by 2025, which aim to improve the global HIV response in order to achieve the targets set out for 2030. This report focused more on societal and legal barriers to delivery of HIV services and, whilst still including the same targets around treatment, also included targets such as 95% of women with HIV should be able to access HIV and sexual and reproductive health services, and less than 10% of PLWH should experience stigma and discrimination. These updated targets are shown in Figure 1.7.

Figure 1.7 UNAIDS HIV targets for 2025

Source: (206)

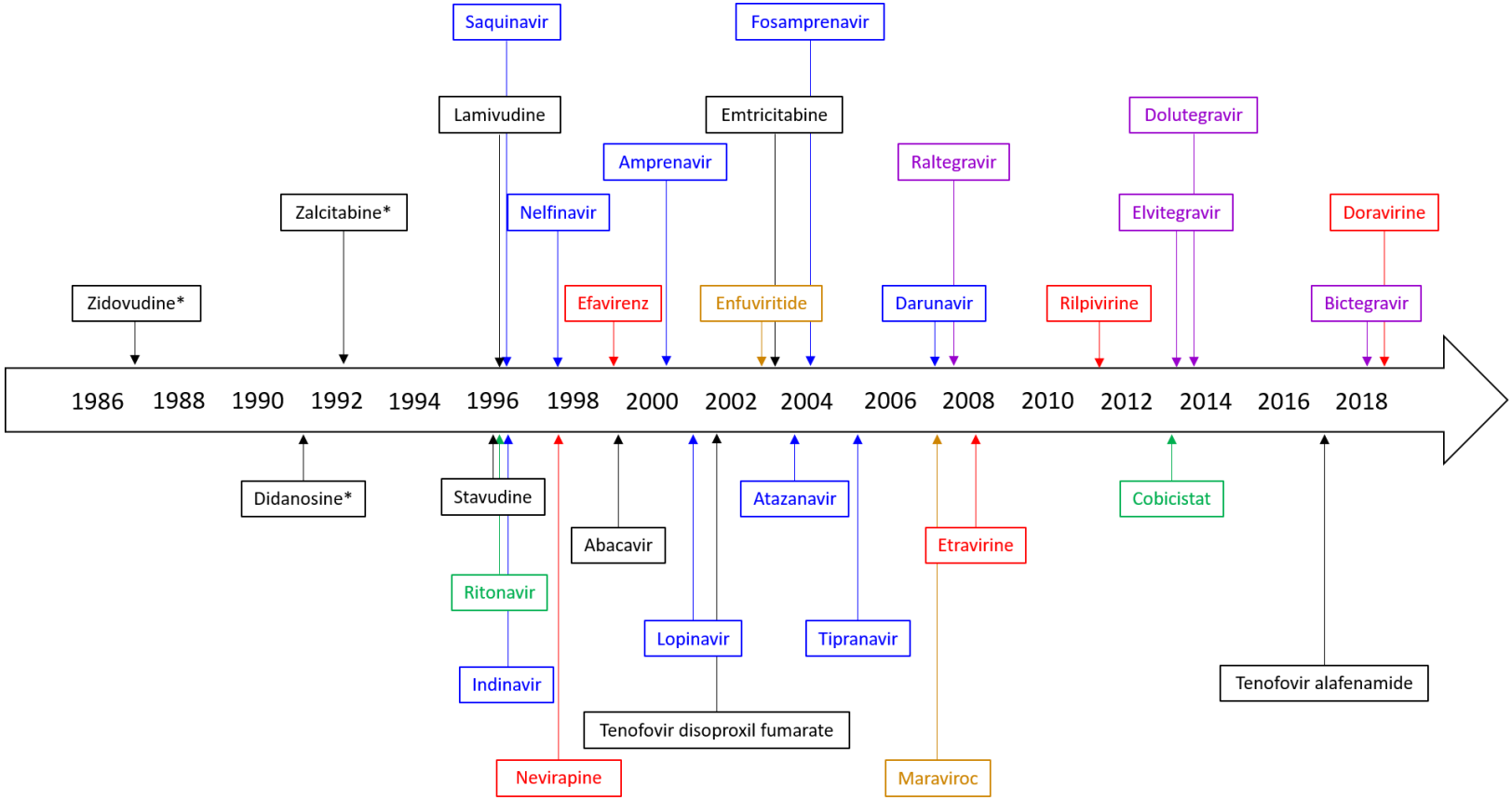
1.8.4 Key populations affected by the pandemic

HIV disproportionally affects specific subgroups of the population. This is caused by factors such as social stigma and discrimination, social inequalities, political factors, and legal inequalities (194,207). UNAIDS published a report called “the Gap Report” in 2014 which was aimed at identifying at risk groups in the population to ensure they are provided with better access to care (194). These groups include adolescent girls and young women, prisoners, migrants, sex workers, and transgender people. Results provided in the report show that 41% of new diagnoses in Europe in 2017 were in migrants and other research has shown that the majority of these individuals acquired HIV post-migration (196,208). Additionally, the prevalence of HIV among sex workers is 12 times greater than among the general population, and this is much higher for transgender women (194,209,210). In order to end the HIV pandemic, it is vital that all groups of the population are able to access services to help treat HIV and reduce the risk of HIV transmission.

1.9 HIV Treatment

From 1996 to 2018, approximately 30 anti-HIV drugs have been approved by the European Medicines Agency (EMA). The information described in the rest of this chapter is on treatment up to 2018, however new developments in HIV treatment from 2019 to 2021 are detailed in Section 1.13 below. A timeline of all anti-HIV drugs approved up to 2018 is shown in Figure 1.8. These drugs are categorised into drug classes depending on which part of the HIV virus life cycle they target (Figure 1.9). The main classes are nucleos(t)ide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), entry inhibitors, and co-receptor antagonists. Below is a discussion of the mechanisms of each drug class and Section 1.4 provides further detail on the HIV virus life cycle.

Figure 1.8 Timeline of antiretroviral drugs approved by the European Medicine Agency (EMA) (211,212)



Nucleoside reverse transcriptase inhibitors; protease inhibitors; non-nucleoside reverse transcriptase inhibitors; integrase strand transfer inhibitors; pharmacokinetic enhancers; other

*approved before the EMA was established in 1995. Therefore approvals given by the US Food and Drug Administration

1.9.1 NRTIs

NRTIs, the first drug class developed to control HIV, inhibit the action of reverse transcriptase enzymes (213). Once the host is infected with HIV, these enzymes are used to convert HIV RNA into DNA by building a chain of nucleotides found in the host cell (214). NRTIs are converted into nucleotide analogues by cellular kinase. As they have a similar structure to the host nucleotides, they are incorporated into the viral DNA chain (213,215). However, it is not possible for the reverse transcriptase enzymes to form the necessary chemical bonds with the NRTIs to continue building the chain, and therefore the viral DNA cannot be completed (213,215).

1.9.2 NNRTIs

NNRTIs also target the reverse transcriptase enzymes, aiming to stop HIV RNA being converted into DNA (213). However, they do this differently to NRTIs (213). NNRTIs bind to reverse transcriptase enzymes near the site where the enzymes act (216,217). This causes a structural change in the enzymes which restricts their activity and makes them incompatible with nucleotides, thus stopping the conversion of HIV RNA to DNA (216,217).

1.9.3 PIs

The final step before the virus is able to infect other cells in the host involves the breakdown of large chains of viral polyproteins into mature and infectious virus particles (214,218,219). This is done using protease enzymes. PIs inhibit the action of protease enzymes and stop the breakdown of the polyprotein chain (220). Whilst new virus particles are still created, they are immature and incapable of infecting new cells, and this slows the spread of infection (220).

1.9.4 INSTIs

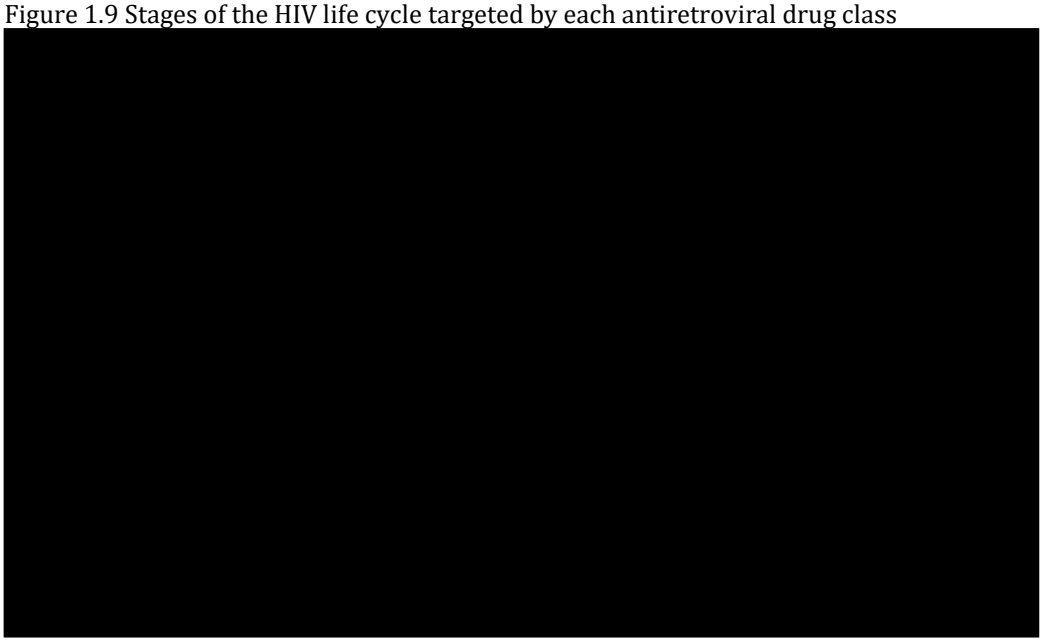
Integrase enzymes act as a catalyst for two reactions that take place during a vital step of viral replication when the viral DNA is first trimmed and then inserted into the host cell DNA (221). INSTIs, one of the latest drug classes developed to control HIV,

block the action of integrase enzymes and thus stop the viral DNA transfer. By doing this, the virus is prevented from infecting the host cell. There is no equivalent enzyme to integrase enzymes in the host cell and therefore INSTIs can block the action of the virus integrase enzyme and are unlikely to interfere with the regular cellular processes of the host (221,222).

1.9.5 Other antiretroviral drug classes

HIV enters the host by binding to CD4 cells. Initially, the HIV cell binds with both the CD4 cell receptor, and a chemokine co-receptor, usually the CCR5 or CXCR4 co-receptor (223,224). The virus particle then fuses to the outer CD4 cell membrane. Two drug classes are used to target this part of the HIV life cycle (213). Co-receptor antagonists block the virus from binding with the co-receptors, and entry or fusion inhibitors stop the fusion of the virus and CD4 cell membrane (223,224). By 2018, there were two approved drugs from these classes: maraviroc (225) and enfuvirtide (226).

Figure 1.9 Stages of the HIV life cycle targeted by each antiretroviral drug class



Source: (227)

1.10 History of HIV treatment

In 1987, six years after HIV was first identified, the first drug to control HIV was approved by the FDA (228). A phase 2 trial comparing a NRTI called Zidovudine (ZDV) to placebo in 282 participants with HIV found that ZDV reduced mortality (n=1 death on ZDV vs. 19 deaths on placebo, p<0.0001) and the frequency of OIs (n=24 OIs on ZDV vs. 45 OIs on placebo) (229). Due to the urgent need for an effective treatment, the trial was terminated early and FDA approval for ZDV was fast-tracked and given the following year. However, there was also a high incidence of serious adverse events observed in the trial, such as anaemia (24.5% on ZDV vs. 4.4% on placebo with haemoglobin <7.5 grams/decilitre, p<0.001) (230), and further research showed that the HIV virus developed resistance to ZDV after prolonged use of approximately 12-18 months (231–233).

Over the following years, as more anti-HIV drugs from the NRTI drug class received approval (234–237), the possibility of giving individuals dual therapy was investigated. Trials comparing dual combinations of ZDV, didanosine (ddI), zalcitabine (ddC), stavudine (d4T) or lamivudine (3TC) found that the risk of an ADE or death was reduced by up to 35% in the dual therapy arms compared to monotherapy arms (238–241). However, this improvement was not as marked in individuals with advanced HIV infection, for example in those with a CD4 count <150 cells/µL or with more than 12 months previous exposure to ZDV (242,243). Additionally, observational studies in the late 1990s reported that several of these drugs were associated with severe adverse drug effects such as lipodystrophy and lactate acidosis causing them to be mostly obsolete as part of contemporary ART (244–246). Other more contemporary NRTIs include abacavir (ABC) approved by the EMA in 1999, tenofovir disoproxil fumarate (TDF) approved in 2002 and emtricitabine (FTC) approved in 2003. These drugs were all shown to be non-inferior to other approved antiretroviral drugs (ARV) (247–254), and whilst there has been some evidence suggesting they are associated with adverse drug effects, for example ABC with myocardial infarction (255) and TDF with kidney disease (256), they are all key components in current treatment guidelines as the backbone of most ART regimens

for ART-naïve adults (84,85,155). More recently, tenofovir alafenamide (TAF) was approved in 2017 (257) and, for shorter term follow-up in RCTs, has been shown to be associated with a lower risk of renal and bone adverse events compared to TDF (258).

In 1996, saquinavir (SQV) became the first drug approved from a second drug class, PIs (259), and was quickly followed by indinavir (IDV) (260) and ritonavir (RTV) (261) in 1996 and nelfinavir (NFV) (262) in 1998. This created the opportunity of using combination antiretroviral therapy (cART) which involved giving individuals a regimen containing three drugs and including drugs from at least two different drug classes. This was beneficial as it was possible to target several parts of the virus life cycle at the same time (Figure 1.9). Trials showed that triple therapy with 2 NRTIs and a PI significantly reduced viral replication and improved clinical endpoints, including increased time to first ADE or death, compared to monotherapy or dual therapy (263,264). The first of these trials reported a 50% reduction in the risk of ADE or death (risk ratio 0.50 [95% CI: 0.38-0.66], p=0.0001) comparing SQV, ZDV and ddC to ZDV and ddC alone in 1,897 participants (260). Further trials showed that cART with other combinations of anti-HIV drugs, such as IDV, ZDV, and 3TC, were more effective at slowing disease progression and improving clinical outcomes for adults with HIV compared to dual or monotherapy (260,265).

Treatment with early PIs, whilst beneficial, was associated with several adverse drug effects, including lipodystrophy and urolithiasis (219,260). Additionally, they required a large number of pills to be taken daily to increase drug concentrations in the blood in order to effectively suppress the virus (266). It was found that, whilst RTV was toxic at high doses (261,267), taking this drug at a low dose could act as a pharmacokinetic booster and, when taken with other PIs, increase the levels of drug concentration in the blood (268,269). However, boosted PI-based regimens were still associated with adverse drug effects, such as gastrointestinal disorders, and a high pill burden (219,266). The approval of atazanavir (ATV) in 2004 provided the opportunity to use a simpler PI-based regimen as this could be taken once-daily (266). ATV can be used boosted or unboosted, and, although it can cause jaundice (270), which to many, is

stigmatising, it is still among the preferred PIs to be used as part of modern ART (84,85,155). Other PIs which have been approved, although are now not very commonly used, include lopinavir (LPV) (271) and amprevanir (APV) (272), which were approved in 2000, fos-amprenavir (FPV) a pro-drug of APV, approved in 2004 (273), and tipranavir (TPV) in 2005 (274). Finally, in 2007, darunavir (DRV) was approved based on results of a phase IIb trial comparing cART with RTV-boosted DRV to other PI-based regimens (275). The trial showed a clear increase in the DRV arm of the proportion of participants with a suppressed VL and no increased risk of adverse drug effects. Whilst initially intended to be used as a salvage therapy drug, it has been shown that DRV also has a high genetic barrier to resistance and is therefore widely used today. However, recent data from the D:A:D study, including 35,711 PLWH, demonstrated an increased incidence of cardiovascular disease with prolonged DRV use (incidence rate ratio 1.59 [95% CI: 1.33–1.91] per 5 years additional use) (276).

Despite the marked improvement in outcomes with cART, there were major limitations to the first available regimens including a high pill burden (277–279), a high incidence of adverse drug effects (220,230,280), drug-drug interactions (281) and lifestyle restrictions (281), as some drugs had to be taken with food and others whilst fasting. New drugs were quickly developed to address these problems. This included combination pills which reduced the number of pills individuals needed to take and therefore improved drug adherence (277,278). The first combination pill to be produced in 1997 was called Combivir (282), combining 3TC and ZDV, and since then 21 combination pills have been produced (283).

The first drug from the NNRTI drug class, nevirapine (NVP), was approved in 1998. Trials showed that regimens with two NRTIs and one NNRTI were virologically superior to two NRTIs with no third agent (284), and non-inferior when using a PI as the third agent (285). Whilst effective at suppressing VL, NVP was also associated with adverse drug effects, such as severe skin rashes (284), and the development of drug-resistant HIV (286,287). New NNRTIs were developed, including efavirenz (EFV) in 1999 and rilpivirine (RPV) in 2011. Studies have since demonstrated that EFV is non-inferior to NVP and associated with fewer immediate adverse drug effects (288).

EFV was therefore very widely used up until a few years ago when it became apparent that it was associated with more psychiatric adverse events including suicide ideation (289). It is now recommended in most guidelines as part of an alternative regimen to be used if no preferred regimens are feasible (84,85,155). A RCT comparing RPV to EFV showed similar efficacy in both arms and a favourable safety profile on the RPV arm with fewer adverse drug effects (16% on RPV vs. 31% on EFV, $p<0.0001$) (290). However, there was a slight increase in virological failure on RPV and it is therefore only recommended as part of a first-line treatment regimen for treatment-naïve adults with HIV whose VL is less than 100,000 copies/mL and CD4 count greater than 200 cells/µl. Other NNRTIs include etravirine (ETR) which was approved in 2008 (291), and most recently doravirine (DOR) approved in 2018 (292,293).

In 2008, INSTIs became one of the most recently approved HIV drug classes. There are four INSTIs on the market – raltegravir (RAL), elvitegravir (EVG), dolutegravir (DTG) and bictegravir (BIC). RAL was the first INSTI to be approved by the EMA in 2008 (228) after the BENCHMRK 1 and 2 trials showed a higher proportion of participants achieving viral suppression on triple combination therapy with RAL compared to placebo (294). This result was consistent across clinically relevant subgroups, such as participants with uncontrolled viremia (VL > 100,000 copies/mL) at baseline (295), and at long-term follow up of 5 years (296). Other trials subsequently showed that regimens containing RAL were generally well tolerated and were non-inferior for virological outcomes compared to NNRTI- (297,298) or PI- (299) based regimens. EVG was approved in 2013; trials comparing EVG pharmacokinetically boosted by cobicistat (COBI) (EVG/c) to RAL (300) and other NNRTI- (301,302) and PI- (303,304) based regimens found that EVG/c was non-inferior for shorter-term virological outcomes, up to 96 weeks.

Both RAL and EVG/c have been shown to be effective in improving virological outcomes and are well tolerated by individuals with HIV (222,296,300,305). However, EVG/c must be prescribed with a pharmacokinetic booster, which increases pill burden, the risk of adverse drug effects, and the risk of drug-drug interactions (306). Additionally, both EVG/c and RAL have been associated with the development of

drug-resistant HIV, albeit relatively rare (307), and there is a high degree of cross-resistance between RAL and EVG/c (308,309). Therefore, second generation INSTIs were developed aiming to address these issues (306).

DTG was the first second-generation INSTI to be approved in 2014 (310). DTG has a higher resistance barrier (307) and has been shown to be non-inferior to other INSTIs (311–313) and ARVs from other drug classes (314,315). There were recently raised concerns over its safety, with one small study conducted in Botswana suggesting an association with neural tube defects among infants if DTG was taken at the time of conception (316). However, updated results show the association was no longer significant and the association has not been found in other studies (317–319). BIC was approved in 2018 with RCTs showing it to be non-inferior to DTG (320,321).

INSTIs, used as part of cART, have been shown to reduce time to virological suppression (298,315,322). Whilst they have been shown to increase the risk of neuropsychiatric adverse events, such as insomnia and dizziness, in particular on DTG, they have a presumed good overall safety profile, based primarily on RCT data (222). They are therefore used with increasing frequency and are recommended in HIV treatment guidelines as part of a first line treatment regimen for those starting ART (84,85,155).

1.11 Treatment strategies

The number of anti-HIV drugs on the market has rapidly increased since 1987 and the wide variety of drugs available allows us to tailor ART regimens based on factors such as patient characteristics and preference, risk profile of the drugs, and concomitant drug use (323). As life expectancy for PLWH has increased (324–326), the prevalence of comorbidities, such as non-AIDS cancer, and hence the need for concomitant medication, has also increased (80,327). The use of several medications at the same time is known as polypharmacy and is increasingly prevalent in older age groups (328). Numerous clinical trials and observational studies have been carried out investigating drug-drug interactions between ARVs and concomitant medication, as

well as adverse drug effects, associated with different ARVs (217,219,329,330). Published treatment guidelines provide recommendations on selecting cART regimens, depending on patient characteristics, such as previous ART experience, comorbidities, and age (84,85,155). These guidelines have evolved over the years and continue to do so today. Current recommendations include initiating a cART regimen with 2 NRTIs as a backbone and an INSTI, boosted PI or NNRTI as the third drug (84,85,155), although there is a trend towards using only unboosted regimens, and therefore excluding boosted PIs and EVG/c, where possible (85). Table 1.4 shows how recommended guidelines have changed over time and regimens which are recommended currently for ART naïve adults.

Table 1.4 European AIDS Clinical Society (EACS), International Antiviral Society (IAS)-USA and British HIV Association (BHIVA) guidelines for first-line treatment regimens in ART-naïve adults with HIV

Year	EACS (84,331–333)		IAS-USA (85,334)		BHIVA (155,335)	
	Backbone	**3rd agent**	**Backbone**	**3rd agent**	**Backbone**	**3rd agent**
1996	-	-	2 NRTIs	-	-	-
1997	-	-	2 NRTIs	PI	2 NRTIs	-
1998	-	-			2 NRTIs	PI or PI/r or NNRTI
2000	-	-	2 NRTIs	NNRTI or PI/r		
2001	-	-	-	-		NNRTI
2002	-	-		NNRTI or PI/r or ABC	-	-
2003	-	-	-	-	2 NRTIs	NNRTI or LPV/r or SQV/r
2004	-	-	ZDV/3TC or ZDV/FTC or ddI/FTC or TDF/3TC or TDF/FTC	EFV or LPV/r or ATV/r or SQV/r or IDV/r	ZDV/3TC or ABC/3TC or TDF/FTC	EFV or LPV/r
2005	ABC or TDF or ZDV + FTC or 3TC	EFV or NVP or FPV/r or LPV/r or SQV/r	-	-		
2006	-	-	ZDV/3TC or ABC/3TC or TDF/FTC	EFV or LPV/r or ATV/r or SQV/r or FPV/r		EFV or LPV/r or FPV/r
2007	ABC/FTC or TDF/FTC		-	-	-	-
2008		EFV or NVP or FPV/r or LPV/r or SQV/r or ATV/r	ABC/3TC or TDF/FTC	EFV or LPV/r or ATV/r or SQV/r or FPV/r or DRV/r	ABC/3TC or TDF/FTC	EFV
2009		EFV or NVP or LPV/r or SQV/r or DRV/r	-	-	-	-
2010	-	-	TDF/FTC	EFV or LPV/r or ATV/r or DRV/r or RAL	-	-

2011	ABC/FTC or TDF/FTC TDF/FTC	EFV or LPV/r or ATV/r or DRV/r NVP or RAL	-	-	-	-
2012	-	-	ABC/3TC or TDF/FTC TDF/FTC	EFV or ATV/r DRV/r or RAL	TDF/FTC	EFV or ATV/r or DRV/r or RAL or EVG/c
2014	ABC/FTC or TDF/FTC TDF/FTC	EFV or ATV/r or DRV/r or RAL or DTG or RPV EVG/c	ABC/3TC or TDF/FTC TDF/FTC	EFV or ATV/r or DTG DRV/r or RAL or EVG/c RPV	-	-
2015	ABC/FTC or TDF/FTC TDF/FTC	DTG DRV/r or RAL or EVG/c or RPV	-	-	TDF/FTC	ATV/r or DRV/r or RAL or EVG/c or DTG or RPV
2016	ABC/3TC or TDF/FTC or TAF/FTC TDF/FTC or TAF/FTC	DTG DRV/r or DRV/c or RAL or EVG/c or RPV	TDF/FTC ABC/3TC or TDF/FTC or TAF/FTC TAF/FTC ABC/3TC or TAF/FTC TDF/FTC or TAF/FTC	EFV DRV/r RAL or EVG/c DTG RPV	-	-
2017			-	-	-	-
2018	TDF/FTC or TAF/FTC ABC/3TC or TDF/FTC or TAF/FTC	DRV/r or DRV/c or RAL or RPV DTG	TDF/FTC TDF/FTC or TAF/FTC	EFV DRV/r or DRV/c or RAL or EVG/c or RPV	-	-

	TAF/FTC	BIC	ABC/3TC or TAF/FTC TAF/FTC	DTG BIC	

Blank space indicates recommendations were the same as those previously listed
- indicates no published guidelines

One important consideration for treating people with HIV is when to start treatment. Originally, initiation of ART was delayed until the CD4 count dropped below a certain threshold. This threshold constantly changed over time and differed between studies, although the most commonly used threshold was a CD4 count <350 cells/μL (336–340). The Strategic Timing of Antiretroviral Therapy (START) study randomised 4,685 participants with a CD4 count >500 cells/μL to start treatment immediately or wait until their CD4 count dropped to 350 cells/μL or they developed AIDS (referred to as the deferred treatment group). An interim analysis of the trial showed that a higher proportion of participants in the deferred treatment group had an ADE, serious non-ADE, or had died compared to the immediate treatment group (4.1% in deferred treatment group vs. 1.8% in immediate treatment group, hazard ratio [HR] 0.43 [95% CI: 0.30-0.62], P<0.001) (104). Based on this result and other supporting studies (150,341), treatment guidelines now recommend starting ART at time of HIV diagnosis regardless of CD4 count, and this has represented a major change in the early ART paradigm (84,85,155).

HIV treatment is generally a lifelong commitment, which can be expensive and carries risks of both short- and long-term toxicities. Therefore, several studies have investigated the effectiveness of using structured treatment interruptions based on CD4 count to try to minimise time spent taking ART. The Strategies for Management of Antiretroviral Therapy (SMART) trial assessed whether it was possible to use these treatment-sparing strategies. The investigators randomised 5,472 participants to continuous treatment with no interruptions or episodic treatment where treatment was only taken when their CD4 count was between 250 cells/μL and 350 cells/μL. OIs or death occurred in 1.7% in continuous treatment vs 4.4% in the episodic treatment group (HR 2.6 [95% CI: 1.9-3.7], P<0.001) (342,343). Several other studies have compared continuous treatment to structured treatment interruptions with mixed results (344–347). Current treatment guidelines do not recommend using treatment interruptions once treatment has been started (84,85,155).

1.12 Treatment limitations

Currently there is no cure for HIV and the aim of anti-HIV drugs is to suppress VL to below the lower limit of detection, which differs on national levels, and to stop the virus reproducing in the host. The current lowest limit of detection available is 20 copies/mL (348). It is therefore necessary to maximise treatment durability. The main reasons for treatment failure include drug toxicity, poor adherence, and the development of drug-resistant HIV, and these reasons are all related (281).

1.12.1 Drug toxicity

Drug toxicities have been shown to be a major contributor to treatment discontinuation and poor ART adherence (349). All ARVs are associated with drug toxicities, however these can vary in frequency and severity. Whilst some toxicities are associated with all ARVs, others are drug-class specific or drug specific. Many clinical trials and observational studies have investigated these toxicities. One example is the D:A:D study, referred to earlier, which was initiated in 1999, and is a collaboration of 11 cohorts with over 49,000 adults living with HIV in Europe, USA, and Australia (350). The purpose of the study was to monitor adverse drug effects associated with ART, in particular cardiovascular disease, liver and renal disease, and non-AIDS-defining cancers.

General toxicities associated with ART include short-term toxicities such as nausea, vomiting, anaemia and headaches (220,329,351), and long-term toxicities such as hepato- and renal toxicity (352–355). Moreover, NRTIs have been shown to be associated with mitochondrial toxicities, which can lead to pancreatitis and peripheral neuropathy (280,356). NNRTIs are generally associated with risk of rash, dysphoria and toxic hepatitis (351,357,358). PIs have been shown to be associated with dyslipidaemia and gastrointestinal side effects, as well as an increased risk of diabetes mellitus and cardiovascular disease (220,329,358–361). Whilst INSTIs are believed to have a more favourable safety profile compared to other drug classes, they have been shown to be associated with neuropsychiatric toxicities (362–364).

However, as INSTIs are the newest drug class, there is currently limited long-term safety data available.

Treatment guidelines include tables of known adverse drug effects for all ARVs, which can be used when deciding which ARVs to prescribe and for monitoring once individuals are on a regimen. Table 1.5 shows adverse drug effects associated with specific ARVs.

Table 1.5 Most common and most severe drug toxicities associated with licensed antiretroviral drugs (84,332,365)

Antiretroviral Drug	**Known toxicities**
Nucleoside Reverse Transcriptase Inhibitors	
Zidovudine	Nail pigmentation, nausea, steatosis, myopathy, rhabdomyolysis, lipoatrophy, dyslipidaemia, hyperlactataemia, anaemia, neutropenia, diabetes mellitus
Didanosine	Pancreatitis, nausea, steatosis, liver fibrosis, ischemic heart disease (IHD), peripheral neuropathy, hyperlactataemia, diabetes mellitus
Zalcitabine	Burning in hands/feet, numbness, pain, tingling
Stavudine	Pancreatitis, steatosis, peripheral neuropathy, lipoatrophy, dyslipidaemia, hyperlactataemia, diabetes mellitus
Lamivudine	Insomnia, nausea, vomiting, abdominal pain, rash, fever
Abacavir	Rash, nausea, diarrhoea, IHD, systemic hypersensitivity syndrome
Tenofovir disoproxil fumarate	Reduced bone mineral density, increase fracture risk, renal impairment
Emtricitabine	Hyperpigmentation
Tenofovir alafenamide	Weight increase. Long term safety data not yet available
Protease Inhibitors	
Indinavir	Nausea, diarrhoea, jaundice, IHD, nephrolithiasis, increase abdominal fat, dyslipidaemia, diabetes mellitus
Saquinavir	Dyslipidaemia, PR and QT prolongation
Nelfinavir	Diarrhoea
Amprenavir	Rash, diarrhoea, nausea
Lopinavir	IHD, decrease eGFR, dyslipidaemia, PR prolongation, diarrhoea, rash
Fosamprenavir	Rash, IHD, dyslipidaemia
Atazanavir	Hyperbilirubinaemia, cholelithiasis, decrease eGFR*, nephrolithiasis, dyslipidaemia, PR prolongation, rash
Tipranavir	Hepatitis, intracranial haemorrhage, dyslipidaemia, rash
Darunavir	Rash, IHD

Non-Nucleoside Reverse Transcriptase Inhibitors	
Nevirapine	Rash, hepatitis, systemic hypersensitivity
Efavirenz	Rash, hepatitis, depression, sleep disturbances, headache, suicidal ideation, dyslipidaemia, gynaecomastia, decrease plasma 25(OH) vitamin D, QTc prolongation
Etravirine	Rash
Rilpivirine	Rash, hepatitis, decrease eGFR, depression, sleep disturbances, headache, QTc prolongation
Doravirine	Sleep disturbances, dizziness, depression, rash
Integrase Strand Transfer Inhibitors	
Raltegravir	Nausea, myopathy, rhabdomyolysis, sleep disturbances, headache, systemic hypersensitivity syndrome, depression, weight increase
Elvitegravir*	Nausea, diarrhoea, decrease eGFR*, sleep disturbances, headache, dyslipidaemia, depression, weight increase
Dolutegravir	Rash, nausea, decrease eGFR, sleep disturbances, headache, systemic hypersensitivity syndrome, myopathy, depression, weight increase
Bictegravir	Decrease eGFR, weight increase
Pharmacokinetic Booster	
Ritonavir	Decrease eGFR
Cobicistat	Decrease eGFR

Abbreviations: QTc-correct QT; eGFR-estimated glomerular filtration rate;
*possibly due to boosting with ritonavir/cobicistat

1.12.2 Adherence

Studies have shown that a decrease in the level of adherence to ART is associated with a higher risk of developing drug-resistant HIV (366,367), higher VL (368,369), lower CD4 counts (370), and a higher risk of mortality (371,372). As it is hard to directly measure adherence during routine clinical practice, individuals are usually assumed to be adherent if their VL is undetectable. The recommended minimum level of adherence required to achieve viral suppression is approximately 95% for individuals on a boosted PI-based regimen (373), although this is lower for other drug classes (374). Whilst drug toxicity is a major contributor to non-adherence, many other factors can also have an impact. Studies have shown that non-adherence is associated with demographic, clinical, and social factors, such as younger age (375,376), concomitant mental illness (377), a lack of social support (378), and substance abuse (379). Over the years, as toxicity profiles of newer ARVs have improved, the proportion of individuals discontinuing treatment or missing doses due to toxicity has reduced (380). Additionally, treatment regimens have become more

convenient with fewer lifestyle restrictions, for example with the introduction of single, combination pills and once-daily pills, and this has also improved adherence levels (381,382). Other strategies to improve adherence further include providing education and support to individuals living with HIV, for example using apps as a reminder to take medication, and addressing structural barriers, such as stigma, which have been shown to be associated with reduced adherence levels (383–387).

1.12.3 Drug resistance

Once the HIV virus has entered the host, it replicates and infects new cells at an extremely high rate (388). This rapid replication process, as described in Section 1.4, is highly prone to error and therefore results in an extremely heterogeneous virus population, with many replicated virus copies including genetic mutations (388,389). A selection of these mutated virus strains will be less susceptible to specific anti-HIV drugs or drug classes. The drug or drug class that the virus is resistant to depends on the stage of the virus life cycle in which the mutation took place, for example a mutation which took place during reverse transcriptase could result in a virus strain resistant to NRTIs or NNRTIs (388–390). Major known resistant mutations include the M184V mutation which results in complete resistance to 3TC and the K65R mutation which can cause resistance to ddC, ABC and TDF (388). Whilst an individual is receiving the particular drugs as part of their ART regimen, these resistant strains become dominant over other virus strains which are susceptible to the treatment (388). Drug-resistant strains have been shown to replicate at a slower rate than non-resistant strains, and therefore if treatment is stopped, a non-resistant virus strain which replicates quickest, known as wild type virus, will become the dominant strain (391). The resistant strains become undetectable, however they remain in latent cells, and if treatment is subsequently restarted, the resistant strain will re-emerge (392,393).

Drug resistance can occur through different mechanisms. Primary or transmitted resistance is when an individual is infected with a strain of HIV which is already resistant to one or more ARVs (394,395), and this occurs in approximately 10% of transmissions in Europe (396–398). Secondary or acquired resistance occurs when

mutations take place under selective drug pressure during ART (388,389). Whilst it is difficult to estimate the prevalence of this type of resistance, amongst individuals with virological failure who had been tested for resistance, a prevalence of approximately 75% has been reported, although this is expected to be lower amongst all individuals exposed to ART (399). Drug-resistant strains are more likely to become the dominant strain if viral suppression is not achieved. This is more common amongst those who received earlier, less effective ART regimens, for example ZDV monotherapy, or those with lower adherence levels (366,388,389). Cross-resistance can also occur when mutations caused by exposure to one ARV result in a mutated virus strain which is resistant to another ARV. This can only happen within drug classes, however it affects all of the ARV drug classes (388). Newer ARVs, for example second generation INSTIs, have a higher genetic barrier to resistance. This means they require several mutations to take place in the virus before it is resistant to the specific drug and these mutations occur less frequently (389).

It is important to generally ensure that individuals with drug-resistant HIV are not prescribed ART regimens containing drugs that the virus is resistant to. Therefore, drug resistance testing is recommended in treatment guidelines for newly diagnosed individuals and those with treatment failure, usually defined as incomplete suppression with a VL greater than 200 copies/mL at 6 months after treatment start, or virological rebound with a VL greater than 50 copies/mL in those with a previously undetectable VL (84,85,155,400).

1.13 Novel developments in HIV treatment

New ARVs are still being tested and approved today. Between 2018 and 2021, 3 anti-HIV drugs have been approved by the EMA: ibalizumab, fostemsavir, and cabotegravir (CAB).

One aim of new ARVs is to specifically target those who have been heavily treated previously and have developed multidrug-resistant HIV. Ibalizumab, an entry inhibitor, and fostemsavir, an attachment inhibitor, have both been shown to be well

tolerated in studies including individuals with HIV who had resistance to at least one ARV in three different drug classes (401,402).

As newer ARVs are more potent and have a higher genetic barrier, the possibility of reducing the number of drugs typically given in ART regimens is also being investigated. Several clinical trials have been carried out comparing dual therapy to triple therapy, with promising results showing good efficacy and tolerability on the dual therapy arm (403). This will be discussed in more detail in Chapter 5.

The possibility of making ART regimens more convenient is still being explored, and the first long-acting injection was approved for use in PLWH. CAB is an INSTI which is available as a tablet and as a two-drug regimen, long-acting injection with RPV, given once every other month (404–406). A phase 3 study comparing CAB plus RPV to an oral triple therapy regimen reported similar rates of virological suppression in both arms. However, CAB was associated with injection-site reactions and pain (406). The regimen involves first taking CAB and RPV as an oral regimen for induction therapy, and if tolerated, individuals are switched to the long-acting injection. There are several requirements for being prescribed this regimen including no history of resistance to CAB or RPV, having a VL <50 copies/mL, and having no history of treatment failure. As the injection needs to be given in clinic and individuals currently taking daily HIV drugs often only attend check-ups once or twice a year, the injections may in fact be less convenient for some individuals who would prefer to take drugs more regularly but attend clinic less regularly.

International treatment guidelines are also constantly being updated with findings from new HIV research. New sets of EACS treatment guidelines were published in 2020 and 2021. In the 2020 guidelines, the dual therapy DTG plus 3TC was added to the list of recommended regimens and information on adverse events and drug-drug interactions with ibalizumab was included (331). In 2021, the dual therapy CAB plus RPV has been added as a switch strategy for individuals who are virologically suppressed, with information added on adverse events and drug-drug interactions associated with this regimen (407). Additionally, DTG is now recommended in a dual

therapy with either FTC or 3TC (previously it was only recommended in dual therapy with 3TC) and DOR is also now recommended as part of an initial triple therapy (407).

Whilst HIV does not currently have a cure, much research is being done to produce one. One potential target for a cure is the CCR5 co-receptor, which, as explained in Section 1.4, is a chemokine co-receptor used by the HIV cell to enter the host. In 2009, a report was published detailing treatment received by an individual living with HIV, known as 'the Berlin patient', soon after he was diagnosed with acute myeloid leukaemia (408). He received two stem cell transplants from donors with a homozygous mutation in their CCR5 gene, along with total body irradiation. This mutation is called delta 32 and leads to a non-functional CCR5 co-receptor (409). Approximately 1% of Western Europeans have this mutation and it results in a high resistance to HIV-1 (409). More recently, in 2017, another individual living with HIV, known as 'the London patient', also received a similar stem cell transplant after being diagnosed with stage 4b Hodgkin lymphoma (410,411). This treatment required only one stem cell transplant and no total body irradiation. Both patients have been in remission from HIV since the transplants and are no longer receiving ART, although follow-up on 'the London patient' is still relatively short. Whilst it is unlikely that this could be used as a widespread cure for HIV, it does provide valuable evidence that the CCR5 receptor is a target for possible cures in the future (411).

Another potential target for a cure is the latently infected CD4+ T-cells (412,413). These cells are infected with HIV but remain suppressed whilst individuals are on ART. If treatment is stopped however, these cells will continue to reproduce the virus. Different cure strategies involving these cells include 'kick and kill' where the latent cells are reactivated so that they can be killed using further treatment (414,415), and 'block and lock' where the aim is to permanently suppress the latent cells, even when the individual is off ART (415). However, the first RCT assessing the impact of 'kick and kill' amongst individuals with HIV showed no additional impact on the reservoir of latent cells compared to ART alone (414). There is currently limited data available assessing the 'block and lock' approach (416).

1.14 Treatment challenges for individuals living with HIV

The rapid development of cART has transformed HIV from a fatal illness to a manageable, chronic condition (80,326). Many factors are associated with life expectancy of individuals with HIV, such as socioeconomic status, substance abuse, and adherence to ART (324).With early HIV diagnosis and effective treatment, the gap between the life expectancy of some groups of individuals living with HIV, for example MSM with a higher CD4 count, and the general population is narrowing (80,326). Nevertheless, there are still many challenges for those living with HIV, in particular for specific groups of the population such as IDUs, migrants, those of non-white ethnicity, and those with a lower CD4 count (417,418).

Whilst there is an increasing proportion of individuals who are on ART, access to treatment is still limited in particular geographical regions and to certain groups of the population (199,419–423). Since the introduction of the "90:90:90 targets" (discussed in Section 1.8.3), there have been substantial improvements in access to ART, however there are still large disparities between countries (79,424,425). Other factors which affect access to treatment include social inequalities, HIV-related stigma, and health insurance coverage (426–430).

Another challenge for individuals with HIV is an increasing prevalence of comorbidities, including cardiovascular disease, kidney disease, and non-AIDS defining cancers (431–433). This is due to many reasons. Firstly, there has been an increase in the incidence of new HIV cases in the older population, and this, coupled with a decreasing mortality rate, has resulted in an aging population living with HIV (434,435). Additionally, studies have shown that the long-term effect of HIV on the immune system, coagulation and inflammation, and long-term exposure to ART, can lead to an increased risk of comorbidities (436–439). Furthermore, many studies have shown that living with HIV is associated with an increased risk of concomitant mental illness, in particular depressive disorders (440–443). This is due to factors such as the psychological burden of having a chronic illness, as well as social stigma associated with HIV (440,444). Similarly, there is a higher risk of HIV amongst those with mental

illness compared to the general population, which also contributes to the high prevalence of concomitant mental illness (445). Finally, there is a higher prevalence of traditional risk factors for comorbidities, including smoking and alcohol use, amongst some subgroups of individuals with HIV (446). It is therefore increasingly important to address these issues, and to prescribe ART regimens which can minimise the risk of further comorbidities and reduce the likelihood of drug-drug interactions with medications for existing comorbidities.

1.15 Focus of thesis

The focus of this thesis is on use and outcomes of contemporary cART in adults living with HIV in Europe and Australia. First, I perform a thorough literature search on treatment discontinuation of INSTIs and clinical outcomes of contemporary ARVs, including the INSTIs DTG, EVG/c, and RAL, the PIs ATV and DRV, and the NNRTIs EFV and RPV. I then use data from the RESPOND and D:A:D studies to address the following aims:

I. to compare the characteristics of those initiating DTG, EVG/c, and RAL, and compare rates of and reasons for discontinuation of INSTIs;
II. to determine the prevalence of 2DRs, describe the characteristics of those starting 2DRs compared to 3DRs, and compare immunological, virological and clinical outcomes with use of 2DRs compared to 3DRs;
III. to assess changes in overall cancer incidence and death due to cancer from 2004-2019, and assess whether these differ between specific subtypes of cancer;
IV. to assess whether there is an association between INSTI use and the incidence of cancer.

Chapter 2 Literature review on contemporary antiretroviral therapy

2.1 Introduction and aims

As mentioned previously, there are over 30 antiretrovirals (ARVs) currently approved for HIV treatment across 6 main drug classes. The focus of my PhD is on contemporary ARVs commonly used in RESPOND, in particular the integrase inhibitors (INSTIs) dolutegravir (DTG), cobicistat boosted elvitegravir (EVG/c), and raltegravir (RAL). Further details on these ARVs are provided in Chapter 1, Section 1.10.

To address the overall aims of this thesis, I carried out two literature reviews; one investigating discontinuation of INSTIs (DTG, EVG/c and RAL), and another investigating clinical outcomes on contemporary ARVs; here I included DTG, EVG/c, and RAL, as well as the protease inhibitors (PIs) atazanavir (ATV) and darunavir (DRV), and the non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz (EFV), and rilpivirine (RPV). I included the PIs and NNRTIs to provide a comprehensive overview of clinical outcomes on contemporary ARVs across the main drug classes. To ensure I included all relevant literature, both searches were carried out in multiple electronic databases: PubMed, Embase and MEDLINE. The search strategy included both medical subject headings (MeSH) terms and free text searches. The specific research questions I aimed to answer in the reviews were as follows:

1. What is the incidence of INSTI discontinuation for people living with HIV (PLWH) in real-life settings?
2. What are the reasons for INSTI discontinuation?
3. What factors are associated with INSTI discontinuation?
4. What is the incidence of clinical outcomes (including cancer, cardiovascular disease (CVD), end stage liver disease (ESLD), and end stage renal disease (ESRD)) on contemporary ARVs for PLWH?

Note that whilst two-drug regimens are a specific focus of Chapter 5 of this thesis, to the best of my knowledge, there are no current studies focusing on clinical outcomes

of two-drug regimens and therefore it was not included in this literature review. Key studies of two-drug regimens are summarised in Chapter 5.

2.2 INSTI discontinuation

2.2.1 Methods

2.2.1.1 Search strategy

The full search strategy for the review addressing research questions 1-3 is included in Appendix I. The main aim of the search was to include all observational studies that addressed discontinuation of INSTIs in PLWH. The search strategy covered the following categories combined by Boolean operators:

1. HIV; and
2. INSTIs or DTG or EVG/c or RAL; and
3. Keywords relating to discontinuation (discontinu* or withdraw* or deprescrib* or cessation* or stop* or switch*)

The search was limited to articles reported in English and published after 1 January 2007, as the first INSTI was approved by the FDA in 2007. The literature search was started in November 2018 and was completed in February 2020.

2.2.1.2 Inclusion and exclusion criteria

To be included in the review, studies had to include adults aged 16 years or older, with confirmed HIV-1, report the total number of participants who discontinued DTG, EVG/c or RAL, and include all discontinuation reasons or state where reasons were unknown. If an article did not include discontinuation reasons, they were excluded. Articles were only included if the full text was available or if all relevant information could be ascertained from the abstract. Conference abstracts and posters were included if they included all relevant information. Randomised controlled trials (RCTs) were excluded from the search as they typically include a highly selected population, for example excluding IDUs, and therefore are unlikely to be representative of PLWH in real-life settings across Europe. They also may underestimate ARV discontinuation in real-life settings due to the motivated population typically enrolled in RCTs (447).

Additionally, whilst RCTs usually report the number who discontinue treatment, it is rarely included as a primary outcome. However, to allow a comparison of discontinuations in observational studies and RCTs, and to put my findings into context, discontinuation of INSTIs in key RCTs is briefly summarised below in Section 2.2.2.5.

2.2.1.3 Data collection

Initially duplicates were removed from the articles identified in the search outlined above. Titles were then screened to deem if the articles were relevant. Of those included based on the titles, abstracts were screened, and finally full texts. Once the relevant articles had been identified, I used a backward snowballing approach to identify any additional articles missed by the review, by scanning the references within the included articles.

The following data was included from the literature review: study characteristics and design including year of study, type of INSTIs included, number of participants on each INSTI in the study, number who discontinued each INSTI during follow-up, reasons for discontinuation, and any other relevant findings, for example, factors associated with discontinuation. Studies from the same cohort were grouped together in the results.

2.2.2 Results

2.2.2.1 Included studies

After removing duplicates, 3177 articles were identified and screened. The inclusion process is shown in Figure 2.1. Of these, 361 articles were included in abstract screening, 44 in the full text screening, and subsequently 19 articles were included in the literature review. The most common reason for articles being excluded were that they investigated discontinuation of different ARVs (n=431) or were results from RCTs (n=333). The articles included in the review and key information extracted from the articles is shown in Table 2.1. Of the articles included, 9 focused on multiple INSTIs, 6 focused on DTG specifically, 1 focused on EVG/c specifically, and 3 focused on RAL. The majority of studies were carried out in Europe, with 1 in USA and 1 in Canada.

Figure 2.1 Study selection process for INSTI discontinuation literature review

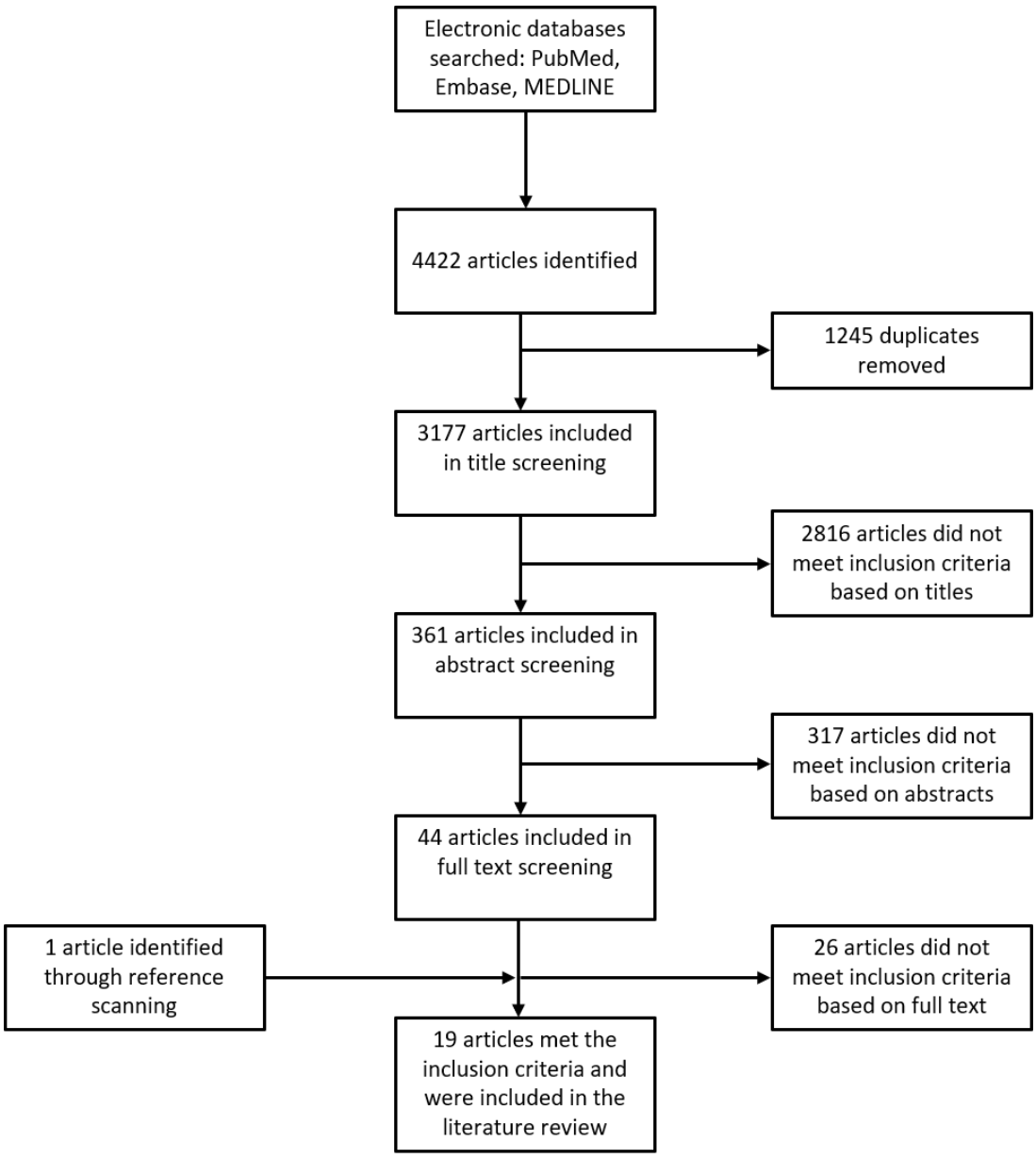


Table 2.1 Summary of 19 articles providing data on INSTI discontinuation

First Author (ref)	Year	Study name or first author affiliation	Design	Country	INSTI type	N on INSTI	N (%) discontin-ued INSTI	Reasons for discontinuation	Other results	Comments
Bonfanti P (448)	2017	Surveillance Cohort Long-Term Toxicity Antiretrovirals (SCOLTA)	Cohort study from July 2014	Italy	DTG	295	29 (10.8%)	Toxicity 16 (55%), simplification 5 (17.2%), virological failure 4 (13.8%), LTFU 2 (6.9%), other 2 (6.9%)	Higher of discontinuation with increasing age (HR 1.04 per 1 year increase [95% CI 1.01- 1.08], p=0.017) and for ART-naïve vs experienced individuals (3.05 [1.39-6.70], p=0.005). Increasing cART duration was associated with a decreasing discontinuation risk (HR not reported).	437 participants on INSTIs were included in the study with 295 having at least 1 follow-up visit

Cid-Silva P (449)	2017	Division of Clinical Virology, University of A Coruña (UDC)	Observational study from January 2015 to January 2017	Spain	DTG	275	29 (10.5%)	Toxicity 28 (96.6%), virological failure 1 (3.4%)	Higher risk of discontinuations due to an AE for females [HR 2.26 [1.12-4.54], p = 0.023) and for those treated with DTG vs EVG/c (2.45 [1.22-4.93], p = 0.012)	
					EVG/c	267	19 (7.1%)	Toxicity 12 (63.1%), virological failure 3 (15.8%), pharmacological interactions 4 (21.1%)		
Cuzin L (450)	2019	Dat'AIDS prevention	Prospective cohort study including INSTI naïve participants from January 2006 to December 2016	France	DTG	6274	786 (12.5%)	Toxicity 450 (57.3%), simplification 30 (3.8%), virological failure 54 (6.9%), other/unknown 252 (32%)	Higher risk of discontinuation due to neuropsychiatric AEs for ART experienced participants vs naïve (HR 1.57 [1.11-1.22], p=0.012) and for those on DTG (2.27 [1.63-3.17], p<0.001 vs EVG/c; 2.46 [2.00-3.04], p<0.001 vs RAL). Risk of discontinuation	
					EVG/c	3421	691 (20.2%)	Toxicity 320 (46.3%), simplification 14 (2.0%), virological failure 110 (15.9%), other/unknown 247 (35.8%)		
					RAL	11620	5910 (50.9%)	Toxicity 1158 (19.6%), simplification 2175		

								(36.8%), virological failure 898 (15.2%), other/unknown 1678 (28.4%)	also increased with increasing CD4 count nadir (1.10 per 100 cells/mm^3 increase [1.05-1.16], p<0.001)	
D'Arminio Monforte A (451)	2019	Italian cohort of antiretroviral-naïve patients (ICONA)	Cohort study including ART naïve participants from January 2011 to June 2018	Italy	DTG	994	55 (5.5%)	Toxicity 26 (47.3%), failure 9 (16.4%), pro-active 6 (10.9%), adherence 6 (10.9%), other 8 (14.5%)	Higher risk of discontinuation due to treatment failure on RAL (HR 2.00 [1.24-3.21], p=0.004) and EVG/c (1.88 [1.20-2.95], p=0.006) vs DTG but no difference in the risk of discontinuation due to toxicity between the INSTIs (1.55 [0.69-3.50], p=0.29 for RAL vs DTG; 1.94 [1.00-3.76], p=0.051 for EVG/c vs DTG)	Pro-active discontinuation defined as regimen modification with a VL≤50 copies/mL to prevent toxicity, improve adherence, simplify the regimen, or reduce pill burden.
					EVG/c	712	70 (9.8%)	Toxicity 31 (44.3%), failure 17 (24.3%), pro-active 6 (8.6%), adherence 2 (2.9%), other 13 (18.6%)		
					RAL	310	121 (39.0%)	Toxicity 11 (9.1%), failure 8 (6.6%), pro-active 76 (62.8%), adherence 12 (9.9%), other 14 (11.6%)		

Leone S (452)	2018	Italian cohort of antiretroviral-naïve patients (ICONA)	Cohort study from April 1997 to June 2016	Italy	DTG	652	70 (10.7%)	Toxicity 10 (14.3%), simplification 25 (35.7%), viral/immunological failure 7 (10.0%), adherence 4 (5.7%), other 14 (20.0%), unknown 10 (14.3%)		
					EVG/c	774	42 (5.4%)	Toxicity 11 (26.2%), simplification 3 (7.1%), adherence 3 (7.1%), other 11 (26.2%), unknown 14 (33.3%)		
					RAL	1134	436 (38.4%)	Toxicity 72 (16.5%), simplification 141 (32.3%), viral/immunological failure 28 (6.4%), adherence 30 (6.9%), other 68 (15.6%), unknown 97 (22.2%)		
Mondi A (453)	2019	Italian cohort of antiretroviral-naïve patients (ICONA)	Cohort study including DTG-naïve participants from January 2015 to	Italy	DTG	1679	121 (7.2%)	Toxicity 66 (54.5%), lack of efficacy 11 (9.1%), simplification 11 (9.1%), adherence issues 6 (5.0%),	Higher risk of discontinuation for participants diagnosed with an ADE (HR 3.38 [1.62-7.05],	

			December 2017					other/unknown 27 (22.3%)	p = 0.001) in the ART naïve group, and for participants on triple therapy with ABC (2.50 [1.06-5.93], p=0.037) or TDF/TAF (3.56 [1.33-9.53], p=0.012) vs dual therapy in the ARTexperienced group	
De Boer M (454)	2016	Leiden University Medical Center (LUMC) and the OLVG Medical Center (OLVG)	Institutional HIV databa-ses from August 2014 to March 2016	The Nethe-rlands	DTG	556	85 (15.3%)	Toxicity 76 (89.4%), not reported 9 (10.6%)	Higher risk of discontinuation due to AEs for participants on triumeq (RR 1.69 [1.00-2.84], p=0.049), or an ABC-containing regimen (1.92 [1.09-3.38], p=0.02), but a lower risk for those on a PI regimen (0.20 [0.05-0.86], p=0.03)	Paper only focused on discontinuations due to AEs, therefore no other reasons provided. As the total number of discontinuations was reported, the paper was included

Derrick CB (455)	2016	University of South Carolina School of Medicine, Columbia	Retrospective cohort study dating back to September 2012, and followed until August 2013	South-east United States	EVG/c	306	20 (6.5%)	Toxicity 5 (25.0%), virological failure 5 (25.0%), acute kidney injury 3 (15%), economic burden 2 (10%), unknown 5 (25.0%)		
Elzi L (456)	2017	Swiss HIV Cohort Study (SHCS)	Cohort study from April 2006 to December 2015	Switz-erland	DTG	1950	204 (10.5%)	Toxicity 75 (36.8%), simplification 22 (10.8%), treatment failure 2 (1.0%), patients wish 44 (21.6%), physicians' decision 26 (12.7%), pregnancy 11 (5.4%), other 18 (8.8%), no information 6 (2.9%)	Higher risk of discontinuation within the first year of treatment for females (HR 1.28 [1.06-1.53], p=0.009), younger participants (0.90 per 10 years older [0.83-0.98], p=0.011), participants with baseline VL > 100,000 (1.49 [1.09-2.02], p=0.011), and those starting RAL vs DTG (1.71	
					RAL	2091	364 (17.4%)	Toxicity 106 (29.1%), simplification 62 (17.0%), treatment failure 10 (2.7%), patients wish 54 (14.8%), physicians' decision 94 (25.8%), pregnancy 3 (0.8%), other 25 (6.9%), no		

								information 10 (2.7%)	[1.38-2.08], p<0.001)	
Hoffmann C (457)	2017	ICH Study Center Hamburg	Retrospective analysis from January 2007 to April 2016	Germa-ny	DTG	985	80 (8.1%)	Toxicity 67 (75.3%), simplification 10 (11.2%), virological failure 1 (1.1%), other 2 (2.2%)	Higher risk of DTG discontinuation due to AEs for females (HR 2.81 [1.46-5.41], p=0.002), participants aged >60 years (2.88 [1.56-5.34], p<0.001), those on ABC (2.63 [1.61-4.29], p=0.0001), and those starting DTG in 2016 vs 2014/15 (8.93 [3.76-21.28], p<0.0001)	Participants could start more than one INSTI regimen therefore n on INSTI is the number of regimens.
					EVG/c	287	47 (16.4%)	Toxicity 27 (56.3%), simplification 8 (17.7%), virological failure 5 (10.4%), other 7 (14.6%)		
					RAL	678	280 (41.3%)	Toxicity 28 (9.0%), simplification 212 (67.9%), virological failure 32 (10.3%), death 32 (10.3%), other 8 (2.6%)		
Lepik K (458)	2018	British Columbia Centre for Excellence in HIV/AIDS (BC-	Cohort study including INSTI naïve PLWH from January 2012	Canada	DTG	519	81 (15.6%)	Toxicity 27 (33.3%), other 39 (48.1%), moved away from BC 8 (9.9%), LTFU 10 (12.3%)		Participants could start more than one INSTI regimen therefore n on

		CfE) Drug Treatment Program (DTP)	to December 2014		EVG/c	394	116 (29.4%)	Toxicity 38 (32.8%), other 57 (49.1%), moved away from BC 8 (6.9%), LTFU 13 (11.2%)		INSTI is the number of regimens
					RAL	551	187 (33.9%)	Toxicity 24 (12.8%), other 144 (77.0%), deceased 43 (23.0%), moved away from BC 9 (4.8%), LTFU 10 (5.3%)		
Menard A (459)	2017	URMITE, UM63, IHU–Méditerranée Infection	Retrospective cohort study from January 2014 to November 2016	South Eastern France	DTG	517	59 (11.4%)	Toxicity 52 (88.1%), virologic failure 4 (6.8%), pregnancy 3 (5.1%)		
Naumann U (460)	2019	The WIP study	Prospective cohort study in routine clinical care in Germany from 2010 to 2014	Germa-ny	RAL	451	67 (14.9%)	Toxicity 22 (32.8%), lack of efficacy 26 (38.8%), poor compliance 5 (7.5%), other 34 (50.7%), unknown 19 (28.4%)		More than reason could be provided for each discontinuation

Peñafiel J (461)	2017	Hospital Clinic, University of Barcelona	Prospective cohort study including ART-naïve participants from 2007 to February 2016	Spain	DTG	212	26 (12.3)	Toxicity 8 (32.0%), simplification 15 (60.0%), medical decision 1 (4.0%), risk of interactions 1 (4.0%)	There were no factors associated with INSTI discontinuation in the first year, however there was a higher risk of DTG discontinuation for treatment experienced individuals (unadjusted IRR 3.11 [1.03-9.39], p=0.033). There was also a higher risk of discontinuation due to AEs for older participants (HR 1.04 [1.02-1.07], p=0.0007).	The paper only reported discontinuations within 1 year
					EVG/c	322	26 (8.1)	Toxicity 16 (66.7%), virological failure 1 (4.2%), risk of interactions 7 (29.2%)		
					RAL	557	71 (12.7)	Toxicity 20 (35.7%), simplification 25 (44.6%), medical decision 8 (14.3%), virological failure 3 (5.4%)		

Roseetti B (462)	2019	Infectious Diseases Unit, Azienda Ospedaliera Universitaria Senese	Cohort study including naïve participants from January 2014 to December 2017	Italy	DTG	132	19 (14%)	Toxicity 13 (68.4%), medical or individual choice 4 (21.1%), proactive switch 2 (10.5%)		
Teira (463)	2018	VACH cohort study	Retrospective cohort study including treatment-experienced participants from August 2016 to June 2017	Spain	DTG	600	49 (8.2%)	Toxicity 14 (28.6%), simplification 8 (16.3%), avoiding long term toxicity 3 (6.1%), virological failure 3 (6.1%), intolerance 1 (2.0%), other 18 (36.7%), unknown 2 (4.1%)		
					EVG/c	1279	51 (4.0%)	Toxicity 7 (13.7%), simplification 7 (13.7%), avoiding long term toxicity 3 (5.9%), virological failure 2 (3.9%), intolerance 2 (3.9%), drug interactions 2 (3.9%), other 24 (47.1%), unknown 4 (7.8%)		

	Todd SEJ (464)	2017	Royal Victoria Hospital	Retrospective case analysis from July 2014 to September 2015	North-ern Ireland	DTG	157	16 (10.2%)	Toxicity 13 (81.3%), pregnancy 2 (12.5%), drug-drug interaction 1 (6.2%)		
	Troya J (465)	2018	The KIRAL study	Retrospective study including ART-experienced participants from December 2007 to January 2016	Spain	RAL	467	91 (19.5%)	Toxicity 27 (29.7%), switch to fixed-dose combination regimens 31 (34.1%), physician's decision 17 (18.7%), virological failure 9 (9.9%), other 9 (9.9%), LTFU or patient's decision 6 (6.6%)		More than reason could be provided for each discontinuation
	Van Halsema C (466)	2016	Monsall Unit, North Manchester General Hospital	Retrospective, observational study from 2007 to November 2012	United Kingd-om	RAL	215	64 (29.8%)	Toxicity 18 (28.1%), simplification 12 (18.8%), virological failure 10 (15.6%), against medical advice 11 (17.2%), end of pregnancy 5 (7.8%), other 8 (12.5%)		

Overall toxicity has been reported in the table; some studies reported the specific toxicities leading to discontinuation and these will be discussed further in the results and discussion below

Abbreviations: HR-hazard ratio, RR-relative risk, LTFU-lost to follow up, AE-adverse event, ADE-AIDS defining event

2.2.2.2 Proportion discontinuing INSTIs

Across all articles included, discontinuation was highest on RAL; the proportion discontinuing RAL ranged from 17% to 50%. For EVG/c, the proportion of participants who discontinued treatment ranged from 4% to 29%, and for DTG, discontinuation ranged from 5% to 15%. Within studies including more than one INSTI, discontinuation was consistently highest on RAL and usually lowest on DTG. One study by Peñafiel et al. reported similar rates of discontinuation on DTG and RAL (12% and 13% respectively), however this study only investigated discontinuations within the first year after starting DTG or RAL (461).

2.2.2.3 Reasons for discontinuation

Overall, 15 articles reported the reasons for DTG discontinuation, and in 13 of these, toxicity was the most common reason; 2 articles reported the main reason as treatment simplification. Similarly, there were 9 articles which reported reasons for EVG/c discontinuation and the most common reason for discontinuation was again toxicity in all papers. In contrast, of the 10 articles reporting reasons for discontinuation on RAL, simplification was most common in 6 of them, toxicity was most common in 3, and lack of efficacy was most common in one.

Across the studies comparing the specific toxicities leading to discontinuation between INSTIs, central nervous system (CNS) toxicities were consistently highest on DTG. For example, Lepik et al. found that, of all participants taking an INSTI, the proportion discontinuing due to CNS toxicities was highest on DTG and lowest on RAL (3.5% DTG, 2.8% EVG/c, 1.6% RAL) (458) and this was similar to results from Peñafiel et al. (3.3% DTG, 0.9% EVG, 1.3% RAL) (461). Papers looking specifically at DTG toxicities reported proportions as high as 6.6% for CNS toxicities (459). For discontinuations due to toxicities on EVG/c and RAL, gastrointestinal toxicities were most common, although this did vary by study, especially for those looking at RAL (451,455,456,458).

2.2.2.4 Factors associated with discontinuation

Several papers looked at factors associated with INSTI discontinuation. Bonfanti et al., Hoffman et al., and Elzi et al. all found that the risk of DTG discontinuation was higher for females and for older individuals (448,456,457). This was also the case in a study by Cid-Silva et al. which focused specifically on discontinuations due to an adverse event (449).

When looking at prior treatment experience, results varied depending on the reason for discontinuation and the type of INSTI included. Bonfanti et al. found that individuals who were ART-naïve had a higher risk of INSTI discontinuation for any reason and that the risk of discontinuation decreased as the duration of cART increased (448). In contrast, Cuzin et al. found that individuals who were ART-naïve had a lower risk of discontinuation, however this was specifically for discontinuations due to CNS adverse events (450). Peñafiel et al. found that there was no difference in the risk of overall INSTI discontinuation based on treatment experience, however when focusing just on DTG discontinuations, the risk was higher for ART-experienced individuals (461).

Several papers compared the risk of discontinuation between INSTIs, after adjusting for baseline characteristics. When looking at discontinuations for any reason, Elzi et al. found that discontinuation risk was higher for RAL compared to DTG (456). However, when looking at discontinuation due to any adverse events and due to CNS adverse events, Cuzin et al. and Cid-Silva et al. found the risk of discontinuation to be higher on DTG compared to the other INSTIs (449,450). Conversely d'Arminio Monforte et al. found no difference in the risk of discontinuation due to any adverse events between the INSTIs (451).

Finally, other ARVs taken at the same time as the INSTI were investigated by De Boer et al. and Hoffman et al. and both found a higher risk of DTG discontinuation for individuals additionally initiating abacavir (ABC) (454,457). De Boer et al. also found a higher risk of DTG discontinuation for those on triumeq, which contains DTG, ABC,

and lamivudine (3TC), compared to other DTG-containing regimens, but a lower risk of discontinuation for those on a PI (454).

2.2.2.5 INSTI discontinuation in RCTs

RAL was approved based on results from the BENCHMRK 1 and 2 RCTs comparing RAL to placebo, first published in 2008 (294,296,467). Across the two trials, there was a total of 462 participants on RAL, of whom 70 (15.2%) discontinued by week 96 of follow-up (467). The most common known reason for discontinuation was due to adverse events, which was reported for 25.7% of discontinuations. By 3 years follow-up, 113 (24.5%) participants had discontinued RAL. The main reasons for discontinuation were withdrawal of consent (n=31), other reasons (n=26), and adverse events (n=23) (296).

Two RCTs were published in 2013, GS-US-236-0102 (study 102) and GS-US-236-0103 (study 103), assessing the efficacy of EVG/c (302,303). Both trials included 353 participants on EVG/c. At week 96 follow-up, 53 (15%) participants had discontinued EVG/c in study 102 and 49 (14%) had discontinued EVG/c in study 103. The most common reasons for discontinuation in study 102 were lost to follow-up (n=26) and adverse events (n=16). In study 103, the most common reason for discontinuation was adverse events (n=15).

Finally for DTG, there were 4 key RCTs: SAILING, SPRING-2, and SINGLE, published in 2013, and FLAMINGO published in 2014 (311,314,315,468). By week 48 follow-up, the proportion discontinuing DTG ranged from 7% in the FLAMINGO trial to 16% in the SAILING trial. The most common reason for discontinuation was lack of efficacy in SAILING and SPRING-2, lost to follow-up in FLAMINGO, and adverse events in SINGLE. Across the trials, out of all participants discontinuing DTG, the proportion discontinuing due to an adverse event ranged from 7.3% to 19.6%.

2.3 Clinical outcomes on contemporary ARVs

2.3.1 Methods

2.3.1.1 Search strategy

The full search strategy for the review addressing research question 4 on the incidence of clinical outcomes on contemporary ARVs for PLWH, is included in Appendix II. The main aim of the search was to include all studies that reported the incidence of CVD, cancer, ESLD, or ESRD on any of the contemporary ARVs listed in Section 2.1. The search strategy covered the following categories combined by Boolean operators:

1. HIV; and
2. INSTIs or DTG or EVG/c or RAL or ATV or DRV or EFV or RPV; and
3. Keywords or MESH terms relating to CVD, cancer or malignancy, ESLD, or ESRD

The search was limited to articles reported in English and published after 1 January 1998, when ATV was approved by the FDA. ATV was the earliest ARV to be approved of the contemporary ARVs being investigated. The literature search began in November 2018 and was completed in February 2020.

2.3.1.2 Inclusion and exclusion criteria

To be included in the review, studies had to include adults, aged 16 years or older, with confirmed HIV-1 and report the incidence of any of the clinical outcomes listed above on any of the ARVs listed above. Articles were not included if they only reported the incidence of the outcome on a group of ARVs, rather than each one individually, unless all ARVs included in the group were of interest in this review (for example, articles were included if they analysed DTG, EVG/c and RAL as a group of INSTIs, but not if they additionally analysed bictegravir as part of the INSTI group, as bictegravir was not of interest in this review). Additionally, articles were not included if they focused on lipid abnormalities associated with the listed outcomes, rather than the outcomes themselves. As with the first literature review, articles were only

included if the full text was available or if all relevant information could be ascertained from the abstract. Conference abstracts and posters were included if they included all relevant information.

2.3.1.3 Data collection

The method for data collection was the same as outlined in Section 2.2.1.3.

The following data was included from the literature review: study characteristics and design, type of ARVs included, type of clinical outcome investigated, number of participants on the ARVs, incidence of the outcome on the ARVs, and any other relevant findings. Again, studies from the same cohort were grouped together in the results.

2.3.2 Results

2.3.2.1 Included studies

After removing duplicates, 3742 articles were identified and screened. The inclusion process is shown in Figure 2.2. Of these, 376 articles were included in abstract screening, 49 in the full text screening, and subsequently 20 articles were included in the literature review. The most common reason for articles being excluded were that they focused on different outcomes (n=455) or different ARVs (n=369). The articles included in the review and key information extracted from the articles is shown in Table 2.2. Of the articles included, 13 focused on CVD, 1 focused on cancer specifically, 2 focused on ESLD, and 1 focused on ESRD. The remaining 3 articles included multiple outcomes. The majority of studies were carried out in Europe and the USA.

Figure 2.2 Study selection process for clinical outcomes on contemporary ARVs literature review

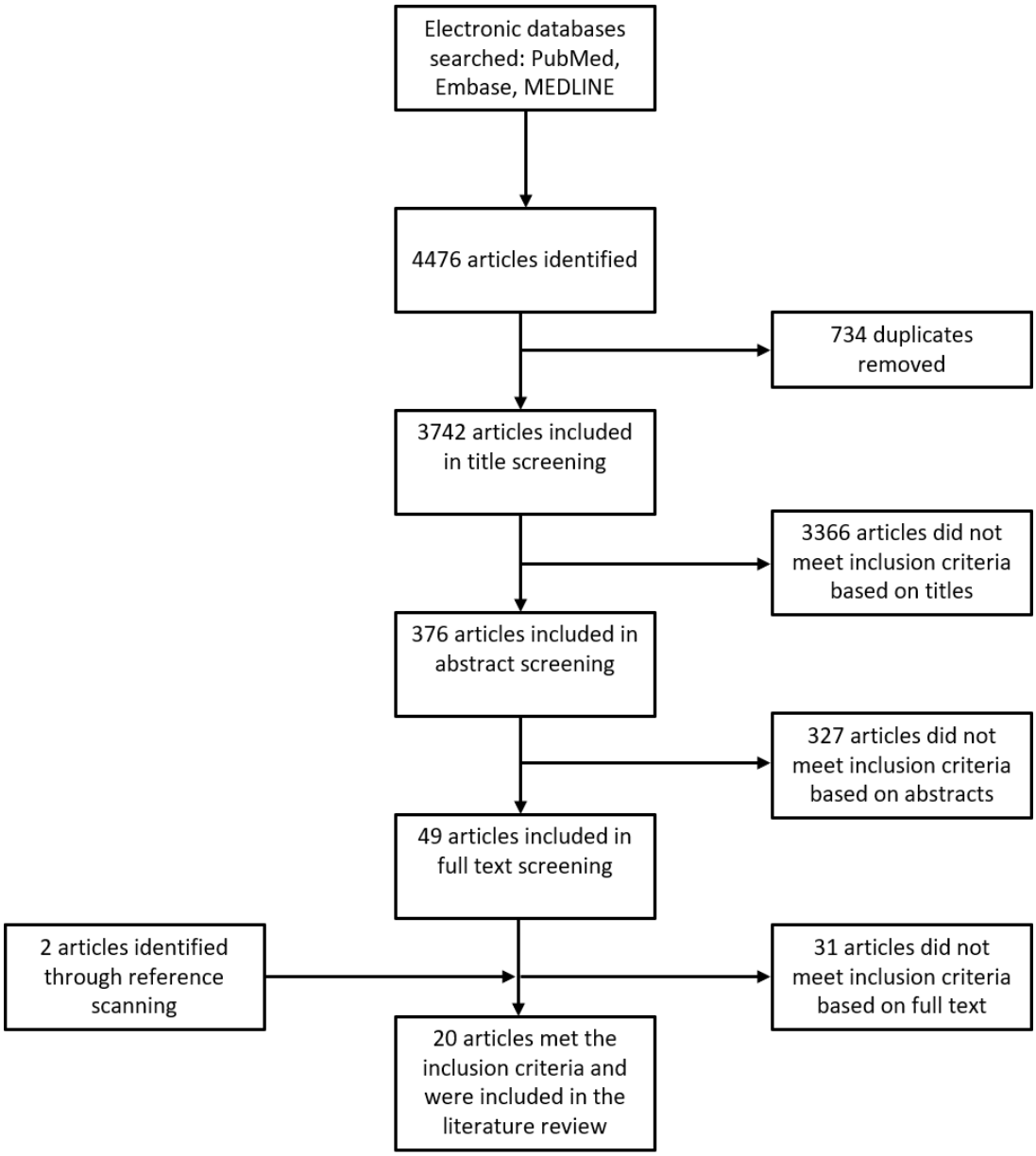


Table 2.2 Summary of 20 articles providing data on clinical outcomes on contemporary ARVs

Author (ref)	Year	Study name or first author affiliation	Design	Country	ARV	N included	Outcome	Main Result	Other results
Antinori A (469)	2019	TMC114-HIV4042 observati-onal study	Observational study in routine clinical settings from 2009 to 2012	Italy	DRV	875	CVD	IR 15/1000 PYFU [95% CI 9-22]	There was no increased risk of CVD with increasing DRV therapy duration (HR 1.02 per 100% increase in duration [95% CI 0.90-1.15], p=0.81) or increasing maximum DRV daily dose (0.91 for 1200 mg vs 800mg [0.28-2.98], p=0.87). The risk of CVD increased with increasing age (HR 3.25 per 25% increase in age [1.80-5.87], p<0.0001) and systolic blood pressure (1.76 per 10% increase [1.28-2.42], p=0.0005).
Opsomer M (470)	2018	Janssen Research and Develop-ment, Beerse, Belgium	Pooled data from 19 Janssen-sponsored, international, phase 2/3/4 studies from 2003 to 2016	Multiple regions	DRV/r	5713	CVD	Pooled estimate: IR 6.15/1000 PYFU [2.91- 11.89]	The risk of CVD was lower for participants using once-daily DRV/r 800/100 mg (IR 0.71/1000 PYFU [0.16-3.05]) vs twice-daily DRV/r 600/100 mg (9.21 [4.94-16.04]). CVD incidence rates did not increase with exposure to

									DRV/r over increasing yearly intervals.
Rosenblatt L (471)	2016	US Medical, Bristol-Myers Squibb, Plainsboro	Retrospective observational cohort using commercial and Medicaid insurance claims databases including ART-naïve participants from January 2007 to December 2013	USA	EFV	Commercial population: 11978 on EFV, 10234 on non-EFV; Medicaid population: 2943 on EFV, 4457 on non-EFV	CVD	Commercial population: EFV – IR 3.43/1000 PYFU [2.72- 4.28], non-EFV – 4.73/1000 PYFU [3.73-5.91]; Medicaid population: EFV – IR 9.55/1000 PYFU [7.17- 12.46], non-EFV – 9.88/1000 PYFU [7.71- 12.46]	In propensity-score-weighted models, participants on EFV regimens had a significantly lower risk of CVD vs non-EFV regimens in the commercial population (HR 0.68 [0.49, 0.93]); there was no significant difference in the medicaid population (0.83 [0.58-1.19]). In both populations, the rates of CVD events were highest among the oldest group of participants aged 55–65. In the commercial population, among participants with ABC use (n = 2029), there was no significant difference in the risk of CVD for EFV vs no EFV (HR 1.33 [0.59-2.99]). Among those without ABC use (n = 20183), there was a significantly lower risk for those on EFV (0.61 [0.43-0.86]).

Desai M (472)	2015	Veterans Health Administ-ration Clinical Case Registry	Longitudinal cohort of US veterans from the Veterans Health Administration Clinical Case Registry from January 1996 to December 2009	USA	ATV	6325	CVD	OR 1.33 [1.06-1.67]	The combination ART regimen with the biggest increase in odds of CVD was EFV plus FTC/TDF (OR 1.45 [1.08-1.96])
					EFV	14268	CVD	OR 1.40 [1.19-1.66]	
LaFleur J (473)	2017	Departm-ent of Pharmac-otherapy, University of Utah College of Pharmacy	Population-based, historical cohort study in Veterans Health Administration hospitals and clinics including ART-naive participants from July 2003 to December 2015	USA	ATV	1529 ATV	MI	IR 5.2/1000 PYFU [2.2-10.2]	Using inverse probability of treatment weighting, the risk of MI and stroke was lower on ATV-regimens vs other PIs (Stroke: HR 0.47 [0.25-0.88]; MI 0.51 [0.33-0.78]), NNRTIs (0.63 [0.41-0.96]; 0.70 [0.53, 0.91]), or INSTIs (0.47 [0.22-0.97]; 0.53 [0.31-0.90])
							Stroke	IR 10.4/1000 PYFU [6.0-16.9]	
					INSTI	611 on INSTI (275 RAL, 203 EVG, 133 DTG)	MI	IR 13.0/1000 PYFU [4.8-28.3]	
							Stroke	IR 33.1/1000 PYFU [18.5-54.6]	

Diaz C (474)	2016	The Instituto Nacional de Infectologia Evandro Chagas (INI) of Fundação Oswaldo Cruz (FIOCRUZ)	Observational, longitudinal, open cohort, including ART experienced participants from January 2000 to December 2010	Brazil	EFV	1982	CVD	Crude IRR per additional year exposure: 0.75 [0.67-0.84], p<0.001; adjusted for baseline characteristics 0.78 [0.69-0.87], p<0.001	Risk of CVD was higher for those age ≥ 40 (IRR 2.30 [1.40-3.2]), with a CD4 nadir ≤ 50 cells/mm^3 (1.73 [1.05-2.40], detectable HIV-RNA (3.39 [2.00-5.00]), prior CVD (2.82 [1.50-5.00]. The risk decreased with increasing percentage time on ART (0.36 [0.20-1.75]. (95% CIs were estimated from a figure).
					ATV/r	627	CVD	Crude: 0.60 [0.45-0.79], p<0.001; adjusted 0.60 [0.45-0.8], p=0.001	
					DRV/r	220	CVD	Crude: 0.71 [0.50-1.02], p=0.067; adjusted 0.65 [0.45-0.95], p=0.027	
					INSTI	180	CVD	Crude 0.82 [0.53-1.28], p=0.39; adjusted 0.78 [0.50-1.22], p=0.28	
Brouwer E (475)	2014	Departm-ent of Pharmacy Practice and Science, University	Cohort study using North Carolina (NC) Medicaid administrative data from 2002 to 2008	USA	ATV	543 ATV vs 2938 non-ATV	MI	IR 5.1/1000 PYFU [1.9-13.6]	There was no significant difference in the risk of CVD on ATV vs using a NNRTI as the 3rd agent: unadjusted HR 1.13 [0.36-3.51], inverse probability weighted HR 1.12 [0.35-3.62]

		of Kentucky							
Durand M (476)	2011	Régie de l'Assuran-ce Maladie du Québec	Nested case–control study within a cohort study using data obtained from the linkage of administrative databases: the Régie de l'assurance-maladie du Québec and Med-Echo database in Quebec, from January 1985 to December 2007	Canada	ATV	68	AMI	Crude OR 1.14 [0.48-2.70], p=0.77; adjusted for baseline characteristics: 1.02 [0.42-2.46], p=0.96	
					EFV	354	AMI	Crude: 1.83 [1.21-2.76], p=0.004; adjusted: 1.83 [1.21-2.76], p=0.004	
Costagliol a D (477)	2020	ANRS-CO4 French Hospital Database on HIV (FHDH)	Case-control study nested in the hospital-based, open cohort from 2006 to 2012	France	ATV	397	MI	Crude OR 1.32 [0.84-2.08]; adjusted for exposure to other ARVs and baseline characteristics 1.54 [0.87- 2.73]	

					DRV	148	MI	Crude 1.14 [0.36-3.59]; adjusted 0.51 [0.11-2.32]	
Engstrom K (478)	2014	Montefio-re Medical Center, Bronx, NY	Longitudinal, cohort study from January 2006 to January 2013	USA	EFV	1625	MI	0%	There was no significant difference for MI on EFV vs ATV (RR 0.32 [0.01-7.81], p = 0.48). There was a higher risk of heart failure on ATV vs EFV (5.94 [2.9-11.8], p<0.0001)
							Heart failure	0.4%	
					ATV/r	1177	MI	0.1%	
							Heart failure	2.1%	
Ryom L (479)	2018	The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study	Multicohort study from January 2009 to February 2016	Europe, USA, and Australia	ATV/r	35711 (6571 exposed at baseline, 9499 exposed by last visit)	CVD	IR increased from 5.03/1000 PYFU [4.69- 5.37] in individuals never exposed to 6.68/1000 PYFU [5.02-8.35] in individuals exposed for more than 6 years	After adjustment for potential confounders, there was no increased risk of CVD with increasing exposure to ATV/r (IRR 1.03 per 5 years increased exposure [0.90-1.18])
					DRV/r	35711 (1428 exposed at baseline, 7964 exposed by last visit)	CVD	IR increased from 4.91/1000 PYFU [4.59-5.23] in individuals never exposed to 13.67/1000 PYFU	After adjustment for potential confounders, there was an increased risk of CVD with increasing exposure to DRV/r (IRR 1.59 per 5 years [1.33-1.91])

								[8.51-8.82] in individuals exposed for > 6 years.	
Worm S (480)	2010	The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study	Multicohort study to February 2008	Europe, USA, and Austral-ia	EFV	33308 included (13522 were exposed to EFV)	MI	No exposure: IR 3/1000 PYFU; <1 year exp: 3.9; 1-2 year exp: 3.8; 2-3 year exp: 3.9; 3-4 year exp: 4.5; 4-5 year exp: 3.2; ≥5 year exp: 4.1 (Estimated from figure in article)	There were no significant association between the risk of MI and cumulative exposure to efavirenz (RR per additional year 1.02 [0.96-1.08])
d'Arminio Monforte A (481)	2013	The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study	Multicohort study from February 2011	Europe, USA, and Austral-ia	ATV	27115 PYFU on ATV - unclear how many participant-ts contributed to PYFU	MI	No exposure: 2.8/1000 PYFU [2.6-3.0]; ≤1 year exp: 3.1 [2.1-4.0]; 1-2 year exp: 3.5 [2.2-4.8]; 2-3 year exp: 2.5 [1.4-4.1]; > 3 year exp: 2.0 [1.2-3.2]	There was no association between cumulative exposure to ATV and risk of MI or stroke, either overall (relative rate/year 0.96 [0.88-1.04]), when boosted with RTV (0.99 [0.90–1.08]), or when unboosted (0.80 [0.61-1.03])
							Stroke	No exposure: 1.7/1000 PYFU [1.6, 1.9]; ≤1 year exp: 2.6 [1.7, 3.4];	

								1-2 year exp: 1.7 [0.9, 2.8]; 2-3 year exp: 1.7 [0.8, 3.1]; > 3 year exp: 1.7 [1.0-2.7]	
Ryom L (482)	2016	The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study	Multicohort study from February 2004 to February 2014	Europe, USA, and Austral-ia	ATV/r	Not reported	ESLD/ Hepatoce-llular carcino-ma	Adjusted for other ARV exposure: IRR 0.71 per 5 years increased exposure [0.44, 1.66], p=0.17	
					EFV	Not reported	ESLD/ Hepatoce-llular carcino-ma	Adjusted for other ARV exposure: 0.80 per 5 years increased exposure [0.63-1.01], p=0.06	
					DRV/r	Not reported	ESLD/ Hepatoce-llular carcino-ma	Adjusted for other ARV exposure: 0.33 per 5 years increased exposure [0.11-1.02], p=0.05	
Ryom L (483)	2014	The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study	Multicohort study from February 2004 to February 2012	Europe, USA, and Austral-ia	ATV/r	7857	Advanced CKD/ ESRD	After adjustment for baseline characteristics compared to never started, started and off ATV/r: IRR 1.52 [0.91-2.54]; started and on ATV/r: 1.52	There was a higher risk of advanced CKD/ESRD for participants with hypertension (IRR 2.48 [1.70-3.62]), diabetes (3.29 [2.18-4.98]), current smokers (1.79 [1.08-2.97]), those with decreasing eGFR (2.05 per 10ml/min lower [1.86-2.26]),

								[0.92-2.51]	and decreasing CD4 (1.37 per halving [1.19-1.56])
Cozzi-Lepri A (484)	2018	EuroSIDA	Prospective cohort study from January 2005 to December 2014	Europe, Israel, and Argenti-na	RAL	1470 RAL cohort (started RAL>21 December 2007) vs 3787 historical cohort (started RAL< 21 December 2007) vs 4467 concurrent cohort (started a different ART regimen> 21 December 2007)	Cancer	RAL cohort: IR 11.1/1000 PYFU [8.4-14.6]; Historical cohort: 12.0 [9.0-16.1]; Concurrent cohort: 8.3 [7.0-9.9]	After adjustment for baseline characteristics, there was no difference in the risk of cancer (RR 0.73 [0.47-1.14], p=0.17 for RAL vs. historical; RR 0.95 [0.65-1.39], p=0.79 for RAL vs. concurrent
Yang R (485)	2011	Departm-ent of Infectious Diseases, Zhongnan	Observational cohort including participants coinfected	China	EFV	190	Advanced liver disease	OR 0.80 [0.43-1.49]	

		Hospital of Wuhan University	with HIV and hepatitis B from September 2004 to April 2010						
Horberg M (486)	2018	Mid-Atlantic Permane-nte Research Institute, Kaiser Permanente Mid-Atlantic States	Observational post-licensure safety study from October 2007 to June 2013	USA	RAL	1757 RAL cohort (started RAL in 2007-2013) vs 2542 historical cohort (started RAL in 2005–2007) vs 3920 concurrent cohort (started a different ART regimen in 2007-2013)	CVD	RAL IR 7.3/1000 PYFU [4.7-9.9]; historical 6.6 [3.8-9.5]; concurrent 4.1 [2.8-5.4]	After adjustment for propensity scores, there was no significant difference in the risk of CVD between the cohorts (RAL vs historical: HR 1.23 [0.57, 2.66], p= 0.60; RAL vs concurrent: 0.95 [0.51, 1.75], p=0.86)
							ADC	RAL 14.4/1000 PYFU [10.7-18.1]; historical 9.3 [5.9-12.7]; concurrent 9.8 [7.8-11.8]	After adjustment for propensity scores, there was a higher risk of ADC in the RAL cohort (RAL vs historical: 2.69 [1.53- 4.71], p<0.001; RAL vs concurrent: 1.85 [1.21-2.82] p<0.001)
							NADC	RAL 19.3/1000 PYFU [15.2-23.5]; historical 7.8 [4.7-10.8]; concurrent 9.1 [7.2-11.0]	After adjustment for propensity scores, there was a higher risk of NADC in the RAL cohort (RAL vs historical: 2.26 [1.29-3.94], p<0.001; RAL vs concurrent: 1.88 [1.26-2.78], p<0.001)

							Hepatic events	RAL 21.7/1000 PYFU [17.1-26.4]; historical 26.8 [20.9-32.6]; concurrent 18.0 [15.2-20.7]	After adjustment for propensity scores, there was no significant difference in the risk of hepatic events between the cohorts (RAL vs historical: 0.92 [0.61-1.39], p=0.69; RAL vs concurrent: 1.25 [0.89-1.75], p=0.20
Troya (487)	2018	The KIRAL study	Observational, retrospective study including ART experienced participants from December 2007 to January 2016	Spain	RAL	467	CVD	2 (0.4%)	
							Cancer	4 (0.8%)	
							Renal insuffici-ency	1 (0.2%)	
INITIO Trial Internatio nal Co-ordinati-ng Committ-ee (488)	2006	INITIO Trial	RCT in outpatient clinic sites from January 2003 to June 2004	Austral-ia, Brazil, Canada, New Zealand, Europe	EFV	297 EFV vs 311 NFV vs 303 EFV & NFV	CVD	EFV 12 events (4.0%); NFV 9 (2.9%); 12 (4.0%) EFV & NFV	
							ADC	EFV 8 (2.7%); NFV 10 (3.2%); EFV & NFV 10 (3.3%)	

Abbreviations: ATV-atazanavir, ATV/r-ritonavir boosted ATV, DRV/r-ritonavir boosted darunavir, ABC-abacavir, EFV-efavirenz, NFV-nelfinavir, NNRTI-non-nucleoside reverse transcriptase inhibitor, MI-myocardial infarction, AMI-acute MI, ADC-AIDS defining cancer, NADC-non-ADC, eGFR-estimated glomerular filtration rate, IR-incidence rate, IRR-IR ratio, CI-confidence interval, HR-hazard ratio, OR-odds ratio, RR-relative risk, PYFU-person years of follow up

2.3.2.2 CVD related outcomes

Of the eight studies included which focused on CVD incidence, 4 included participants on INSTIs: 2 of these looked at RAL and 2 focused on INSTIs as a class.

One study investigating CVD whilst on RAL found the incidence rate (IR) of CVD was 7.3/1000 person-years of follow-up (PYFU) for participants on RAL-containing regimens and 4.1/1000 PYFU for participants who were on other regimens; after adjustment for potential confounders using propensity scores, there was no significant difference in the risk of CVD between the groups (RAL vs non-RAL hazard ratio (HR) 0.95 [95% CI: 0.51-1.75], p=0.86) (486).

Diaz et al. included INSTIs as a class and reported no difference in the risk of CVD with increasing exposure to INSTIs (adjusted HR per additional year of INSTI exposure 0.78 [95% CI: 0.50-1.22], p=0.28) (474). Additionally, LaFleur et al. investigated the incidence of myocardial infarction (MI) and stroke on INSTIs, and reported IRs of 13.0/1000 PYFU and 33.1/1000 PYFU, respectively (473). LaFleur et al. also reported the incidence of MI and stroke on ATV-containing regimens to be 5.2/1000 PYFU and 10.4/1000 PYFU, respectively (473). After adjustment for potential confounders, the incidence of MI and stroke on ATV was found to be lower than on INSTIs (stroke HR 0.47 [0.22-0.97]; MI HR 0.53 [0.31–0.90]), PIs (MI HR 0.47 [0.25-0.88]; stroke HR 0.51 [0.33-0.78]) and NNRTIs (MI HR 0.63 [0.41-0.96]; stroke HR 0.70 [0.53-0.91]). Other studies investigating the incidence of CVD on ATV also found no increased CVD risk with increasing ATV exposure. In the D:A:D study, Ryom et al. reported an IR of 5.03/1000 PYFU in participants with no exposure to ritonavir-boosted ATV (ATV/r) increasing to 6.68/1000 PYFU for participants with more than 6 years exposure to ATV/r (479), however after adjustment for potential confounders, there was no difference in the risk of CVD with increasing ATV/r exposure (IR ratio (IRR) 1.03 per 5 years increased exposure [95% CI: 0.90-1.18]). In contrast, Diaz et al. found that the risk of CVD decreased with increasing ATV/r exposure (IRR 0.60 per 1 year increased exposure [0.45-0.81], p=0.001) (474).

When looking at the IR of CVD on DRV/r, Antinori et al. reported an IR of 15.0/1000 PYFU for those ever exposed to DRV/r (469), whilst Ryom et al. showed an increasing incidence from 4.91/1000 PYFU in those never exposed to DRV/r compared to 13.67/1000 PYFU in those with more than 6 years exposure (479). Ryom et al. also showed that, after adjustment for potential confounders, the risk of CVD increased with increasing exposure to DRV/r (IRR 1.59 per 5 years increased exposure [1.33-1.91]). This result was not replicated in other studies, however there are considerable differences between the studies in terms of study design, length of follow-up, sample size, and the definition of CVD used (469,470,477).

Finally, for EFV, Desai et al. and Durand et al. reported higher odds of CVD for those exposed to EFV compared to those not exposed (472,476). Conversely, Diaz et al. found a decreasing risk of CVD with increasing exposure to EFV (IRR per additional year exposure 0.78 [0.69-0.87], p<0.001) (474), and when looking specifically at MIs, Worm et al. reported no increased risk of MI with increasing EFV exposure (relative risk (RR) per additional year exposure 1.02 [0.96-1.08]) (480).

2.3.2.3 Cancer related outcomes

Two articles compared the incidence of cancer in a cohort of participants on RAL-containing regimens to a cohort of participants on regimens containing other ARVs. Using data from the EuroSIDA cohort study, Cozzi-Lepri et al. reported an IR of any cancer of 11.1/1000 PYFU for participants on RAL compared to 8.3/1000 PYFU for participants on other ARVs; however after adjustment for potential confounders, there was no difference in the risk of cancer on RAL (RR 0.98 [0.67-1.41], p=0.90) (484). In contrast, Horberg et al. found a higher adjusted risk of AIDS-defining cancers (ADC) and non-ADC (NADC) on RAL (ADC: IR 14.4/1000 PYFU on RAL vs 9.8/1000 PYFU on non-RAL, HR 1.85 [1.21-2.82], p<0.001; NADC: 19.3/1000 PYFU on RAL vs 9.1/1000 PYFU on non-RAL, HR 1.88 [1.26-2.78], p<0.001) (486). Troya et al. also looked at clinical outcomes on RAL in a cohort of ART-experienced participants and reported that 4 (0.8%) participants had cancer (487).

Finally, one article compared the number of AIDS-defining events, including ADCs, for participants on 2 NRTIs plus EFV, nelfinavir (NFV) or both in the INITIO RCT, and found similar numbers across the groups (n=8 [2.7%] with ADC on EFV only vs 10 [3.2%] on NFV only vs 10 [3.3%] on EFV plus NFV) (488).

2.3.2.4 Liver related outcomes

Three articles investigated the incidence of liver toxicity whilst on the ARVs of interest. Horberg et al. reported an IR of 21.7/1000 for hepatic events (not defined within the manuscript) on RAL and 18.0/1000 PYFU for participants on other ARVs with no difference in the adjusted risk of hepatic events between the groups (adjusted HR 1.25 [0.89-1.75], p=0.20) (486).

Yang et al. investigated the incidence of advanced liver disease (defined as liver cirrhosis, hepatocellular carcinoma, or severe reactivation of a pre-existing chronic hepatitis B) on EFV in a cohort of participants coinfected with HIV and hepatitis B and found no difference in the risk on EFV (unadjusted odds ratio [OR] 0.80 [0.43-1.49], p=0.48) (485).

Finally, Ryom et al. reported the incidence of ESLD or hepatocellular carcinoma on ATV/r, EFV, and DRV/r in the D:A:D study and found no change in the incidence with increasing exposure to any of the ARVs (482).

2.3.2.5 Renal related outcomes

Two of the articles included in the review reported renal toxicity. In a cohort of 467 ART-experienced participants on RAL, Troya et al. reported renal insufficiency (not defined within the manuscript) for 1 (0.2%) participant (487).

Finally, one article from the D:A:D study reported the incidence of advanced chronic kidney disease or ESRD on several ARVs, including ATV/r (483). This article showed a higher incidence for participants who were on ATV/r compared to those who had never started ATV/r (IRR 1.52 [95% CI: 0.92-2.51]), and a higher incidence for participants who had started ATV/r but were no longer on it (IRR 1.52 [0.91-2.54]), although neither result was statistically significant.

2.4 Discussion

Across the 19 articles included in the literature review investigating INSTI discontinuation, discontinuation was consistently highest on RAL, with one study reporting discontinuation as high as 50%, and lowest on DTG. The most common reason for DTG and EVG/c discontinuations was toxicity and the most common reason for RAL discontinuations was simplification. The most common toxicity for DTG was CNS toxicity, and for RAL and EVG/c, it was gastrointestinal toxicity.

The proportions of participants discontinuing INSTIs due to toxicity reported in these studies were generally higher than proportions reported in RCTs. In RCTs investigating INSTIs, discontinuations due to toxicity generally occurred in less than 2% of participants, however in many of the studies included in this review, the proportion discontinuing for toxicity was between 5% and 10% (301,313–315). This difference in proportions likely reflects the selected population included in RCTs. Additionally, individuals in RCTs are under formal care which may result in them being less likely to discontinue.

The risk of discontinuation was also found to be higher for females, older individuals, and those taking ABC at the same time as the INSTI, and these results were fairly consistent across the studies included. It is unclear why the proportion discontinuing INSTIs is higher for females and suggests further research is needed on the safety of INSTIs in females, who are often underrepresented in HIV research.

The majority of the 20 studies included in the literature review on clinical outcomes focused on CVD. Studies looking at INSTIs did not find a difference in the risk of CVD, either when comparing regimens containing RAL to regimens without RAL, or when investigating increasing exposure to INSTIs as a class. One study comparing ATV to INSTIs, PIs, and NNRTIs, found that the incidence of CVD was lowest on ATV compared to other drug classes. For DRV, there were mixed results, with one study showing an increasing risk of CVD with increasing exposure to DRV, and others showing no difference in the risk with increasing exposure.

There were very few studies reporting the incidence of cancer, ESLD or ESRD on individual ARVs of interest. Two studies reporting cancer on RAL showed conflicting results, with one reporting no difference in the risk of cancer on RAL and the other reporting a higher risk on RAL, although this result was split by ADC and NADC. For liver toxicity, there was no difference in the risk of events on RAL, EFV, ATV/r, or DRV/r in the three studies reporting on this, and for renal toxicity, there was an increased risk on ATV, although this result was not statistically significant.

There are some limitations to this literature review. Firstly, only papers written in English were included and therefore studies from non-English speaking countries may have been excluded. I did not exclude studies based on sample size and the wide range of sample sizes included in the study may limit how generalisable some of the findings are. Additionally, some of the studies included in the clinical outcomes review had relatively small sample sizes and therefore may be underpowered to detect a difference in the risk of clinical events on individual ARVs. Finally, some of the clinical endpoints were non-specific, for example hepatic events or renal insufficiency, and there was not enough detail provided in the article to enable me to accurately classify these events. In terms of the overall quality of the studies included, it is clear that some of the studies are limited by their sample size, short follow-up time, unclear outcome definition, and a lack of heterogeneity in those performed in single centres. This likely explains some of the differences in results between studies and indicates the results found in this review should be interpreted with caution.

This review highlights significant gaps in the literature which I will address in my PhD. None of the studies reporting on INSTI discontinuation were performed in international settings and therefore they were unable to include a comparison of discontinuations by region. This could be important as access to specific ARVs, and the reasons for discontinuing ARVs, may differ between countries. As RESPOND includes many countries across Europe, as well as Australia, I will be able to compare discontinuation across regions in my analyses (in Chapter 4).

Of the articles looking at clinical outcomes, there are none focusing specifically on DTG, EVG/c, or RPV. This is likely due to the lack of follow-up on the more recently approved ARVs. Additionally, it is unclear whether any studies included more contemporary regimens, such as dual therapy. These are both issues I aim to address in my thesis (in Chapter 5 and Chapter 7). Finally, as mentioned above, the sample size of several of the studies may be too small to accurately compare clinical outcomes across ARVs. As RESPOND has approximately 30,000 participants and uses centrally validated clinical endpoints, it will be better powered to answer questions that smaller cohorts cannot.

Chapter 3 Methods

All analyses in this thesis were undertaken using data from the International Cohort Consortium of Infectious Diseases (RESPOND). Additionally, Chapter 6 also uses data from the Data Collection of Adverse Events of Anti-HIV Drugs (D:A:D) study. This chapter describes the structure of and data collection in RESPOND, as well as an overview of D:A:D, and the statistical methods used to analyse the RESPOND and D:A:D data.

3.1 The International Cohort Consortium of Infectious Diseases (RESPOND)

RESPOND began in 2017 as a collaboration of 14 observational cohort studies from across Europe and Australia. In 2015, cohorts who had taken part in previous European collaborations, such as the D:A:D study and EuroSIDA cohort, were invited to continue collaboration in RESPOND.

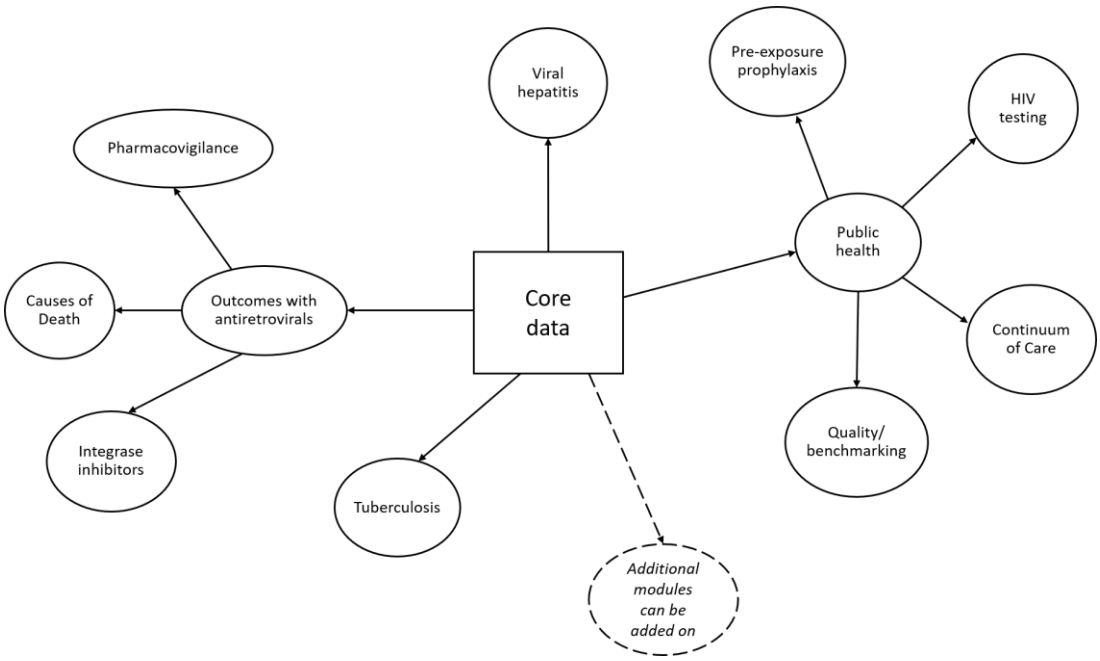
The D:A:D study was a multi-cohort study running from 1999 until 2016, including more than 49,000 people living with HIV (PLWH) from Europe, USA, and Australia (489). D:A:D used systematic data collection and robust event adjudication to assess whether exposure to specific antiretrovirals (ARVs) was associated with an increased risk of cardiovascular disease, other organ diseases, and cancers. Funding for D:A:D ceased in 2016, however many questions remained unanswered and it was felt that a similar, large multi-cohort study on contemporarily treated PLWH was needed to investigate outcomes of modern treatments, such as integrase inhibitors (INSTIs), and to look at the long-term safety profiles of these ARVs. RESPOND therefore was designed to build on the same basic methodology as D:A:D. More detail is given on D:A:D in Section 3.2 below.

The largest cohort contributing to RESPOND is EuroSIDA and much of the infrastructure used in RESPOND is based on that of EuroSIDA, as well as D:A:D. EuroSIDA is a cohort study including more than 22,000 PLWH in Europe, Israel, and Argentina (490). It was initiated in 1994 and has set the standard for European HIV collaborations, publishing over 300 papers on topics ranging from temporal trends in mortality amongst PLWH to uptake and efficacy of antiretroviral therapy (ART) (490).

The overall aim of RESPOND is to build a large and dynamic cohort consortium to allow a response to unmet research needs, both on HIV and other infectious diseases (491). The consortium includes HIV cohorts, scientific collaborators, community representatives, and financial supporters from the pharmaceutical industry. RESPOND uses modular data collection, which allows the research agenda to remain flexible; there is a core module which includes key data, for example demographics, on all individuals involved in RESPOND and then additional modules are added to this covering different research areas. This structure is shown in Figure 3.1. Outside of the core module, cohorts in RESPOND are able to decide which modules to contribute data to. The additional modules focus on topics such as pharmacovigilance, comorbidities and coinfections, and public health. The specific aims of different modules currently in RESPOND are discussed further in Section 3.1.1. Data collected in each of the modules is pooled into a common data repository. The size of this data repository allows RESPOND to answer a wide range of research questions, which individual cohorts may be too small to answer.

In 2017, there were more than 26,000 PLWH enrolled in RESPOND from 14 cohorts. The cohorts included in RESPOND and the number of participants they originally contributed are shown in Table 3.1. Between 2017 and 2020, the existing cohorts continued to contribute participants to RESPOND, 2 additional cohorts joined the collaboration, and one existing cohort split into 2, making it a total of 17 collaborating cohorts. New cohorts joining RESPOND must satisfy several requirements including contributing data annually from at least 1000 PLWH, having a dedicated data manager, committing to meeting the RESPOND timelines, and carrying out regular quality assurances on the data provided. The full list of requirements for new cohorts is available on the CHIP website (492) and the data items required are detailed in Section 3.1.4.

Figure 3.1 Proposed and existing modules in RESPOND



Circles coming off core data represent the scientific areas in RESPOND; these are similar to the scientific interest groups shown in Figure 3.3. Circles coming off the scientific areas represent specific projects within the groups

Table 3.1 Cohorts involved in RESPOND

Cohort	**Geographical region[4]**	**Number of participants enrolled in RESPOND in 2017***	**Number of participants enrolled in RESPOND in 2020***
Austrian HIV Cohort (AHIVCOS)	Austria	3,920	4,331
The Australian HIV Observational Database (AHOD)	Australia	661	389
CHU Saint-Pierre	Belgium	1,574	1,593
The AIDS Therapy Evaluation in the Netherlands (ATHENA) national observational HIV cohort[1]	Netherlands	-	1,482
University Hospital Cologne-University Hospital Bonn[2]	Germany	1,083	1,556
EuroSIDA Cohort[3]	Europe	10,051	10,306
Frankfurt HIV Cohort Study	Germany	44	187
Georgian National AIDS Health Information System (AIDS HIS)	Georgia	272	488
Italian Cohort Naive Antiretrovirals (ICONA)	Italy	650	1,315
Modena HIV Cohort	Italy	1,286	1,444
Nice HIV Cohort	France	483	968
PISCIS Cohort Study	Spain	650	650
Royal Free HIV Cohort Study	United Kingdom	3,410	3,417
San Raffaele Scientific Institute	Italy	895	1,109
Swedish InfCare HIV Cohort[1]	Sweden	-	650
Swiss HIV Cohort Study (SHCS)	Switzerland	1,300	3,300

*Different versions of the database are used for each chapter in this thesis. Details of this are given in Table 3.2 and the corresponding chapters

[1]cohorts added in 2018

[2]these cohorts split into two for the second data download in 2018

[3]see Figure 3.2 for more details on the countries included in EuroSIDA

[4]Countries are grouped into geographical regions for all RESPOND analyses, as follows: Western Europe: Austria, Belgium, France, Germany, Luxembourg, Switzerland; Southern Europe: Argentina, Greece, Israel, Italy, Portugal, Spain; Northern Europe: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East Central Europe: Bosnia-Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia, Slovenia, Slovakia; Eastern Europe: Belarus, Estonia, Georgia, Latvia, Lithuania, Russia, Ukraine; Australia.

Figure 3.2 Location of centres included in EuroSIDA

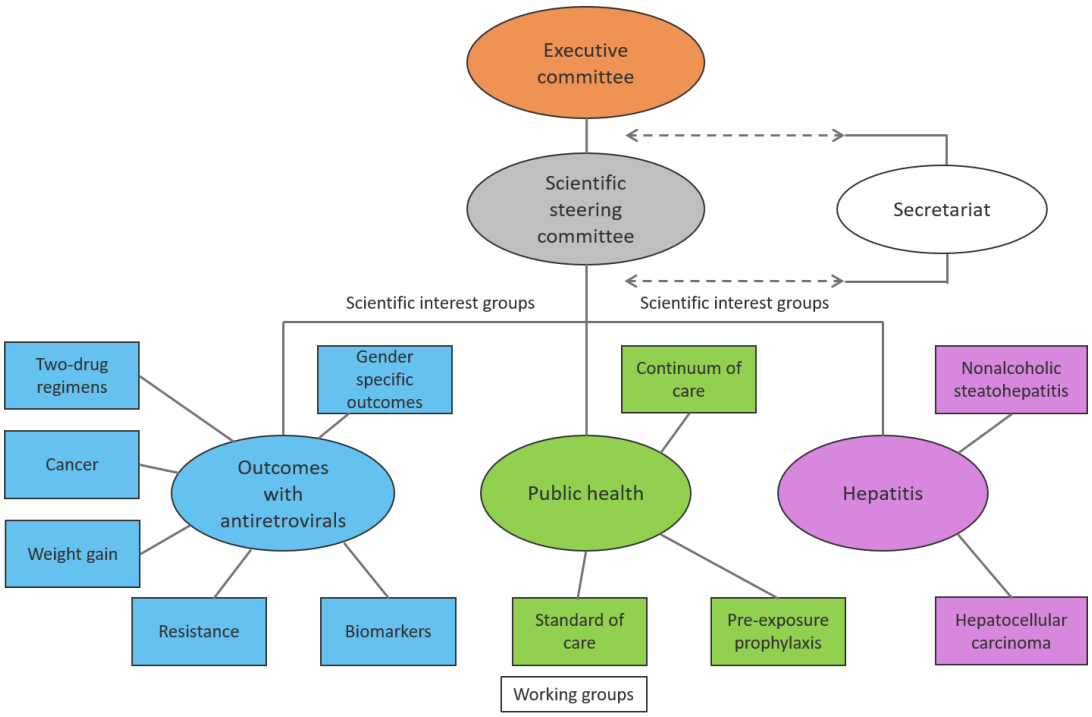
Source: (493)

3.1.1 Organisation

RESPOND is managed by the coordinating centre at The Centre of Excellence for Health, Immunity and Infections (CHIP), Department of Infectious Diseases at Rigshospitalet, Copenhagen, Denmark and the statistical centre at University College London (UCL). The consortium comprises the executive committee, the scientific steering committee (SSC), scientific interest groups (SIGs), and smaller project-oriented working groups. Members of the RESPOND study group are listed in Appendix III and the structure of RESPOND is shown in Figure 3.3. The role of the executive committee is to oversee the consortium and ensure the objectives of RESPOND are being met. The SSC is responsible for reviewing and approving new research projects within RESPOND, as well as reviewing the scientific output from these projects, and monitoring the general scientific progress of RESPOND. There are three SIGs: (i) the outcomes with ARVs SIG, (ii) the public health SIG, and (iii) the hepatitis SIG. These groups are responsible for generating ideas for specific projects within RESPOND and discussing the analyses undertaken, and each have specific aims, discussed further below. All projects in this thesis were included in the outcomes with ARVs group. Within each SIG in RESPOND, specific working groups may be set up to focus on a particular project. A working group was set up to discuss

the project comparing outcomes of two-drug regimens to three-drug regimens, which is presented in Chapter 5, and a cancer working group were involved in discussing the project assessing cancer trends, presented in Chapter 6. Communication between each of the groups in RESPOND, as well as the organisation of regular meetings for each group, is facilitated by the RESPOND secretariat, and I was responsible for coordinating the outcomes with ARVs SIG during the course of my PhD (see section 3.1.6.3).

Figure 3.3 Structure of RESPOND



3.1.1.1 Aims of the Outcomes with ARVs SIG

The aims of the outcomes with ARVs SIG include monitoring uptake of contemporary ARVs, evaluating immunological and virological outcomes of these ARVs, and assessing their short- and long-term safety profiles. Additionally, the group aims to assess whether outcomes of ARVs differ in sub-groups of the population, including those defined by age, gender, CD4 count, and coinfections and comorbidities.

3.1.1.2 Aims of the Hepatitis SIG

The aims of the hepatitis group are to study the long-term effects of treatment for viral hepatitis B and hepatitis C, and to assess factors associated with the

development of hepatic and extra-hepatic morbidity and mortality in individuals coinfected with HIV and hepatitis B or hepatitis C.

3.1.1.3 Aims of the Public Health SIG

The public health group aim to study pre-exposure prophylaxis (PrEP) use among individuals newly diagnosed with HIV and assess the prevalence of drug resistance before starting ART in those exposed to PrEP. They also aim to improve understanding of the HIV continuum of care and develop tools to better estimate the number of individuals at different stages of the continuum.

3.1.2 Governance

Cohorts are requested to provide data from a random selection of individuals at their clinic, with approximately half taking INSTIs and half taking boosted protease inhibitors or non-nucleoside reverse transcriptase inhibitors. They are reimbursed for a specific number of participants enrolled into RESPOND, which is determined by the executive committee. Cohorts can then contribute data on additional participants as data in-kind. All data from reimbursed participants is included in all RESPOND analysis projects, however cohorts can decide whether to include data from participants contributed in-kind to each analysis; to date, cohorts have generally included all data in all projects.

Projects using data from RESPOND must be approved by the SSC. The process involves completing a project proposal form, as shown in Appendix IV, which is then sent to the relevant SIG for discussion. Once finalised, the proposal is sent to nominated reviewers in the SSC who recommend whether the project should be accepted, modified, or rejected. New projects in RESPOND are encouraged and any research group is able to submit a project proposal to the SSC, although funding for the project may need to be applied for externally to RESPOND.

Projects involved in RESPOND are published under a collective RESPOND group authorship. Writing committees are then determined for each project, with cohorts contributing reimbursed data receiving one authorship and cohorts additionally contributing data in-kind receiving two authorships. External funders and additional

authors can be included for each project, provided they satisfy the International Committee of Medical Journal Editors (ICJME) authorship requirements.

Further details on the governance and procedures in RESPOND are included on the RESPOND website (494).

3.1.3 Enrolment and inclusion in RESPOND

Enrolment of participants into RESPOND began in 2017. The inclusion criteria in RESPOND is as follows:

(i) Confirmed HIV-1 infection

(ii) Age 18 years or older at RESPOND baseline (defined below)

(iii) Have signed informed consent forms for involvement in the RESPOND consortium and data repository, and for involvement in specific projects within RESPOND, if this is required by local or national legislation.

To further be included in studies within the outcomes with ARVs group, the following inclusion criteria must be satisfied:

(iv) Individuals receiving an INSTI based ART regimen must have started the INSTI for the first time after 1st January 2012 and have a CD4 count and viral load (VL) measurement within 12 months prior to or 3 months after starting the INSTI

(v) Individuals who have not started an INSTI must have a CD4 and VL measurement within 12 months prior to or 3 months after RESPOND baseline.

Further details on the inclusion criteria can be found in the RESPOND protocol (491) and RESPOND Outcomes Study protocol (495). RESPOND baseline is defined as the latest of the date that participants were first seen at their local cohort, the date of starting an INSTI for participants who started an INSTI, and 1st January 2012. The date 1st January 2012 was chosen for several reasons. Firstly, as RESPOND began enrolment in 2017, it was felt that cohorts would be able to provide quality data, including clinical events, on the previous 5 years. Additionally, a main focus of

RESPOND is on INSTIs and by 2012, INSTIs were routinely being used as first-line treatment rather than only for salvage therapy.

There are further inclusion and exclusion criteria for each specific analysis project in RESPOND, and inclusion into each analysis project in this thesis are detailed in the corresponding chapters and in Table 3.2 below.

Table 3.2 Summary of data used in each thesis chapter

Thesis chapter	Title	Database version used*	N included in database	N included in analysis	Key inclusion criteria
4	Uptake and discontinuat-ion of integrase inhibitors	DS0	26,279	9,702	Started DTG, EVG/c or RAL after the latest of local cohort enrolment and 1st January 2012, aged ≥ 16, had a CD4 count and VL measurement prior to or within 6 months after starting an INSTI
5	Virological, immunologi-cal, and clinical outcomes of two-drug regimens	DS1	29,432	9,791	Antiretroviral treatment experienced started an eligible regimen during follow-up and after 1 January 2012, aged ≥ 18, had a CD4 count and VL measurement 1 year prior to or within 12 weeks after starting the regimen of interest
6	Trends in cancer incidence in different contemporary ART-eras amongst people living with HIV	DS2 and merger 17 of the D:A:D data	33,185 in DS2, 49,706 in merger 17	31,200 in DS2, 45,355 in merger 17 (9,919 were in both datasets)	Aged ≥ 18, had any follow-up data, for those in RESPOND: had a CD4 count and VL measurement 1 year prior to or 12 weeks after baseline
7	Integrase Inhibitor Use and cancer incidence in a large cohort setting	DS2	33,185	29,340	Aged ≥ 18, had a CD4 count and VL measurement 1 year prior to or within 12 weeks after baseline

*DS0 refers to the first version of the database, DS1 to the second version, and DS2 to the third version

3.1.4 Data collection

Cohorts included in RESPOND collect data on participants during routine clinical visits. The data is submitted to CHIP at the time of enrolment, and annually thereafter. At the time of enrolment, data is also retrospectively collected on the previous 5 years, and earlier if it is available. Figure 3.4 shows the enrolment and data collection process in RESPOND. Table 3.3 shows the key data items collected in RESPOND. Data items are split into those which cohorts must provide and those which are encouraged for cohorts to additionally provide; these are indicated in Table 3.3. The deadline for submitting data annually is the end of November. Data is submitted by cohorts by either transferring their database using the RESPOND Electronic Submission Tool (REST) or by manually entering data using the Research Electronic Data Capture (REDCap) web application. Cohorts are provided with guidance for data submission in the RESPOND Standard Operating Procedure (SOP) (496). The format of the data follows the HIV Cohorts Data Exchange Protocol (HICDEP) format; further detail can be found at: https://hicdep.org/.

Automated checks are implemented in REST and REDCap by CHIP which alert cohorts if the data is incomplete or there are any systematic errors detected, for example a participant is receiving 5 or more ARVs concurrently for more than one day. This allows the cohorts to correct the data before submission. The data is then received by CHIP where further checks are performed within a week of data submission to identify any remaining systematic errors in the data. Missing data is queried with the cohorts, and they are requested to resubmit the corrected data. The process is repeated until the end of January when no further data submission can be made. The data undergoes a final evaluation and decisions are made whether to implement on-site monitoring at specific cohorts based on the quality of the data received.

Detailed definitions of the events collected, as well as the validation algorithm, are described in the RESPOND manual of operations (MOOP) (490). All serious non-AIDS events and all AIDS defining cancers collected, which occur after 12 months prior to the last cohort visit before RESPOND enrolment must be submitted separately using a specific case report form (CRF) on REDCap. Prospectively occurring events are

reported in real time and for participants who have died, a Coding Causes of death (CoDe) form must also be submitted (497). The CoDe form provides a standardised method for identifying the underlying cause of death in PLWH and therefore ensures consistency in the reporting across clinics. This can be important in cohort studies which play a key role in monitoring mortality trends in populations of PLWH (497).

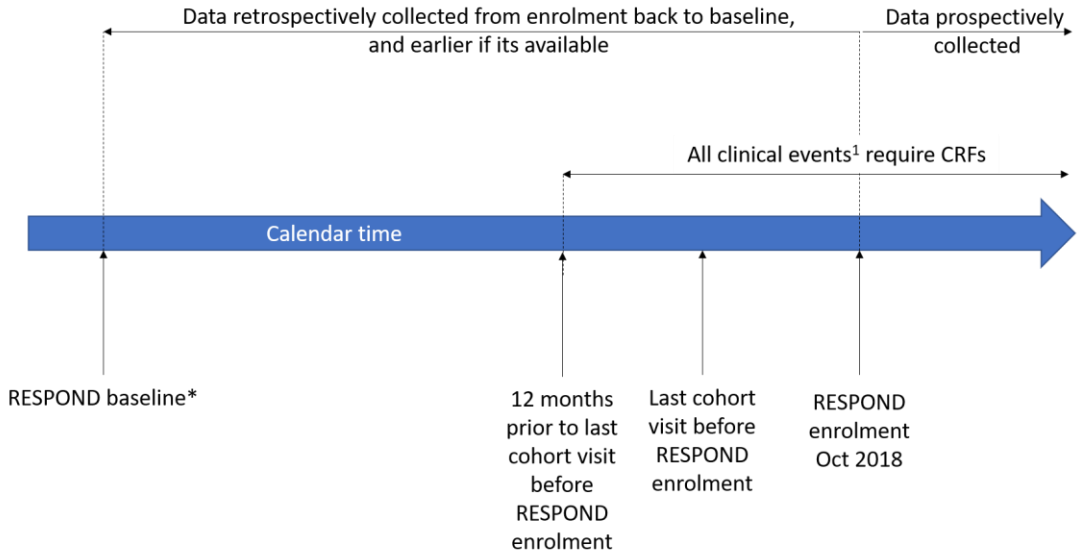
Once the final data has been received at CHIP in January, a list of any pending events requiring CRFs which have not been received, are sent to each centre to be completed. CRFs used in RESPOND can be found on the CHIP website (490). The event definitions are based primarily on those developed by D:A:D between 1999-2016 (498). Once the CRFs are received, the events are validated by a specially trained medical doctor at CHIP using a prespecified algorithm, as described in the MOOP (490). Events are classified as definite, possible, or null/insufficient data. Events with too little information to be validated are queried with the clinics. Additionally, if there is likely to be an event missing, for example if a myocardial infarction is reported to have been treated with an invasive cardiovascular procedure, with no CRF submitted for the latter, this would also be queried. The validation process is supervised by a senior medical doctor previously involved with the event validation in D:A:D to ensure consistency over time. Events which are unclear, as well as a random selection of other events, are discussed with external experts. Further checks are done annually by comparing events which have been reported in REST and REDCap to those submitted using a CRF. Pending event forms are queried with the cohorts in March and again in May to ensure they are submitted before the database deadline which is 1st July. Any remaining events requiring a CRF are queried in August for inclusion in the data submission for the following year.

Events which occur outside the validation period specified above do not need an event form, however those which occurred after 1st January 2012 are checked to ensure they are not duplicate events. Primary RESPOND analyses are therefore performed on a mixture of validated and non-validated events. Sensitivity analyses are then performed on validated events only. This is a particular strength of the RESPOND consortium as this method ensures events in RESPOND are robust, and it

is therefore possible to reliably assess comorbidity trends in PLWH and carry out large-scale, post-marketing pharmacovigilance surveillance.

After the data is submitted and cleaned at CHIP, it is then transferred to the statistical centre at UCL, where further detailed data checks and cleaning are performed. This is explained below in Section 3.1.5. The datasets are transferred in July each year. The initial data download in 2018 was called "DS0" and each subsequent download was numbered consecutively. The version of the database used for each analysis project in this thesis, as well as the number of participants included and key inclusion criteria, is shown in Table 3.2.

Figure 3.4 Data collection process in RESPOND for participants enrolled in October 2018



*RESPOND baseline defined as latest of local cohort enrolment, date of INSTI start, 1st January 2012
[1]events include AIDS and non-AIDS defining cancer, myocardial infarction, stroke, invasive cardiovascular procedures, end-stage liver and renal disease, bone fractures

Table 3.3 Data items collected in RESPOND outcomes with antiretrovirals module

Demographics and basic information	Date of birth[1], date first seen at clinic[1], gender[1], country of origin, ethnicity, height, weight[1], date of first HIV-1-antibody positive test[1], date of first HCV-antibody positive test[1], mode of HIV-1 transmission[1], prior smoking status, current smoking status, alcohol abuse, injecting drug use
Infection-related Laboratory data	HIV-RNA[1], HCV antibody[1], HCV-RNA[1], HBV surface antigen[1], HCV-genotype, HCV subtype, HLA B*5701, CD4[1], CD8, blood samples
Other Laboratory data	ALT and/or AST, platelets, alkaline phosphatase, INR, haemoglobin, serum creatinine, total cholesterol, HDL, LDL, haemoglobin A1c and/or glucose, bilirubin, album, triglycerides
Medical treatment	All treatment for HIV[1], HCV[1], hypertension[1], diabetes[1], dyslipidaemia[1], tuberculosis[1], thrombosis[1], including start and stop dates, and reasons for discontinuations
Paraclinical data	Bone mass density, proteinuria (dipstick), blood pressure, liver trans elastography (fibro scan), acoustic radiation force impulse, liver biopsy (metavir stage), hepatocellular carcinoma screening (abdominal CT and ultrasound)
Clinical events	AIDS defining event[1], myocardial infarction[1,2], stroke[1,2], invasive cardiovascular procedures[1,2], end-stage liver disease[1,2], end-stage renal disease[1,2], AIDS and non-AIDS defining cancer[1,2], bone fractures[1,2], pregnancy
Previous clinical events	Cancer[1], diabetes[1], AIDS defining event[1], myocardial infarction[1], stroke[1], invasive cardiovascular procedures[1], pregnancies

Abbreviations: HCV – hepatitis C; RNA - ribonucleic acid; HBV – hepatitis B; HLA – human leukocyte antigen; ALT - alanine transaminase; AST - aspartate amino transferase; INR - international normalised ratio; HDL - high-density lipoproteins; LDL - low-density lipoproteins; CT - computerized tomography;

[1]Variables are required for inclusion in RESPOND

[2]if event occurs after 12 months prior to the last cohort visit before RESPOND enrolment, it must be submitted separately using a specific case report form (CRF)

Note that not all cohorts provide data on all of the data items listed

3.1.5 Data cleaning

The data is downloaded by CHIP as multiple SAS (Statistical Analysis Software, Cary NC, USA) files corresponding to the different datasets included. This data is then used by myself, as well as other statisticians at UCL and by statisticians from different cohorts.

Once the data is received, I help to coordinate data cleaning among the statisticians to ensure there is consistency amongst all versions of the data. To clean the data, I convert the SAS files into Stata files and carry out multiple checks and transformations on the data. This includes removing dates and values which are outside of the expected clinical range for each variable, converting each type of measurement to a common unit and removing measurements where the units are unclear, and removing duplicate entries from the datasets. Specific variables in the datasets are automatically calculated by the IT team at CHIP. To ensure these are correct, I manually calculate them again using the same algorithms and investigate any discrepancies.

Some comorbidity definitions used in RESPOND analyses take into account data from several different variables and therefore require further data manipulation. For example, diabetes is defined as a reported diagnosis of diabetes, the use of anti-diabetic medication, a random glucose measurement of 11.1 mmol/L or above, a Haemoglobin A1c measurement of 6.5% or above, or 48 mmol/mol or above. Other comorbidities use a composite definition, for example cardiovascular disease is defined as a myocardial infarction, invasive cardiovascular procedure, or stroke. To create these definitions, I merge variables from different datasets together and create a new events dataset including all of the relevant data.

Any issues I find with the data are queried with CHIP, either by email communication, by organising a meeting between the IT team and statistical team, or by reporting them on MantisBT, which is a web-based bug tracking system. These issues are either dealt with and a new version of the data is transferred, or, if they require querying with the cohorts, they are addressed for the next data download.

From DS2 onwards, data cleaning is carried out concurrently by different users of the data and the programming code used to clean the datasets is shared to ensure consistency. As more users of the data joined the collaboration, each person cleaned different datasets, and these were double checked by another statistician to ensure they were correct. The final, clean datasets were then shared amongst the group. I coordinate regular meetings between the data users in which we discuss completeness of the data and data cleaning. I also help to resolve any discrepancies between different versions of the data.

Once the initial data cleaning is completed, I am responsible for reporting summaries of the completeness of specific variables created for each cohort, either by reporting the percentage of participants missing the variable of interest or by reporting the incidence of the variable. Table 3.4 shows the completeness of key variables in the DS0 version of the database. Each year, these summaries are compared to previous versions of the database to ensure that the completeness of the data has improved. The summaries are also sent to CHIP to ensure that they agree. An overview of the data completeness is fed back to the RESPOND consortium at an SSC meeting and improvement of data quality is addressed at the annual RESPOND retreat (see Section 3.1.6.4). I am also responsible for creating summaries for the events included in RESPOND and comparing event rates to prior years; more detail on this is included below.

Finally, rules are created to determine whether to include each cohort for specific outcomes in analysis projects, depending on whether the percentage of missing data is too high or the incidence rate too low for that variable. The threshold for inclusion is often set at 80% for completeness and incidence rates are compared across cohorts to determine the threshold for inclusion. Cohorts who do not meet the threshold for inclusion for a specific outcome are recorded as unknown for all participants for that outcome.

Table 3.4 Completeness of key variables in DS0 version of the database

Variable	Proportion of participants with data
Date of birth	100
Gender	100
Ethnicity	86.0
Weight	88.7*
Height	70.3
Smoking	69.1*
HIV transmission group	94.0
HIV viral load	99.9*
CD4 count	99.7*
Antiretroviral therapy data	96.8*
Hepatitis B	82.7
Hepatitis C	87.3

*Proportion of participants with at least one measurement at any time

3.1.5.1 Event completeness

The event data is recorded in three separate datasets; one showing all electronically reported (validated and unvalidated) clinical events and procedures, one including AIDS defining events, and a third including only events submitted on a CRF for validation in RESPOND. Initially, I compare the number of specific events in each dataset with a doctor at CHIP responsible for the event validation to ensure they agree. I also try to identify any anomalies in the data and whether there are any missed events in the validation dataset by comparing the number of events, by cohort, to previous versions of the datasets. As some comorbidity definitions are a combination of many different events, these definitions also need to be verified.

Once the events have been cleaned, I calculate the incidence rates for specific events, overall and by cohort. This is done for all events submitted across the datasets in RESPOND and then again just for events which have been validated and determined as an event. The incidence rates are also calculated for different time periods and in each version of the dataset to assess whether the incidence of events is increasing over time. The cohorts are then informed of the overall incidence rates in the consortium and the specific incidence rates in their cohort to try to identify whether event reporting is incomplete if observed rates differ from the expected rates.

3.1.6 RESPOND meetings

Within RESPOND, regular meetings take place between the different working groups and committees. This section provides an overview of some of the meetings I take part in.

3.1.6.1 RESPOND team meetings

A biweekly meeting takes place between the statistical centre at UCL and the coordinating centre at CHIP. The aim of this meeting is to discuss topics across RESPOND and EuroSIDA, and covers areas such as funding for cohorts contributing data, agenda items for upcoming meetings with the wider consortium, and progress on data collection.

3.1.6.2 Coordination meetings at CHIP

Approximately 3 times a year, I attend face to face meetings at CHIP. During these visits, we discuss any topics usually covered during the RESPOND team meetings, as well as the progress of ongoing projects in RESPOND and ideas for new projects. During the coronavirus pandemic in 2020-2021, these meetings took place virtually.

3.1.6.3 Outcomes with ARVs SIG meetings

Meetings with the outcomes with ARVs SIG are held approximately every 3 months to discuss the progress of new and ongoing projects within the group. As part of the RESPOND secretariat, I was responsible for organising these meetings throughout the course of my PhD. This includes finding a date for a teleconference, circulating any documents that need reviewing by the group, for example new project proposals and outcomes of analyses, writing and circulating an agenda before the meeting, and writing up the minutes of the meeting. I also often present results from projects I am working on at these meetings.

3.1.6.4 RESPOND retreat

I am also involved in organising the RESPOND retreat, mentioned above. The retreat is held annually and is attended by representatives from UCL, CHIP, and each of the cohorts. It is held in conjunction with The International Workshop on HIV and Hepatitis Observational Databases (IWHOD). It is usually held over 2 days and includes discussions of new and existing projects in RESPOND, discussions on data

quality, data management, and other topics. It was not held in 2020-2021 due to the coronavirus pandemic.

3.1.7 Ethics and funding

Each study contributing to RESPOND is required to obtain ethical approval from their local ethics committees. If required by the local or national ethics committee, informed consent by the participants is also obtained, as explained in Section 3.1.3.

RESPOND initially received funding from ViiV Healthcare LLC and Gilead Sciences. Additional support has been provided by the following cohorts contributing data in-kind and/or statistical support: Austrian HIV Cohort Study (AHIVCOS), The Australian HIV Observational Database (AHOD), Le Centre Hospitalier Universitaire (CHU) Saint-Pierre, University Hospital Cologne, EuroSIDA Cohort, Frankfurt HIV Cohort Study, Georgian National AIDS Health Information System (HIS), Modena HIV Cohort, San Raffaele Scientific Institute, Swiss HIV Cohort Study (SHCS), and the Royal Free HIV Cohort Study. From 2021, RESPOND also obtained funding from Merck & Co.

A further project in the RESPOND consortium called the Common Action against HIV/tuberculosis/hepatitis C across Regions of Europe (CARE) East Cohort Study is funded by the European Union's Horizon 2020 Research and Innovation programme. This study includes participants from the Russian Federation, Ukraine, and Georgia, and aims to investigate clinical outcomes in individuals with HIV and in individuals co-infected with HIV and hepatitis C from Eastern Europe.

3.2 D:A:D

As mentioned above, the D:A:D study was a multi-cohort study including more than 49,000 PLWH. Data from the D:A:D study is used in Chapter 6 of this thesis assessing cancer trends. D:A:D was also organised by the coordinating centre at CHIP. The study was initiated based on a request from the EMA with the main objective being to assess associations between exposure to different ARVs and myocardial infarction and other cardiovascular diseases (489). All cardiovascular disease and death events were centrally validated from 1999. In 2004, the focus expanded to other non-AIDS events including end stage renal and liver disease, and cancer. Participants were

enrolled in D:A:D during three enrolment cohorts in 1999-2001, 2001-2004, and 2004-2009. The cohorts included in D:A:D and the number of participants enrolled from each cohort as of 2016 is shown in Table 3.5. D:A:D used the same data collection processes and event validation algorithm that was subsequently adapted by RESPOND, and is described in Section 0 (498). The data items collected in D:A:D are similar to those collected in RESPOND (Table 3.3). The following data items were collected in D:A:D:

- demographics and CVD risk factors, including age, sex, ethnicity, cohort, prior CVD events, smoking status, height, weight, hypertension,
- HIV-related factors including CD4 counts, VL, HIV risk group, time of HIV diagnosis, AIDS-related events, and ART,
- data on clinical events including myocardial infarctions, strokes, invasive cardiovascular procedures, diabetes mellitus, death, cancer, ESLD, and ESRD,
- data on hepatitis serology,
- laboratory data including blood glucose, creatinine, haemoglobin, lipids, bilirubin, aspartate amino transferase, alanine amino transferase, and platelets,
- data on other drugs, such as lipid lowering drugs, anti-hypertensive, anti-diabetic drugs, and drugs used to treat AIDS-related events.

Table 3.5 Cohorts involved in D:A:D

Cohort	**Geographical region**	**Number of participants enrolled in D:A:D in 2016**
Swiss HIV Cohort Study (SHCS)	Switzerland	7,897
The AIDS Therapy Evaluation in the Netherlands (ATHENA) national observational HIV cohort	Netherlands	12,461
Community Programs for Clinical Research on AIDS (CPCRA)	USA	3,056
Nice HIV Cohort	France	1,611
Aquitaine Cohort	France	3,334
Barcelona Antiretroviral Surveillance Study (BASS)	Spain	682
HIVBIVUS	Sweden	965
EuroSIDA Cohort*	Europe	12,000
The Australian HIV Observational Database (AHOD)	Australia	844
Italian Cohort Naive Antiretrovirals (ICONA)	Italy	3,938
CHU Saint-Pierre	Belgium	2,918

*see Figure 3.2 for more details on the countries included in EuroSIDA

3.3 Statistical methods

This section provides an overview of some of the statistical methods used in the results chapters of this thesis. Further details on specific methods used in each results chapter are provided in the appropriate chapter.

3.3.1 Regression analysis

Regression analysis is used to evaluate how the change in one or more variables (called explanatory or independent variables), $x_1, x_2, \ldots, x_n$ (n≥1), affects another variable (called the dependent variable or outcome), *y* (499). Univariable regression refers to a regression model with a single explanatory variable included and multivariable regression refers to a regression model including multiple explanatory variables. An example of a situation where regression would be used would be to determine whether an individual's total cholesterol is associated with their risk of a heart attack. Here, heart attack is the outcome and total cholesterol is the explanatory variable. The type of outcome determines which regression model is most appropriate to use and this will be discussed more below.

3.3.1.1 Linear regression

Linear regression is used when the outcome of interest is a continuous variable, for example weight or total cholesterol (500). The model used for linear regression is as follows:

$$y = \beta_0 + \beta_1 x_1 + \ldots + \beta_n x_n + \varepsilon \quad (3.1)$$

where *y* is the outcome, $x_1, \ldots, x_n$ are a set of *n* explanatory variables, $\beta_0, \ldots, \beta_n$ are the regression parameters, and ε represents a random error term, which is assumed to be N(0, σ^2). The regression parameter β_i shows the change in the expected value of *y* for each unit increase in x_i, when all other explanatory variables remain constant. For example, if the outcome is weight in kilograms, x_1 is age in years and β_1 is equal to 1.5, this would imply that for each year increase in age, average weight increases by 1.5 kilograms, if all other variables were held constant.

3.3.1.2 Logistic regression

Logistic regression is used for a binary outcome and provides the odds ratio for the outcome occurring (501,502). A binary variable has only two possible outcomes, for example success or failure of a treatment. The model used for logistic regression is as follows:

$$logit(\pi) = log(\frac{\pi}{1-\pi}) = \beta_0 + \beta_1 x_1 + \ldots + \beta_n x_n \quad (3.2)$$

where π represents the probability of the outcome, y, occurring. The parameter β_i from this regression model can be interpreted as the change in the log odds of achieving the outcome for each unit increase in x_i, whilst holding all other variables constant; odds ratios can be achieved by exponentiating β_i.

3.3.1.3 Multinomial logistic regression

An extension of logistic regression is multinomial logistic regression, and this is used when there are more than two possible outcomes, for example if the outcome is type of painkiller prescribed with 3 different options: paracetamol, ibuprofen, and aspirin (501,502). In multinomial logistic regression, a reference category for the outcome is chosen and then the log odds of achieving each other potential outcome is compared to this reference group through a series of logistic regression models. In the example above, if paracetamol is chosen as the reference group, the results of the multinomial logistic regression model will show the log odds of being prescribed ibuprofen vs paracetamol, and the log odds of being prescribed aspirin vs paracetamol. The model for multinomial logistic regression is as follows:

$$logit(\pi_j) = \log(\frac{\pi_j}{\pi_1}) = \beta_{j0} + \beta_{j1} x_1 + \ldots + \beta_{jn} x_n \quad (3.3)$$

where the outcome y can take j possible options, y=1 has been chosen as the reference group, and π_j represents the probability of the outcome being category j. There will be *j-1* logistic regression models simultaneously run and *j-1* sets of regression parameters $\beta_{j0}, \ldots, \beta_{jn}$ estimated. For example, a 3-level outcome would effectively be turned into two 2-level outcomes and logistic regression would be run on each of these 2-level outcomes. The regression parameters are interpreted in the

same way as logistic regression, however each set of parameters is conditional on the outcome only taking the value *1* (the reference group) or *j* (the group being compared). It is possible to fit a series of separate logistic regression models for each comparison of the outcome categories, however fitting them all simulatenously in a multinomial logistic regression model is more efficient (501).

3.3.1.4 Poisson regression

Poisson regression is used when the outcome of interest is a count outcome or a rate. A count outcome is the absolute number of times an outcome occurs, for example the number of AIDS-defining events in a clinical trial, whereas a rate outcome is the number of times an outcome occurs relative to another quantity, usually a unit of time, for example the number of adverse drug reactions per year in a cohort study (502–504). Modelling the outcome as a rate can be useful when each individual is followed for a different length of time, and therefore the probability of experiencing an event will differ for each person. The Poisson regression model for a count outcome is as follows:

$$\log(\mu) = \beta_0 + \beta_1 x_1 + \ldots + \beta_n x_n \quad (3.4)$$

where μ is the mean of outcome, *y*, for example the mean number of AIDS-defining events across participants in the clinical trial in the example above. The regression parameter, β_i shows the change in the log of the mean of the outcome for each unit increase in x_i; exponentiating these parameters shows the multiplicative change in the mean of the outcome.

When the outcome is a rate, rather than a count, the Poisson regression model takes the form:

$$\log(\lambda) = \beta_0 + \beta_1 x_1 + \ldots + \beta_n x_n \quad (3.5)$$

where λ is the rate of the outcome. The rate, λ, is equal to the mean number of events (μ)/follow-up time (t), and therefore the log of λ can be expressed as:

$$\log(\lambda) = \frac{\log(\mu)}{\log(t)} = \log(\mu) - \log(t) \qquad (3.6)$$

The Poisson regression model shown in equation (3.5) can therefore be rearranged as follows:

$$\log(\mu) = \log(t) + \beta_0 + \beta_1 x_1 + \ldots + \beta_n x_n \qquad (3.7)$$

Here, the term *log(t)* accounts for the different follow-up times experienced by different individuals and is termed the offset; the parameter estimate for the offset is constrained to equal 1 (502–504). The regression parameters now show the change in the log rate of the outcome and exponentiating them shows the multiplicative change in the rate of the outcome.

3.3.1.5 Negative binomial regression

One assumption of the Poisson regression model is that the mean and variance of the outcome are the same (505). When the variance is larger than the mean, it is referred to as overdispersion. One situation where overdispersion commonly occurs is if the outcome is relatively rare and so many people do not experience it (505). One option to deal with this is to use a negative binomial regression model, which includes an extra term in the model to account for the overdispersion. Estimates are interpreted in the same way as the Poisson regression model, however, standard errors for regression parameters from this model tend to be larger than from the Poisson regression model and therefore confidence intervals are wider (505). This is because, when overdispersion is present, the standard errors are often underestimated in the Poisson regression model.

3.3.1.6 Survival analysis

Survival analysis is used when analysing the time to an outcome or event occurring, for example time to hospital discharge (502,503). The time at which the outcome occurs is called the survival time. Individuals are followed for different lengths of time from a pre-defined baseline until the occurrence of the event. A common feature of survival analysis is the use of censoring (506). Individuals who have not experienced the outcome of interest by the end of follow-up are censored at a pre-specified time

point, such as the date of final visit. For these individuals, we know that they did not experience the outcome at the point of censoring, however we do not know whether they experienced the outcome after censoring, and if so, when they experienced the outcome, and this must be accounted for in the analysis. An important assumption of most survival analysis models is that censoring is uninformative about event times, which means that the likelihood that an individual is censored, and for those that are, the time at which the individual is censored, does not provide any information regarding when the individual may experience the outcome (506).

There are multiple analysis models which can be used to analyse survival data, each with different assumptions. In this thesis, I have used the Cox proportional hazards model (507). The model is:

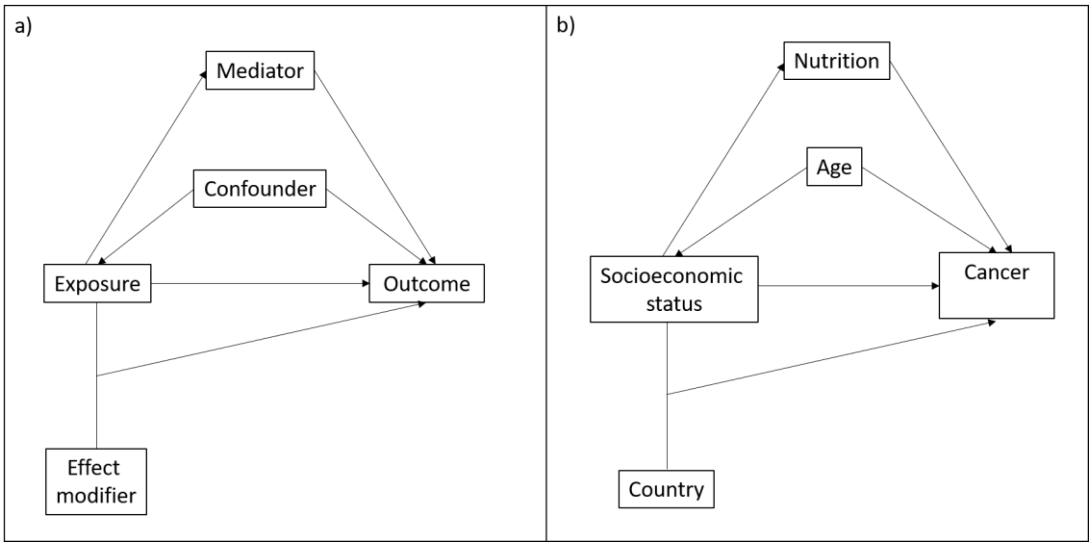
$$\log\left(h(t)\right) = \log\left(h_0(t)\right) + \beta_1 x_1 + \ \ldots \ + \beta_n x_n \quad (3.8)$$

where *t* represents the survival time, *h(t)* is the hazard function, defined below, $h_0(t)$ is the hazard function when all independent variables are set to 0, and β_i is the change in the hazard of the outcome for each unit change in variable x_i. The hazard function is defined as the instantaneous probability of the outcome occurring during the time interval between time *t* and time $t + \delta$, as δ gets very small, given the individual has not experienced the outcome at time *t*. The Cox proportional hazards model assumes that the multiplicative effect of x_i on the hazard ratio is constant over time and this is known as the proportional hazards assumption (506,507).

3.3.2 Confounders, effect modifiers, and mediators

A common issue that arises in the analysis of observational data is the effect that other measured or unmeasured variables may have on the association between an independent variable of interest and an outcome. In this section, I will refer to the independent variable as an exposure. These other variables could be confounders, effect modifiers, or mediators, and each of these is defined below. Figure 3.5 shows an overview of how each of these variables may affect the association between an exposure and an outcome, and an example of a situation in which this may occur.

Figure 3.5 The relationship between different variables in an analysis of observational data: a) an overview, b) an example



In the figures, an arrow pointing from one box to another shows that the variable in the first box influences the variable in the second

3.3.2.1 Confounders

The definition of a confounder is a variable which influences both the exposure and the outcome, but it does not lie on the causal pathway between the exposure and outcome (508). For example, when looking at the association between socioeconomic status and the risk of cancer, as in Figure 3.5, age may be a confounding variable as it may be that older people have a higher socioeconomic status compared to younger people as they have been working for longer, and older people are generally at higher risk of cancer. However, age is not on the pathway from socioeconomic status to cancer, as socioeconomic status cannot affect a person's age. If age were not properly accounted for, it may seem as if a higher socioeconomic status was associated with a higher risk of cancer, which is unlikely to be correct.

Confounding can be dealt with at the design stage or the analysis stage of a study. At the design stage, the following methods could be used to account for confounding (508):

- Randomisation, where participants are randomly assigned to each exposure group and so the confounding variables are balanced between groups. This is generally the gold standard for designing medical studies as it ensures the groups are balanced for known and unknown confounders. However, in many settings, randomisation is not possible.
- Restriction, where only participants with similar characteristics, in relation to known confounding variables are included in the study.
- Matching, where the participants in the unexposed group are chosen to have similar characteristics to those in the exposed group, in relation to known confounding variables.

Confounding can also be dealt with at the analysis stage by adjusting for any known and measured confounding variables in a multivariable regression model or by stratifying the results according to different categories of the confounding variable (504,509). The results from an adjusted regression model show the association between the exposure and the outcome, whilst holding all other variables in the model constant, thereby eliminating the effects of these variables. Residual confounding is likely to remain an issue in cohort studies if there is missing data on any of the variables or they have not been recorded in the data with enough detail. Additionally, there is likely to be unmeasured confounding from other variables which were not recorded, as well as confounding from unknown variables which were not chosen as confounders (508). It is not possible to formally test whether a variable is a confounder and variables believed to be confounders are usually chosen a priori based on scientific literature.

Often confounders are fixed at baseline. However, in some situations, the effect of the confounder may vary over time; these are known as time-varying confounders (510). Time-varying confounding often occurs when the exposure of interest also changes over time, for example when the exposure is cumulative exposure to a drug.

It is important to adjust for time-varying confounders correctly, if they are present, to accurately estimate the effect of a time-varying exposure on an outcome. As time-varying confounders are measured repeatedly, the repeat measurements within participants are likely to be correlated, and this must be accounted for in the regression model. Therefore, time-varying confounders can be adjusted for in a regression model accounting for correlated data (see below, Section 3.3.3). Examples of time-varying confounders are CD4 count, smoking status, or blood pressure (511). The disadvantage of using time-varying confounders is in a situation where the past value of the exposure has affected the value of the time-varying confounder and this, in turn, affects the outcome. In this case, the time-varying confounder will also be a mediator (see below, Section 3.3.2.3) and cannot be adjusted for in the model. There are methods for handling this situation using causal methods (510), (511), however in this thesis, I have accounted for it by fixing the confounder at baseline. This method may not fully account for the effect of the confounder over time, however it is a simpler and more easily interpretable solution.

3.3.2.2 Effect modifiers

Another type of variable which may affect the association between an exposure and outcome is an effect modifier. This is a variable where the association between the exposure and outcome differs depending on the value or category of this variable (508). For simplicity, the effect modifier is assumed to be categorical in this section, however the definition also applies to a continuous variable. In the example in Figure 3.5, country may be an effect modifier, as in countries with better social support, the effect of socioeconomic status on the risk of cancer may be weaker, however in countries with little or no social support, this effect may be much stronger. It is possible to test whether a variable is an effect modifier by including an interaction term in the regression model between the exposure and the effect modifier (508,509,512). It is then possible to calculate the association between exposure and outcome in each category of the effect modifier, and the p-value for the interaction term shows whether the association differs significantly across the categories. To avoid multiple testing, variables believed to be effect modifiers should again be chosen a priori based on scientific literature.

3.3.2.3 Mediators

Finally, a mediator is a variable which lies on the causal pathway between an exposure and outcome (508,513). This can happen if the exposure causes a change in the mediator, which in turn affects the outcome. In the example in Figure 3.5, nutrition may be a mediator, as individuals with lower socioeconomic status may not be able to afford nutritious food, and bad nutrition could in turn lead to an increased risk of cancer. A mediator provides information on the mechanism behind the association between the exposure and outcome and should not be accounted for in an analysis model, otherwise the association may be underestimated (513). It is possible to identify if a variable is a mediator through mediation analysis, however this is outside the scope of this thesis.

3.3.3 Handling correlated data

Standard regression models assume that all observations are independent. There are many scenarios where this assumption does not hold, for example in longitudinal data collection where multiple measurements are taken on the same participant over time or in cluster randomised trials where groups of participants receive the same treatment. In these situations, measurements from the same participant or same cluster are likely to be correlated. This correlation should be accounted for in the analysis model. There are multiple types of models which can account for correlated data including generalised estimating equations (GEEs) and mixed models. In Chapter 7 of this thesis, assessing the association between INSTI use and cancer incidence, I use GEEs to account for correlated data. In GEEs, any regression model can be used (514,515). A working correlation structure is then specified which describes the correlation between measurements (516–519). The type of structure chosen depends on the structure of the data and the type of correlation between measurements. I have used an unstructured correlation structure, which allows the correlation between every pair of measurements to be different. Whilst other structures can be more appropriate for longitudinal data, for example the autoregressive structure, as this assumes measurements taken closer together are more highly correlated than measurements taken further apart, it does not allow for visits to be unevenly spaced, which occurs in my data (517,519). Robust standard

errors can then be specified and this means that the model will estimate the standard errors to account for any misspecification in the correlation structure (519).

3.3.4 Handling missing data

Missing data is a common issue in medical research and, in particular, observational studies; it can lead to a loss of information, thereby reducing statistical power, and, in certain situations, it can also lead to biased results (520,521). There are many different methods for handling missing data in an analysis and the validity of each method relies on assumptions about the relationship between the likelihood of the data being missing and the variables included in the analysis (522). These assumptions are that the missing data is:

i) missing completely at random (MCAR), which means the likelihood of the missing data is unrelated to any of the variables included in the analysis, for example, an individual's laboratory data is missing because their blood sample was accidentally damaged;

ii) missing at random (MAR), which means the likelihood of missing data is dependent on other variables which have been observed, for example, age is missing for some participants in a cohort because a specific centre did not collect data on age; or

iii) missing not at random (MNAR), which means the likelihood of missing data is dependent on the missing data itself, for example, individuals with a lower CD4 count were more likely to miss their clinic appointment and therefore not have their CD4 count measured.

It is usually not possible to verify these assumptions on the data collected and therefore, it can be useful to use more than one method to handle missing data to test the robustness of the analysis results. Below, I outline three methods of handling missing data which I have used in analyses in this thesis.

3.3.4.1 Including an unknown category

For categorical variables with missing data, an unknown or missing category can be included. This method includes the maximum number of participants, however it can lead to biased results in some situations, for example when the data is MNAR (521). Additionally, it cannot be used for continuous variables, and it is difficult to interpret the results for the participants in the unknown category.

3.3.4.2 Complete case analysis

Complete case analysis restricts the analysis to only include participants with data recorded on all of the variables included in the model. This method can be unbiased in certain situations, for example if the likelihood of a participant having all data recorded is independent of the outcome, after accounting for all other variables included in the analysis model (520,523). However, if there is a lot of missing data, this can result in a large number of participants being excluded from the analysis, which will reduce statistical power.

3.3.4.3 Multiple imputation

Multiple imputation creates multiple versions of the dataset where missing values are replaced by predictions from regression models (524–526). One specific example of this is multivariate imputation by chained equations (MICE). In this method, each variable with missing data is, in turn, treated as a dependent variable in a regression model, with all other variables included as independent variables in the model. To begin the process, imputed values are chosen for all variables with missing data by randomly sampling with replacement from the observed values in the dataset (524). Then, as each variable is cycled through, the recorded values plus the imputed values of each other variable are used in the regression model. Predictions are then generated from these regression models to replace the missing data. In order to reflect the uncertainty in the predictions, residual error is added to the imputed values. The variables are cycled through multiple times to create a single imputed dataset. This whole process is then repeated several times in order to create multiple different datasets with imputed values in place of the missing data. Each dataset is analysed individually to produce separate regression parameter estimates and then these estimates are combined using Rubin's Rules (525). The overall estimate is

calculated as an average of the separate estimates and the variance of this estimate is calculated, taking into account both the variance within each imputed dataset and the variance between the different imputed datasets.

MICE is a flexible method which can be used for different types of variables, i.e. continuous, binary, categorical, and it makes use of all of the data. Results from MICE are unbiased if the missing data is MCAR or MAR (524).

3.4 Software

All analyses in this thesis were performed using Stata/SE 15.0, Stata/MP 16.0, and SAS 9.4 (Statistical Analysis Software, Cary NC, USA).

Chapter 4 Uptake and discontinuation of integrase inhibitors

4.1 Introduction

Integrase strand transfer inhibitors (INSTIs) are one of the latest antiretroviral drug classes to be approved by the EMA. The mechanism of INSTIs is detailed in Chapter 1, Section 1.9.4. Briefly, INSTIs inhibit the action of integrase enzymes which act as a catalyst to enable the HIV genome to integrate into the host DNA (221,222). There are five INSTIs which have been approved by the EMA. Raltegravir (RAL) was the first to be approved in 2008 (294,467), followed by cobicistat-boosted elvitegravir (EVG/c) in 2013 (303,527), dolutegravir (DTG) in 2014 (314,315,468,528), bictegravir (BIC) in 2018 (320,321), and cabotegravir (CAB) in 2021 (529,530).

Several RCTs and small observational studies have shown lower rates of short-term adverse events, lower rates of discontinuation, and non-inferiority for virological and immunological outcomes on INSTIs compared to NNRTIs (298,301,315,527,531,532), and boosted PIs (PI/b) (299,304,314,322,533,534). INSTIs are therefore recommended in most treatment guidelines, including the European AIDS Clinical Society (EACS; Figure 4.1), the International AIDS Society (IAS), and Department of Health and Human Services (DHHS), as part of first-line treatment regimens for adults living with HIV (85,331,535).

Figure 4.1 Recommendations for initial regimens for people living with HIV starting antiretroviral therapy in EACS guidelines

Source: (331)

Figure 4.2 shows adverse events known to be associated with INSTI use, included in EACS guidelines, Version 10.1. Commonly reported adverse events associated with INSTIs include headache, nausea, and sleep disturbances (363). Additionally, EVG/c and DTG may cause inhibition of the renal tubular secretion of creatinine, causing an artefactual increase in creatinine plasma levels, which is not reflective of a declining renal function (315,322,536). Another adverse event recently shown to be associated with INSTIs is weight gain. Several RCTs and observational studies have shown greater weight gain with INSTIs compared to NNRTIs and PI/b (537–541). This effect seems to be particularly pronounced on DTG, and the reason for this is currently unclear; it may be because DTG is commonly prescribed with tenofovir alafenamide (TAF) which has also been shown to be associated with weight gain, although another study in RESPOND has shown DTG was still associated with weight gain even when not prescribed with TAF (542), or because INSTIs cause less adverse events and therefore impair appetite less than other ARVs with higher levels of adverse events (537,543). As INSTIs are a relatively new drug class, the clinical implications of this adverse event are unclear, however weight gain generally, both in PLWH and in the general

population, has been shown to be associated with an increased risk of comorbidities, including dyslipidaemia, cardiovascular disease (CVD), and diabetes (543–546).

Figure 4.2 Known adverse effects associated with INSTIs listed in EACS guidelines

Source: (331)

Whilst the frequency of drug-drug interactions on INSTIs as a drug class is relatively low compared to other ARVs, it is higher on EVG/c, due to the pharmacokinetic enhancement with COBI (331). Some of these interactions may be treatment limiting, for example individuals coinfected with HIV and tuberculosis should not be co-administered EVG/c and rifampicin, and individuals coinfected with HIV and hepatitis C (HCV) should not be co-administered EVG/c and several direct acting antiviral drugs (331).

In Chapter 2, I completed a literature review investigating the prevalence of and reasons for discontinuation of INSTIs in observational studies of adults living with HIV and in key RCTs. The review showed that discontinuation was highest on RAL, mainly due to treatment simplification, and usually lowest on DTG (450–452,457,458,461). The main reason for discontinuation of DTG and EVG/c was toxicity, with nervous system toxicities being most common on DTG and gastrointestinal toxicities being

most common on EVG/c. The risk of discontinuation was also higher in certain subgroups such as females and older individuals (448–451,454,456,457). Further, the proportion of individuals discontinuing INSTIs due to toxicity was higher in observational studies compared to RCTs (294,303,314,315,467,468,527,528). The review highlighted some significant gaps in the literature, for example there were no studies performed in international settings allowing for a comparison of INSTI discontinuation between geographical regions. Access to INSTIs may differ between countries as individuals in countries with fewer treatment options available may discontinue their current treatment less frequently. Most of the studies included were relatively small and it was unclear in many studies whether there was a standardised method for recording the reason for discontinuation. Finally, individuals with prior or existing comorbidities are often not recruited into RCTs, which can limit how generalisable their results may be to PLWH. Due to the presumed favourable safety profile of INSTIs, it is likely that a higher proportion of those with existing comorbidities are receiving INSTIs in routine clinical practice. Therefore, a large, international collaboration is needed to provide a representative overview of the characteristics of those initiating INSTIs and those discontinuing INSTIs.

In this chapter I describe the characteristics of individuals initiating RAL, EVG/c, and DTG in the RESPOND cohort, compare the reasons for discontinuation of each INSTI, and assess factors associated with discontinuation of INSTIs. Discontinuations are split into those which occurred within 6 months after INSTI start and those which occurred after 6 months after INSTI start.

4.1.1 Aims

The aims of this chapter are to:

(i) identify baseline characteristics associated with initiating DTG, EVG/c, and RAL for the first time from ART-naïve or ART-experienced status;
(ii) compare rates of discontinuation and reasons for discontinuation of DTG, EVG/c, and RAL;

(iii) identify baseline characteristics associated with discontinuation of first INSTI regimen.

4.2 Methods

This analysis was performed on the first version (version DS0) of the RESPOND database with a data cut-off of 1st October 2017. Baseline was defined as the date of first INSTI start after 1st January 2012. Individuals were followed until the latest of the most recent CD4 count, VL, or ART start date, drop out date as defined by the cohort, or date of death. If this date was after the data cut-off, individuals were censored at 1st October 2017.

4.2.1 Inclusion criteria

The inclusion criteria for RESPOND are detailed in Chapter 3, Section 3.1.3. For this analysis, individuals from RESPOND were included if they:

(i) started any regimen containing DTG, EVG/c or RAL after the latest of the date they were enrolled into their local cohort or 1st January 2012;
(ii) were aged ≥ 16 when starting the INSTI;
(iii) had a CD4 count and VL measurement prior to or within 6 months after starting the INSTI.

4.2.2 Outcomes

4.2.2.1 INSTI uptake

The first outcome was defined as initiation of DTG, EVG/c, or RAL after the latest of 1st January 2012 or the date of local cohort enrolment. Individuals starting more than one INSTI during follow-up were included in the first INSTI group they were exposed to. BIC and CAB were not assessed in this analysis as they were approved by the EMA after the data cut-off date.

4.2.2.2 INSTI discontinuation

The second outcome was defined as discontinuation of the first INSTI regimen during follow-up, provided individuals had been on the INSTI for a minimum of 7 days. 7 days

was chosen to rule out minor data errors. Discontinuation was not counted if an individual switched from a single tablet regimen to its individual components, or vice versa, while remaining on the same INSTI, provided there was no interruption between treatments. Additionally, discontinuation was not counted if the other ARVs in the regimen changed, provided the INSTI component remained the same.

Discontinuations were split into those which occurred within 6 months of INSTI initiation and those which occurred after 6 months of initiation. This was aimed at identifying short-term toxicities (≤6 months after INSTI start) and longer-term toxicities (>6 months after INSTI start).

4.2.3 Potential confounders

All potential confounders, defined prior to or at INSTI initiation, considered in this analysis are described in Table 4.1.

Table 4.1 Baseline demographic and clinical characteristics included in analyses

Variable	Categories	Comments
Year of starting the INSTI	Continuous (per 1 year later)	
Age	Continuous (per 10 years later)	
Gender	Male; female	
HIV risk group	MSM; IDU; heterosexual sex; other; unknown or missing	
Ethnicity	White; Black; other; unknown or missing	
CD4 cell nadir prior to INSTI start	Continuous (per 100 cells increase)	Taken as the lowest CD4 count prior to initiation. If no CD4 count was measured prior to initiation, the first measurement within 6 months after INSTI start was used
CD4 count at INSTI start	Continuous (per 100 cells increase)	Taken as the most recent CD4 count before initiation. If no CD4 count was measured prior to initiation, the first measurement within 6 months after INSTI start was used (median difference between CD4 count prior to initiation and initiation = 18 days)
Smoking status	Past; current; never; unknown or missing	
ART experience and viral suppression status	ART naïve; ART experienced with VL <400 copies/mL; ART experienced with VL ≥400 copies/mL*	VL was taken as the most recent VL before initiation. If no VL was measured prior to initiation, the first measurement within 6 months after INSTI start was used (median difference between VL prior to initiation and initiation = 26 days)
Viral hepatitis C	No; yes; unknown	Defined by use of anti-HCV medication, a positive HCV antibody test, a positive HCV RNA qualitative test, HCV RNA >615 IU/mL, and/or a positive genotype test
Viral hepatitis B	No; yes; unknown	Defined by a positive HBV surface antigen test and/or HBV DNA >357 IU/mL
Hypertension	No; yes; unknown	Confirmed by use of anti-hypertensives at any time before INSTI start or if the most recent systolic or diastolic blood pressure measurement before INSTI start was higher than 140 or 90 mmHg, respectively
Diabetes	No; yes; unknown	Defined as reported diabetes diagnosis or use of antidiabetic medication or a random glucose

		measurement of 11.1 mmol/L or above, a Haemoglobin A1c measurement of 6.5% or above, or 48 mmol/mol or above
Prior AIDS-defining event	No; yes; unknown	Composite diagnosis as defined by the CDC list of AIDS-defining conditions (547,548)
Prior non-AIDS defining cancer	No; yes; unknown	
Prior end stage liver disease	No; yes; unknown	Composite diagnosis of ascites (where extrahepatic reasons are excluded), hepatic encephalopathy grade III-IV, hepatorenal syndrome, endoscopically verified variceal bleeding, spontaneous bacterial peritonitis, liver transplantation (549)
Prior cardiovascular disease	No; yes; unknown	Composite diagnosis of myocardial infarction, stroke or invasive cardiovascular procedure (549)
Prior fracture	No; yes; unknown	Includes pathological, osteoporotic, and traumatic fractures (549)
Prior chronic kidney disease	No; yes; unknown	Two consecutive measurements of eGFR measured at least 3 months apart ≤60 mL/min if the first eGFR was >60 mL/min or a 25% decline if first eGFR was <60 mL/min. eGFR was calculated using the CKD-EPI creatinine equation (550)
Geographical region	Western Europe; Northern Europe/Australia; Southern Europe; Eastern/East Central Europe	Due to low numbers, Australia was combined with Northern Europe in the analysis models, and Eastern Central Europe was combined with Eastern Europe. For further details, see Chapter 3, Table 3.1 footnote
INSTI type	RAL; EVG/c; DTG	Only included in the discontinuation model

Abbreviations: MSM – men who have sex with men; IDU – injecting drug use; HCV – hepatitis C; RNA - ribonucleic acid; HBV – hepatitis B; CKD – chronic kidney disease; eGFR - estimated glomerular filtration rate; CKD-EPI - Chronic Kidney Disease Epidemiology Collaboration. Continuous variables were checked to see if there was a linear relationship with the outcome before fitting as continuous

*Note, in later chapters, viral suppression is defined as VL<200 copies/mL. This is because a central RESPOND proposal was approved re-defining viral suppression as VL<200 copies/mL after this analysis was completed. The proposal showed that only 0.6% of all VL measurements would be excluded when using VL<200 copies/mL (as the limit of detection was higher than 200 for these measurements or was missing).

4.2.4 Reasons for discontinuation

For each drug discontinuation one underlying reason was provided by the participating cohort at the clinician's judgement. Reasons were grouped into treatment failure, toxicity, patient or physician choice (without further details), treatment simplification, other, and unknown. Further detail on the discontinuation reasons included in each group is provided in Table 4.2.

Table 4.2 Reasons for discontinuation

Category	Reasons
Toxicity	Abnormal fat redistribution, concern of cardiovascular disease, cardiovascular toxicity, dyslipidaemia, hypersensitivity reaction, toxicity predominantly from abdomen/gastrointestinal tract, toxicity related to liver, pancreas, kidneys, nervous system, neuropsychiatric toxicity, headache, toxicity predominantly from endocrine system, diabetes, other toxicity
Treatment simplification	Simplified treatment available, treatment too complex
Treatment failure	Treatment failure, virological failure, partial virological failure, immunological failure – CD4 count drop, clinical progression, resistance (based on test result), death; if the discontinuation reason was reported as other causes or unknown and the viral load at date of discontinuation (± 3 months) was greater than 400 copies/mL, this was counted as treatment failure
Patient/physician choice	Patient's wish/decision, non-compliance, failure to complete course of treatment, physician's decision
Other	Toxicity concerns during pregnancy, pregnancy – switch to a more appropriate regimen, pregnancy intended, pregnancy ended, comorbidity, availability of more effective treatment, drug interaction, protocol change, regular treatment termination, change in treatment (not due to side effects, failure, poor adherence, or contra-indication), structured treatment interruption, study treatment commenced, study treatment completed, other causes
Unknown	Unknown or reason missing (and not classified as treatment failure)

Discontinuation due to toxicity was further broken down into the following categories: nervous system toxicities, abdomen or gastrointestinal tract toxicities, kidney toxicities, hypersensitivity reactions, patient or physician choice, and other. Patient or physician choice was included as a marker of potential toxicity for this analysis as this has been done in previous EuroSIDA analyses (551) and toxicity was

likely to be a major contributor to the decision to discontinue. The specific toxicities included in each group are provided in Table 4.3.

Table 4.3 Reasons for discontinuation due to toxicity

Category	Reasons
Patient/physician choice	Patient's wish/decision, non-compliance, failure to complete course of treatment, physician's decision
Toxicity – nervous system	Toxicity predominantly from nervous system, peripheral neuropathy, neuropsychiatric toxicity, headache
Toxicity– abdomen/gastrointestinal tract	Toxicity predominantly from abdomen/gastrointestinal tract, liver toxicity, pancreas toxicity
Toxicity – kidneys	Toxicity predominantly from kidneys
Hypersensitivity reaction	Hypersensitivity reaction
Toxicity– other/unspecified	Toxicity predominantly from endocrine system, diabetes, unspecified side effects, other toxicity

4.2.5 Statistical methods

4.2.5.1 INSTI uptake

Baseline characteristics were summarised and compared between INSTIs; categorical variables were summarised using totals and percentages, whilst continuous variables were summarised using median and interquartile range.

Multinomial logistic regression was used to assess associations between baseline demographic and clinical characteristics and the likelihood of starting RAL compared to DTG and of starting EVG/c compared to DTG. DTG was chosen as the reference category because it was the most commonly used INSTI and also most recently approved. Each variable listed in Table 4.1 was included separately in univariable models and then all variables were fitted simultaneously in a multivariable model.

Results of the INSTI uptake analysis were stratified by those who were ART-naïve, ART-experienced with VL <400 copies/mL and ART-experienced with VL ≥400 copies/mL, to determine whether characteristics associated with INSTI choice differed according to whether the INSTI was part of an initial regimen or a switch strategy. Additionally, a prespecified subgroup analysis was performed to assess

whether the effect of gender on the choice of INSTI, differed between age groups, in the whole analysis population. This was done by fitting an interaction term between gender and age in the multivariable model. Other subgroup analyses were performed assessing whether the effect of having each comorbidity listed in Table 4.1, on the choice of INSTI, differed by age. These analyses were also performed by fitting an interaction term in the multivariable model between age and each subgroup of interest.

In all analysis models, an unknown category was used to account for missing data for categorical variables or where variables were reported as unknown. As some cohorts were missing data on specific comorbidities, I did not adjust for cohort in the primary analysis. Analyses were repeated including cohort as an explanatory variable and excluding comorbidities. Additionally, the models were rerun using multiple imputation by chained equations to account for missing data with 10 imputations and using Rubin's rules to combine results (525). Further details on this method are given in Chapter 3, Section 3.3.4.3.

Analyses were also repeated only including those starting an INSTI from 2015, when DTG, EVG/c and RAL were all approved by the EMA. Finally, the primary analysis model was additionally adjusted for the nucleoside reverse transcriptase inhibitor (NRTI) backbones (for those on a NRTI backbone) included in the INSTI-based regimen.

4.2.5.2 INSTI discontinuation

Discontinuation of DTG, EVG/c, and RAL within 6 months after INSTI start was summarised using Kaplan Meier (KM) estimates. Reasons for discontinuation were compared between INSTIs. Cox proportional hazards models were used to assess factors associated with time to discontinuation within 6 months after INSTI start, including all variables listed in Table 4.1. Each variable was included in univariable models and then all were fitted simultaneously in a multivariable model. Individuals were censored at final follow up, defined in Section 4.2 above.

Prespecified subgroup analyses were performed by fitting an interaction term in the multivariable model between INSTI type and each of gender, age, HIV risk group, prior ART-experience, HBV and HCV status, and each comorbidity listed in Table 4.1.

As above, an unknown category was used to account for missing data for categorical variables. Cohort was not adjusted for in the primary analysis. Additional analyses were performed including cohort and excluding comorbidities, and accounting for missing data using multiple imputation by chained equations.

As a sensitivity analysis, body mass index (BMI) was additionally adjusted for in the primary analysis model. Finally, models were rerun including discontinuations after 6 months after INSTI start only and including INSTI discontinuation due to toxicity only.

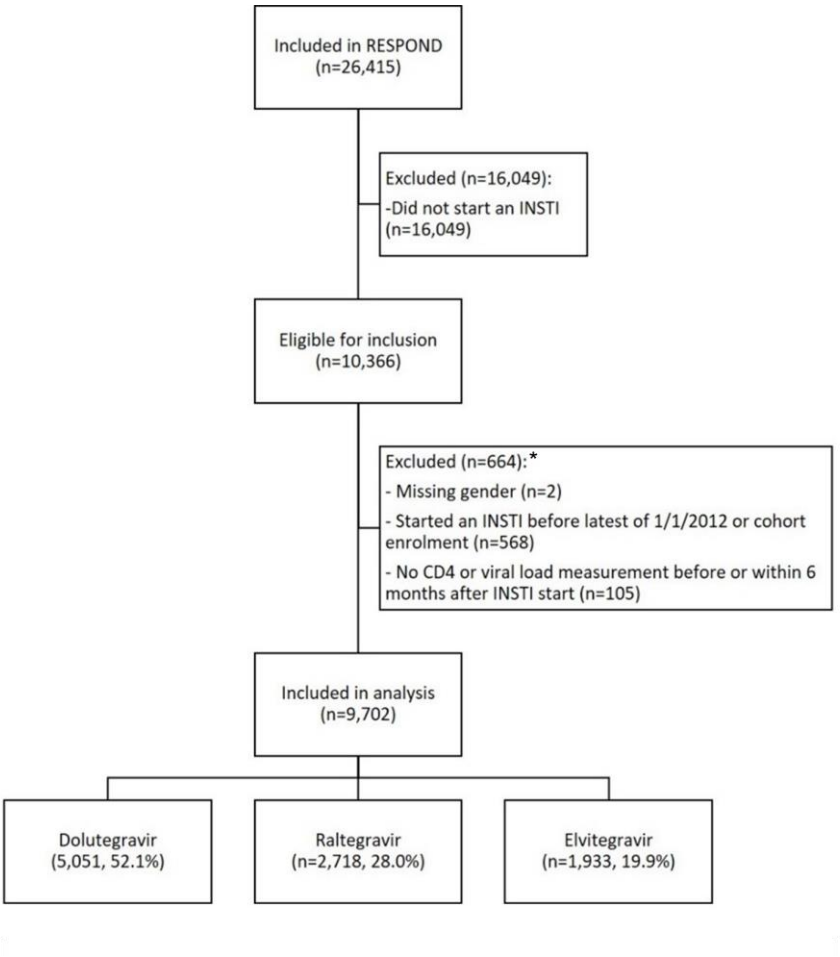
4.3 Results

4.3.1 Participants starting INSTIs

There were 26,415 individuals from 14 cohorts included in version DS0 of the RESPOND database. In total, 10,366 participants started an INSTI and of these, 9,702 (93.6%) were included in the analysis. The reasons for exclusion from the analysis were as follows (more than one reason could apply): 568 started an INSTI before the latest of 1st January 2012 or local cohort enrolment, 105 did not have a CD4 count or VL measurement before or within 6 months after INSTI start, and 2 had missing information on gender. The demographic and clinical characteristics of those included and excluded from the analysis were compared at RESPOND baseline, defined as the latest of local cohort enrolment, INSTI start for those who started an INSTI, and 1st January 2012. In general, characteristics were similar. However, a higher proportion of those included were from Western Europe compared to those excluded (53.0% of those included were in Western Europe vs 39.4% of those excluded) and a lower proportion were in Northern Europe (13.1% vs 59.2.%, $p<0.0001$). This was because more individuals in Northern Europe had started an INSTI before cohort enrolment or 1st January 2012 compared to the other geographical regions.

Of those included, 5,051 (52.1%) started DTG, 1,933 (19.9%) started EVG/c and 2,718 (28.0%) started RAL. Figure 4.3 shows the study flow for participants and the number of participants included in each group in the analysis.

Figure 4.3 Flow chart showing inclusion/exclusion process



*More than one reason can apply

4.3.2 Baseline characteristics

Baseline demographic characteristics of INSTI users are presented in Table 4.4 and Figure 4.4. The median age of INSTI users was 48 years (interquartile range [IQR] 39-54) and the majority were male (75.5%), of white ethnicity (70.4%) and ART-experienced with a suppressed VL (67.4%). The proportion who were ART-naïve was highest on EVG/c (30.4% on EVG/c, 20.5% on RAL, 23.5% on DTG, p<0.0001). The majority of all individuals included in the analysis were in the men who have sex with men (MSM) HIV risk group, however this proportion was also highest on EVG/c (51.3% on EVG/c, 41.2% on RAL, 44.4% on DTG, p<0.0001).

Across the INSTIs, there was a relatively high incidence of prior AIDS defining events (ADEs, 21.0% on DTG, 28.3% on RAL, 13.2% on EVG/c, p<0.0001; Figure 4.5) and comorbidities, including hypertension, diabetes, and prior CVD (proportion with at least one comorbidity: 37.6% on DTG, 33.1% on RAL, 27.7% on EVG/c, p<0.0001), although these were lowest on EVG/c.

The median date of starting an INSTI was August 2015 (IQR September 2014-July 2016). Due to the earlier release of RAL, the median date of starting RAL (February 2014 [January 2013-April 2015]) was earlier than for EVG/c (December 2015 [October 2014-November 2016]) and DTG (January 2016 [May 2015-October 2016], p<0.0001).

Table 4.4 Baseline characteristics of INSTI users, overall and by INSTI type - n (%) unless stated otherwise

		Overall		Dolutegravir		Raltegravir		Elvitegravir/c	
Total		9702	(100)	5051	(52.1)	2718	(28.0)	1933	(19.9)
Gender	Male	7322	(75.5)	3765	(74.5)	1998	(73.5)	1559	(80.7)
	Female	2378	(24.5)	1286	(25.5)	720	(26.5)	372	(19.2)
	Transgender	2	(0.0)	0	(0.0)	0	(0.0)	2	(0.1)
Ethnicity	White	6835	(70.4)	3691	(73.1)	1875	(69.0)	1269	(65.6)
	Black	1023	(10.5)	482	(9.5)	325	(12.0)	216	(11.2)
	Other	417	(4.3)	218	(4.3)	110	(4.0)	89	(4.6)
	Unknown	1427	(14.7)	660	(13.1)	408	(15.0)	359	(18.6)
Body mass index	<18.5	369	(3.8)	203	(4.0)	107	(3.9)	59	(3.1)
	18.5-<25	3887	(40.1)	2233	(44.2)	859	(31.6)	795	(41.1)
	≥25	2580	(26.6)	1469	(29.1)	569	(20.9)	542	(28.0)
	Unknown	2866	(29.5)	1146	(22.7)	1183	(43.5)	537	(27.8)
Smoking status	Never	2451	(25.3)	1402	(27.8)	548	(20.2)	501	(25.9)
	Current	2627	(27.1)	1488	(29.5)	607	(22.3)	532	(27.5)
	Previous	924	(9.5)	505	(10.0)	243	(8.9)	176	(9.1)
	Unknown	3700	(38.1)	1656	(32.8)	1320	(48.6)	724	(37.5)
ART experien-ce	Naïve	2330	(24.0)	1185	(23.5)	557	(20.5)	588	(30.4)
	Experienced VL < 400 cps/mL	6541	(67.4)	3529	(69.9)	1798	(66.2)	1214	(62.8)
	Experienced VL ≥ 400 cps/mL	831	(8.6)	337	(6.7)	363	(13.4)	131	(6.8)
HIV risk	Men who have sex with men	4356	(44.9)	2244	(44.4)	1121	(41.2)	991	(51.3)
	injecting drug use	1396	(14.4)	735	(14.6)	460	(16.9)	201	(10.4)
	Heterosexual	3164	(32.6)	1669	(33.0)	911	(33.5)	584	(30.2)
	Other	256	(2.6)	124	(2.5)	95	(3.5)	37	(1.9)
	Unknown	530	(5.5)	279	(5.5)	131	(4.8)	120	(6.2)
Continuous variables, median (IQR)									
INSTI start date, mm/yy		08/15	(09/14, 07/16)	01/16	(05/15, 10/16)	02/14	(01/13, 04/15)	12/15	(10/14, 11/16)
Age, years		48	(39, 54)	48	(39, 55)	48	(41, 54)	45	(36, 53)
CD4 cell nadir, cells/mm³		213	(91, 350)	215	(93, 349)	179	(68, 311)	262	(138, 404)
CD4 count at INSTI start, cells/mm³		552	(350, 761)	578	(369, 788)	507	(297, 714)	560	(386, 756)

Figure 4.4 Geographical region of INSTI users, stratified by INSTI

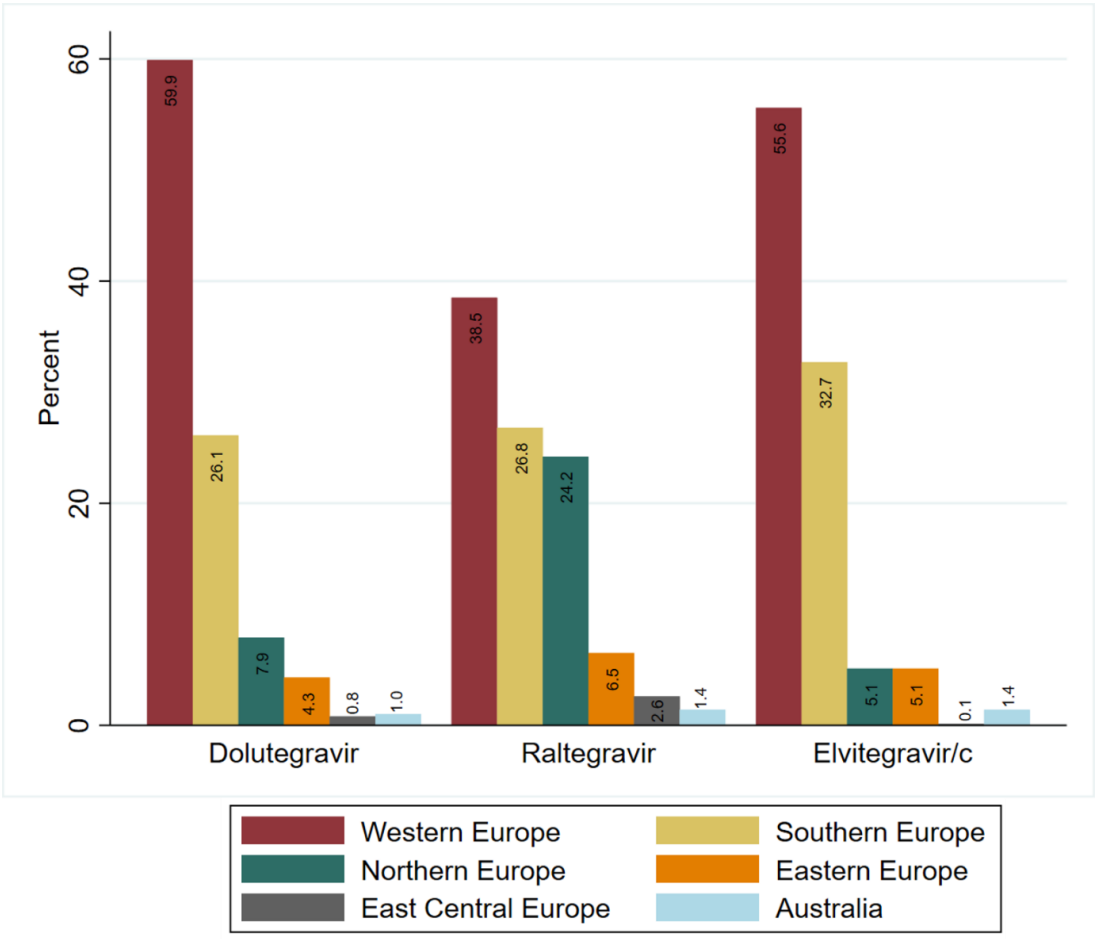
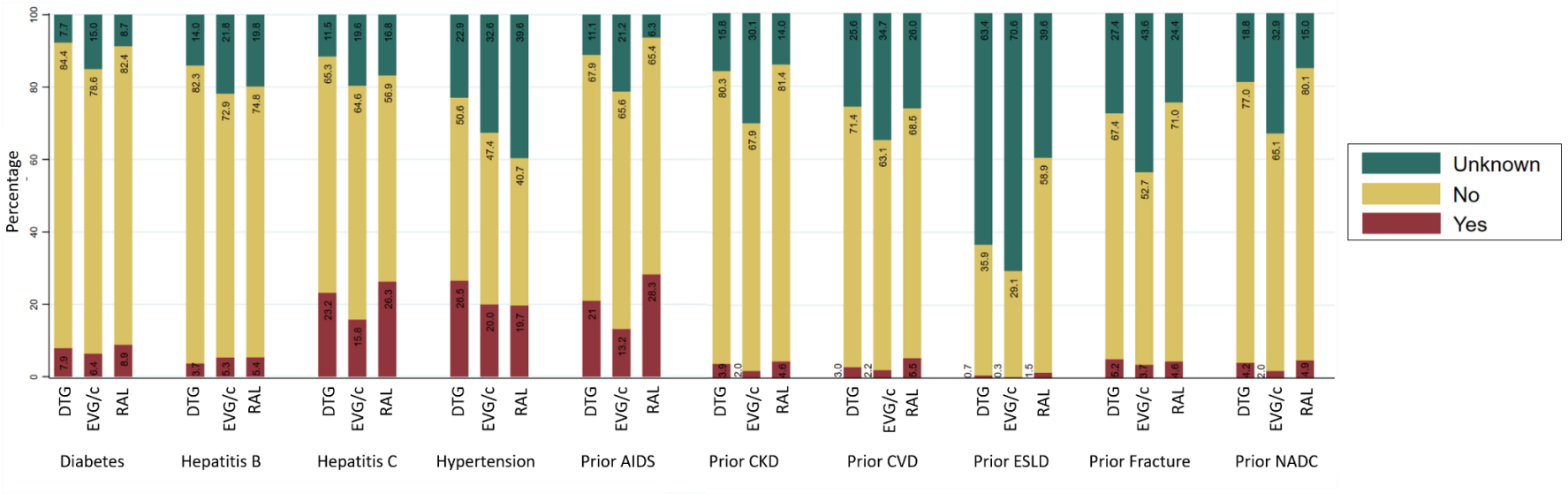


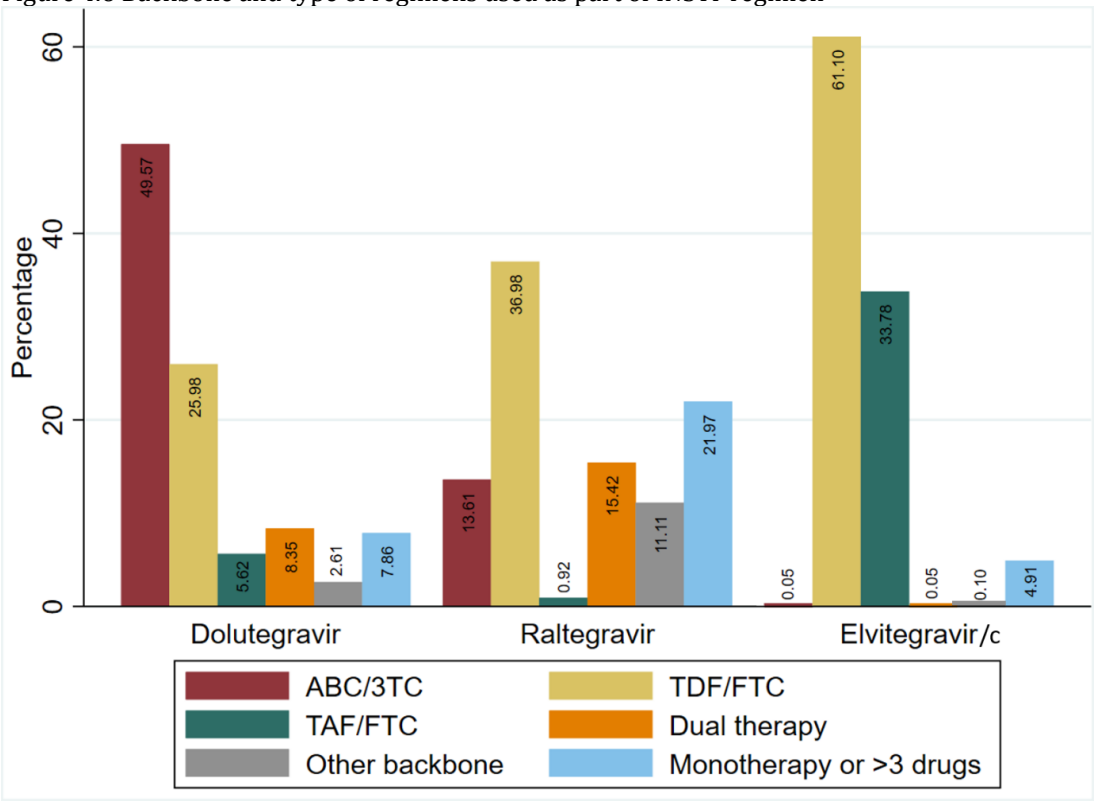
Figure 4.5 Prior comorbidities of individuals starting INSTIs, stratified by INSTI type



Abbreviations: CKD-chronic kidney disease; CVD-cardiovascular disease; ESLD-end stage liver disease; NADC-non-AIDS defining cancer

Of those on DTG and EVG/c, 35.1% and 88.4% were on single tablet regimens, respectively. Figure 4.6 shows the NRTI backbones used for each INSTI. The most commonly used backbone for DTG was abacavir (ABC) and lamivudine (3TC) (49.6%) and for EVG/c and RAL, tenofovir disoproxil fumarate (TDF) with emtricitabine (FTC) (61.1% and 37.0%, respectively).

Figure 4.6 Backbone and type of regimens used as part of INSTI-regimen



Abbreviations: ABC-abacavir; 3TC-lamivudine; TDF-tenofovir disoproxil fumarate; FTC-emtricitabine; TAF-tenofovir alafenamide

4.3.3 INSTI uptake

Results from univariable and multivariable multinomial logistic regression models assessing factors associated with starting each INSTI are presented in Table 4.5 and Table 4.6, respectively. Results of the univariable and multivariable models were similar. After adjustment, the likelihood of starting RAL or EVG/c compared to DTG decreased over time, although at a faster rate for RAL (RAL vs DTG risk ratio [RR] per year increase in INSTI start 0.25 [0.23-0.26], p<0.0001; EVG/c vs DTG 0.63 [0.57-0.69], p<0.0001). Participants in Eastern and Southern Europe were more likely to start RAL or EVG/c compared to those in Western Europe, with a higher increase seen for RAL

(Eastern Europe: RAL vs DTG 6.82 [5.07-9.19], EVG/c vs DTG 1.36 [1.02-1.81]; Southern Europe: RAL vs DTG 3.00 [2.36-3.81], EVG/c vs DTG 1.23 [0.99-1.52], p<0.0001). Increasing age at INSTI initiation was associated with an increased likelihood of starting RAL (1.14 per 10-year increase [1.06-1.22], p<0.0001) but a decreased likelihood of starting EVG/c (0.91 [0.86-0.97], p=0.002) compared to DTG. Female gender was also associated with a decreased likelihood of starting EVG/c (0.68 [0.58-0.80], p<0.0001) compared to starting DTG.

When looking at previous ART experience, the likelihood of starting RAL compared to DTG was higher for participants who were ART-naïve (1.29 [1.03-1.63]) or ART-experienced with VL≥400 copies/mL (1.56 [1.22-2.00], p<0.0001) compared to those who were ART-experienced with VL<400 copies/mL. Similarly, the likelihood of starting RAL was also higher for those in the injecting drug use (IDU; 1.37 [1.06-1.76]) or heterosexual sex (1.33 [1.10-1.60], p=0.009) risk categories for HIV acquisition, compared to MSM. Increasing CD4 count at INSTI initiation was associated with an increased probability of starting EVG/c (200-349 vs <200 cells/mm^3: 1.75 [1.34-2.27]; 350-499 vs <200 cells/mm^3: 1.88 [1.45-2.44]; ≥500 vs <200 cells/mm^3: 1.66 [1.27-2.17], p<0.0001) with no difference for RAL (p=0.16) compared to starting DTG.

Participants with HBV coinfection were more likely to start RAL (1.60 [1.19-2.17], p=0.007) or EVG/c (1.68 [1.30-2.19], p=0.0005) compared to DTG, and those with HCV coinfection were also more likely to start RAL (1.39 [1.13-1.72], p=0.008) but were less likely to start EVG/c (0.80 [0.66-0.98], p=0.007). In general, participants with comorbidities were more likely to start RAL but less likely to start EVG/c compared to DTG.

Table 4.5 Associations between baseline characteristics and choice of INSTIs – univariable analysis

			Raltegravir vs Dolutegravir			Elvitegravir/c vs Dolutegravir		
Variable	**Reference**	**Group**	**RR***	**(95% CI)**	**p-value**	**RR***	**(95% CI)**	**p-value**
INSTI start, per 1-year increase			0.30	(0.28, 0.31)	<0.0001	0.81	(0.77, 0.85)	<0.0001
Geographical region[1]	Western Europe	Southern Europe	1.60	(1.42, 1.79)	<0.0001	1.35	(1.20, 1.52)	<0.0001
		Northern Europe/ Australia	4.45	(3.88, 5.11)		0.78	(0.69, 0.96)	
		Eastern Europe	2.80	(2.32, 3.38)		1.10	(0.87, 1.41)	
Age, per 10-year increase			1.05	(1.01, 1.09)	0.03	0.83	(0.80, 0.87)	<0.0001
Gender	Male	Female	1.06	(0.95, 1.17)	0.32	0.70	(0.61, 0.80)	<0.0001
Ethnicity	White	Black	1.33	(1.14, 1.54)	0.0003	1.30	(1.10, 1.55)	<0.0001
		Other	0.99	(0.78, 1.26)		1.19	(0.92, 1.53)	
		Unknown	1.22	(1.06, 1.39)		1.58	(1.37, 1.83)	
Smoking status	Never	Current	1.04	(0.91, 1.20)	<0.0001	1.00	(0.87, 1.15)	0.004
		Previous	1.23	(1.03, 1.48)		0.98	(0.80, 1.19)	
		Unknown	2.04	(1.80, 2.30)		1.22	(1.07, 1.40)	
ART experience	Experienced, VL<400 cps/mL	Naive	0.92	(0.82, 1.04)	<0.0001	1.44	(1.28, 1.62)	<0.0001
		Experienced, VL≥400 cps/mL	2.11	(1.80 ,2.48)		1.13	(0.91, 1.40)	
HIV risk	MSM	IDU	1.25	(1.09, 1.44)	0.0008	0.62	(0.52, 0.74)	<0.0001
		Heterosexual	1.09	(0.98, 1.22)		0.79	(0.70, 0.89)	
		Other	1.53	(1.16, 2.02)		0.68	(0.46, 0.98)	
		Unknown	0.94	(0.75, 1.17)		0.97	(0.78, 1.22)	
CD4 nadir, cells/mm³	<200	200-349	0.76	(0.68, 0.85)	<0.0001	1.41	(1.24, 1.60)	<0.0001
		350-499	0.67	(0.58, 0.79)		1.68	(1.44, 1.96)	
		≥500	0.70	(0.59, 0.83)		1.67	(1.42, 1.98)	
CD4 count at INSTI start, cells/mm³	<200	200-349	0.87	(0.73, 1.04)	<0.0001	1.79	(1.41, 2.26)	<0.0001
		350-499	0.71	(0.60 ,0.83)		1.85	(1.49, 2.30)	
		≥500	0.60	(0.52 ,0.69)		1.55	(1.28, 1.89)	
Hepatitis C	No	Yes	1.29	(1.16, 1.45)	<0.0001	0.69	(0.59, 0.79)	<0.0001
		Unknown	1.67	(1.45, 1.91)		1.72	(1.49, 1.99)	
Hepatitis B	No	Yes	1.60	(1.28, 2.00)	<0.0001	1.59	(1.24, 2.04)	<0.0001
		Unknown	1.55	(1.37, 1.76)		1.75	(1.53, 2.01)	
Hypertension	No	Yes	0.92	(0.82, 1.04)	<0.0001	0.80	(0.70, 0.92)	<0.0001
		Unknown	2.15	(1.93, 2.40)		1.52	(1.34, 1.72)	
Diabetes	No	Yes	1.16	(0.98, 1.37)	0.07	0.87	(0.70, 1.07)	<0.0001
		Unknown	1.15	(0.97, 1.37)		2.07	(1.76, 2.44)	
Prior AIDS	No	Yes	1.40	(1.25, 1.56)	<0.0001	0.65	(0.56, 0.76)	<0.0001
		Unknown	0.59	(0.49, 0.71)		1.97	(1.71, 2.27)	
Prior NADC	No	Yes	1.14	(0.91, 1.43)	0.0001	0.56	(0.39, 0.79)	<0.0001
		Unknown	0.77	(0.68, 0.87)		2.07	(1.84, 2.33)	
Prior ESLD	No	Yes	1.22	(0.78, 1.93)	<0.0001	0.52	(0.22, 1.24)	<0.0001
		Unknown	0.38	(0.35, 0.42)		1.37	(1.23, 1.54)	

Prior CVD	No	Yes	1.90	(1.50, 2.40)	<0.0001	0.84	(0.59, 1.18)	<0.0001
		Unknown	1.06	(0.95, 1.18)		1.53	(1.37, 1.72)	
Prior fracture	No	Yes	0.84	(0.68, 1.05)	0.005	0.92	(0.70, 1.21)	<0.0001
		Unknown	0.84	(0.76, 0.94)		2.04	(1.82, 2.28)	
Prior CKD	No	Yes	1.17	(0.93, 1.47)	0.04	0.60	(0.42, 0.85)	<0.0001
		Unknown	0.87	(0.77, 1.00)		2.25	(1.99, 2.55)	

Abbreviations: RR-risk ratio; CI-confidence interval; cps-copies
*Results from a univariable, multinomial logistic regression
[1]Due to low counts, Australia is grouped with Northern Europe and Eastern Central Europe is grouped with Eastern Europe.

Table 4.6 Associations between characteristics at INSTI start and choice of INSTIs – multivariable analysis

			Raltegravir vs Dolutegravir			Elvitegravir/c vs Dolutegravir		
Variable	**Reference**	**Group**	**RR***	**(95% CI)**	**p-value**	**RR***	**(95% CI)**	**p-value**
INSTI start, per 1-year increase			0.25	(0.23, 0.26)	<0.0001	0.63	(0.57, 0.69)	<0.0001
Geographic-al region[1]	Western Europe	Southern Europe	3.00	(2.36, 3.81)	<0.0001	1.23	(0.99, 1.52)	<0.0001
		Northern Europe/ Australia	1.15	(0.86, 1.52)		0.68	(0.52, 0.90)	
		Eastern Europe	6.82	(5.07, 9.19)		1.36	(1.02, 1.81)	
Age, per 10-year increase			1.14	(1.06, 1.22)	<0.0001	0.91	(0.86, 0.97)	0.002
Gender	Male	Female	0.98	(0.82, 1.17)	0.80	0.68	(0.58, 0.80)	<0.0001
Ethnicity	White	Black	1.00	(0.77, 1.30)	<0.0001	1.24	(1.00, 1.54)	0.003
		Other	0.98	(0.68, 1.42)		1.14	(0.87, 1.50)	
		Unknown	2.04	(1.55, 2.68)		1.48	(1.17, 1.86)	
Smoking status	Never	Current	1.03	(0.85, 1.24)	0.25	1.10	(0.94, 1.29)	0.65
		Previous	1.08	(0.85, 1.38)		1.04	(0.84, 1.28)	
		Unknown	1.30	(1.00, 1.71)		1.03	(0.82, 1.29)	
ART experience	Experien-ced, VL<400 cps/mL	Naive	1.29	(1.03, 1.63)	<0.0001	0.99	(0.82, 1.19)	0.61
		Experience-ed, VL≥400 cps/mL	1.56	(1.22, 2.00)		1.12	(0.88, 1.41)	
HIV risk	MSM	IDU	1.37	(1.06, 1.76)	0.009	1.01	(0.80, 1.28)	0.68
		Heterosex-ual	1.33	(1.10, 1.60)		1.10	(0.94, 1.29)	
		Other	1.69	(1.11, 2.57)		0.88	(0.59, 1.32)	
		Unknown	1.06	(0.78, 1.45)		0.99	(0.77, 1.26)	
CD4 nadir, cells/mm³	<200	200-349	0.97	(0.81, 1.16)	0.57	1.09	(0.94, 1.27)	0.70
		350-499	0.93	(0.73, 1.18)		1.07	(0.88, 1.31)	
		≥500	1.14	(0.85, 1.53)		1.06	(0.84, 1.35)	
CD4 count at INSTI start, cells/mm³	<200	200-349	0.92	(0.70, 1.21)	0.16	1.75	(1.34, 2.27)	<0.0001
		350-499	0.84	(0.64, 1.10)		1.88	(1.45, 2.44)	
		≥500	0.76	(0.58, 0.99)		1.66	(1.27, 2.17)	
Hepatitis C	No	Yes	1.39	(1.13, 1.72)	0.008	0.80	(0.66, 0.98)	0.007
		Unknown	1.03	(0.71, 1.50)		1.39	(1.01, 0.93)	
Hepatitis B	No	Yes	1.60	(1.19, 2.17)	0.007	1.68	(1.30, 2.19)	0.0005
		Unknown	1.14	(0.84, 1.55)		0.98	(0.74, 1.29)	
Hypertensi-on	No	Yes	0.90	(0.76, 1.07)	<0.0001	0.85	(0.73, 0.98)	0.005
		Unknown	35.73	(22.98, 55.55)		0.39	(0.19, 0.81)	
Diabetes	No	Yes	1.20	(0.95, 1.51)	0.31	1.07	(0.85, 1.34)	0.11
		Unknown	1.02	(0.66, 1.59)		0.68	(0.47, 0.98)	
Prior AIDS	No	Yes	1.29	(1.09, 1.52)	<0.0001	0.71	(0.60, 0.84)	0.0001
		Unknown	0.02	(0.01, 0.04)		0.65	(0.40, 1.07)	
Prior NADC	No	Yes	1.23	(0.89, 1.70)	<0.0001	0.67	(0.47, 0.97)	0.10
		Unknown	6.00	(4.19, 8.59)		1.06	(0.71, 1.57)	
Prior ESLD	No	Yes	1.38	(0.74, 2.59)	0.0003	0.54	(0.21, 1.42)	0.06
		Unknown	0.64	(0.50, 0.80)		0.81	(0.67, 0.98)	

Prior CVD	No	Yes	2.34	(1.69, 3.24)	<0.0001	1.00	(0.70, 1.44)	0.01
		Unknown	0.16	(0.11, 0.24)		0.46	(0.27, 0.76)	
Prior fracture	No	Yes	0.60	(0.43, 0.83)	<0.0001	1.06	(0.80, 1.40)	<0.0001
		Unknown	0.34	(0.23, 0.49)		2.71	(1.83, 4.01)	
Prior CKD	No	Yes	1.32	(0.94, 1.83)	0.007	0.76	(0.52, 1.10)	<0.0001
		Unknown	1.89	(1.18, 2.93)		5.08	(3.28, 7.86)	

*Results from a multivariable, multinomial logistic regression; all variables were fitted in the model simultaneously

[1]Due to low counts, Australia is grouped with Northern Europe and Eastern Central Europe is grouped with Eastern Europe.

4.3.3.1 Sensitivity analyses

A summary of the main results from the sensitivity analyses are shown in Table 4.7. Analyses were rerun using multiple imputation to account for missing data, rather than fitting unknown categories, with similar results found. Due to the collinearity between missing data and cohort, analyses adjusting for cohort instead of comorbidities were performed, and also showed similar results.

As a post hoc analysis, I also repeated analyses only including those starting an INSTI from 2015 (when DTG, EVG/c and RAL were all approved). This included 6595 participants (4403 on DTG, 1354 on EVG/c, 838 on RAL). The likelihood of starting EVG/c compared to DTG increased over time from 2015 (RR 1.44 per year later [1.33-1.57], p<0.0001), as shown in Table 4.7. This effect was reversed in the overall analysis where the likelihood of starting EVG/c compared to DTG decreased over time; other results were similar when limited to those starting an INSTI after 2015. Adjusting additionally for the nucleoside backbone did not change the findings in the primary analysis, except for HBV coinfection, which was no longer associated with choice of INSTI (RAL vs DTG: 1.27 [0.93-1.75], p=0.21; EVG/c vs DTG: 1.00 [0.73-1.36], p=0.61).

Table 4.7 Summary of main results from sensitivity analyses assessing predictors of the choice of INSTI

Using multiple imputation to account for missing data (n=9702 included)

			Raltegravir vs Dolutegravir			Elvitegravir/c vs Dolutegravir		
Variable	**Reference**	**Group**	**RR***	**(95% CI)**	**p-value**	**RR***	**(95% CI)**	**p-value**
INSTI start, per 1-year increase			0.26	(0.25,0.28)	<0.001	0.79	(0.75,0.83)	<0.001
Geographical region[1]	Western Europe	Southern Europe	2.86	(2.42,3.37)	<0.001	1.43	(1.25,1.65)	<0.001
		Northern Europe/ Australia	5.35	(4.46,6.42)		0.78	(0.63,0.97)	
		Eastern Europe	7.74	(5.95,10.06)		1.47	(1.13,1.91)	
Age, per 10-year increase			1.11	(1.04,1.19)	0.002	0.94	(0.89,1.00)	0.04
Gender	Male	Female	0.97	(0.82,1.15)	0.73	0.71	(0.60,0.84)	<0.001
ART experience	Experienced, VL<400 cps/mL	Naive	1.19	(0.97,1.46)	0.007	1.17	(0.97,1.41)	0.14
		Experienced, VL≥400 cps/mL	1.44	(1.14,1.81)		1.19	(0.94,1.50)	
Hepatitis C	No	Yes	1.47	(1.10,1.97)	0.01	0.77	(0.59,1.01)	0.06
Hepatitis B	No	Yes	1.64	(1.05,2.55)	0.03	1.84	(1.37,2.47)	<0.001
Prior AIDS	No	Yes	1.27	(1.08,1.48)	0.003	0.73	(0.61,0.86)	<0.001
Prior NADC	No	Yes	1.17	(0.86,1.60)	0.31	0.65	(0.45,0.94)	0.02
Prior CVD	No	Yes	2.00	(1.50,2.69)	<0.001	0.93	(0.66,1.31)	0.67

Adjusting the primary analysis model for cohort instead of comorbidities (n=9702 included)

			Raltegravir vs Dolutegravir			Elvitegravir/c vs Dolutegravir		
Variable	**Reference**	**Group**	**RR***	**(95% CI)**	**p-value**	**RR***	**(95% CI)**	**p-value**
INSTI start, per 1-year increase			0.27	(0.25, 0.29)	<0.0001	0.82	(0.78, 0.86)	<0.001
Age, per 10-year increase			1.10	(1.03, 1.17)	0.003	0.88	(0.83, 0.93)	<0.001
Gender	Male	Female	0.96	(0.81, 1.14)	0.62	0.67	(0.57, 0.79)	<0.001
ART experience	Experienced, VL<400 cps/mL	Naive	1.29	(1.03, 1.62)	<0.001	1.02	(0.85, 1.23)	0.50
		Experienced, VL≥400 cps/mL	1.71	(1.35, 2.17)		1.15	(0.91, 1.45)	

Restricting the primary analysis to individuals starting an INSTI after 1st January 2015 (n=6595 included)

			Raltegravir vs Dolutegravir			Elvitegravir/c vs Dolutegravir		
Variable	**Reference**	**Group**	**RR***	**(95% CI)**	**p-value**	**RR***	**(95% CI)**	**p-value**
INSTI start, per 1-year increase			0.60	(0.53,0.68)	<0.001	1.44	(1.33,1.57)	<0.001
Geographical region[1]	Western Europe	Southern Europe	2.41	(1.78,3.26)	<0.001	1.31	(1.03,1.67)	<0.001
		Northern Europe/ Australia	1.03	(0.68,1.56)		0.61	(0.43,0.86)	
		Eastern Europe	4.25	(3.01,6.01)		1.22	(0.89,1.67)	
Age, per 10-year increase			1.09	(1.00,1.19)	0.06	0.96	(0.90,1.03)	0.24
Gender	Male	Female	0.99	(0.79,1.25)	0.94	0.72	(0.59,0.87)	<0.001
ART experience	Experienced, VL<400 cps/mL	Naive	1.61	(1.18,2.21)	0.006	0.88	(0.71,1.09)	0.31
		Experienced, VL≥400 cps/mL	1.41	(1.02,1.96)		1.10	(0.83,1.45)	
Hepatitis C	No	Yes	1.28	(0.98,1.67)	0.18	0.83	(0.66,1.04)	0.09

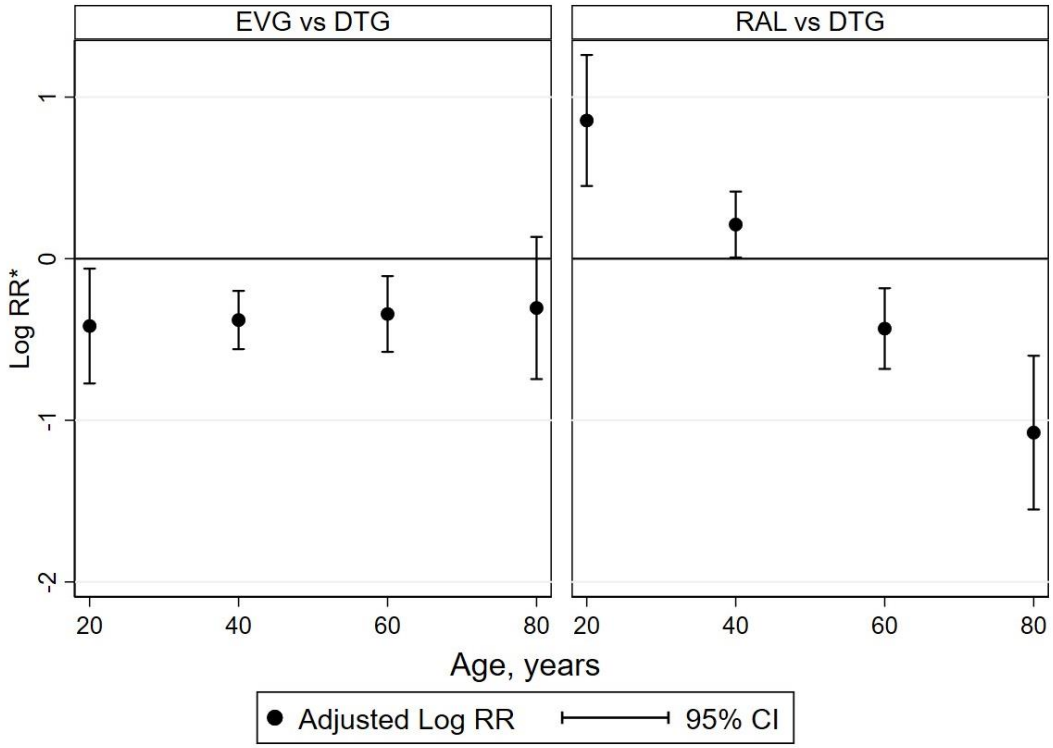
		Unknown	1.02	(0.61,1.70)		1.29	(0.88,1.90)	
Hepatitis B	No	Yes	1.39	(0.93,2.06)	0.26	1.87	(1.40,2.51)	<0.001
		Unknown	0.99	(0.65,1.49)		1.10	(0.79,1.53)	
Prior AIDS	No	Yes	1.37	(1.11,1.70)	<0.001	0.78	(0.64,0.94)	0.03
		Unknown	0.03	(0.02,0.06)		1.18	(0.59,2.35)	
Prior NADC	No	Yes	0.95	(0.63,1.46)	<0.001	0.59	(0.39,0.89)	0.01
		Unknown	4.81	(2.91,7.96)		0.60	(0.33,1.08)	
Prior CVD	No	Yes	2.40	(1.59,3.62)	<0.001	1.03	(0.68,1.57)	0.92
		Unknown	0.11	(0.06,0.19)		0.87	(0.41,1.84)	

Results are from multivariable multinomial logistic regression model adjusted for the same variables as in the primary analysis (other than when cohort was adjusted for instead of comorbidities). Other results from sensitivity analyses are not shown

4.3.3.2 Subgroup analyses

There was a significant interaction between age and gender (p-value for interaction <0.0001) when comparing RAL to DTG, showing that females were more likely to start RAL compared to males in younger age groups but were less likely to start RAL compared to males in older age groups (Figure 4.7). Other prespecified subgroup analyses between age and having hepatitis B (HBV), HCV, and each comorbidity listed in Table 4.1, were non-significant. Results were additionally stratified by ART experience at baseline, with similar results seen for individuals who were ART naïve, ART experienced with VL<400 copies/mL, and ART experienced with VL ≥400 copies/mL (Table 4.8).

Figure 4.7 Association between gender and INSTI uptake, by age group



*Log RR comparing females to males estimated from a multinomial logistic regression model including an interaction between age and gender, adjusted for year of starting INSTI, geographical region, ethnicity, smoking status, HIV risk group, antiretroviral treatment experience, CD4 nadir, CD4 count at INSTI start, hepatitis B, hepatitis C, hypertension, diabetes, prior AIDS, non-AIDS cancers, end stage liver disease, cardiovascular disease, fracture, chronic kidney disease

Table 4.8 Associations between characteristics at INSTI start and choice of INSTIs, stratified by ART experience at INSTI start – multivariable analysis

Raltegravir vs Dolutegravir

			ART naïve			ART experienced, VL<400			ART experienced, VL≥400		
Variable	**Reference**	**Group**	**RR***	**(95% CI)**	**p-value**	**RR***	**(95% CI)**	**p-value**	**RR***	**(95% CI)**	**p-value**
INSTI start, per 1 calendar year later			0.27	(0.23, 0.30)	<0.0001	0.23	(0.22, 0.25)	<0.0001	0.17	(0.13, 0.22)	<0.0001
Geographical region[1]	Western Europe	Southern Europe	3.18	(1.77,5.72)	<0.0001	3.00	(2.26,3.98)	<0.0001	7.23	(2.50,20.88)	<0.0001
		Northern Europe/ Australia	4.97	(1.17,21.08)		1.03	(0.75,1.41)		0.92	(0.31,2.74)	
		Eastern Europe	15.93	(4.75,53.40)		6.40	(4.53,9.03)		17.24	(6.34,46.86)	
Age, per 10-year increase			1.17	(1.03,1.33)	0.02	1.14	(1.05,1.25)	0.003	0.89	(0.69,1.16)	0.39
Gender	Male	Female	1.47	(0.97,2.23)	0.07	0.90	(0.73,1.13)	0.37	0.66	(0.37,1.16)	0.15
Ethnicity	White	Black	1.77	(1.01,3.10)	0.24	0.83	(0.60,1.16)	<0.0001	0.80	(0.34,1.85)	0.53
		Other	0.95	(0.49,1.83)		0.94	(0.58,1.54)		1.60	(0.43,5.87)	
HIV risk	MSM	IDU	1.79	(0.84,3.80)	0.22	1.25	(0.94,1.68)	0.08	1.53	(0.61,3.82)	0.91
		Heterosexual	1.12	(0.76,1.67)		1.38	(1.09,1.74)		1.22	(0.60,2.45)	
		Other	2.50	(0.95,6.54)		1.26	(0.75,2.11)		1.58	(0.37,6.71)	
CD4 at INSTI start, cells/mm³	<200	200-349	0.45	(0.12,1.71)	0.49	0.94	(0.61,1.46)	0.12	1.03	(0.50,2.09)	1.00
		350-499	0.33	(0.08,1.34)		0.88	(0.58,1.34)		1.05	(0.48,2.29)	
		≥500	0.36	(0.08,1.59)		0.74	(0.50,1.09)		1.00	(0.46,2.17)	
Hepatitis C	No	Yes	1.29	(0.67,2.48)	0.33	1.61	(1.27,2.05)	<0.0001	0.78	(0.36,1.70)	0.58
Hepatitis B	No	Yes	2.25	(0.83,6.07)	0.10	1.37	(0.96,1.94)	0.14	3.02	(1.18,7.72)	0.03
Hypertension	No	Yes	0.77	(0.43,1.36)	0.003	0.98	(0.81,1.20)	<0.0001	0.60	(0.32,1.14)	<0.0001
Diabetes	No	Yes	0.73	(0.25,2.11)	0.35	1.32	(1.03,1.70)	0.07	0.70	(0.25,1.95)	0.36
Prior AIDS	No	Yes	2.15	(1.32,3.49)	<0.0001	1.18	(0.97,1.43)	<0.0001	1.86	(1.08,3.23)	0.001
Prior NADC	No	Yes	1.13	(0.30,4.23)	0.40	1.23	(0.86,1.75)	<0.0001	1.54	(0.40,5.94)	<0.0001
Prior CVD	No	Yes	5.24	(0.60,45.50)	0.24	2.27	(1.61,3.20)	<0.0001	4.04	(0.76,21.37)	0.006
Prior fracture	No	Yes	1.91	(0.48,7.62)	0.01	0.58	(0.41,0.84)	<0.0001	0.32	(0.10,0.98)	0.02

Elvitegravir/c vs Dolutegravir										
			ART naïve			ART experienced, VL<400			ART experienced, VL≥400		
Variable	**Reference**	**Group**	**RR***	**(95% CI)**	**p-value**	**RR***	**(95% CI)**	**p-value**	**RR***	**(95% CI)**	**p-value**
INSTI start, per 1 calendar year later			0.63	(0.57,0.69)	<0.0001	0.94	(0.88,1.00)	0.06	0.77	(0.62,0.95)	0.02
Geographical region[1]	Western Europe	Southern Europe	1.99	(1.24,3.17)	<0.0001	1.16	(0.89,1.50)	0.005	1.77	(0.63,5.01)	0.75
		Northern Europe/ Australia	3.25	(0.84,12.54)		0.67	(0.50,0.90)		1.13	(0.40,3.18)	
		Eastern Europe	10.78	(3.52,33.02)		1.12	(0.81,1.55)		1.28	(0.46,3.54)	
Age, per 10-year increase			1.00	(0.90,1.10)	0.95	0.89	(0.82,0.95)	0.001	0.77	(0.59,0.99)	0.04
Gender	Male	Female	0.59	(0.40,0.88)	0.009	0.71	(0.58,0.86)	<0.0001	0.58	(0.32,1.02)	0.06
Ethnicity	White	Black	1.14	(0.67,1.92)	0.41	1.19	(0.92,1.55)	0.02	1.87	(0.88,4.00)	0.16
		Other	1.17	(0.74,1.84)		1.10	(0.77,1.59)		2.61	(0.82,8.30)	
HIV risk	MSM	IDU	0.52	(0.26,1.06)	0.45	1.10	(0.83,1.45)	0.61	2.51	(1.00,6.28)	0.11
		Heterosexual	1.02	(0.73,1.42)		1.15	(0.95,1.40)		0.80	(0.39,1.63)	
		Other	1.17	(0.45,3.05)		0.92	(0.58,1.46)		0.50	(0.08,3.17)	
CD4 at INSTI start, cells/mm³	<200	200-349	0.97	(0.30,3.07)	0.010	1.86	(1.14,3.02)	0.04	2.28	(1.13,4.58)	0.07
		350-499	2.72	(0.82,9.02)		1.75	(1.10,2.80)		1.01	(0.44,2.32)	
		≥500	2.30	(0.67,7.85)		1.53	(0.97,2.41)		1.18	(0.55,2.57)	
Hepatitis C	No	Yes	1.36	(0.79,2.36)	0.11	0.67	(0.53,0.84)	0.001	0.79	(0.36,1.76)	0.83
Hepatitis B	No	Yes	2.10	(0.90,4.86)	0.10	1.75	(1.31,2.33)	<0.0001	0.87	(0.29,2.66)	0.52
Hypertension	No	Yes	0.68	(0.42,1.09)	0.27	0.84	(0.72,1.00)	0.03	1.15	(0.66,2.02)	0.39
Diabetes	No	Yes	1.44	(0.67,3.10)	0.64	0.96	(0.75,1.24)	0.07	2.46	(1.02,5.92)	0.005
Prior AIDS	No	Yes	0.73	(0.41,1.28)	0.55	0.72	(0.60,0.87)	0.002	0.60	(0.33,1.08)	0.12
Prior NADC	No	Yes	0.24	(0.03,1.90)	0.40	0.71	(0.49,1.03)	0.16	0.46	(0.05,3.91)	0.59
Prior CVD	No	Yes	0.00	(0.00,NE)	1.00	1.03	(0.71,1.50)	0.007	2.55	(0.49,13.15)	0.46
Prior fracture	No	Yes	0.34	(0.04,2.85)	0.61	1.15	(0.86,1.54)	0.002	0.37	(0.10,1.38)	0.06

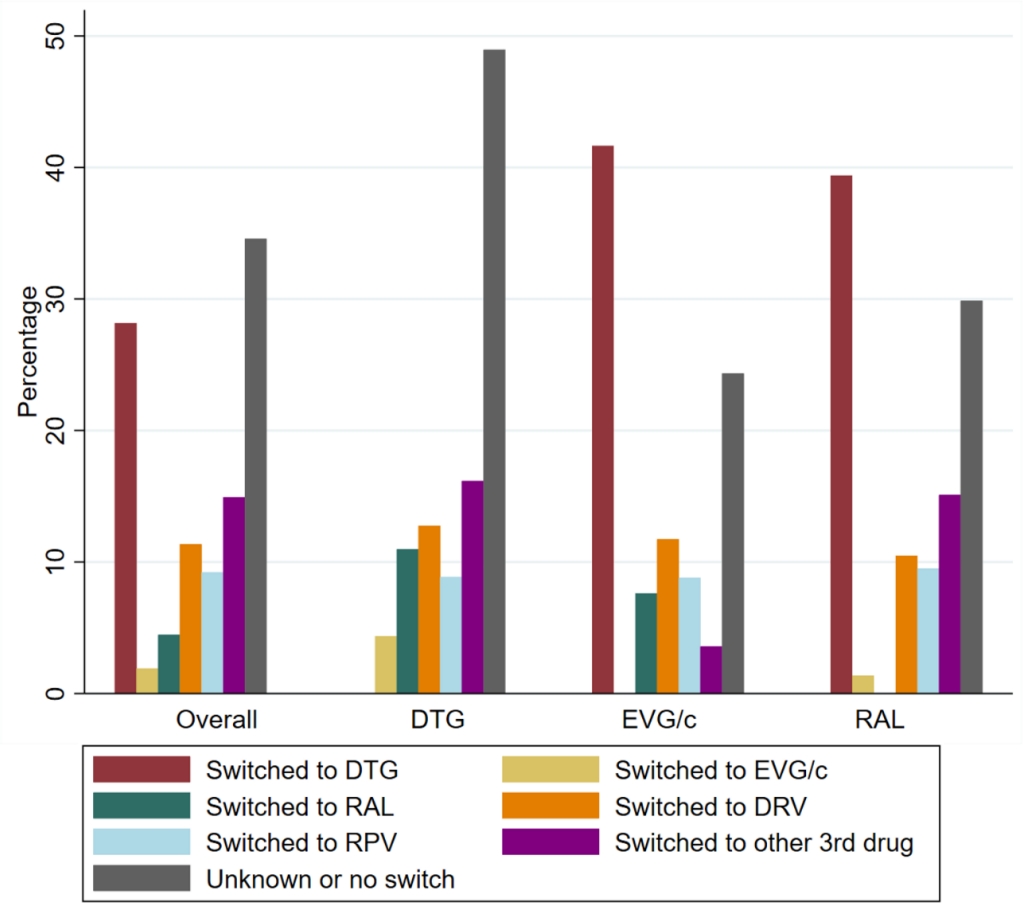
*Results from a multivariable, multinomial logistic regression; all variables were fitted in the model simultaneously.
Unknown categories were used for missing data for categorical variables (data not shown)

4.3.4 INSTI discontinuation

4.3.4.1 Overview

Median follow-up time was longest on RAL (33.4 months IQR [16.7-48.3]), compared to EVG/c (17.7 [7.6-31.7]) and DTG (17.1 [8.5-26.2]) as this was the first INSTI licensed for use. Of all INSTI users, 9669 (99.7%) were on the INSTI for at least 7 days and were considered in the discontinuation analysis. Overall, 2105 (21.7%) persons discontinued an INSTI during follow-up; the proportion who discontinued was highest on RAL (1145 (42.5%) RAL, 619 (12.3%) DTG, 341 (17.6%) EVG/c). Amongst those discontinuing, median time to discontinuation was 12.2 months (IQR 4.4-24.0) on RAL, 6.3 months (2.7-14.0) on DTG, and 8.9 months (3.2-18.4) on EVG/c. Figure 4.8 shows the 3rd drugs that individuals switched to after INSTI discontinuation. Approximately 28.2% of those who discontinued an INSTI switched to DTG (for those not on DTG originally), 11.4% switched to darunavir (DRV), and 9.2% switched to rilpivirine (RPV).

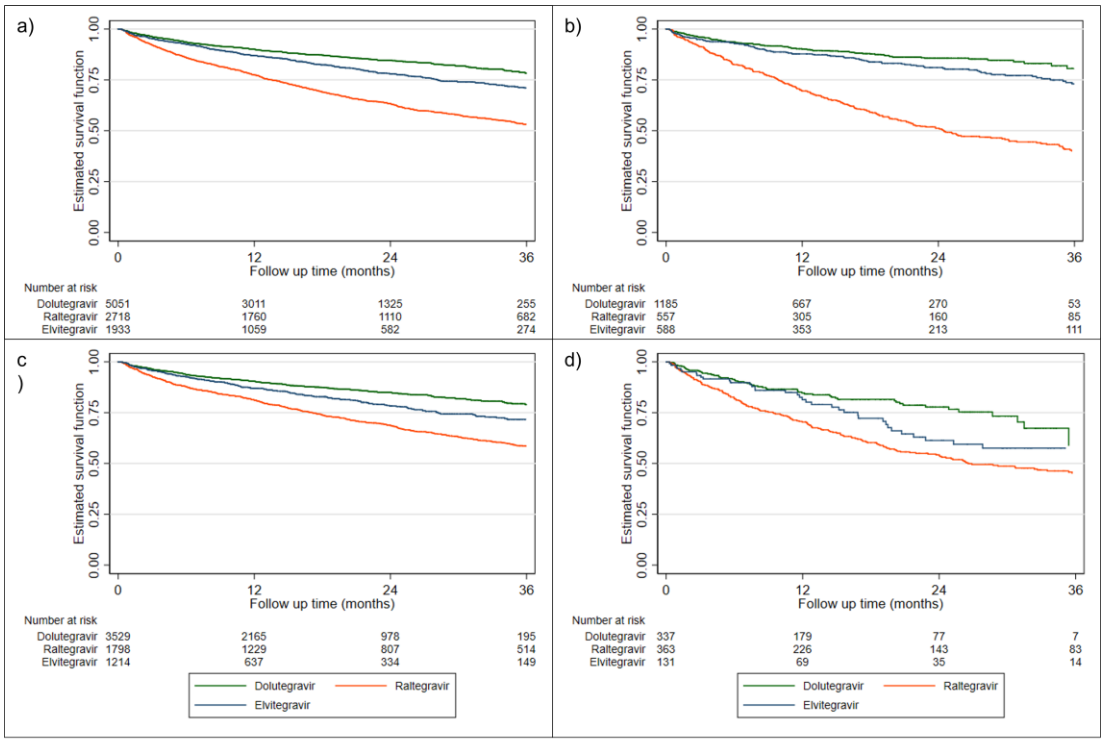
Figure 4.8 3rd drugs switched to after discontinuing an INSTI



89 participants switched to more than one 3rd drug
Other 3rd drug includes efavirenz, etravirine, nevirapine, atazanavir, saquinavir, nelfinavir, amprenavir, lopinavir

KM plots of discontinuation, overall and stratified by prior ART-experience are shown in Figure 4.9. The overall KM estimate of discontinuation at 6 months after INSTI start was 8.9% (95% CI: 8.3-9.5) and was highest on RAL (14.0% [12.7-15.4] RAL vs. 6.4% [5.7-7.2] on DTG, 7.4% [6.3-8.8] on EVG/c; p<0.0001), and this was consistent regardless of prior ART-experience. The overall KM estimate of discontinuation at 1 and 2 years were 10.0% (9.1-10.9) and 15.4% (14.2-16.7) for DTG, 13.1% (11.5-14.9) and 22.0% (19.7-24.5) for EVG/c, and 22.6% (21.0-24.3) and 36.7% (34.7-38.7) for RAL. Discontinuation of RAL was highest in 2014 and 2015 when DTG and EVG/c were both approved by the EMA.

Figure 4.9 Kaplan Meier plots of INSTI discontinuation: (a) overall; (b) in antiretroviral treatment-naïve individuals; (c) in antiretroviral treatment-experienced individuals with a viral load < 400 copies/mL; (d) in antiretroviral treatment-experienced individuals with a viral load ≥ 400 copies/mL



4.3.4.2 Reasons for discontinuation of INSTI

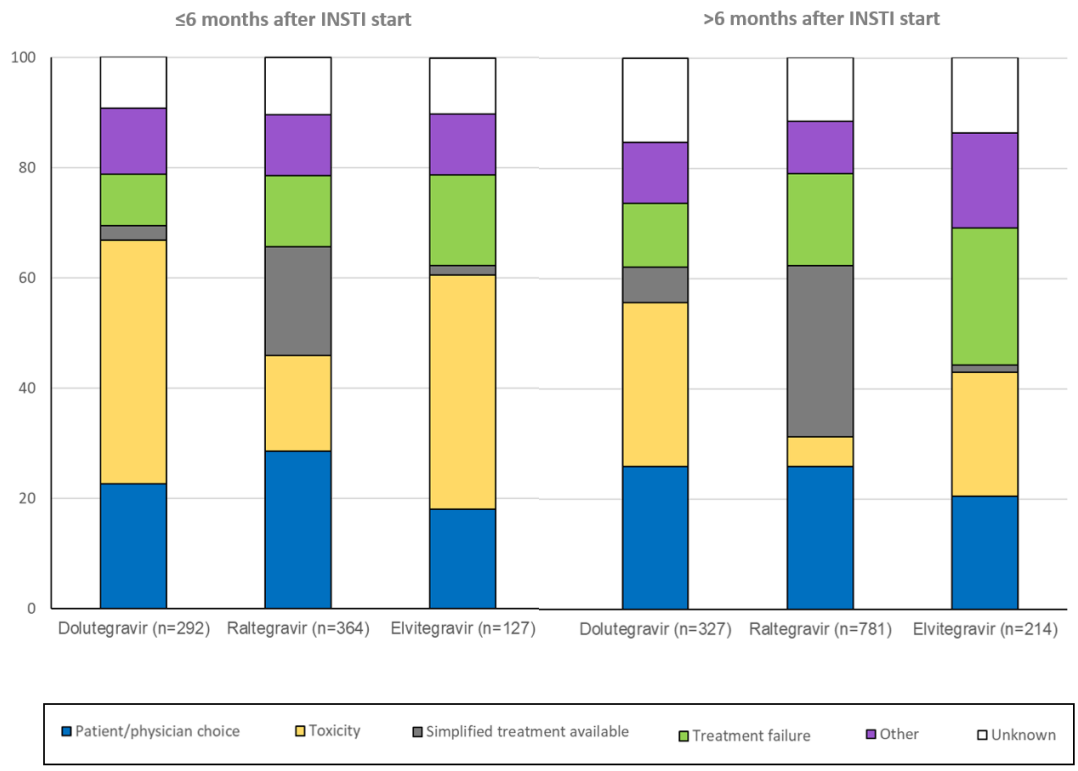
Overall, the most common reasons for INSTI discontinuation were patient or physician choice (24.9%), followed by toxicity (20.6%). For discontinuations of DTG and EVG/c, the most common reason was toxicity (36.5% DTG and 29.9% EVG/c), whilst for discontinuations of RAL, it was treatment simplification (27.5%). Of those participants who discontinued RAL due to treatment simplification, the majority switched to DTG (60.9%). Reasons for discontinuation differed between those which occurred within 6 months after INSTI start and those which occurred after 6 months after INSTI start, and these are presented, by INSTI, in Figure 4.10.

By 6 months after INSTI start, 783 (8.1%) individuals had discontinued an INSTI (292 (5.8%) on DTG, 127 (6.6%) on EVG/c, 364 (13.4%) on RAL) and the most commonly reported reason for discontinuation was toxicity (31.4% overall), followed by patient or physician choice (24.6% overall). Reasons for discontinuation were similar for DTG

and EVG/c, with discontinuation due to toxicity accounting for almost half of all discontinuations in these groups (44.2% and 42.5% respectively). Conversely, of all discontinuations on RAL, the main reason reported was patient or physician choice (28.6%). Discontinuations for treatment simplification accounted for a significantly higher proportion of discontinuations on RAL compared to DTG or EVG/c (19.8% on RAL, 2.7% on DTG, 1.6% on EVG/c, p<0.0001).

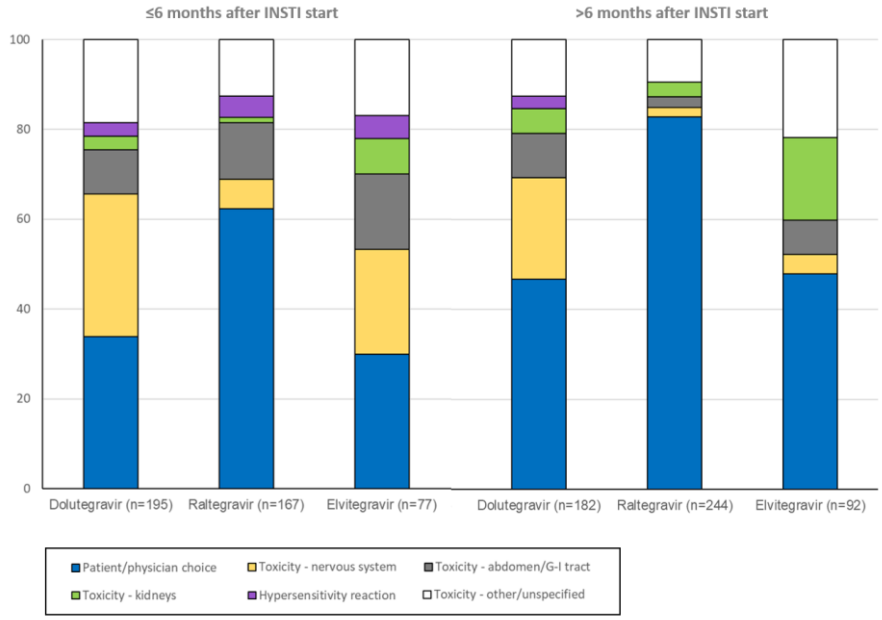
Overall, 1,322 (13.6%) individuals discontinued an INSTI more than 6 months after INSTI start: 327 (6.5%) on DTG, 214 (11.1%) on EVG/c, 781 (28.7%) on RAL. Of those, the most commonly reported reason was patient or physician choice (25.0% overall). For discontinuations of DTG and EVG/c, toxicity remained the most common reason (29.7% and 22.4%, respectively), and treatment simplification was the most common reason on RAL (31.1%).

Figure 4.10 Reasons for INSTI discontinuation split by discontinuations ≤6 months and >6 months after INSTI start



Discontinuations due to toxicity, within 6 months and after 6 months after INSTI start, were broken down and compared between INSTIs, as shown in Figure 4.11. Overall, 439 individuals discontinued an INSTI due to toxicity within 6 months after INSTI start and 518 discontinued due to toxicity after 6 months after INSTI start. Within 6 months, nervous system toxicity accounted for a higher proportion of toxicity discontinuations on DTG compared to the other INSTIs (31.8% on DTG, 23.4% on EVG/c, 6.6% on RAL, p<0.0001) and this was also the case for discontinuations after 6 months (22.5% on DTG, 4.4% on EVG/c, 2.1% on RAL, p<0.0001). Nervous system toxicities included neuropsychiatric toxicities, headache, and peripheral neuropathy, although the type of nervous system toxicity was not reported for the majority of discontinuations. As EFV has been shown to be associated with nervous system toxicities, I assessed how many of those discontinuing DTG due to nervous system toxicities had previously discontinued EFV for the same reason. Of 62 individuals discontinuing DTG due to nervous system toxicities by 6 months, 8 (12.9%) had previously discontinued EFV because of nervous system toxicities, and of 42 individuals discontinuing for nervous system toxicities after 6 months, 6 (14.3%) had previously discontinued EFV for nervous system toxicities.

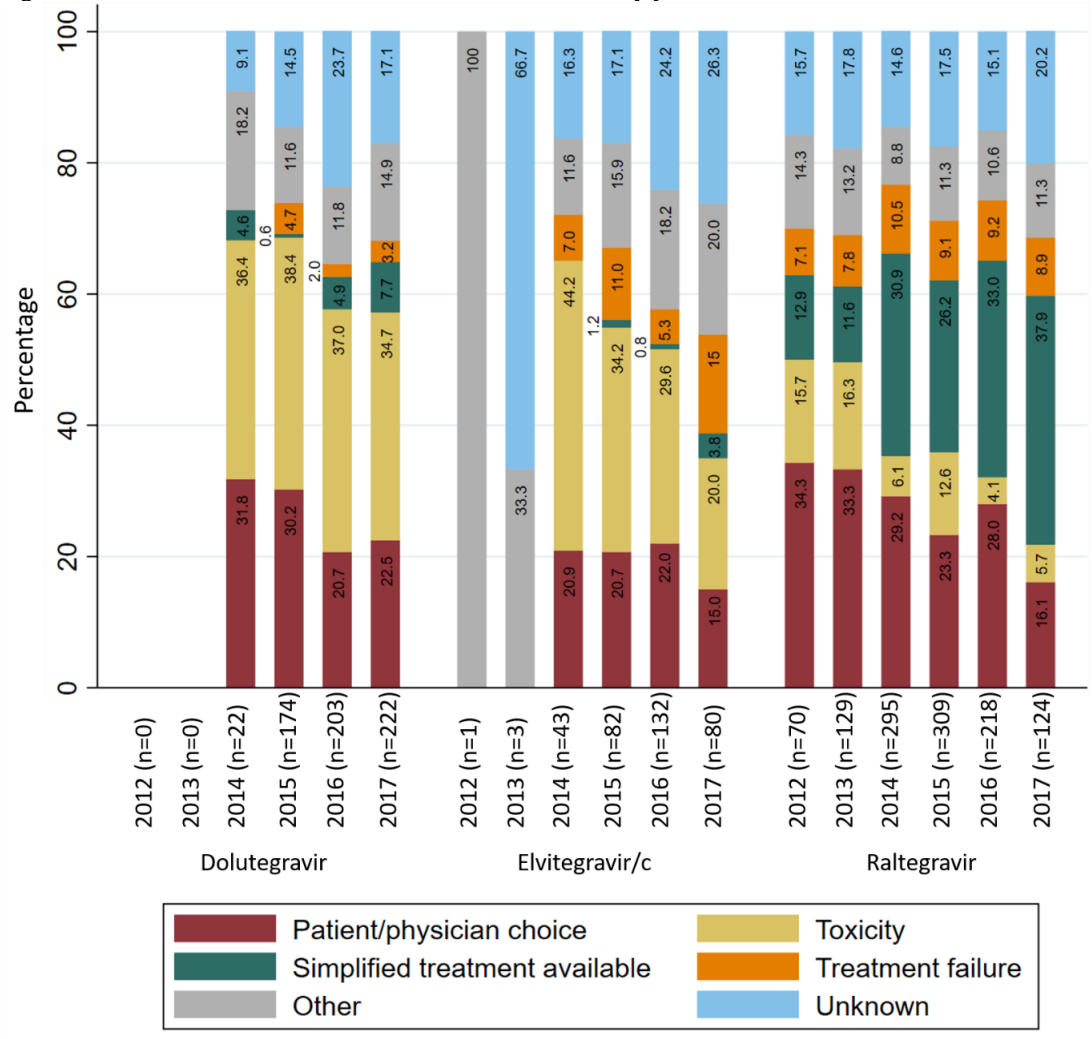
Figure 4.11 Reasons for toxicity discontinuation split by discontinuations ≤6 months and >6 months after INSTI start



Abbreviations: G-I – gastrointestinal

Reasons for discontinuation of each INSTI was stratified by calendar year, as shown in Figure 4.12, to assess whether specific reasons have become more common over time. Reasons for discontinuation remained similar over time on DTG. The proportion of discontinuations due to patient or physician choice or toxicity decreased over time on RAL, and discontinuations due to treatment simplification increased. Finally, discontinuations due to toxicity decreased over time on EVG/c, although the number of discontinuations, by year, in this group were relatively small. The reasons for discontinuation were also compared between males and females with similar results found (Table 4.9).

Figure 4.12 Reasons for discontinuation of each INSTI, by year of discontinuation



n in brackets shows the number of participants who discontinued the INSTI each year

Table 4.9 Reasons for INSTI discontinuation for males and females

		Males (n=7322)		Females (n=2378)	
All discontinuations	Total discontinued	1530	(20.9)	575	(24.2)
	Reasons for discontinuation				
	Patient/Physician Choice	368	(24.1)	156	(27.1)
	Toxicity	311	(20.3)	122	(21.2)
	Simplified treatment available	245	(16.0)	104	(18.1)
	Treatment failure	123	(8.0)	32	(5.6)
	Other	196	(12.8)	70	(12.2)
	Unknown	287	(18.8)	91	(15.8)
Discontinuations within 6 months	Total discontinued	549	(7.5)	234	(9.8)
	Reasons for discontinuation				
	Patient/Physician Choice	128	(23.3)	65	(27.8)
	Toxicity	171	(31.2)	75	(32.1)
	Simplified treatment available	55	(10.0)	27	(11.5)
	Treatment failure	29	(5.3)	6	(2.6)
	Other	83	(15.1)	22	(9.4)
	Unknown	83	(15.1)	39	(16.7)
Discontinuations after 6 months	Total discontinued	981	(13.4)	341	(14.3)
	Reasons for discontinuation				
	Patient/Physician Choice	240	(24.5)	91	(26.7)
	Toxicity	140	(14.3)	47	(13.8)
	Simplified treatment available	190	(19.4)	77	(22.6)
	Treatment failure	94	(9.6)	26	(7.6)
	Other	113	(11.5)	48	(14.1)
	Unknown	204	(20.8)	52	(15.3)

4.3.4.3 Associations between baseline characteristics and INSTI discontinuation

Results from unadjusted and adjusted Cox proportional hazards models assessing factors associated with INSTI discontinuation within the first 6 months after INSTI start are presented in Table 4.10. The adjusted risk of discontinuation was higher for RAL (hazard ratio [HR] 3.03, [95% CI: 2.47-3.71]) and EVG/c (1.37 [1.10-1.70], p<0.0001) compared to DTG. Individuals who started an INSTI later were more likely to discontinue it (1.11 per year later [1.04-1.18], p=0.001), as were females (1.28 [1.06-1.55], p=0.01), those with uncontrolled viremia compared to a suppressed VL in ART-experienced participants (1.36 [1.07-1.73], p=0.046), and those with HCV (1.32 [1.06-1.66], p=0.007) or prior NADC (1.55 [1.13-2.12], p=0.001). Conversely, those in Southern (0.58 [0.43-0.78]) and Eastern Europe (0.31 [0.20-0.50], p<0.0001) were less likely to discontinue compared to those in Western Europe. Results were similar in univariable and multivariable models except for INSTI start where there was

a decreasing risk of discontinuation as year of INSTI start increased in univariable models and an increasing risk of discontinuation in multivariable models. Similar results were seen for discontinuations greater than 6 months after INSTI initiation, as shown in Table 4.11.

Table 4.10 Associations between baseline characteristics and INSTI discontinuation in the first 6 months after INSTI start

			Univariable model*			Multivariable model*		
Variable	**Reference**	**Group**	**HR**	**(95% CI)**	**p-value**	**HR**	**(95% CI)**	**p-value**
INSTI type	DTG	RAL	2.27	(1.94, 2.64)	<0.001	3.03	(2.47, 3.71)	<0.001
		EVG/c	1.17	(0.95, 1.44)		1.37	(1.10, 1.70)	
INSTI start, per 1 year later			0.89	(0.85, 0.94)	<0.001	1.11	(1.04, 1.18)	0.001
Geographic-al region[1]	Western Europe	Southern Europe	0.83	(0.70, 0.98)	<0.001	0.58	(0.43, 0.78)	<0.001
		Northern Europe	1.03	(0.84, 1.27)		0.89	(0.64, 1.25)	
		Eastern Europe	0.43	(0.28, 0.66)		0.31	(0.20, 0.50)	
Age category	<30	30-39	1.07	(0.81, 1.41)	0.32	1.04	(0.78, 1.39)	0.19
		40-49	0.88	(0.67, 1.16)		0.84	(0.63, 1.12)	
		≥50	0.98	(0.75, 1.27)		0.95	(0.70, 1.28)	
Gender	Male	Female	1.34	(1.15, 1.56)	<0.001	1.28	(1.06, 1.56)	0.01
Ethnicity	White	Black	1.14	(0.92, 1.42)	0.56	0.96	(0.74, 1.25)	0.58
		Other	0.88	(0.60, 1.27)		0.79	(0.54, 1.15)	
		Unknown	1.00	(0.82, 1.22)		0.89	(0.66, 1.21)	
HIV risk	MSM	IDU	1.18	(0.96, 1.46)	0.09	0.89	(0.67, 1.19)	0.68
		Heterose-xual	1.24	(1.06, 1.45)		1.01	(0.82, 1.25)	
		Other	1.05	(0.66, 1.67)		0.75	(0.46, 1.22)	
		Unknown	0.97	(0.69, 1.36)		0.92	(0.65, 1.31)	
Smoking status	Never	Current	1.04	(0.85, 1.27)	0.10	0.96	(0.77, 1.19)	0.46
		Previous	1.10	(0.84, 1.44)		1.13	(0.86, 1.50)	
		Unknown	1.23	(1.03, 1.48)		0.85	(0.64, 1.15)	
ART experience	Experience-ed, VL<400 cps/mL	Naive	1.15	(0.98, 1.36)	<0.001	1.10	(0.87, 1.39)	0.046
		Experien-ced, VL≥400 cps/mL	1.68	(1.36, 2.08)		1.36	(1.07, 1.73)	
CD4 nadir, cells/mm³	<200	200-349	0.87	(0.74, 1.03)	0.41	1.05	(0.86, 1.28)	0.68
		350-499	0.91	(0.73, 1.13)		1.13	(0.86, 1.47)	
		≥500	1.00	(0.80, 1.25)		1.20	(0.88, 1.64)	
CD4 count at INSTI start, cells/mm³	<200	200-349	0.70	(0.54, 0.91)	<0.001	0.76	(0.58, 1.01)	0.06
		350-499	0.63	(0.50, 0.80)		0.69	(0.51, 0.91)	
		≥500	0.63	(0.52, 0.77)		0.71	(0.54, 0.95)	
Hepatitis C	No	Yes	1.18	(1.00, 1.36)	0.13	1.32	(1.06, 1.66)	0.007
		Unknown	0.99	(0.80, 1.22)		0.70	(0.46, 1.06)	
Hepatitis B	No	Yes	0.96	(0.68, 1.36)	0.87	0.93	(0.66, 1.33)	0.39
		Unknown	1.04	(0.87, 1.25)		1.24	(0.89, 1.74)	
	No	Yes	0.87	(0.73, 1.05)	0.15	0.92	(0.75, 1.11)	0.64

Hypertensi-on		Unknown	1.06	(0.90, 1.24)		0.91	(0.59, 1.39)	
Diabetes	No	Yes	0.82	(0.62, 1.08)	0.26	0.82	(0.62, 1.10)	0.39
		Unknown	0.89	(0.69, 1.14)		1.11	(0.65, 1.90)	
Prior AIDS	No	Yes	1.08	(0.92, 1.28)	0.01	1.01	(0.84, 1.21)	0.04
		Unknown	0.71	(0.55, 0.92)		2.18	(1.19, 4.01)	
Prior NADC	No	Yes	1.47	(1.08, 1.99)	0.004	1.55	(1.13, 2.12)	0.001
		Unknown	0.83	(0.69, 1.00)		0.61	(0.41, 0.92)	
Prior ESLD	No	Yes	1.11	(0.53, 2.36)	0.16	0.99	(0.46, 2.11)	0.52
		Unknown	1.15	(1.00, 1.33)		1.16	(0.90, 1.50)	
Prior CVD	No	Yes	1.16	(0.82, 1.66)	0.52	1.15	(0.79, 1.68)	0.002
		Unknown	1.07	(0.92, 1.26)		2.16	(1.41, 3.30)	
Prior fracture	No	Yes	0.84	(0.59, 1.20)	0.95	0.85	(0.59, 1.22)	0.54
		Unknown	0.97	(0.83, 1.14)		1.14	(0.76, 1.70)	
Prior CKD	No	Yes	0.83	(0.56, 1.24)	0.03	0.79	(0.52, 1.19)	0.001
		Unknown	0.77	(0.63, 0.94)		0.37	(0.22, 0.62)	

*Results from a Cox proportional hazards model; all variables were fitted simultaneously in the multivariable model

[1]Due to low counts, Australia is grouped with Northern Europe and Eastern Central Europe is grouped with Eastern Europe.

Table 4.11 Associations between characteristics at 6 months after INSTI start and risk of discontinuation after 6 months after INSTI start

			Univariable model*			Multivariable model*		
Variable	**Reference**	**Group**	**HR**	**(95% CI)**	**p-value**	**HR**	**(95% CI)**	**p-value**
INSTI type	DTG	RAL	2.91	(2.54,3.32)	<0.0001	3.91	(3.30,4.63)	<0.0001
		EVG/c	1.57	(1.32,1.87)		1.67	(1.39,2.00)	
INSTI start, per 1 year later			0.83	(0.79,0.87)	<0.0001	1.10	(1.04,1.17)	<0.0001
Geographic-al region[1]	Western Europe	Southern Europe	1.30	(1.15,1.48)	<0.0001	1.07	(0.87,1.33)	0.01
		Northern Europe	0.97	(0.82,1.16)		1.13	(0.88,1.46)	
		Eastern Europe	0.88	(0.70,1.12)		0.69	(0.52,0.92)	
Age category	<30	30-39	1.22	(0.96,1.55)	0.29	1.26	(0.99,1.62)	0.05
		40-49	1.09	(0.86,1.37)		1.04	(0.81,1.33)	
		≥50	1.08	(0.86,1.35)		1.03	(0.80,1.32)	
Gender	Male	Female	1.12	(0.99,1.27)	0.07	1.15	(0.99,1.34)	0.07
Ethnicity†	White	Black	1.07	(0.89,1.28)	0.002	1.07	(0.86,1.32)	0.17
		Other	0.70	(0.50,0.97)		0.71	(0.51,1.00)	
		Unknown	1.24	(1.08,1.43)		0.91	(0.72,1.16)	
HIV risk	MSM	IDU	1.27	(1.08,1.48)	0.01	0.98	(0.79,1.21)	0.23
		Heterosexu-al	1.06	(0.94,1.20)		0.89	(0.75,1.05)	
		Other	0.85	(0.59,1.21)		0.70	(0.48,1.01)	
		Unknown	0.98	(0.76,1.26)		0.86	(0.66,1.13)	
Smoking status	Never	Current	0.98	(0.84,1.14)	0.68	0.92	(0.78,1.08)	0.42
		Previous	1.07	(0.88,1.30)		1.06	(0.87,1.30)	
		Unknown	1.25	(1.09,1.43)		0.88	(0.68,1.13)	
ART experience	Experien-ced, VL<400 cps/mL	Naive	1.10	(0.97,1.25)	<0.0001	1.08	(0.91,1.28)	<0.0001
		Experience-ed, VL≥400 cps/mL	2.34	(1.76,3.10)		2.12	(1.57,2.85)	
CD4 nadir, cells/mm³	<200	200-349	0.88	(0.77,1.00)	0.25	0.95	(0.82,1.10)	0.82
		350-499	0.95	(0.80,1.12)		1.03	(0.84,1.26)	
		≥500	0.92	(0.76,1.12)		0.97	(0.77,1.23)	
CD4 count at INSTI start, cells/mm³	<200	200-349	0.89	(0.71,1.12)	<0.0001	1.02	(0.81,1.29)	0.29
		350-499	0.78	(0.62,0.96)		0.91	(0.72,1.15)	
		≥500	0.69	(0.57,0.83)		0.87	(0.69,1.09)	
Hepatitis C	No	Yes	1.18	(1.04,1.35)	0.003	1.08	(0.91,1.29)	0.56
		Unknown	1.25	(1.06,1.47)		1.12	(0.82,1.53)	
Hepatitis B	No	Yes	0.90	(0.69,1.17)	0.04	0.84	(0.64,1.09)	0.37
		Unknown	1.19	(1.03,1.37)		1.06	(0.81,1.38)	
Hypertensi-on	No	Yes	0.95	(0.83,1.08)	0.004	1.00	(0.87,1.16)	0.001
		Unknown	1.20	(1.05,1.36)		0.51	(0.35,0.73)	
Diabetes	No	Yes	0.94	(0.78,1.13)	0.12	0.91	(0.75,1.10)	0.61
		Unknown	1.19	(0.99,1.43)		1.05	(0.70,1.57)	
Prior AIDS	No	Yes	1.04	(0.92,1.19)	0.31	0.95	(0.83,1.10)	0.007
		Unknown	1.14	(0.96,1.36)		2.05	(1.30,3.24)	
Prior NADC	No	Yes	1.17	(0.90,1.53)	0.13	1.18	(0.90,1.54)	0.03
		Unknown	1.12	(0.99,1.28)		0.69	(0.50,0.94)	
Prior ESLD	No	Yes	1.03	(0.57,1.87)	0.12	0.92	(0.50,1.68)	0.005

		Unknown	1.12	(1.01,1.25)		1.40	(1.14,1.71)	
Prior CVD	No	Yes	1.00	(0.76,1.32)	<0.0001	0.91	(0.68,1.22)	<0.0001
		Unknown	1.38	(1.23,1.56)		2.37	(1.68,3.35)	
Prior fracture	No	Yes	1.12	(0.88,1.43)	0.001	1.22	(0.95,1.56)	0.29
		Unknown	1.25	(1.10,1.40)		1.01	(0.73,1.38)	
Prior CKD	No	Yes	0.91	(0.69,1.19)	0.18	0.87	(0.66,1.15)	0.02
		Unknown	1.13	(0.98,1.31)		0.58	(0.38,0.87)	

*Results from a Cox proportional hazards model; all variables were fitted simultaneously in the multivariable model

[1]Due to low counts, Australia is grouped with Northern Europe and Eastern Central Europe is grouped with Eastern Europe.

4.3.4.4 Sensitivity analyses

Table 4.12 shows a summary of the main results from each sensitivity analysis carried out. As a post hoc analysis, I additionally adjusted for BMI in the multivariable model to investigate whether BMI was associated with discontinuation, as BMI has previously been shown to be associated with risk of drug toxicity (364). Results remained similar and BMI was not associated with the risk of discontinuation (p=0.27). I also reran analyses only including those starting an INSTI from 2015 and adjusting for cohort rather than comorbidities in the main analysis, both with similar results. Cohorts who provided data on only a sample of their participants, rather than all participants, were asked to ensure at least half of them were on INSTIs, and this could result in selection bias and affect how representative the results are of PLWH in Europe and Australia. I therefore repeated the main analysis only in cohorts providing data on more than 95% of their participants; this included 5580 individuals from 8 cohorts and showed similar results. Finally, I performed an analysis assessing predictors of INSTI discontinuation due to toxicity only and again found similar results.

Table 4.12 Summary of main results from sensitivity analyses assessing predictors of discontinuation within 6 months of INSTI start

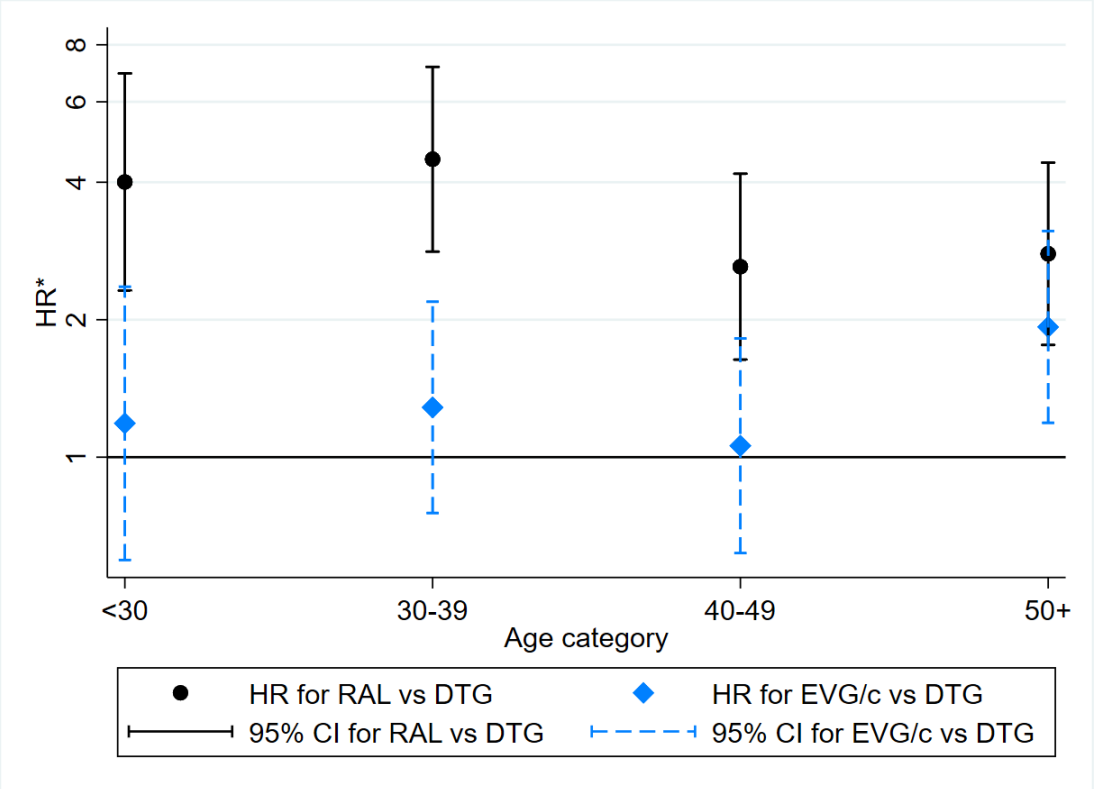
Sensitivity analysis	N included	Variable	Group	HR	(95% CI)	P-value
Additionally adjusting for baseline BMI in the primary analysis model	9702	INSTI type, vs DTG	RAL EVG/c	2.99 1.36	(2.44, 3.67) (1.10, 1.69)	<0.0001
		INSTI start, per year later		1.11	(1.04, 1.18)	0.001
Only including individuals starting an INSTI after 1/1/2015 in the primary analysis model	6595	INSTI type, vs DTG	RAL EVG/c	3.04 1.38	(2.36, 3.92) (1.07, 1.77)	<0.0001
		INSTI start, per year later		0.91	(0.79, 1.04)	0.18
Restricting the primary analysis to cohorts who provided data on >95% of their participants	5580	INSTI type, vs DTG	RAL EVG/c	3.72 1.56	(2.86, 4.84) (1.19, 2.04)	<0.0001
		INSTI start, per year later		1.12	(1.03, 1.21)	0.006
Adjusting for cohort instead of comorbidities in the primary analysis model	9702	INSTI type, vs DTG	RAL EVG/c	2.5 1.22	(2.07, 3.02) (0.99, 1.51)	<0.0001
		INSTI start, per year later		1.08	(1.01, 1.14)	0.019
Assessing predictors of discontinuation due to toxicity only	9702	INSTI type, vs DTG	RAL EVG/c	1.90 1.33	(1.44,2.50) (1.01,1.74)	<0.001
		INSTI start, per year later		1.05	(0.96,1.14)	0.28

Results are from multivariable Cox proportional hazards models adjusted for the same variables as in the primary analysis (other than when cohort was adjusted for instead of comorbidities). Other results from sensitivity analyses are not shown

4.3.4.5 Subgroup analyses

Prespecified subgroup analyses showed a significant interaction between INSTI type and age group, shown in Figure 4.13 (p-value for interaction 0.001). Across all age groups, the risk of discontinuation was higher on RAL than on DTG; however, the difference between RAL and DTG decreased slightly in older age groups. There was an increased risk of discontinuation of EVG/c compared to DTG in the oldest age group (≥50 years); however, there was no difference in the risk on EVG/c compared to DTG in lower age groups. Other subgroup analyses were run for INSTI type and each of gender, HIV risk group, prior ART experience, HBV and HCV status, and each comorbidity; all of which were non-significant.

Figure 4.13 Risk of INSTI discontinuation, by age category



*HR comparing INSTI types estimated from a Cox proportional hazards model including an interaction between INSTI type and age category, adjusted for year of starting INSTI, geographical region, gender, ethnicity, smoking status, HIV risk group, antiretroviral treatment experience, CD4 nadir, CD4 count at INSTI start, hepatitis B, hepatitis C, hypertension, diabetes, prior AIDS, non-AIDS cancers, end stage liver disease, cardiovascular disease, fracture, chronic kidney disease

4.4 Discussion

In this chapter, I compared demographic and clinical characteristics of almost 10,000 individuals starting DTG, EVG/c, and RAL. I also compared reasons for discontinuation of each INSTI and investigated factors associated with discontinuation, both for discontinuations within 6 months after INSTI start and after 6 months after INSTI start. I found that as the year of INSTI start increased, the likelihood of starting RAL or EVG/c decreased compared to DTG, with a greater decline for RAL. Discontinuation was highest on RAL, mainly due to treatment simplification, and the main reason for discontinuation of DTG and EVG/c was toxicity. Whilst the proportion discontinuing due to toxicity was highest on DTG, this proportion was low across all INSTIs.

Subgroup analyses of INSTI uptake showed that females were more likely to start RAL compared to males in lower age groups but were less likely to start RAL compared to males in older age groups. This may be partly because treatment guidelines recommend RAL for pregnant women (or women wishing to conceive), in particular those starting follow-up late or whose VL is not fully suppressed at the third trimester (331,552). Additionally, data from a small study in Botswana suggested there may be an association between DTG and neural tube defects among infants if DTG was taken at the time of conception (317). Whilst more recent data suggests this association is not as strong as originally thought (319), those results were not available at the time of data collection for this study and therefore, this may further contribute to younger females being more likely to take RAL compared to DTG. In older age groups, treatment simplification may be a higher priority for menopausal women; therefore, regimens containing DTG are likely to be favoured over RAL.

Furthermore, this analysis showed that those with HBV coinfection were more likely to start RAL or EVG/c, and those with prior CVD were also more likely to start RAL compared to DTG. Treatment guidelines recommend using TDF or tenofovir alafenamide containing regimens in HBV coinfected individuals (85,331,553). After adjustment for NRTI backbone the association between HBV and choice of INSTI was no longer significant, suggesting the backbone was likely driving this treatment

choice rather than the INSTI. Results from the D:A:D study have shown that ABC is associated with an increased risk of CVD and is commonly prescribed with DTG as part of a single tablet regimen with 3TC (439). However, after adjusting for backbone, the association between CVD and the likelihood of starting RAL remained highly significant suggesting this decision was not driven by ABC and requires further research.

During follow up, the risk of discontinuation was significantly higher on RAL compared to DTG or EVG/c, mainly due to treatment simplification. I found the rate of discontinuation on RAL was higher than reported in many of the studies included in the literature review in Chapter 2 (451,452,456,458,460,461,465,466). In the review, the proportion discontinuing RAL ranged from 17% to 50%, however, only 2 out of 10 studies found the proportion discontinuing RAL to be above 40% (450,457). This is likely because the cut off for follow-up in this study was the end of 2017, which was later than other studies and therefore reflects the increasing availability of newer INSTIs. This is also an observational study which is likely to have higher rates of discontinuation compared to RCTs. For all INSTIs, the risk of discontinuation increased with later year of INSTI start, which may be related to the growing availability of post marketing information on adverse events associated with INSTIs and greater availability of treatment options (146,331,363,554–557). Additionally, the risk of discontinuation was up to 3 times higher in Western Europe compared to other European regions, which may also reflect the wider range of available treatment options in Western Europe (558).

The risk of INSTI discontinuation was also higher for females compared to males. This is in line with studies carried out by Hoffman et al. (559) and Llibre et al. (560), who reported an increased risk among females of DTG discontinuation and INSTI discontinuation due to adverse events, respectively. Studies have suggested that the higher rates of adverse events in females are due to a lower BMI and difference in fat/water distribution leading to higher drug exposure (559,561). Additionally, the association between INSTIs, in particular DTG, and weight gain appears to be more pronounced in Black females (538,540); after adjusting for BMI in this analysis,

however, there remained a significantly higher risk of discontinuation for all females. Additionally, I found similar rates of discontinuation due to toxicity for females and males (32% and 31% of discontinuations, respectively). These results suggest that further research should be carried out on the safety of INSTIs in females, who are often underrepresented in HIV research. The results also showed that those with HCV had an increased risk of discontinuation. This is a similar result to those by Grint et al. who reported higher ART discontinuation for those with HCV in 9,535 individuals from the EuroSIDA study (562). However, the study did not include participants on INSTI-based regimens. The increased risk of INSTI discontinuation for those with HCV could be because those with HCV are more likely to be in the IDU risk group and the risk of treatment discontinuation has been shown to be higher in this group as well (563,564). IDU status and HCV status are often collinear, and the relationship is therefore difficult to disentangle. Finally, subgroup analyses showed that INSTI users in older age groups were more likely to discontinue EVG/c compared to DTG, and this is likely due to the increased frequency of drug-drug interactions on EVG/c, for example with simvastatin, which is commonly used to treat high cholesterol, or amlodipine, used to treat high blood pressure (331,565).

The most common reasons for INSTI discontinuation within 6 months after INSTI start were patient/physician choice and toxicity. However, of those starting an INSTI, the proportion discontinuing within 6 months due to toxicity was relatively low on all INSTIs (3.9% DTG, 4.0% EVG/c, 6.1% RAL). This is an important and reassuring real-world finding showing that toxicities are not leading to high rates of INSTI discontinuation. The most common individual toxicity was from the nervous system for DTG and EVG/c and from the abdomen/gastrointestinal tract for RAL. This is in line with several observational studies that have reported higher rates of DTG discontinuation due to neuropsychiatric adverse events compared to other INSTIs (362–364,454,459,559,560). As is the case with several other recent observational studies and case report series (364,442,454,459,559,560,566,567), these results show a higher rate of discontinuation due to toxicity than reported in RCTs, especially on DTG. As discussed in the literature review in Chapter 2, this likely reflects the selected population participating in clinical trials and reflects the need for further

investigation. Beyond 6 months after INSTI initiation, the most common individual toxicity for EVG/c was renal, likely attributable to the coformulation with TDF in the single tablet regimen TDF/FTC/EVC/c and the artefactual increase in creatinine caused by cobicistat (568). Reasons for discontinuation on each INSTI remained fairly similar over time although discontinuations of RAL due to treatment simplification did increase, likely due to the approval of more contemporary ARVs which are available as single tablet regimens. The most common ARVs individuals switched to after discontinuing an INSTI were DTG, DRV, and RPV, all of which are available as single tablet regimens.

4.4.1 Strengths and limitations

There are some limitations to this analysis. As mentioned in Chapter 3, Section 3.1.2, individuals enrolled into RESPOND are not randomly selected as cohorts are asked to ensure a minimum number of individuals included are on INSTIs, as this is a key research area in RESPOND. Therefore, the proportion of INSTI users in RESPOND is likely higher than in the general population of PLWH, and results from this chapter should be interpreted with this in mind. Rerunning the analysis restricted to 8 cohorts who provided data on more than 95% of their participants, irrespective of INSTI use, and may therefore be more representative, showed similar results. This did however include fewer participants (n=5580). As this is a cohort study, it is not possible to rule out confounding by indication, as those starting INSTIs may be different from those starting other drug classes, for example they may have more comorbidities. Additionally, it is not possible to fully adjust for all factors associated with the choice of INSTI or discontinuation of INSTIs. For example, resistance data is not currently collected in RESPOND, and this may affect the choice of any ARV. INSTIs are a relatively new drug class, and there are likely to be differences in marketing, pricing and access to the drugs on national levels, which have not been fully accounted for in the analysis, and follow up for DTG, in particular, may still be limited. There is also a relatively high proportion of missing data, particularly for comorbidities, and completeness of the data varies between cohorts. However, analyses using multiple imputation to account for missing data, and adjusting for cohort instead of

comorbidities, showed similar results. Finally, the reasons for discontinuation of INSTIs are those reported in patient notes and the proportion of unknown reasons, as well as the distribution of known reasons, differs considerably between cohorts. Only one reason was provided per discontinuation, and the reasons given are limited, for example, patient or physician choice may cover a wide range of reasons including concerns regarding toxicity, drug-drug interactions, and issues with treatment adherence. However, all cohorts used the HIV Cohorts Data Exchange Protocol standard for data reporting and have previously participated in the development of this standard (569).

There are also several strengths to this analysis. RESPOND is a large, pan-European, heterogeneous study based in real-world settings which makes these findings generalisable to the wider population of adults living with HIV. Existing literature addressing these topics are typically from RCTs or smaller observational studies on national, rather than international levels. The large size of RESPOND means it is possible to identify factors associated with uptake and discontinuation and compare results between different subgroups. It is also possible to look at shorter- and longer-term reasons for discontinuation. Additionally, reasons for discontinuation were reported using the HICDEP format which standardises reporting. Finally, whilst DTG is the most widely used INSTI and EVG/c is no longer recommended as first-line treatment for PLWH, all three INSTIs included in this analysis have been used by a significant number of individuals in RESPOND, and therefore it was possible to perform intraclass comparisons of INSTIs.

4.4.2 Conclusions

In this chapter I found that uptake of DTG compared to EVG/c or RAL has increased over calendar time, and more in Western Europe compared to other European regions. INSTI discontinuation was low overall and mainly due to toxicity in the first 6 months and patient or physician choice thereafter. Discontinuation was significantly higher for RAL, primarily due to treatment simplification, whilst discontinuation due to nervous system toxicities was highest on DTG. Females were more likely to discontinue an INSTI, as were those with HCV or prior NADC, whilst

those in Southern and Eastern Europe were less likely to discontinue an INSTI. These findings highlight the need for further research to better understand adverse events of INSTIs and longer-term follow-up to assess clinical events on INSTIs as well as discontinuation.

4.4.3 Publications

The results from the chapter were presented at The International Workshop on HIV and Hepatitis Observational Databases (IWHOD) 2019 as a poster and the EACS Conference 2019 as an oral presentation. The manuscript has been published in the Journal of Acquired Immune Deficiency Syndromes (JAIDS) (570). The conference poster and presentation and published manuscript are included in Appendices V, VI, and VII, respectively.

Chapter 5 Virological, immunological, and clinical outcomes of two-drug regimens

5.1 Introduction

Since the mid-1990s when antiretrovirals (ARVs) from more than one drug class became available, combination antiretroviral therapy (ART) has traditionally included three ARVs (331). Use of three-drug regimens (3DRs) has been shown to be effective in reducing VL, maintaining viral suppression, and increasing CD4 counts (123,281,571). However, as there is currently no cure for HIV, ART is a lifelong commitment, and there are concerns around drug-drug interactions, polypharmacy, and long-term toxicities (572–575). With an aging HIV population, the prevalence of non-AIDS comorbidities is increasing, and it is therefore becoming increasingly important to reduce the potential risks associated with long-term ART usage (575–577).

The emergence of new ARVs with a higher barrier against resistance and more potent antiretroviral activity, including second-generation INSTIs and boosted darunavir (DRV/b), has led to more interest in reducing ART to two-drug regimens (2DRs). There are five 2DRs recommended by the majority of current treatment guidelines as switch strategies for individuals with a VL below the limit of detection and without historical resistance or hepatitis B co-infection: dolutegravir (DTG) plus rilpivirine (RPV), DTG plus lamivudine (3TC), boosted atazanavir (ATV/b) plus 3TC, DRV/b plus 3TC (331,535,578), and DRV/b plus RPV (331). Additionally, DTG plus 3TC is widely recommended as an initial regimen for ART-naïve individuals with a VL < 500,000 copies/mL and without hepatitis B co-infection (331,578,579).

Several RCTs and observational studies have shown good virological and immunological efficacy of contemporary 2DRs (580–588). Further details on these studies are given below. However, despite this increasing evidence, data comparing clinical outcomes of 2DRs and 3DRs remains scarce. Large studies with long follow-up are needed to assess clinical outcomes and RCTs are rarely long enough to assess

them. In Chapter 2, I completed a literature review of studies assessing clinical outcomes and contemporary ARVs, however none of the studies included looked specifically at 2DRs.

5.1.1 Review of 2DRs

To identify key studies investigating 2DRs, I searched PubMed using the following search strategy:

1. HIV; and
2. Antiretroviral therapy; and
3. Keywords relating to dual therapy ('dual therapy' or 'dual regimen' or 'two drug' or 'class-sparing' or 'nucleoside-sparing' or 'NRTI-sparing' or 'N(t)RTI-sparing' or 'simplification').

Once the relevant articles had been identified, I used a backward snowballing approach to identify any additional articles missed by the review, by scanning the references within the included articles. Table 5.1 shows a summary of key studies assessing different dual therapies as initial treatment for ART-naïve individuals and switch therapies for ART-experienced individuals.

One of the first randomised trials to assess dual therapy in the modern ART-era was the ACTG-5142 RCT published in 2008 (589). This trial compared boosted lopinavir (LPV/r) plus efavirenz (EFV) to triple therapy containing EFV or LPV/r in ART-naïve participants and found a similar virological efficacy on both arms but more drug resistance in the dual therapy arm. LPV/r was also assessed as a dual therapy with TDF in the KALEAD trial (590) but this was shown to have lower virological efficacy compared to the triple therapy arm.

Many trials have assessed dual therapy containing maraviroc (MVC), either as an initial therapy for ART-naïve individuals or as a switch therapy for ART-experienced individuals (591–596). These trials showed mixed results but generally a lower virological efficacy on the dual therapy arm compared to triple therapy. Therefore,

dual therapies containing MVC are rarely used, and are not part of the recommended 2DR strategies (331,535,578,579).

With the approval of INSTIs and DRV/r from 2007, trials of dual therapy began to show more promising results. RAL combined with DRV/r as initial therapy was non-inferior to standard treatment for participants with CD4 counts greater than 200 cells/µL in the NEAT 001 trial, however there was also a higher rate of development of drug resistance in the dual therapy arm (597,598). Other trials have shown good efficacy of dual therapy with RAL combined with LPV/r (588,599,600), etravirine (ETR) (601,602), or nevirapine (NVP) (603). RAL has also been assessed as dual therapy combined with boosted or unboosted ATV, however studies of this regimen have shown a higher rate of virological rebound (604), drug resistance (605), and hyperbilirubinemia (605) compared to triple therapy.

DTG has been assessed as dual therapy for treatment-experienced individuals combined with 3TC (606), DRV/b (607,608), or RPV (580,609), all showing non-inferiority compared to the triple therapy arm. Additionally, results from the Gemini 1 and 2 trials assessing DTG plus 3TC as initial therapy for treatment-naïve individuals showed non-inferiority compared to DTG, 3TC, and emtricitabine (FTC) (585,610).

As well as in dual therapy with INSTIs, DRV/b has also been assessed as dual therapy in combination with 3TC (581,611) and RPV (612), both showing non-inferiority compared to triple therapy.

Other dual therapies which have shown promising results in trials include 3TC plus boosted ATV (583,613) and LPV/r plus 3TC (584,614). Finally, cabotegravir (CAB) is a new INSTI which is prescribed as a dual therapy, combined with RPV, long-acting intramuscular injection. Results from the LATTE and LATTE-2 trials showed CAB plus RPV was non-inferior to CAB plus abacavir/3TC (615,616).

Table 5.1 Summary of key studies assessing dual therapy – all randomised trials, unless stated otherwise

Study name or first author (ref)	Year	Dual therapy	Comparator	2DR as initial or switch therapy	Country(ies)	Overall number of participants in study	Number of participants on dual therapy	Summary of results
ACTG-5142 (589)	2008	LPV/r + EFV	EFV or LPV/r + 2 NRTIs	Initial	South Africa, United States	753	250	VL suppression at 96 weeks was higher in triple therapy group. There was a higher rate of drug resistance on dual therapy
KALEAD (590)	2010	LPV/r + TDF	LPV/r + 2 NRTIs	Initial	Italy	152	72	VL suppression was similar in both groups at 24 weeks (p=0.47)
Pulido* (592)	2016	MVC + ATV/r	Continue current triple ART	Initial	Spain	98	32	VL suppression was similar in both groups at 48 weeks (p=0.37)
VEMAN (593)	2015	MVC + LPV/r	LPV/r + TDF/FTC	Initial	Italy	50	26	Virological efficacy and safety at 48 weeks was similar between groups
MARCH (594)	2016	MVC + PI[†]	MVC or PI/r[†] + 2 NRTIs	Switch	International	397	158	Dual therapy was significantly inferior for VL suppression at 48 weeks
MODERN (596)	2016	MVC + DRV/r	MVC + TDF/FTC	Initial	Europe, United States, Canada, Australia	797	396	Dual therapy was significantly inferior for VL suppression at 48 weeks
GUSTA (595)	2017	MVC + DRV/r	Continue current triple ART	Switch	Italy	165	82	Excess viral failures found in dual therapy arm at 48 weeks (p=0.005)
PROGRESS (588)	2012	LPV/r + RAL	LPV/r + TDF/FTC	Initial	Europe, United States, Puerto Rico, Canada	206	101	VL suppression was similar in both groups at 96 weeks (p=0.77)

KITE (600)	2012	LPV/r + RAL	Continue current triple ART	Switch	United States	60	40	VL suppression was similar in both groups at 48 weeks (p=0.70)
CCTG-589 (599)	2016	LPV/r + RAL	EFV + TDF/FTC	Initial	United States	51	26	VL suppression was similar in both groups at 48 weeks (p=0.99)
GARDEL (614)	2014	LPV/r + 3TC	LPV/r + 3TC/FTC	Initial	United States, Mexico, Chile, Peru, Argentina, Spain	426	217	VL suppression was similar in both groups at 48 weeks (p=0.17)
OLE (584)	2015	LPV/r + 3TC	LPV/r + 3TC or FTC + 3rd NRTI	Switch	Spain, France	250	123	Treatment response was similar in both groups at 48 weeks (p=0.92) with treatment failure defined as unsuppressed VL, death of any cause, new AIDS event, loss to follow-up, or permanent change or interruption of randomised treatment
SPARTAN (605)	2012	RAL + unboosted ATV	ATV/r + TDF/FTC	Initial	Europe, Latin America, United States	93	63	VL suppression was similar in both groups at 24 weeks. Incidence of resistance to RAL and grade 4 hyperbilirubinemia was higher on dual therapy
HARNESS (604)	2016	RAL + ATV/r	ATV/r + TDF/FTC	Switch	United States, Europe	109	72	There was a higher virological rebound rate and treatment discontinuation at 24 weeks on dual therapy arm
SPARE (617)	2013	RAL + DRV/b	LPV/r + TDF/FTC	Switch	Japan	58	28	VL suppression was similar in both groups at 48 weeks, a non-significant higher proportion in the dual therapy group achieved >10% improvement in eGFR (p=0.27)

RADAR (618)	2014	RAL + DRV/b	DRV/r + TDF/FTC	Initial	United States	85	42	Dual therapy arm did not achieve similar virologic efficacy at week 48 but was better with regard to markers of bone health
ANRS 143/NEAT 001 (597,598)	2014	RAL + DRV/b	DRV/r + TDF/FTC	Initial	Europe	805	401	Treatment response was similar in both groups at 32 weeks with treatment failure defined as unsuppressed VL, death of any cause, new AIDS event, new serious non-AIDS event, or discontinuation of treatment due to insufficient virological response; there was a higher rate of resistance-associated mutation on dual therapy
PROBE (612)	2016	DRV/b + RPV	Continue current triple ART	Switch	Italy	60	30	VL suppression was similar in both groups at 48 weeks
DUAL (581)	2017	DRV/b + 3TC	Continue DRV/r + TDF/FTC or ABC/3TC	Switch	Spain	249	129	VL suppression was similar in both groups at 48 weeks
ANDES (611)	2018	DRV/b + 3TC	DRV/b + 3TC/TDF	Initial	Argentina	145	75	VL suppression was similar in both groups at 48 weeks
DUALIS (608,619)	2017	DTG + DRV/b	Continue DRV/r + 2 NRTIs	Switch	Germany	263	131	VL suppression was similar in both groups at 48 weeks
SWORD 1 & 2 (580)	2018	DTG + RPV	Continue current triple ART	Switch	International	1028	516	VL suppression was similar in both groups at 48 weeks

GEMINI 1 & 2 (585,610)	2018	DTG + 3TC	DTG + TDF/FTC	Initial	International	1441	719	VL suppression was similar in both groups at 48 weeks
ATLAS-M (613)	2017	3TC + ATV/b	ATV/r + 2 NRTIs	Switch	Italy	266	133	VL suppression was similar in both groups at 48 weeks
SALT (583)	2017	3TC + ATV/b	ATV/r + 2 NRTIs	Switch	Spain	286	133	VL suppression was similar in both groups at 96 weeks
LATTE/LATTE-2 (615,616)	2017	CAB + RPV	CAB + ABC/3TC	Switch	Canada, France, Germany, Spain, United States	286	230	VL suppression was similar in all groups at 96 weeks

Abbreviations: /b-boosted with ritonavir or cobicistat; /r-ritonavir boosted; LPV/r-boosted lopinavir; EFV-efavirenz; TDF-tenofovir disoproxil fumarate; MVC-maraviroc; ATV-atazanavir; PI-protease inhibitor; DRV- darunavir; RAL-raltegravir; 3TC-lamivudine, RPV-rilpivirine; NRTI-nucleoside reserve transcriptase inhibitor; FTC-emtricitabine; ABC-abacavir, CAB-cabotegravir

*observational study

† PIs: ATV/r, LPV/r, DRV/r, saquinavir/r, fosamprenavir/r, indinavir/r

5.1.2 Aims

Whilst there are many studies looking at virological and immunological outcomes of a wide range of 2DRs, as outlined above, data on clinical outcomes remains scarce. As mentioned above, large studies with long follow-up are needed to assess clinical outcomes and RCTs and small observational studies are not usually able to do this.

The aims of this chapter are to:

(i) determine the prevalence of 2DRs in RESPOND and describe the characteristics of those starting 2DRs compared to 3DRs;
(ii) compare immunological, virological and clinical outcomes with use of 2DRs compared to 3DRs.

5.2 Methods

This analysis was performed on the second version (version DS1) of the RESPOND database with a data cut-off of 1st October 2018. Baseline was defined as the date of first eligible regimen start after the latest of date of enrolment into the local cohort or 1st January 2012. Individuals were followed until the latest of the most recent CD4 count, VL measurement, or ART start date, drop out date as defined by the cohort, or date of death. If this date was after the data cut-off, individuals were censored at 1st October 2018.

5.2.1 Inclusion criteria

The inclusion criteria for RESPOND are detailed in Chapter 3, Section 3.1.3. For this analysis, individuals from RESPOND were included if they:

(i) were ART-experienced and switched to an eligible regimen after the latest of the date they were enrolled into their local cohort or 1st January 2012;
(ii) were aged ≥ 18 at regimen start;
(iii) had a CD4 count and VL measurement within 12 months prior to or 12 weeks after starting the regimen of interest;

(iv) had not taken both ARVs prior to regimen start for individuals starting an eligible 2DR or had not taken the 3rd agent prior to regimen start for those starting an eligible 3DR.

ART-naïve individuals were excluded from the analysis as the majority of 2DRs are currently recommended as switch strategies (331) and only 3% of those starting 2DRs in RESPOND were ART-naïve.

5.2.2 Eligible 2DRs and 3DRs

Eligible regimens, as listed in Table 5.2, were chosen a priori by a RESPOND 2DR working group, which was led by myself, and consisted of core RESPOND staff, pharmaceutical industry representatives, and clinicians from cohorts included in RESPOND. I drafted a proposal for which regimens to include, detailed the current data available in the literature on each regimen, and the number of participants in RESPOND taking the regimens. The final list was then decided on via email communication with the group. In order to reflect 2DRs currently being prescribed in real-world settings, eligible 2DRs were chosen to include those currently recommended in treatment guidelines, as well as other 2DRs which have been shown to be non-inferior to 3DRs in RCTs or observational studies and have at least 20 individuals in RESPOND taking them. Eligible 2DRs consisted of exactly two active drugs including DRV/b, LPV/b, ATV/b, 3TC, RAL, DTG, RPV, or ETR. Eligible 3DRs consisted of exactly 2 NRTIs and DRV/b or LPV/b, boosted or unboosted ATV, RAL, DTG, RPV or ETR being the third ARV. The third ARV was chosen to include the same ARVs as used in the 2DRs.

Participants starting 2DRs during follow-up were included from the date of starting the 2DR. Participants starting eligible 3DRs were identified from those not starting 2DRs and were included from the date of starting the 3DR. Participants starting more than one eligible 2DR or more than one eligible 3DR during follow-up were only included once and only on the first 2DR or 3DR they started.

Table 5.2 Eligible regimens included in the analysis

Eligible two-drug regimens	Eligible three-drug regimens
RAL + DRV/b	2 NRTIs + DRV/b
3TC + DRV/b	2 NRTIs + ATV or ATV/b
RAL + ETR	2 NRTIs + RAL
DTG + 3TC	2 NRTIs + DTG
DTG + RPV	2 NRTIs + RPV
3TC + ATV/b	2 NRTIs + ETR
DTG + DRV/b	2 NRTIs + NVP
RAL + NVP	
RPV + DRV/b	

Abbreviations: DRV – darunavir; RAL – raltegravir; 3TC – lamivudine; ETR – etravirine; DTG – dolutegravir; RPV – rilpivirine; ATV – atazanavir; NVP – nevirapine NRTI – nucleoside reverse transcriptase inhibitor; /b – ritonavir or cobicistat boosted

5.2.3 Outcomes

5.2.3.1 Immunological outcomes

The immunological outcome, measured at 6 (±3 months) and 12 (±3 months) months follow-up, was a CD4 count increase from baseline of greater than 100 cells/mm^3 or greater than 25% (620).

5.2.3.2 Virological outcomes

The virological outcomes, measured at 6 (±3 months) and 12 (±3 months) months follow-up were (620):

I. VL < 200 copies/mL. Individuals with missing outcome or ART-regimen change were excluded for this outcome;
II. composite treatment outcome (cTO) success with cTO failure defined as at least one of: VL ≥ 200 copies/mL, missing VL, any ART-regimen change, AIDS event, or death.

5.2.3.3 Clinical outcomes

The clinical outcome was occurrence of any severe clinical event during follow-up, which was a composite outcome of AIDS (cancer and non-cancer), non-AIDS defining cancer (NADC), cardiovascular disease (CVD, defined as invasive cardiovascular procedures, myocardial infarction, or stroke), end stage liver disease (ESLD), end stage renal disease (ESRD), and death (490). Individuals were followed until the first

severe event of any type, or last follow-up (defined in Section 5.2), whichever occurred first.

5.2.4 Potential confounders

All potential confounders, defined prior to or at eligible regimen start, considered in this analysis are described in Table 5.3.

Table 5.3 Baseline demographic and clinical characteristics included in analyses

Variable	Categories	Comments
Year of starting the regimen	Continuous (per 1 year later)	
Age	Continuous (per 10 years later)	
Gender	Male; female	
HIV risk group	MSM; IDU; heterosexual sex; other; unknown or missing	
Ethnicity	White; Black; other; unknown or missing	
Body mass index	<18.5; 18.5-<25; ≥25; missing	
Smoking status	Past; current; never; unknown or missing	
CD4 cell nadir prior to regimen start	Continuous (per 100 cells increase)	Taken as the lowest CD4 count prior to regimen start. If no CD4 count was measured, the first measurement within 12 weeks after regimen start was used
CD4 count at regimen start	Continuous (per 100 cells increase)	Taken as the most recent CD4 count within 12 months prior to regimen start. If no CD4 count was measured, the first measurement within 12 weeks after regimen start was used (median difference between CD4 count and regimen start = 22 days)
CD8 count at regimen start	Continuous (per 100 cells increase)	Taken as the most recent CD8 count within 12 months prior to regimen start. If no CD8 count was measured, the first measurement within 12 weeks after regimen start was used (median difference between CD8 count and regimen start = 21 days)
Viral suppression status at regimen start	VL <200 copies/mL; VL ≥200 copies/mL	VL was taken as the most recent VL within 12 months before regimen

		start. If no VL was measured prior to regimen start, the first measurement within 12 weeks after regimen start was used (median difference between VL prior to regimen start and regimen start = 21 days)
Viral hepatitis C	No; yes; unknown	Defined by use of anti-HCV medication, a positive HCV antibody test, a positive HCV RNA qualitative test, HCV RNA >615 IU/mL, and/or a positive genotype test
Viral hepatitis B	No; yes; unknown	Defined by a positive HBV surface antigen test and/or HBV DNA >357 IU/mL
Hypertension	No; yes; unknown	Confirmed by use of anti-hypertensives at any time before regimen start or if the most recent systolic or diastolic blood pressure measurement before regimen start was higher than 140 or 90 mmHg, respectively
Diabetes	No; yes; unknown	Defined as reported diabetes diagnosis, use of antidiabetic medication, a random glucose measurement of 11.1 mmol/L or above, or a Haemoglobin A1c measurement of 6.5% or above, or 48 mmol/mol or above (549)
Prior AIDS (non-cancer)	No; yes; unknown	Composite diagnosis as defined by the CDC list of AIDS-defining conditions (547,548)
Prior AIDS cancer	No; yes; unknown	Composite diagnosis of Kaposi's sarcoma, non-Hodgkin lymphoma, cervical cancer (549)
Prior non-AIDS defining cancer	No; yes; unknown	Any non-AIDS cancer excluding skin cancers (expect malignant melanoma) and pre-cancers (549)
Prior end stage liver disease	No; yes; unknown	Composite diagnosis of ascites (where extrahepatic reasons are excluded), hepatic encephalopathy grade III-IV, hepatorenal syndrome, endoscopically verified variceal bleeding, spontaneous bacterial peritonitis, liver transplantation (549)
Prior end stage renal disease	No; yes; unknown	Composite diagnosis of dialysis for more than three months or kidney transplant (549)
Prior cardiovascular disease	No; yes; unknown	Composite diagnosis of myocardial infarction, stroke or invasive cardiovascular procedure (549)

Prior fracture	No; yes; unknown	Includes pathological/osteoporotic, and traumatic fractures (549)
Prior chronic kidney disease	No; yes; unknown	Two consecutive measurements of eGFR measured at least 3 months apart ≤60 mL/min if the first eGFR was >60 mL/min or a 25% decline if first eGFR was <60 mL/min. eGFR was calculated using the CKD-EPI creatinine equation (550)
Prior chronic liver enzyme elevation	No; yes; unknown	Two consecutive measurements of ALT >50 IU/L for males or >35 IU/L for females, measured between 6 months and 2 years apart.
Prior dyslipidaemia	No; yes; unknown	Defined as total cholesterol>239.4mg/dL or HDL cholesterol<34.7mg/dL or triglyceride >203.55mg/dL or use of lipid lowering treatments (621)
Geographical region	Western Europe; Northern Europe/Australia; Southern Europe; Eastern/East Central Europe	Due to low numbers, Australia was combined with Northern Europe in the analysis models, and Eastern Central Europe was combined with Eastern Europe. For further details, see Chapter 3, Table 3.1 footnote
Number of previous ARVs exposed to	Continuous (per 1 ARV increase)	
Number of previous drug classes exposed to	Continuous (per 1 drug class increase)	
Prior total ART duration	Continuous (per 1 year increase)	
5 year D:A:D CVD risk score	<1, 1-<5, 5-<10, ≥10, unknown	Calculated using method described by Friis-Møller et al. (622)

Abbreviations: MSM – men who have sex with men; IDU – injecting drug use; VL – viral load; HCV – hepatitis C; RNA - ribonucleic acid; HBV – hepatitis B; CKD – chronic kidney disease; eGFR - estimated glomerular filtration rate; CKD-EPI - Chronic Kidney Disease Epidemiology Collaboration; ALT - Alanine aminotransferase; IU - international units per litre; HDL - high-density lipoproteins

Continuous variables were checked to see if there was a linear relationship with the outcome before fitting as continuous

5.2.5 Statistical methods

I summarised baseline characteristics for those starting an eligible 2DR or 3DR; categorical variables were summarised using totals and percentages, whilst continuous variables were summarised using median and interquartile range (IQR). Reasons for discontinuing the previous regimen before starting an eligible regimen were compared between those starting 2DRs and those starting 3DRs. Reasons were only considered if the previous regimen was discontinued within 7 days before starting the eligible regimen. The specific statistical methods used for each outcome are detailed below. Analyses were performed using Stata/SE 15.0 (StataCorp LLC). All p-values are two sided with a p-value <0.05 defined as statistically significant.

5.2.5.1 Immunological and virological outcomes

The nearest VL or CD4 count to 6- and 12-months follow-up, within 3 months either side, were included in analyses of virological and immunological outcomes. The proportion of participants achieving each virological and immunological outcome, listed in Section 5.2.3.1 and Section 5.2.3.2, at 6- and 12-months follow-up was compared between regimen types. Analyses of 6- and 12-month outcomes only included individuals with the potential for at least 6- and 12-months follow-up, respectively. This was calculated on a cohort level. The median date of participants' final visit was calculated for each cohort. If there was at least 6 months between regimen start and the median last visit date, individuals in that cohort were included in the 6-month outcomes analysis, and if there was at least 12 months, individuals were also included in the 12-month outcomes analysis (623).

Reasons for virological or immunological failure were summarised. For those who had cTO failure (defined in Section 5.2.3.2) due to treatment discontinuation, the reasons for discontinuation were also compared between regimens.

I then used logistic regression to compare outcomes between regimen types, adjusted for baseline characteristics listed in Table 5.3. Sensitivity analyses were performed defining virological and cTO success using a VL<50 copies/mL instead of a VL<200 copies/mL.

In all analysis models, an unknown category was used to account for missing data for categorical variables or where variables were reported as unknown. As some cohorts were missing data on specific comorbidities, I did not adjust for cohort in the primary analysis. Analyses were repeated including cohort as an explanatory variable and excluding comorbidities. Additionally, the models were rerun using multiple imputation by chained equations to account for missing data with 10 imputations and using Rubin's rules to combine results (525). Further details on this method are given in Chapter 3, Section 3.3.4.3.

5.2.5.2 Clinical outcomes

I summarised the crude incidence rate of each severe clinical event included in the composite clinical outcome, individually, and compared these between 2DRs and 3DRs using Poisson regression. I then used Poisson regression to compare the incidence of any severe clinical event between regimen types, adjusted for baseline characteristics. Each characteristic was adjusted for separately in univariable models and those with p-value <0.1, or those determined to be a likely confounder a priori, were simultaneously included in a multivariable model.

Results of the multivariable model were compared according to the reason for discontinuing the previous regimen (toxicity vs other) before starting the 2DR or 3DR. Other prespecified subgroup analyses included age, gender, CD4 count, and VL at regimen start. All subgroup analyses were performed by fitting an interaction term between regimen type and the subgroup of interest.

As explained in Chapter 3, Section 0, all prospectively collected events in RESPOND are submitted using a case report form and these events are then centrally validated by a clinician at the RESPOND coordinating centre. For this chapter, I performed a sensitivity analysis which only included events which had been centrally validated. Other sensitivity analyses included comparing only 2DRs which are currently recommended in treatment guidelines to 3DRs where the third ARV was the same as those included in the recommended 2DRs. At the time of analysis, recommended

2DRs were DTG plus RPV, DTG plus 3TC, ATV/b plus 3TC, DRV/b plus 3TC, and DRV/b plus RPV. Corresponding 3DRs included DTG or RPV or ATV/b or DRV/b plus 2 NRTIs.

Analyses were also performed comparing the incidence of the most common individual clinical events: AIDS (non-cancer), NADC, CVD, and death. Due to the fact that fewer events were included in this analysis, there was reduced power, and therefore the models were only adjusted for key baseline characteristics: age, CD4 count at regimen start, smoking status, and number of ARVs previously exposed to. Further analyses were performed allowing participants to start more than one eligible regimen during follow-up and comparing the incidence of any severe clinical event between regimen types using generalised estimating equations with Poisson regression, adjusted for potential confounders, and including a random effect for participant and robust standard errors.

For the main analysis, any event which occurred after regimen discontinuation was attributed to the regimen participants started at baseline. I performed a sensitivity analysis censoring participants at date of regimen discontinuation and only including events if they occurred before discontinuation.

As above, an unknown category was used to account for missing data for categorical variables. Cohort was not adjusted for in the primary analysis; however, analyses were repeated including cohort and excluding comorbidities. Missing data was also accounted for using multiple imputation by chained equations. Finally, I performed a complete case analysis, where individuals with missing data on any variable included in the regression model, were excluded from the analysis.

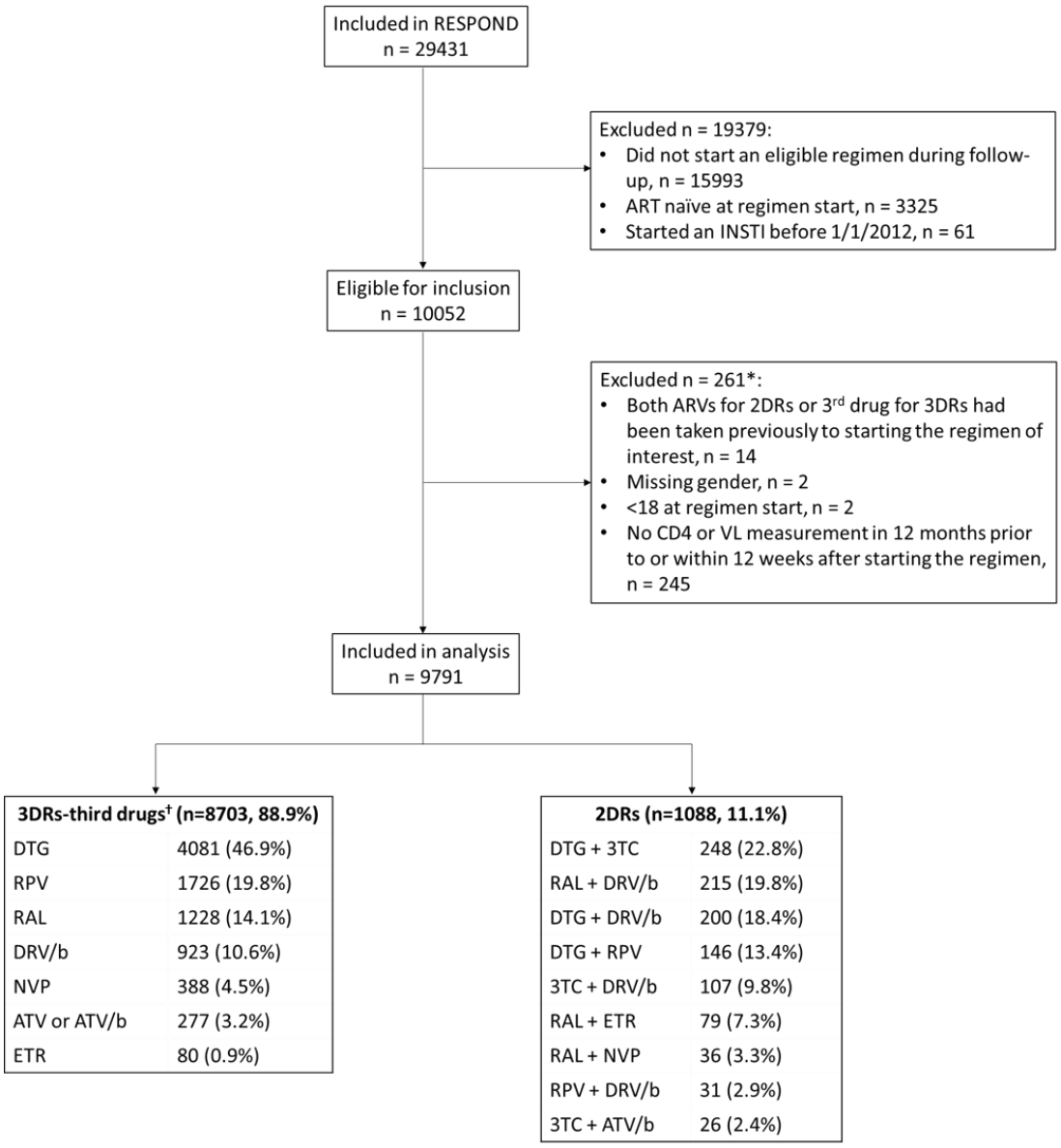
5.3 Results

5.3.1 Participants included

There were 29,431 individuals from 17 cohorts included in version DS1 of the RESPOND database. In total, 10,052 participants started an eligible regimen during follow-up and of these, 9791 (97.4%) were included in the analysis. The reasons for exclusion from the analysis were as follows (more than one reason could apply): 245 did not have a CD4 count or VL measured in the 12 months prior to or 12 weeks after starting the regimen, 14 individuals had taken both ARVs in the 2DR or the 3rd ARV in the 3DR before starting the regimen of interest, 2 were <18 years at regimen start, and 2 did not have information on gender. A larger proportion of those excluded from the analysis were injecting drug users compared to those included (26.3% excluded vs 16.4% included); other baseline characteristics were similar. The study flow for this chapter is shown in Figure 5.1.

Of the 9791 individuals included, 1088 (11.1%) started an eligible 2DR and 8703 (88.9%) started an eligible 3DR. The most common 2DRs were DTG plus 3TC (22.8%), RAL plus DRV/b (19.8%), and DTG plus DRV/b (18.4%). The most common 3DR was DTG plus 2 NRTIs (46.9%) with the most common NRTI backbones being tenofovir disoproxil fumarate/FTC (45.0%), ABC/3TC (40.5%), and tenofovir alafenamide/FTC (9.5%).

Figure 5.1 Study flow chart



*More than one reason can apply
†3DRs consisted of 2 nucleoside reverse transcriptase inhibitors plus the 3rd drug listed. 3DRs were chosen so the 3rd drugs include the same ARVs listed in the 2DRs
Note, starting an INSTI before 1/1/2012 is an exclusion criterion for RESPOND, however 61 participants were erroneously included in the RESPOND database and then excluded from any analyses

5.3.2 Baseline characteristics

Baseline characteristics of participants are presented in Table 5.4. The median age at regimen start was higher for those on 2DRs (52.6 years [interquartile range, IQR, 46.7-59.0] 2DRs vs 47.7 [39.7-54.3] 3DRs, p<0.001). The majority of individuals on both regimen types had a suppressed VL (86.4% on 2DRs vs 87.9% on 3DRs, p=0.16) and CD4 count at regimen start was similar (622 cells/μL [409-814] 2DRs vs 605 [424-809] 3DRs, p=0.55). Participants on 2DRs had been exposed to more ARVs prior to starting the regimen of interest (8 ARVs [5-11] vs 6 [4-8], p<0.001). Regimen type differed between geographical regions, with the majority of participants on 2DRs being in Southern Europe (45.8% 2DRs vs 20.3% 3DRs) and on 3DRs in Western Europe (38.4% vs 52.1%, global p<0.001, Figure 5.2). Figure 5.3 shows the proportion of individuals with an AIDS defining event or comorbidity prior to starting the regimen of interest. There was a higher proportion of prior AIDS defining events on 2DRs (29.3% 2DRs vs. 21.7% 3DRs, p<0.001). Approximately 89% of participants had at least one comorbidity, which was mainly driven by dyslipidaemia, and there was a higher proportion of most comorbidities in those on 2DRs, including diabetes (9.8% vs. 6.9%, p<0.001), dyslipidaemia (73.5% vs 66.5%, p<0.001), and prior CVD (7.1 vs 3.3%, p<0.001).

Table 5.4 Characteristics of participants at regimen start

		Overall		Two-drug regimens		Three-drug regimens	
		n	(%)	n	(%)	n	(%)
Total		9791	(100)	1088	(11.1)	8703	(88.9)
Gender	Male	7048	(72.0)	795	(73.1)	6253	(71.9)
	Female	2738	(28.0)	293	(26.9)	2445	(28.1)
	Transgender	3	(0.0)	0	(0.0)	3	(0.0)
Ethnicity	White	6976	(71.2)	829	(76.2)	6147	(70.6)
	Black	1125	(11.5)	108	(9.9)	1017	(11.7)
	Other	416	(4.2)	40	(3.7)	376	(4.3)
	Unknown	1274	(13.0)	111	(10.2)	1163	(13.4)
Body mass index	<18.5	363	(3.7)	53	(4.9)	310	(3.6)
	18.5-<25	4182	(42.7)	430	(39.5)	3752	(43.1)
	25+	2923	(29.9)	257	(23.6)	2666	(30.6)
	Unknown	2323	(23.7)	348	(32.0)	1975	(22.7)
Smoking status	Never	2764	(28.2)	259	(23.8)	2505	(28.8)
	Current	2836	(29.0)	237	(21.8)	2599	(29.9)
	Previous	1162	(11.9)	128	(11.8)	1034	(11.9)
	Unknown	3029	(30.9)	464	(42.6)	2565	(29.5)
HIV VL, copies/mL	< 200	8588	(87.7)	940	(86.4)	7648	(87.9)
	≥ 200	1203	(12.3)	148	(13.6)	1055	(12.1)
HIV risk	MSM	4037	(41.2)	406	(37.3)	3631	(41.7)
	IDU	1536	(15.7)	193	(17.7)	1343	(15.4)
	Heterosexual	3469	(35.4)	393	(36.1)	3076	(35.3)
	Other	337	(3.4)	34	(3.1)	303	(3.5)
	Unknown	412	(4.2)	62	(5.7)	350	(4.0)
Continuous variables, median (IQR)							
Regimen start, mm/yy		07/15	(04/14, 08/16)	12/15	(11/14, 01/17)	07/15	(03/14, 07/16)
Age, years		48	(40, 55)	53	(47, 59)	48	(40, 54)
CD4 count nadir, cells/mm³		202	(91, 309)	170	(68, 280)	206	(96, 312)
CD4 count at reg start, cells/mm³		608	(423, 810)	622	(409, 814)	605	(424, 809)
CD8 cell count at reg start, cells/mm³		790	(572, 1087)	827	(580, 1120)	786	(571, 1081)
Number of ARVs previously exposed to		6	(4,9)	8	(5,11)	6	(4,8)
Time since starting antiretroviral therapy, years		10	(5,17)	14	(6,19)	10	(5,16)

Abbreviations: MSM-men who have sex with men; IDU-injecting drug use; IQR-interquartile range

Baseline is defined as the date of starting a regimen of interest

Figure 5.2 Geographical region of individual starting 2DRs or 3DRs, stratified by regimen type

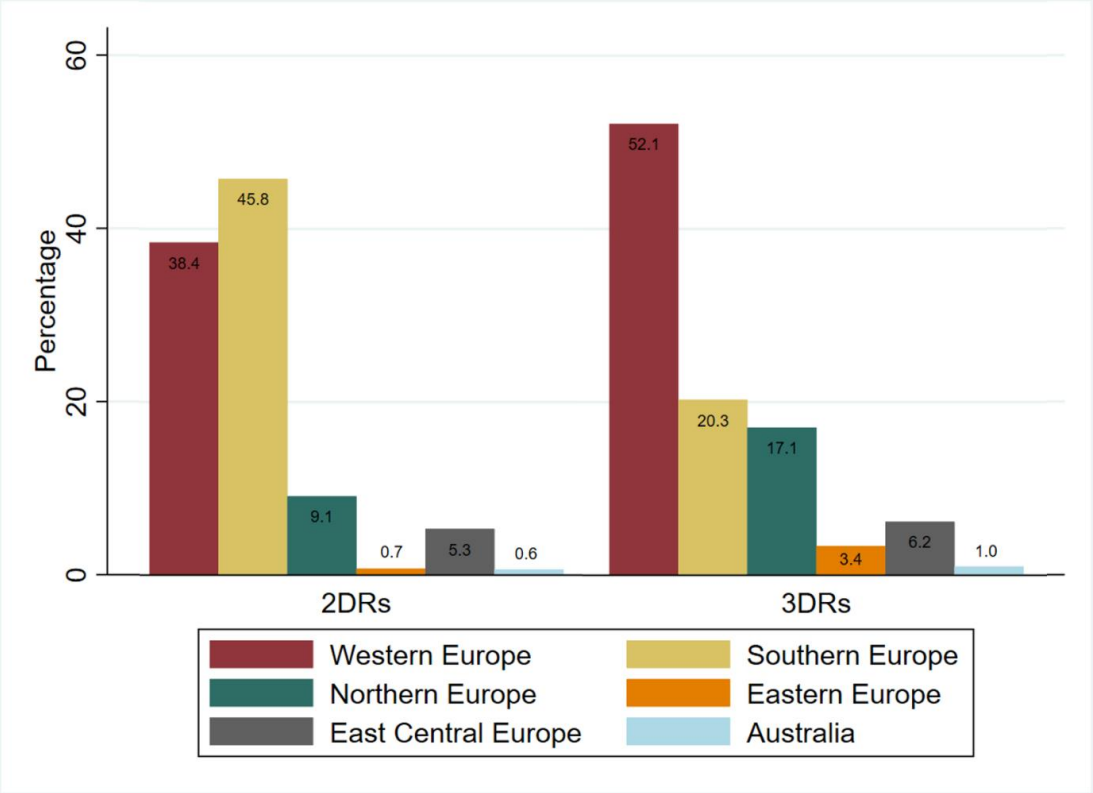
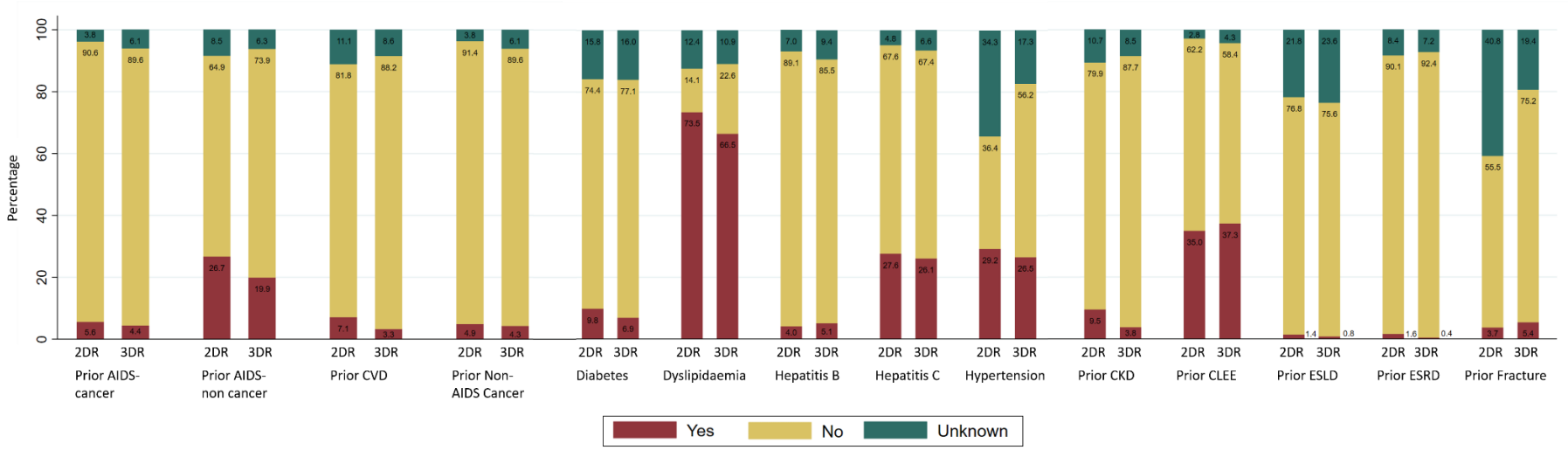


Figure 5.3 Prior comorbidities of individual starting 2DRs or 3DRs, stratified by regimen type



Abbreviations: CVD-cardiovascular disease; CKD-chronic kidney disease; CLEE-chronic liver enzyme elevation; ESLD-end stage liver disease; ESRD-end stage renal disease

Of those who started a 2DR or 3DR, 1006 (92.5%) and 8071 (92.7%) discontinued their previous regimen within 7 days of starting the new regimen, respectively. The most common reason for discontinuation of the previous regimen was toxicity for both regimen types (28.6% amongst those on 2DRs vs 28.8% on 3DRs; p=0.91, Figure 5.4). Amongst those discontinuing for toxicity, the most common type of toxicity was related to the nervous system for those starting 3DRs (28.3%) and renal impairment for 2DRs (37.9%, Figure 5.5). Additionally, treatment simplification was reported for a larger proportion of discontinuations amongst participants starting a 3DR (8.6% amongst those on 2DRs vs 14.1% on 3DRs; p<0.001).

Figure 5.4 Reason for discontinuing the previous regimen before starting a 2DR or 3DR, stratified by regimen type

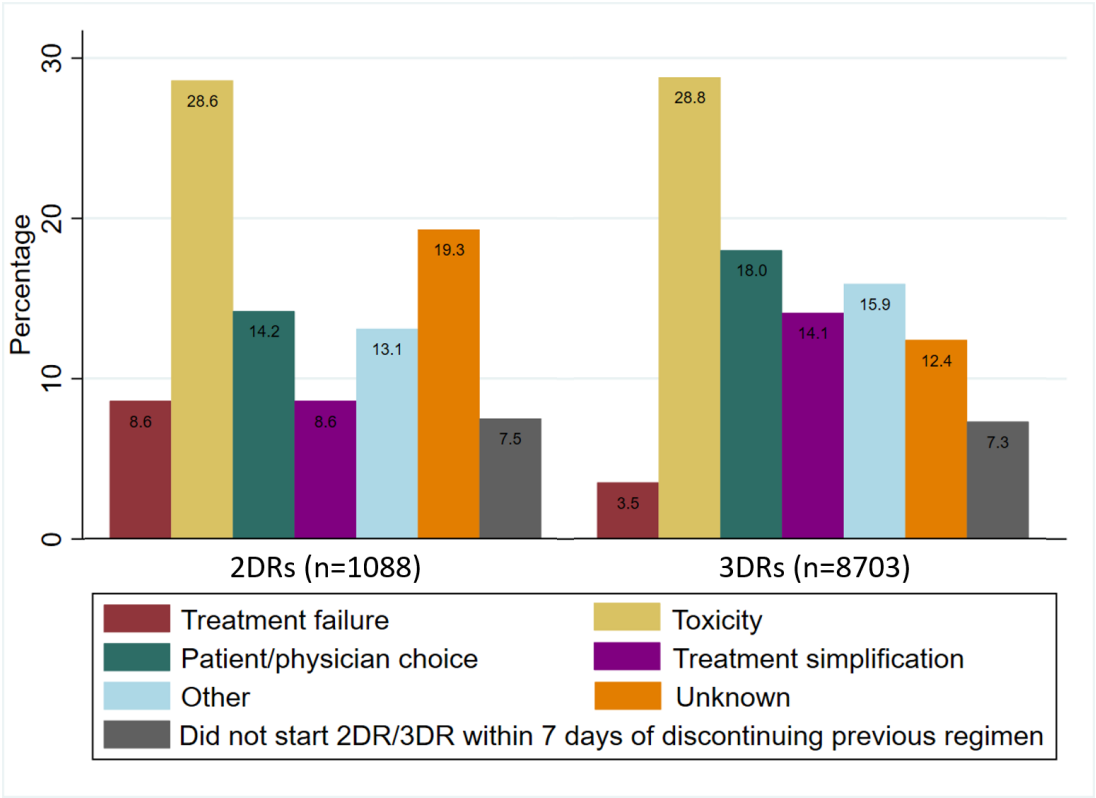
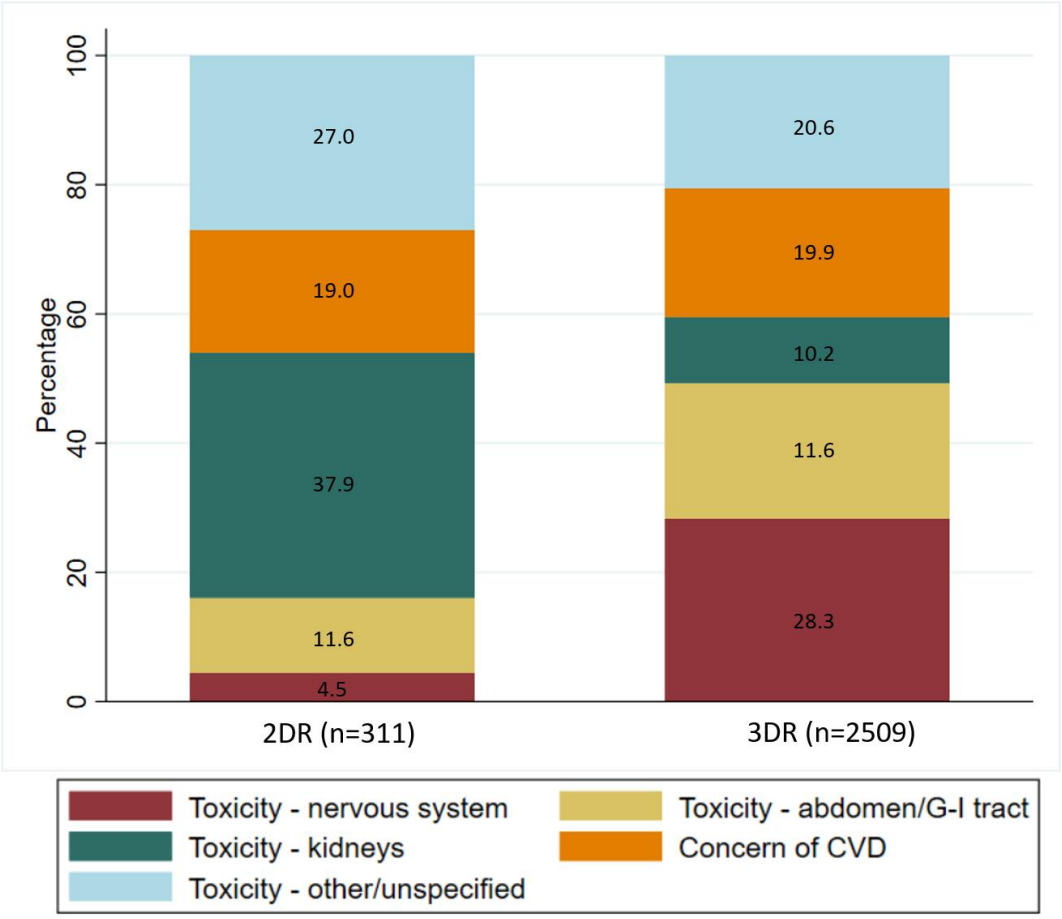


Figure 5.5 Reasons for toxicity discontinuations of the previous regimen before starting a 2DR or 3DR, by regimen type



5.3.3 Immunological outcomes

Summary results from immunological outcomes at 6 months follow-up are shown in Table 5.5. Overall, 94.9% of individuals had at least 6 months potential follow-up and were included in the analysis. Of these, 27.7% achieved a CD4 count increase of more than 100 copies/mL or more than 25% compared to baseline CD4 count and this proportion was similar between 2DRs and 3DRs (27.0% 2DRs vs 27.8% 3DRs). This result was also similar after adjusting for potential confounders (odds ratio [OR] comparing 2DR to 3DR: 0.97 [95% CI: 0.82-1.16], p=0.70, Figure 5.6).

Overall, 88.1% of individuals had at least 12 months potential follow-up (Table 5.7). Again, similar proportions achieved a CD4 count increase on 2DRs and 3DRs (28.4% 2DRs vs 30.1% 3DRs) and this was consistent after adjusting for potential confounders (OR comparing 2DR to 3DR: 0.92 [0.76-1.12], p=0.34, Figure 5.7).

5.3.4 Virological outcomes

Virological outcomes at 6 months follow-up are summarised in Table 5.5. A similar proportion of those on 2DRs and 3DRs achieved VL<200 copies/mL at 6 months follow-up (85.6% 2DRs vs 83.9% 3DRs) and cTO success (74.2% 2DRs vs 73.0% 3DRs). Results were similar when defining virological and cTO success using a VL<50 copies/mL. The main reason for cTO failure was missing VL (12.4% 2DRs vs 13.4% 3DRs) and ART-regimen change (12.5% 2DRs vs 13.0% 3DRs). For those who had cTO failure due to ART-discontinuation, the reasons for discontinuation are shown in Table 5.6; the most common reasons for discontinuation of a 2DR or 3DR was toxicity (29.1% and 29.1% of discontinuations of 2DRs and 3DRs), followed by patient or physician choice (23.8% 3DRs, 15.5% 2DRs). Of those discontinuing for toxicity, the most common type of toxicity was nervous system toxicity for both regimen types (29.1% 3DRs, 33.3% 2DRs). Figure 5.6 shows the odds of achieving viral suppression and cTO success, both using a VL of 200 copies/mL and of 50 copies/mL to define suppression, after adjustment for baseline characteristics. There was no difference between the type of regimen and the odds of achieving any of the outcomes ($p>0.1$ for all outcomes).

As with immunological outcomes, virological outcomes at 12 months follow-up were consistent with 6 month results, showing no difference between regimen types (Table 5.7 and Figure 5.7). Again, ART-regimen change and missing VL were the most common reasons for cTO failure, and for those who had cTO failure due to ART-discontinuation, toxicity was the most common reason for discontinuation of both regimen types (Table 5.8). For those who discontinued due to toxicity, nervous system toxicity remained the most common toxicity type for 2DRs and 3DRs (26.1% 3DRs, 24.0% 2DRs).

Table 5.5 Summary of immunological and virological outcomes at 6 months

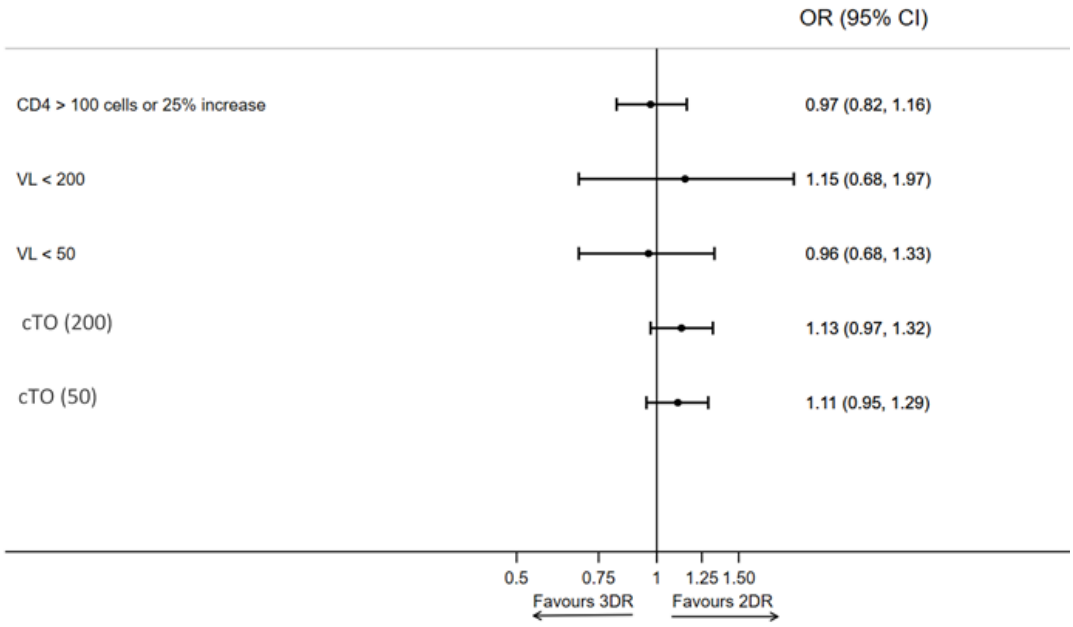
		All		Two-drug regimens		Three-drug regimens		
		n	(%)	n	(%)	n	(%)	P
All		9791	(100)	1088	(11.1)	8703	(88.9)	
Potential follow-up	No	495	(5.1)	68	(6.3)	427	(4.9)	0.06
	Yes	9296	(94.9)	1020	(93.8)	8276	(95.1)	
Amongst those with 6 months potential follow-up								
CD4 increase > 100 or 25%	No	5242	(56.4)	587	(57.5)	4655	(56.2)	0.73
	Yes	2578	(27.7)	275	(27.0)	2303	(27.8)	
	Unknown*	1476	(15.9)	158	(15.5)	1318	(15.9)	
VL < 200 copies/mL	No	244	(2.6)	21	(2.1)	223	(2.7)	0.30
	Yes	7819	(84.1)	873	(85.6)	6946	(83.9)	
	Unknown*	1233	(13.3)	126	(12.4)	1107	(13.4)	
VL < 50 copies/mL	No	568	(6.1)	66	(6.5)	502	(6.1)	0.35
	Yes	7399	(79.6)	823	(80.7)	6576	(79.5)	
	Unknown*	1329	(14.3)	131	(12.8)	1198	(14.5)	
Start new ARV	No	8203	(88.2)	903	(88.5)	7300	(88.2)	0.76
	Yes	1093	(11.8)	117	(11.5)	976	(11.8)	
Stop ARV	No	8159	(87.8)	910	(89.2)	7249	(87.6)	0.14
	Yes	1137	(12.2)	110	(10.8)	1027	(12.4)	
Any regimen change	No	8092	(87.0)	892	(87.5)	7200	(87.0)	0.69
	Yes	1204	(13.0)	128	(12.5)	1076	(13.0)	
Death	No	9240	(99.4)	1013	(99.3)	8227	(99.4)	0.71
	Yes	56	(0.6)	7	(0.7)	49	(0.6)	
AIDS	No	9236	(99.4)	1011	(99.1)	8225	(99.4)	0.32
	Yes	60	(0.6)	9	(0.9)	51	(0.6)	
cTO (200)	No	2495	(26.8)	263	(25.8)	2232	(27.0)	0.42
	Yes	6801	(73.2)	757	(74.2)	6044	(73.0)	
cTO (200) – on treatment n=7041	No	340	(4.83)	47	(5.9)	293	(4.7)	0.15
	Yes	6701	(95.2)	755	(94.1)	5946	(95.3)	
cTO (50)	No	2817	(30.3)	296	(29.0)	2521	(30.5)	0.34
	Yes	6479	(69.7)	724	(71.0)	5755	(69.5)	
cTO (50) – on treatment n=6956	No	570	(8.2)	76	(9.5)	494	(8.0)	0.15
	Yes	6386	(91.8)	722	(90.5)	5664	(92.0)	

*CD4/VL missing at 6 months follow-up
cTO (200) refers to cTO success using a VL <200 copies/mL with cTO failure defined as at least one of: VL ≥ 200 copies/mL, missing VL, any ART-regimen change, AIDS event, or death. cTO (50) refers to cTO success using a VL <50 copies/mL
On treatment: excluding missing VL or ART change

Table 5.6 Reasons for discontinuation of two- or three- drug regimens at 6 months after starting regimen

	All		Two-drug regimens		Three-drug regimens	
	n	(%)	n	(%)	n	(%)
Included	9791	(100)	1088	(11.1)	8703	(88.9)
With 6 months follow-up	9296	(94.9)	1020	(93.8)	8276	(95.1)
Any stop	1137	(12.2)	110	(10.8)	1027	(12.4)
Reason for discontinuation amongst those who discontinued within 6 months follow-up						
Toxicity	331	(29.1)	32	(29.1)	299	(29.1)
Simplified treatment available	182	(16.0)	15	(13.6)	167	(16.3)
Treatment failure	42	(3.7)	7	(6.4)	35	(3.4)
Patient/Physician Choice	261	(23.0)	17	(15.5)	244	(23.8)
Other	181	(15.9)	12	(10.9)	169	(16.5)
Unknown	140	(12.3)	27	(24.5)	113	(11.0)

Figure 5.6 Virological and immunological outcomes comparing 2DRs to 3DRs at 6 months follow-up



cTO (200) refers to cTO success using a VL <200 copies/mL with cTO failure defined as at least one of: VL ≥ 200 copies/mL, missing VL, any ART-regimen change, AIDS event, or death. cTO (50) refers to cTO success using a VL <50 copies/mL

All models adjusted for age, ethnicity, smoking status, viral load at baseline, CD4 nadir, CD4 at baseline, prior AIDS, region. CD4 outcome model additionally adjusted for hypertension. VL outcome models additionally adjusted for HIV risk group, prior CVD. cTO outcome models additionally adjusted for hepatitis C, gender, HIV risk group.

Table 5.7 Summary of virological and immunological outcomes at 12 months

		All		Two-drug regimens		Three-drug regimens		
		n	(%)	n	(%)	n	(%)	P
All		9791	(100)	1088	(11.1)	8703	(88.9)	
Potential follow-up	No	1165	(11.9)	160	(14.7)	1005	(11.5)	0.002
	Yes	8626	(88.1)	928	(85.3)	7698	(88.5)	
Amongst those with 12 months potential follow-up								
CD4 increase > 100 or 25%	No	4373	(50.7)	458	(49.4)	3915	(50.9)	0.07
	Yes	2583	(29.9)	264	(28.4)	2319	(30.1)	
	Unknown*	1670	(19.4)	206	(22.2)	1464	(19.0)	
VL < 200 copies/mL	No	201	(2.3)	21	(2.3)	180	(2.3)	0.10
	Yes	7001	(81.2)	731	(78.8)	6270	(81.4)	
	Unknown*	1424	(16.5)	176	(19.0)	1248	(16.2)	
VL < 50 copies/mL	No	498	(5.8)	55	(5.9)	443	(5.8)	0.27
	Yes	6623	(76.8)	694	(74.8)	5929	(77.0)	
	Unknown*	1505	(17.4)	179	(19.3)	1326	(17.2)	
Start new ARV	No	6888	(79.9)	760	(81.9)	6128	(79.6)	0.10
	Yes	1738	(20.1)	168	(18.1)	1570	(20.4)	
Stop ARV	No	6809	(78.9)	761	(82.0)	6048	(78.6)	0.02
	Yes	1817	(21.1)	167	(18.0)	1650	(21.4)	
Any regimen change	No	6716	(77.9)	741	(79.8)	5975	(77.6)	0.12
	Yes	1910	(22.1)	187	(20.2)	1723	(22.4)	
Death	No	8535	(98.9)	917	(98.8)	7618	(99.0)	0.68
	Yes	91	(1.1)	11	(1.2)	80	(1.0)	
AIDS	No	8564	(99.3)	919	(99.0)	7645	(99.3)	0.34
	Yes	62	(0.7)	9	(1.0)	53	(0.7)	
cTO (200)	No	3159	(36.6)	346	(37.3)	2813	(36.5)	0.66
	Yes	5467	(63.4)	582	(62.7)	4885	(63.5)	
cTO (200) – on treatment n=5679	No	281	(5.0)	45	(7.2)	236	(4.7)	0.006
	Yes	5398	(95.0)	579	(92.8)	4819	(95.3)	
cTO (50)	No	3423	(39.7)	369	(39.8)	3054	(39.7)	0.96
	Yes	5203	(60.3)	559	(60.2)	4644	(60.3)	
cTO (50) – on treatment n=5615	No	475	(8.5)	65	(10.5)	410	(8.2)	0.06
	Yes	5140	(91.5)	557	(89.5)	4583	(91.8)	

*CD4/VL missing at 12 months follow up

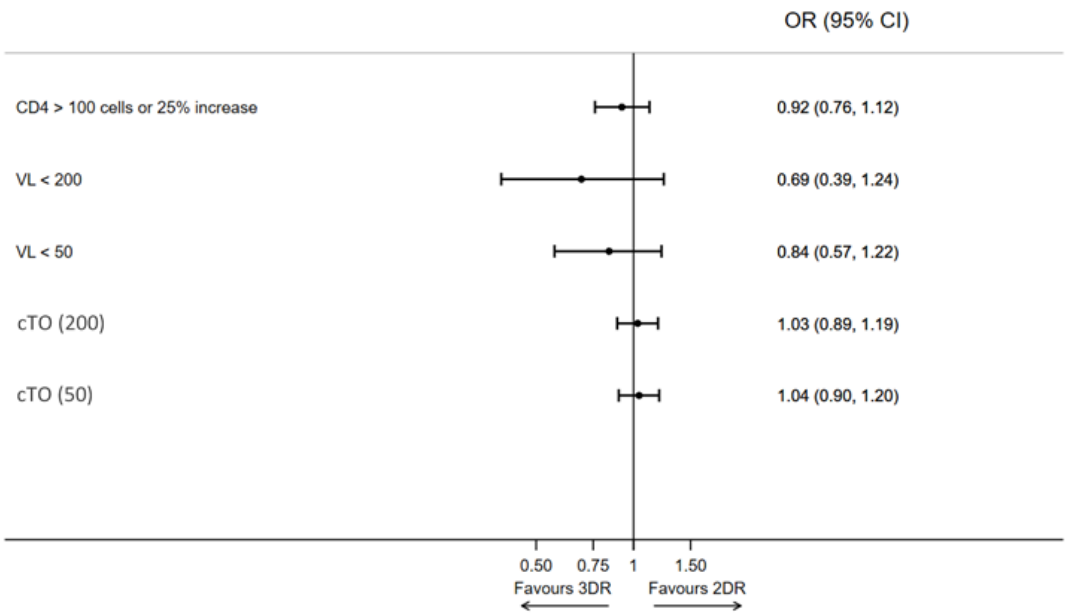
cTO (200) refers to cTO success using a VL <200 copies/mL with cTO failure defined as at least one of: VL ≥ 200 copies/mL, missing VL, any ART-regimen change, AIDS event, or death. cTO (50) refers to cTO success using a VL <50 copies/mL

On treatment - excluding missing VL or ART change

Table 5.8 Reasons for discontinuation of two- or three- drug regimens at 12 months after starting regimen

	All		Two-drug regimens		Three-drug regimens	
	n	(%)	n	(%)	n	(%)
Included	9791	(100)	1088	(11.1)	8703	(88.9)
With 12 months follow-up	8626	(88.1)	928	(85.3)	7698	(88.5)
Any stop	1817	(21.1)	167	(18.0)	1650	(21.4)
Reason for discontinuation amongst those who discontinued within 12 months follow-up						
Toxicity	451	(24.8)	42	(25.1)	409	(24.8)
Simplified treatment available	333	(18.3)	25	(15.0)	308	(18.7)
Treatment failure	71	(3.9)	11	(6.6)	60	(3.6)
Patient/Physician Choice	401	(22.1)	19	(11.4)	382	(23.2)
Other	325	(17.9)	26	(15.6)	299	(18.1)
Unknown	236	(13.0)	44	(26.3)	192	(11.6)

Figure 5.7 Virological and immunological outcomes comparing 2DRs to 3DRs at 12 months follow-up

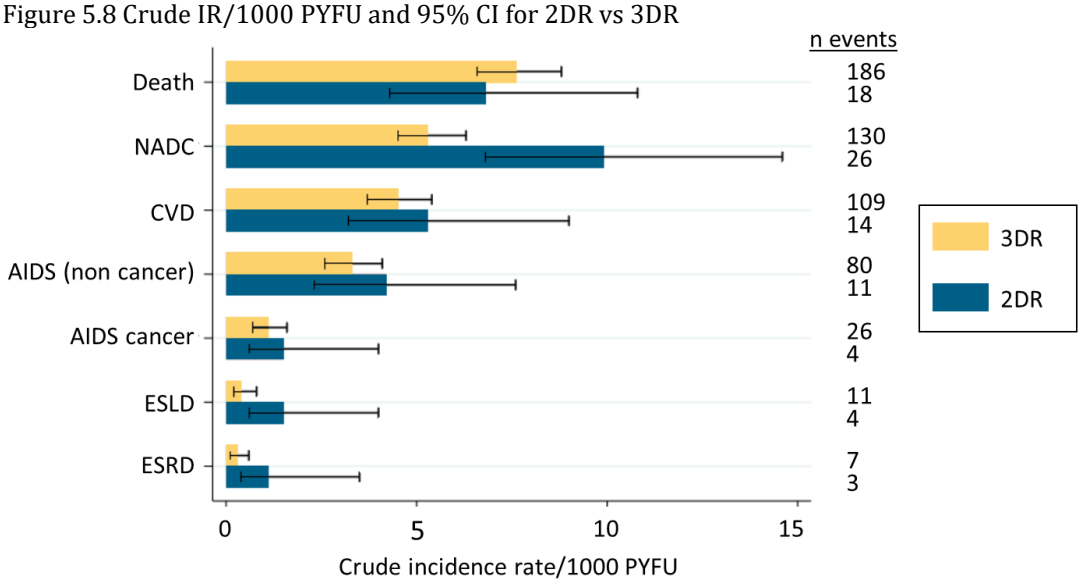


cTO (200) refers to cTO success using a VL <200 copies/mL with cTO failure defined as at least one of: VL ≥ 200 copies/mL, missing VL, any ART-regimen change, AIDS event, or death. cTO (50) refers to cTO success using a VL <50 copies/mL.
All models adjusted for year of regimen start, age, smoking status, risk group, VL at baseline, CD4 nadir, CD4 at baseline, hepatitis C, AIDS, region. CD4 additionally adjusted for hypertension, diabetes, and chronic liver enzyme elevation. VL additionally adjusted for ethnicity. cTO additionally adjusted for chronic kidney disease.

5.3.5 Clinical outcomes

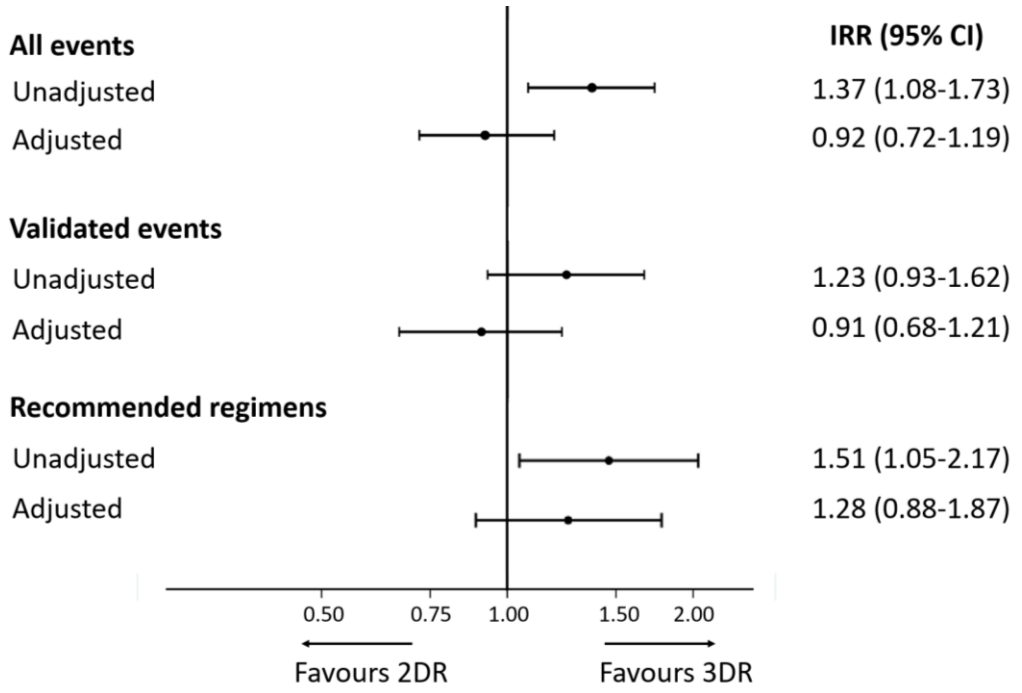
Overall, median follow-up was 2.6 years (IQR 1.4-3.8) and higher for those on 3DRs (2.7 [1.4-3.8]) compared to 2DRs (2.2 [1.2-3.2]). During a total follow-up of 27,159 years, there were 619 severe clinical events (as defined in Section 5.2.3.3, incidence rate [IR] 23.3/1000 PYFU [95% CI 21.6-25.2]): 540 events for participants on 3DRs (22.5/1000 PYFU [20.7-24.5]) and 79 for participants on 2DRs (30.9/1000 PYFU [24.8-38.5]). Overall, the most common events were death (IR 7.5/1000 PYFU [6.5-8.6]) and NADC (5.8/1000 PYFU [4.9-6.8]). Figure 5.8 shows the crude IRs and 95% CIs of each severe event by regimen type. With the exception of death, the crude IR of each event was higher on 2DRs, although some of the event rates have wide confidence intervals due to the small number of events, and the confidence intervals for 2DRs and 3DRs overlap for all events except NADC.

Figure 5.8 Crude IR/1000 PYFU and 95% CI for 2DR vs 3DR



The unadjusted IR of any severe event was higher on 2DRs (IR ratio [IRR] 1.37 [95% CI: 1.08-1.73], p=0.009), as shown in Figure 5.9. After adjustment for age, the difference was attenuated and no longer significant (IRR 1.08 [0.85-1.37], p=0.54); results were similar after adjustment for a wide range of baseline characteristics (IRR 0.92 [0.72-1.19]; p=0.53).

Figure 5.9 Incidence rate ratio comparing events on two-drug regimens vs three-drug regimens



All events and validated events - adjusted analyses adjusted for age, gender, ethnicity, BMI, smoking status, HIV risk group, HIV viral load at regimen start, nadir CD4 count, CD4 count at regimen start, viral hepatitis C, viral hepatitis B, prior hypertension, prior diabetes, prior AIDS defining event (excluding cancer), prior AIDS cancer, prior non-AIDS cancer, prior end stage liver disease, prior cardiovascular disease, prior fracture, prior chronic kidney disease, prior dyslipidaemia, number of drugs previously exposed to
Recommended regimens - adjusted analysis adjusted for age, gender, ethnicity, smoking status, CD4 count at regimen start, viral hepatitis C, prior AIDS defining event (excluding cancer), prior non-AIDS cancer, prior cardiovascular disease, prior chronic kidney disease, number of drugs previously exposed to
Recommended regimens included-2DRs: DTG plus RPV, DTG plus 3TC, ATV/b plus 3TC, DRV plus 3TC, DRV plus RPV; 3DRs: DTG or RPV or ATV/b or DRV plus 2 NRTIs

5.3.5.1 Sensitivity analyses

Of the 619 clinical events experienced during follow-up, 462 were in the RESPOND validation period (as defined in Chapter 3, Section 0), and 444 (96.1%) were centrally validated. The IR of validated events was 28.1/1000 PYFU (95% CI: 25.4-31.0) for 3DRs and 34.6/1000 PYFU (26.7-44.7) for 2DRs. The crude IRR of validated events for 2DRs versus 3DRs was 1.23 (0.93-1.62; p=0.14), and as in the main analysis, was not significant after adjustment for baseline characteristics (0.91 [0.68-1.21], p=0.52; Figure 5.9). Again, the change in result after adjustment for baseline characteristics was mainly driven by age.

As treatment guidelines only recommend a subset of all the 2DRs used by RESPOND participants and therefore included in this analysis reflecting real-life 2DR use, I restricted the analyses to only include participants on recommended 2DRs compared to corresponding 3DRs. The included regimens are listed in Section 5.2.5.2 and Figure 5.9 footnote. This analysis included 558 participants (51.3%) on approved 2DRs and 7007 (80.5%) on corresponding 3DRs. Differences in baseline characteristics between 2DRs and 3DRs in this analysis were similar to those in the primary analysis, apart from a higher proportion on recommended 2DRs having suppressed VL compared to corresponding 3DRs (96.1% vs 88.0%, p<0.0001); in the main analysis the proportion with a suppressed VL was similar on 2DRs vs 3DRs (86.4% vs 87.9%, p=0.16).

There were 363 events during 18,133 PYFU on 3DRs (IR 20.0/1000 PYFU [95% CI: 18.1-22.2]) and 32 events during 1059 PYFU on 2DRs (30.2/1000 PYFU [21.4-42.7]). There was a similar distribution of events as in the main analysis. As in the primary analysis there was a higher crude incidence of events on 2DRs (IRR 1.51 [95% CI: 1.05-2.17], p=0.026; Figure 5.9); after adjustment however, there was no longer a significant difference between regimen types (IRR 1.28 [0.88-1.87], p=0.20). As before, this non-significant result after adjustment was mainly driven by age.

I also repeated analyses allowing participants to start more than one eligible regimen during follow-up. Results of this analysis, as well as other sensitivity analyses, are shown in Figure 5.10. There were 1175 2DRs and 10,306 3DRs included in this sensitivity analysis, and after adjustment for baseline characteristics, there remained a similar incidence of events on 2DRs and 3DRs (adjusted IRR 1.04 [0.75-1.45], p=0.81). The analysis was then rerun including recurrent events, provided the recurrent event was of a different type to any prior event, and this also showed similar results. In total, an additional 150 events were included and the adjusted IRR comparing 2DRs to 3DRs was 0.82 (95% CI: 0.65-1.03, p=0.10). The most common types of recurrent events were NADC followed by death (experienced by 39 participants) or multiple different AIDS events (experienced by 24). I also assessed specifically the number of additional deaths that would be included if recurrent events were allowed. There were 85 more deaths included, however these occurred

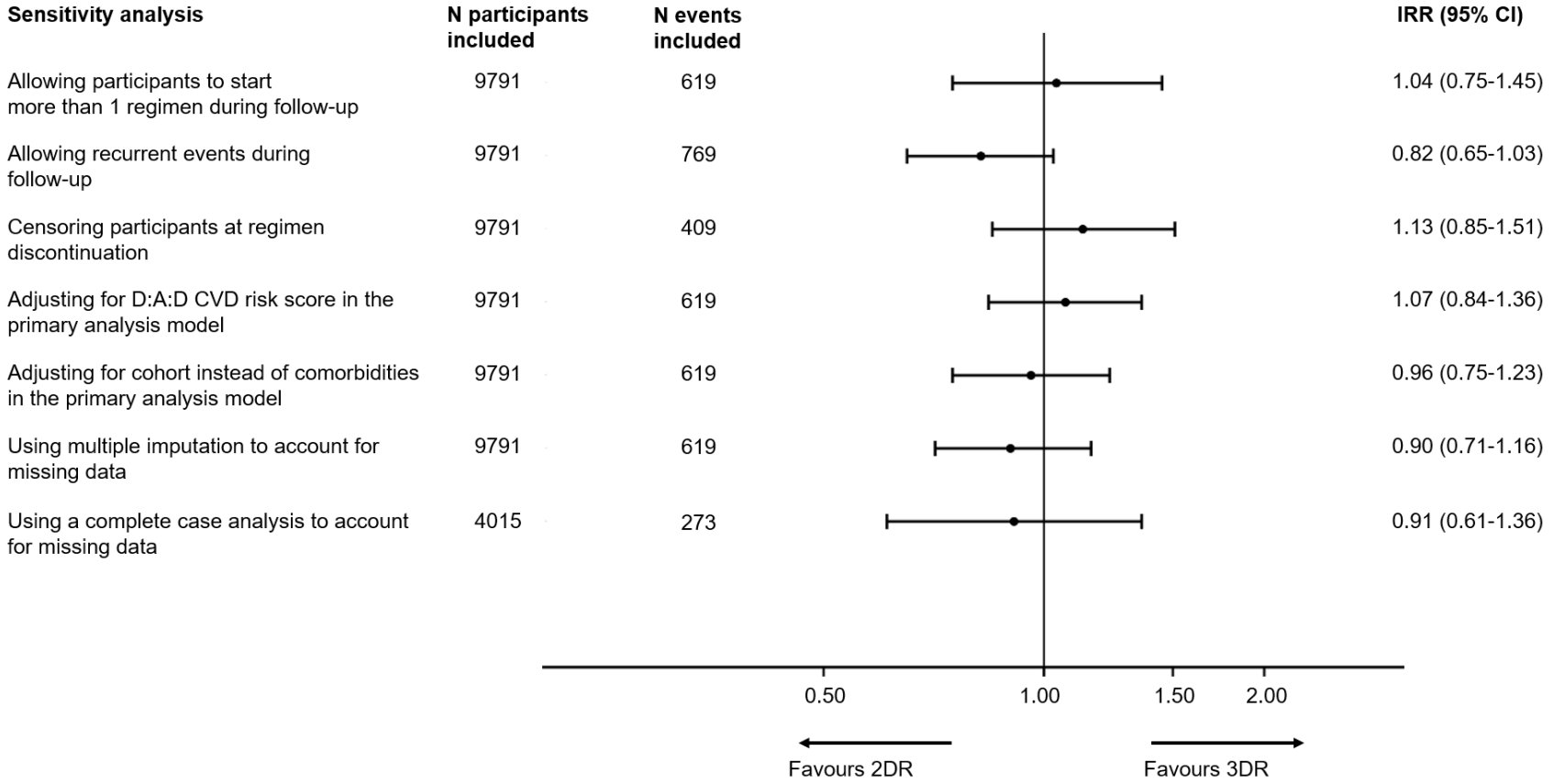
for a similar proportion of participants on 2DRs and 3DRs (0.9% 3DR vs 0.6% 2DR, p=0.40).

For the main analysis, if an event occurred after treatment discontinuation, the event was still attributed to the regimen participants started at baseline. As a sensitivity analysis, I repeated the analysis censoring individuals who discontinued their regimen at the date of regimen end. For this analysis, there were 63 events during 2569 PYFU on 2DRs (IR/1000 PYFU 24.5 [95% CI: 18.8-31.4]) and 346 events during 24097 PYFU on 3DRs (IR/1000 PYFU 14.4 [12.9-16.0]), and the adjusted incidence of events was similar for 2DRs compared to 3DRs (adjusted IRR 1.13 [0.85-1.51], p=0.39).

I repeated analyses using multiple imputation to account for missing data and performed a complete case analysis, both with similar results. As some cohorts were missing data on specific comorbidities, models were rerun adjusting for cohort rather than comorbidities, again showing similar results.

To explore the effect of previous ARV exposure on the results, the main analysis was repeated, adjusting for the D:A:D CVD risk score, which accounts for previous exposure to ARVs (622), instead of the variables used to calculate the score individually, which showed similar results. D:A:D CVD risk score was assessed rather than the CKD risk score as CVD was one of the events included in the composite clinical endpoint. Finally, the role of the NRTI backbone was also assessed for those on 3DRs to investigate whether the incidence of events was driven by the backbone rather than the 3rd drug. This was because some NRTIs have been shown to be associated with an increased risk of specific clinical events, for example TDF has been shown to be associated with ESRD (624) and ABC with CVD (439). This analysis was done by comparing the IRs on each 3DR before and after adjusting for the backbone but showed similar results.

Figure 5.10 Results of sensitivity analyses comparing the adjusted incidence of events on 2DRs to 3DRs



Note, analysis allowing participants to start more than 1 regimen during follow-up included 11,481 regimens from 9791 participants

In an exploratory analysis, with more limited power, focused on individual events, there was a non-significant lower incidence on 2DRs of death (0.69 [0.42-1.12], p=0.13) and CVD (0.80 [0.45-1.41], p=0.44), but a higher incidence of NADC (1.35 [0.88-2.09], p=0.17) and non-cancer AIDS events (IRR 1.27 [0.67-2.43], p=0.47), after adjustment (Table 5.9). As the event rates were lower when looking at specific events and the analyses were adjusted for a limited number of potential confounders, these estimates have wide confidence intervals, and the results should be interpreted with caution.

Table 5.9 Comparison of the incidence of individual severe clinical events between two- and three- drug regimens

				Univariable			Multivariable*		
			N events	**IRR**	**(95% CI)**	**P**	**IRR**	**(95% CI)**	**P**
Death	Regimen Type	3DR	186	1			1		
		2DR	18	0.90	(0.55, 1.46)	0.66	0.69	(0.42, 1.12)	0.13
NADC	Regimen Type	3DR	130	1			1		
		2DR	26	1.86	(1.22, 2.84)	0.004	1.35	(0.88, 2.09)	0.17
CVD	Regimen Type	3DR	109	1			1		
		2DR	14	1.19	(0.68, 2.08)	0.54	0.80	(0.45, 1.41)	0.44
AIDS – non cancer	Regimen Type	3DR	80	1			1		
		2DR	11	1.28	(0.68, 2.40)	0.44	1.27	(0.67, 2.43)	0.47

*Multivariable model adjusted for age, CD4 count at regimen start, smoking status, number of drugs previously exposed to

5.3.5.2 Subgroup analyses

In a pre-specified subgroup analysis, there was a significant interaction between regimen type and VL at regimen start (interaction p=0.011); this showed there was no difference in the adjusted incidence of events between regimen types for those with a suppressed VL (VL<200 copies/mL) at regimen start (IRR 1.12 [95% CI: 0.85-1.48]), however, surprisingly, in those with uncontrolled viremia (VL≥200 copies/mL), there was a lower incidence of events on 2DRs versus 3DRs (0.51 [0.30-0.89]). Similar results were seen when defining uncontrolled viremia as VL≥50 copies/mL (interaction p=0.03). This did not appear to be driven by any specific event, however the number of events on 2DRs for those with uncontrolled viremia was extremely low. All other subgroup analyses were non-significant.

5.4 Discussion

In this chapter, I compared immunological, virological, and clinical outcomes between ART-experienced individuals on 2DRs and 3DRs in a large, heterogenous cohort setting. I included almost 10,000 participants: 1088 on 2DRs and 8703 on 3DRs. I found that a similar proportion of individuals on 2DRs and 3DRs achieved CD4 count recovery, VL<200 copies/mL, and cTO success at 6- and 12- months follow-up. I also found a similar incidence of severe clinical events on 2DRs versus 3DRs, after adjusting for baseline characteristics, primarily age. Immunological and virological outcomes have been extensively compared between 2DRs and 3DRs in the literature, however data comparing clinical outcomes remains scarce. While several surrogate markers for clinical outcomes, such as inflammation, and immune activation biomarkers have been compared between 2DR and 3DR, with mixed results found (580,585,625,626), this is one of the first large studies comparing hard clinical outcomes. Some baseline characteristics, for example age and the presence of comorbidities, were notably different between the groups, suggesting there is likely to be confounding by indication present. However, the results were highly consistent across a wide range of sensitivity analyses, including restricting the analysis to centrally validated events and to individuals starting guideline recommended regimens only.

Subgroup analyses showed consistent results amongst those with a suppressed VL at regimen start. Interestingly, there was a lower incidence of events on 2DRs versus 3DRs in those with uncontrolled viremia, although this group did include smaller numbers. This may be because the proportion of participants with comorbidities amongst those with uncontrolled viremia on 2DRs was lower than amongst those with a suppressed VL, which was not the case for those on 3DRs, although prior comorbidities was adjusted for in the model. However additional research is needed to investigate this finding further.

For the primary analysis, I included all 2DRs which had previously been shown to be non-inferior to 3DRs in RCTs and observational studies, regardless of whether they

are recommended in guidelines. This was to better reflect current clinical practice across the regions included. Sensitivity analyses were then performed including 2DRs recommended in international guidelines only, which showed a higher, although non-significant incidence of clinical events on 2DRs. This analysis, however, included considerably smaller numbers and the results have wide confidence intervals. It is expected that there may be a higher short-term incidence of events on 2DRs, as older individuals and those with prevalent or increased risk of comorbidities were more likely to be prescribed 2DRs in this analysis. Further research of individual clinical events with longer follow-up on 2DRs is needed to assess if the disease trajectories may be altered or not by using 2DRs which are expected to be less toxic.

Further, results from exploratory analyses comparing the incidence of the most common individual events suggests that NADC and AIDS (non-cancer) rates may be higher for 2DR, but death and CVD rates lower. Again, these analyses were limited by power, and large studies with longer follow-up time are needed to investigate each of these endpoints further. Van Wyck et al. (626) and Calza et al. (601) both showed a decrease in lipids with DTG plus 3TC and RAL plus etravirine, respectively, compared to 3DRs, suggesting the risk of CVD may subsequently be lower on 2DRs. Although other studies comparing lipids on 2DRs have shown mixed results and changes in lipids may only partially affect the risk of CVD (580,581,585). Additionally, Serrano-Villar et al. found increased long-term inflammation on 2DRs (627), the clinical implications of which warrant further investigation. I was also not able to investigate whether event rates differed according to specific 2DRs, due to limited power, and this may again show different results for specific events.

Switching from 3DRs to 2DRs has several potential advantages. Using 2DRs may cause fewer drug-drug interactions, which is important as the population with HIV is aging and the prevalence of non-AIDS comorbidities increasing (575,628). Avoiding ARVs shown to be associated with an increased risk of toxicities, such as renal and bone toxicities (i.e. for TDF), may further lead to fewer toxicities on 2DRs, although this requires further research with longer follow-up and comparison with newer 3DRs such as those including tenofovir alafenamide (580,612,629). Additionally, 2DRs

provide a simpler regimen for those not currently on fixed combination pills, and some 2DRs have been shown to be more cost effective than many 3DRs (332,629,630). Whilst most treatment guidelines recommend specific 2DRs as switch strategies, their use in Europe is increasing, and many guidelines now recommend DTG plus 3TC as a possible initial regimen for ART-naïve individuals (331,535,578). It is therefore important to compare the longer-term clinical outcomes of 2DRs versus 3DRs, data which will not be available from randomised clinical trials. Whilst many studies have shown 2DRs are non-inferior to 3DRs for short-term virologic and immunologic endpoints, data comparing clinical endpoints outside these findings in RESPOND remains scarce (580,581,632,582–588,631).

5.4.1 Strengths and limitations

There are some limitations to this analysis. As this is an observational study, confounding by indication may affect the results, especially as 2DRs are newer and perhaps only prescribed to individuals with specific demographic and clinical characteristics. Whilst I have adjusted for a wide range of baseline characteristics, residual confounding cannot be excluded. Additionally, there is a relatively high proportion of missing data, for example for smoking status, and variability in data completeness between cohorts. I did, however, perform several sensitivity analyses to handle missing data, all showing similar results. Finally, the primary outcome of severe clinical events was analysed as a composite endpoint due to the low incidence of specific events, and 2DRs and 3DRs were analysed as groups. Specific regimens included in 2DRs and 3DRs were specified a priori and reflect real-world settings where individuals are treated with a range of regimens. As mentioned above, the results may differ for specific clinical events or for specific 2DRs or 3DRs.

There are, however, several strengths to this analysis. This is one of the first studies assessing clinical outcomes of 2DRs and a subset of the clinical events in RESPOND are centrally validated by clinicians at the RESPOND coordinating centre. RESPOND is a large and heterogeneous sample, from real-world settings, providing results which are generalisable to people living with HIV in Europe and Australia. Further, due to

the size of the study, I was able to include a variety of 2DRs and assess relatively uncommon clinical endpoints.

5.4.2 Conclusions

In conclusion, virological and immunological outcomes were similar between 2DRs and 3DRs. After accounting for demographic and clinical characteristics, there was also a similar incidence of severe clinical events on 2DRs and 3DRs. 2DRs appear to be a viable treatment option with regards to clinical outcomes, although further research on resistance and long-term durability of 2DRs, as well as research on individual 2DRs and individual clinical events is needed.

5.4.3 Publications

The results from this project were presented at the Conference on Retroviruses and Opportunistic Infections (CROI) 2020 as a virtual poster (appendix VIII) and the manuscript has been published in Clinical Infectious Diseases (CID) (633) (appendix IX).

Chapter 6 Trends in cancer incidence in different contemporary ART-eras amongst people living with HIV

6.1 Introduction

Cancer is one of the leading causes of death, both in the general population, and in people living with HIV (PLWH) (80,634–637). In the general population in the European Union, the most common cancers in 2020 were breast cancer (13.3% of all cancers diagnosed), colorectal cancer (12.7%), prostate cancer (12.5%), and lung cancer (11.9%) (638). Figure 6.1 shows the most common cancers diagnosed in the general population in Europe in 2020, split by males and females.

Figure 6.1 Most common cancers diagnosed in Europe in 2020, split between males and females

Source: (638)

Several studies have shown that the incidence of cancer is higher amongst PLWH compared to the general population. One study in the USA with follow-up from 1996-2012 and including 448,258 PLWH, 3,093,033 person-years of follow-up (PYFU) and 21,294 cancers, showed a higher risk compared to the general population of all cancer, AIDS-defining cancers (ADCs), defined as Kaposi's sarcoma, non-Hodgkin

lymphoma, and cervical cancer, and several non-ADCs (NADCs), including liver cancer, lung cancer, and Hodgkin lymphoma (639). This was measured using standardised incidence ratios (SIRs) where the observed number of cancers amongst PLWH is divided by the expected number estimated from the general population; a SIR greater than one shows an increased risk of cancer amongst PLWH. The SIR for any cancer during follow-up was 1.69 (95% CI: 1.67-1.72) showing a 69% higher risk of cancer for PLWH. For ADCs, the risk was almost 14 times higher for PLWH (SIR 13.97 [13.63-14.32]) and for NADCs, it was 21% higher (SIR 1.21 [1.19-1.23]), however this was mostly driven by virus-related NADCs, such as anal cancer and liver cancer. When looking by year of follow-up, the authors reported that these SIRs had decreased over time, although they were still above 1 in 2012. Similar findings have been reported in several other studies (640,641). Additionally, it has been shown that some types of cancers are diagnosed at a younger age in PLWH, for example the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) study showed that lung cancer, anal cancer, oral cavity/pharynx cancers, kidney cancers, and myelomas were all diagnosed at a median of 2-4 years younger in PLWH compared to the general population, although this only included follow-up from 1996-2008 (642).

The most common cancers amongst PLWH have changed drastically since the mid-1990s when combination ART was introduced. Immunodeficiency or lower CD4 counts has been shown to be associated with an increased risk of ADCs and some NADCs (643). Therefore, prior to the widespread use of ART, when PLWH commonly experienced immunodeficiency, ADCs were the predominant cancers (644). Since then, however, the incidence of ADCs has significantly decreased (80,635,644–646). The Veterans Aging Cohort Study (VACS), including 44,787 PLWH and 329,084 PYFU, reported the incidence of ADCs decreased from 288/100,000 PYFU in 1997-2000 to 129/100,000 PYFU in 2009-2012 (647). At the same time, there has been an increase in the burden of NADCs (635,648,649) which is likely attributable, in part, to the fact that the population of PLWH is aging. Several studies have assessed changes in the incidence of cancers amongst PLWH with mixed results. Whilst some have shown that cancer incidence has remained steady after accounting for age, others have reported

an increased risk of NADCs over time and an increased risk compared to the general population without HIV (645–647,650–654). The Antiretroviral Therapy Cohort Collaboration (ART-CC) study including 83,586 PLWH reported that the most common NADCs during 2006-2015 were lung cancer (n=255, 17.7% of NADCs diagnosed), Hodgkin lymphoma (n=196, 13.6%), and anal cancer (n=124, 8.6%) (655). Similar results were reported in several cohort studies with follow-up up to 2010 (650,653,656), however there is limited data available in more recent years, when even more effective and less toxic ARVs have become available.

The reasons for changes in the incidence of NADCs amongst PLWH is likely to be multifaceted. As effective treatment for HIV has become widely used, the life expectancy of PLWH has increased (635,649). This has led to an increase in the burden of several age-associated comorbidities, including cancer (80,634,648). Additionally, the prevalence of risk factors for cancer, such as smoking, drug use, and alcohol use is relatively high amongst some subgroups of PLWH (657). HIV also affects the natural history of common coinfections, such as hepatitis B (HBV), hepatitis C (HCV), and Epstein Barr virus (EBV) which have been shown to be associated with an increased risk of specific cancers such as hepatocellular carcinoma, the incidence of which has been going up over time, and non-Hodgkin and Hodgkin lymphoma (648,658–660). As HBV, HCV, and EBV share some similar transmission routes to HIV, for example through injecting drug use for hepatitis or bodily fluids for EBV, the incidence of these infections has been shown to be higher amongst PLWH (661,662). Tenofovir disoproxil fumarate is an ARV used for treatment of both HIV and HBV, providing an opportunity to treat both infections at the same time, and there is a vaccine available for HBV, although the global prevalence remains high (661). Studies have shown that infection-related cancers, such as those related to the human papillomavirus (HPV), are also more prevalent amongst PLWH (663,664). HPV causes most cervical cancers, as well as many cancers of the anus, rectum, vagina, vulva, penis, and oropharynx. With the introduction of a vaccine for HPV, however, some of these HPV-associated cancers are now potentially preventable (663). Whist the introduction of ART reduced the risk of ADCs through improvements in immune function, it may also reduce the risk of NADCs through reducing HIV-associated

inflammation and coagulation (665–667). On the other hand, whilst ART is effective at improving immune function and lowering HIV VL, it is a lifelong commitment and there are long-term toxicities associated with ART use (331). Previous studies have shown that older PIs, for example, have been associated with an increased risk of anal cancer (668–670). No other associations between ART and NADCs have been reported; however, as cancer is a relatively rare outcome that develops over many years, there are few large studies assessing whether more contemporary ARVs are associated with an increased risk of NADCs or whether cancer trends have changed throughout different ART-eras, for example before and after second generation INSTIs were introduced.

As lifestyle factors and ART use have changed over time, it is likely that cancer trends differ between different types of cancers, for example cancers related to BMI, to smoking, or to infection. It is therefore important for analyses assessing changes in cancer incidence to look at these groups of cancers separately. Whilst it may appear that there is no change in the incidence of cancer over time, it could be that the incidence of infection-related cancers is decreasing over time, whilst the incidence of BMI-related cancers may be increasing.

As treatment for some cancers has improved over time, age-standardised mortality due to cancer has decreased (671). In the USA, the rate of death due to cancer has decreased by 1.4% per-year in females and 1.8% per-year in males from 2001-2018 (672). Globally, the age-standardised death rate has decreased by 15% from 1990-2017, although the change in death over time differs between countries and between different types of cancers, for example death due to stomach cancer has substantially decreased globally from 19.3/100,000 individuals in 1990 to 11.0/100,000 in 2017, whilst death due to liver cancer has only slightly decreased from 10.8/100,000 in 1990 to 10.2/100,000 in 2017, and death due to pancreatic cancer has slightly increased from 5.1/100,000 in 1990 to 5.6/100,000 in 2017 (673).

For this Chapter, I combined data from RESPOND including follow-up from 2012-2019 with data from the D:A:D study including follow-up from 2004-2016 to assess cancer

trends over time. D:A:D and RESPOND use the same underlying methodology and collect similar data. Additionally, many cohorts contributed data to both collaborations. By using data from both studies and including a longer follow-up, the chapter focuses both on overall cancer trends and a comparison of cancer trends across different ART-eras.

6.1.1 Aims

The aims of this chapter are to:

(iii) assess changes in overall cancer incidence from 2004-2016 in D:A:D and 2012-2019 in RESPOND;

(iv) assess whether cancer trends differ between specific subtypes of cancers, including infection-related cancers, BMI-related cancers, and smoking-related cancers;

(v) compare cancer trends between different subgroups of the D:A:D and RESPOND populations;

(vi) assess whether the incidence of death due to cancer has increased from 2004-2016 in D:A:D and 2012-2019 in RESPOND.

6.2 Methods

This analysis was performed on the final merger 17 of the D:A:D database with a data cut-off of 1st February 2016 and on the third update (version DS2) of the RESPOND database with a data cut-off of 31st December 2019. Database versions for RESPOND and D:A:D are explained further in Chapter 3, Section 3.1.4 and Section 3.2, respectively.

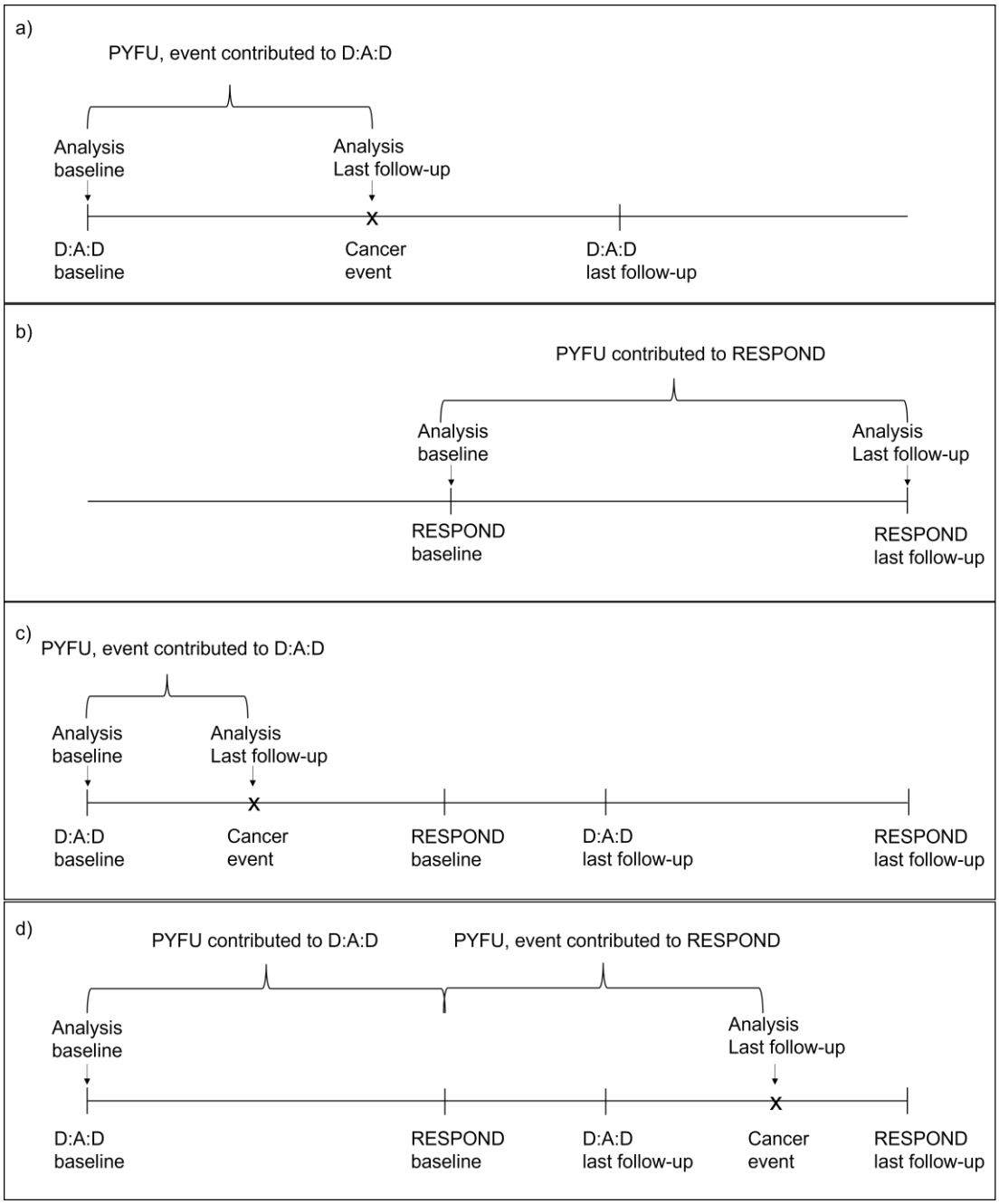
For D:A:D, baseline was defined as the latest of date of entry into D:A:D and 1st January 2004, when systematic collection of cancer events was initiated. Individuals were followed until the earliest of first cancer event or 6 months after last clinic visit (as has been used in previous D:A:D analyses (479)). If this date was after the data cut-off, individuals were censored at 1st February 2016. Six months after last clinic visit was used to define last follow-up for D:A:D as some cohorts in D:A:D captured

mortality data from national surveillance datasets. Therefore, to ensure follow-up was not artificially extended for individuals who were lost to follow-up from their clinic but had a date of death in national datasets, all individuals were censored 6 months after last clinic visit and only deaths which occurred within this timeframe were included.

For RESPOND, baseline was defined as the latest of local cohort enrolment and 1st January 2012. Individuals were followed until the earliest of first cancer event or final-follow up, with final follow-up defined as the latest of the most recent CD4 count, VL measurement, or ART start date, drop out date as defined by the local cohort, or date of death. If this date was after the data cut-off, individuals were censored at 31st December 2019.

Individuals who were included in both D:A:D and RESPOND were followed from the earliest of D:A:D baseline or RESPOND baseline until the latest of D:A:D final follow-up or RESPOND final follow-up. Figure 6.2 shows how events and follow-up were assigned to D:A:D and RESPOND depending on whether a participant was enrolled in D:A:D only, RESPOND only, or both collaborations.

Figure 6.2 Participant follow-up for: a) an individual only enrolled in D:A:D; b) an individual only enrolled in RESPOND; c) an individual enrolled in D:A:D and RESPOND with an event prior to RESPOND baseline; d) an individual enrolled in D:A:D and RESPOND with an event after RESPOND baseline



6.2.1 Inclusion criteria

The inclusion criteria for RESPOND is detailed in Chapter 3, Section 3.1.3 and for D:A:D has been published previously (446) (available at: https://chip.dk/Research/Studies/DAD/Study-Documents). For this analysis, individuals from RESPOND and D:A:D were included if they:

(i) were aged 18 years or older at baseline;
(ii) had any follow-up data.

Additionally, individuals from RESPOND were excluded if they did not have a CD4 count and VL measurement either 1 year prior to or within 12 weeks after baseline, or if they had missing information on gender. These exclusion criteria were not applied to individuals from D:A:D as this has not been done in previous D:A:D analyses, however, for consistency, I performed a sensitivity analysis applying the same exclusion criteria to individuals from D:A:D as well.

6.2.2 Outcomes

The primary outcome was any incident cancer during follow-up. Pre-cancers, relapse of a primary cancer, and basal or squamous cell skin cancers were not collected. The definition and methodology of cancers is similar in both D:A:D and RESPOND; further detail on the cancer definition is provided in the RESPOND and D:A:D manual of operations (490,674). Individuals who had cancer prior to baseline were included in the main analysis. For these individuals, cancer during follow-up was only counted if the type of cancer during follow-up was different from the one which occurred prior to baseline, for example anal cancer before baseline and Hodgkin lymphoma after baseline. If the type of cancer prior to baseline was unknown, no cancers during follow-up were counted. A sensitivity analysis was performed excluding individuals with any cancer prior to baseline.

Cancers were split into ADCs and NADCs, and were separately categorised into infection-related cancers, smoking-related cancers, and BMI-related cancers. Cancers included in each category are shown in Table 6.4 and Table 6.5 below. These

categories were chosen by a cancer working group and confirmed by an external oncologist. Each cancer type could be included in more than one category, if appropriate, for example colon cancer was included as a smoking-related cancer and a BMI-related cancer. As each cancer category was analysed independently, including the same cancers in multiple categories did not bias the results.

The final outcome was death due to cancer. Causes of death are classified using the Coding Of causes of Death Form (CoDE). As detailed in Chapter 3, Section 3.1.4, the CoDE form provides a standardised method for identifying causes of death in PLWH across the clinics (497). For this outcome, individuals were followed from baseline until earliest of final follow-up (as defined above in Section 6.2) or 1st February 2016 for individuals in D:A:D or 31st December 2019 for individuals in RESPOND.

6.2.3 Potential confounders

All potential confounders considered in this analysis are described in Table 6.1. The same confounders were adjusted for in both D:A:D and RESPOND. Age, gender, HIV risk group, ethnicity, CD4 cell nadir, CD4 count, prior ART-experience and viral suppression status, and geographical region, were all defined prior to or at baseline. The remaining confounders were fitted as time-updated variables.

Table 6.1 Potential confounders considered in analyses

Variable	Categories	Comments
Age	Continuous (per 10 years later)	
Gender	Male; female	
HIV risk group	MSM; IDU; heterosexual sex; other; unknown or missing	
Ethnicity	White; Black; other; unknown or missing	Some cohorts were prohibited from reporting ethnicity
Body mass index[1]	<18.5 kg/m^2; 18.5-<25 kg/m^2; ≥25 kg/m^2; missing	
Smoking status[1]	Past; current; never; unknown or missing	
CD4 cell nadir prior to baseline	Continuous (per 100 cells increase)	Taken as the lowest CD4 count prior to baseline. If no CD4 count was measured, the first measurement within 12 weeks after baseline was used
CD4 count at baseline	Continuous (per 100 cells increase)	Taken as the most recent CD4 count within 12 months prior to baseline. If no CD4 count was measured, the first measurement within 12 weeks after baseline was used (median difference between CD4 count and baseline = 35 days)
Prior ART-experience and viral suppression status at baseline	ART-naïve; ART-experienced with VL <200 copies/mL; ART-experienced with VL ≥200 copies/mL	VL was taken as the most recent VL within 12 months before baseline. If no VL was measured prior to baseline, the first measurement within 12 weeks after baseline was used (median difference between VL and baseline = 33 days)
Viral hepatitis C[1]	No; yes; unknown	Defined by use of anti-HCV medication, a positive HCV antibody test, a positive HCV RNA qualitative test, HCV RNA >615 IU/mL, and/or a positive genotype test
Viral hepatitis B[1]	No; yes; unknown	Defined by a positive HBV surface antigen test and/or HBV DNA >357 IU/mL
Hypertension[1]	No; yes; unknown	Confirmed by use of anti-hypertensives at any time before baseline or if the most recent systolic or diastolic blood pressure measurement before baseline was higher than 140 or 90 mmHg, respectively

Diabetes[1]	No; yes; unknown[2]	Defined as reported diabetes diagnosis or use of antidiabetic medication (490)
Prior AIDS (non-cancer)[1]	No; yes; unknown	Composite diagnosis as defined by the CDC list of AIDS-defining conditions (547,548)
Prior AIDS cancer[1]	No; yes; unknown[2]	Composite diagnosis of Kaposi's sarcoma, non-Hodgkin lymphoma, cervical cancer (490)
Prior non-AIDS defining cancer[1]	No; yes; unknown[2]	Any non-AIDS cancer, excluding skin cancers (expect malignant melanoma) and pre-cancers (490)
Prior end stage liver disease[1]	No; yes; unknown[2]	Composite diagnosis of ascites (where extrahepatic reasons are excluded), hepatic encephalopathy grade III-IV, hepatorenal syndrome, endoscopically verified variceal bleeding, spontaneous bacterial peritonitis, liver transplantation (490)
Prior end stage renal disease[1]	No; yes; unknown[2]	Composite diagnosis of dialysis more than three months or kidney transplant (490)
Prior cardiovascular disease[1]	No; yes; unknown	Composite diagnosis of myocardial infarction, stroke or invasive cardiovascular procedure (675)
Prior chronic kidney disease[1]	No; yes; unknown	Two consecutive measurements of eGFR measured at least 3 months apart $\leq$60 mL/min if the first eGFR was >60 mL/min or a 25% decline if first eGFR was <60 mL/min. eGFR was calculated using the CKD-EPI creatinine equation in RESPOND and the CG formula in D:A:D (550,676)
Prior dyslipidaemia[1]	No; yes; unknown[2]	Defined as total cholesterol>239.4mg/dL or HDL cholesterol<34.7mg/dL or triglyceride >203.55mg/dL or use of lipid lowering treatments (621)
Geographical region	Western Europe; Northern Europe/Australia; Southern Europe; Eastern/East Central Europe; USA	Due to low numbers, Australia was combined with Northern Europe in the analysis models, Eastern Central Europe was combined with Eastern Europe, and USA was combined with Western Europe. For further details, see Chapter 3, Table 3.1 footnote.
Exposure to protease inhibitors[1]	No; yes	
Exposure to integrase strand transfer inhibitors[1]	No; yes	

Exposure to non-nucleoside reverse transcriptase inhibitors[1]	No; yes	

Abbreviations: MSM – men who have sex with men; IDU – injecting drug use; RNA - ribonucleic acid; CKD – chronic kidney disease; eGFR - estimated glomerular filtration rate; CKD-EPI - Chronic Kidney Disease Epidemiology Collaboration; CG – Cockcroft-Gault; HDL - high-density lipoproteins;
Continuous variables were checked to see if there was a linear relationship with the outcome before fitting as continuous
[1]Variables were fitted as time-updated in analysis models
[2]Unknown category was only reported for participants in RESPOND

6.2.4 Statistical methods

I initially combined data from D:A:D and RESPOND into one dataset. Multiple cohorts in the collaborations had contributed data from the same individuals into D:A:D and RESPOND. These cohorts were contacted, and they all supplied the participant IDs for individuals doubly enrolled so that they could be identified in the datasets. Their data from the two cohorts was combined to ensure they were not included in analyses twice. For individuals with conflicting data in the two collaborations, I used data from D:A:D until the date of RESPOND baseline and then used data from RESPOND thereafter. For example, if systolic blood pressure measurements differed between those reported in the D:A:D data and those reported in the RESPOND data, or if there were additional systolic blood pressure measurements included in one of the datasets, I included all systolic blood pressure measurements recorded in the D:A:D data from D:A:D baseline until RESPOND baseline, and included the measurements recorded in the RESPOND data from RESPOND baseline onwards.

I summarised the baseline characteristics of all participants included in the analysis and compared them between participants enrolled in D:A:D, participants enrolled in RESPOND, and those enrolled in both collaborations. Additionally, I compared baseline characteristics between those who went on to have cancer during follow-up and those who did not.

The crude incidence and age-standardised incidence of any cancer during follow-up was estimated for the following time periods: 2004-2005, 2006-2007, 2008-2009, 2010-2011, 2012-2013, 2014-2015, 2016-2017, and 2018-2019. Incidence rates were

standardised according to the age distribution of the combined D:A:D and RESPOND cohorts in 2015 (677). Confidence intervals for standardised incidence rates were calculated using Dobson's method (678).

I used Poisson regression to assess the association between cancer incidence and calendar year of follow-up, adjusted for potential confounders, listed in Table 6.1. As clinical events were fitted as time-updated, and the incidence of several of these, in particular AIDS events, are affected by CD4 count and VL, CD4 count and VL were fixed at baseline. Additionally, as prior ART-experience and viral suppression status was correlated with exposure to PIs, INSTIs, and NNRTIs, the primary model only included ART-experience and viral suppressions status. I then ran another model excluding ART-experience but including time-updated exposure to PIs, INSTIs, and NNRTIs, and including baseline VL as a continuous variable. I also reran the primary model with all confounders fixed at baseline.

Crude and age-standardised incidence rates were calculated separately for ADCs and NADCs, and for smoking-related cancers, infection-related cancers, and BMI-related cancers. Adjusted Poisson regression models were also rerun for each of these cancer types.

Analyses were repeated only including events which had been centrally validated; this included all events in D:A:D with a case report form which were then validated, and only events in RESPOND which occurred during the RESPOND validation period (defined as 12 months prior to the last local cohort visit before RESPOND enrolment onwards).

I carried out several subgroup analyses to assess whether cancer trends over time differed according to gender, ethnicity, age, HIV risk group, region, ART exposure and viral suppression status, CD4 nadir, immunosuppression status (defined as CD4 count below 350 cells/mm^3), or whether individuals had hepatitis B, hepatitis C, or a prior AIDS event. These were done by including an interaction between time period and the subgroup of interest in the Poisson regression models, adjusted for age.

To compare cancer trends between different ART-eras, I compared the incidence of each type of cancer between individuals in D:A:D, who were generally treated with older ARVs, and individuals in RESPOND who were generally treated with more contemporary ARVs. I also compared cancer trends before and after 2014, as DTG, the first 2nd generation INSTI, was approved in 2014.

Finally, the crude and age-standardised incidence of death due to cancer was calculated in each time period.

In all analyses, missing data for categorical variables was accounted for by including an unknown category in the regression models. The analysis was then repeated using complete case analysis where individuals with missing data on any variables included in the multivariable Poisson regression model were excluded.

Analyses were performed using Stata/SE 17.0 (StataCorp LLC). All p-values are two sided with a p-value <0.05 defined as statistically significant.

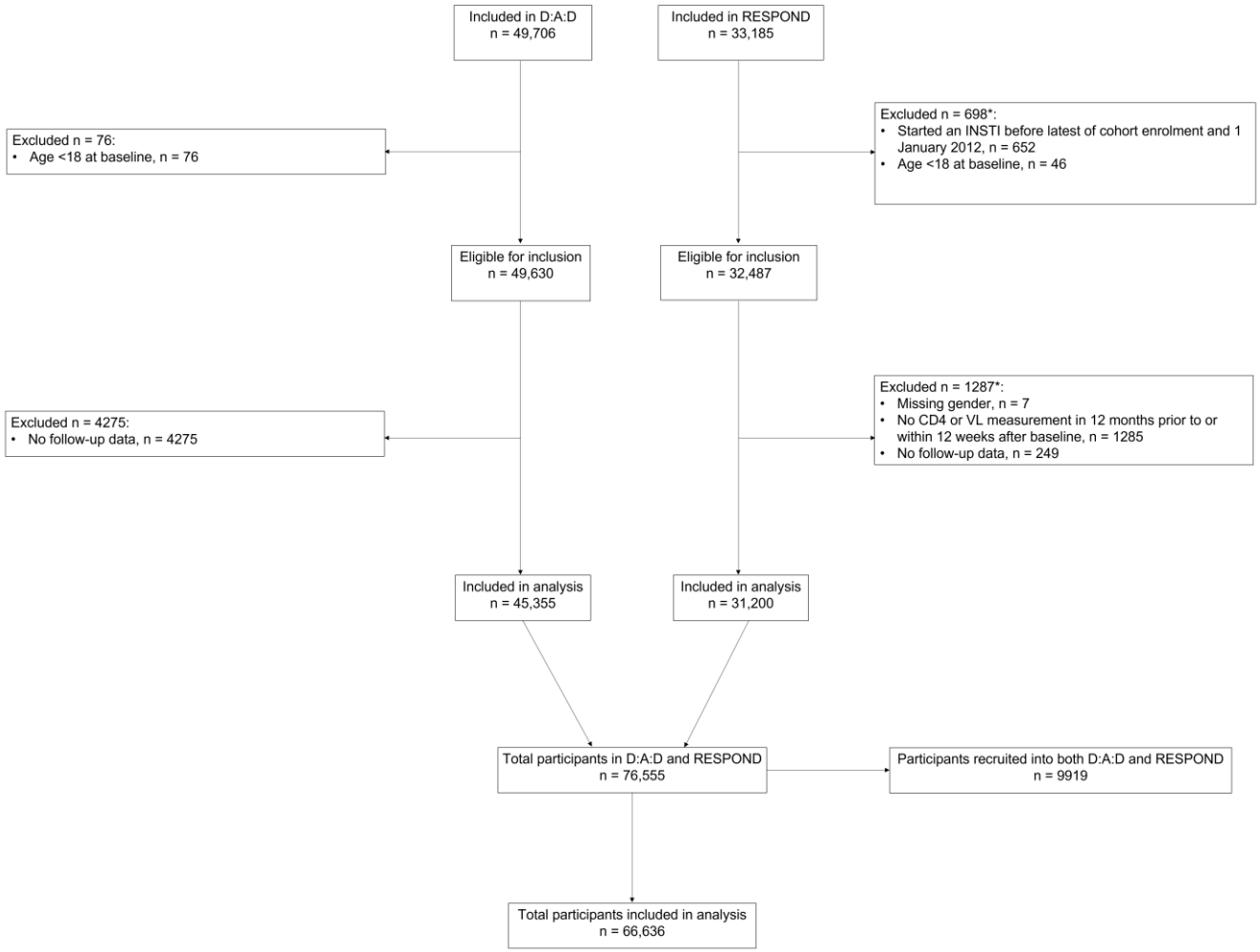
6.3 Results

6.3.1 Participants included

There were 49,706 participants from 11 cohorts included in merger 17 of the D:A:D database and 33,185 participants from 17 cohorts included in version DS2 of the RESPOND database. In total, 7 cohorts recruited participants into both D:A:D and RESPOND.

Of 49,630 eligible participants in D:A:D, 45,355 (91.4%) were included in the analysis. All participants excluded from D:A:D did not have any follow-up data after baseline. Of 32,487 eligible participants in RESPOND, 31,200 (96.0%) were included in the analysis. The reasons for exclusion from the analysis for RESPOND participants were as follows (more than one reason could apply): 1285 did not have a CD4 count or VL measured in the 12 months prior to or within 12 weeks after baseline, 249 had no follow-up data, and 7 were missing information on gender. Overall, there were 9919 participants enrolled in both D:A:D and RESPOND. Therefore, there was a total of 66,636 participants included in the analysis. The study flow for this chapter is shown in Figure 6.3.

Figure 6.3 Study flow for the analysis



6.3.2 Baseline characteristics

Baseline characteristics of individuals included in the analysis are shown in Table 6.2, and compared between those in RESPOND, those in D:A:D, and those recruited into both cohort collaborations. Median baseline age overall was 41 years (interquartile range, IQR, 34-48) and 74% of individuals were male. Just over one third of individuals were ART-naïve (35% ART-naïve, 46% ART-experienced with VL<200 copies/mL, 18% ART-experienced with VL≥200 copies/mL). Approximately half of participants were either current or previous smokers (24% never smokers, 34% current smokers, 13% previous smokers, 29% unknown) and 63% had a prior comorbidity.

Participants in D:A:D were younger than those in RESPOND (median [IQR] age 41 [34-47] years in D:A:D vs 43 [34-50] in RESPOND vs 40 [34-47] in both; p<0.0001) and baseline VL was higher in D:A:D (400 [50-24700] copies/mL in D:A:D vs 68 [36-33601] in RESPOND vs 50 [50-6540] in both; p=0.0001; Table 6.2). There was also a higher proportion of current smokers in D:A:D, although a higher proportion of participants in RESPOND have unknown smoking status (38% current smokers in D:A:D vs 24% in RESPOND vs 39% in both; p<0.0001), and a higher proportion in D:A:D had a prior comorbidity (66% in D:A:D vs 52% in RESPOND vs 81% in both; p<0.0001); the proportion of participants with each comorbidity is shown in Figure 6.4.

Table 6.2 Baseline characteristics, overall and by cohort

		Overall (n=66,636)		Only in D:A:D (n=35,436)		Only in RESPOND (n=21,281)		In both cohorts (n=9919)	
		n	(%)	n	(%)	n	(%)	n	(%)
Gender	Male	49425	(74.2)	26175	(73.9)	16077	(75.5)	7173	(72.3)
	Female	17159	(25.8)	9255	(26.1)	5175	(24.3)	2729	(27.5)
	Transgender	45	(0.1)	0*	(0.0)	29	(0.1)	16	(0.2)
Ethnicity	White	37193	(55.8)	15268	(43.1)	14585	(68.5)	7340	(74.0)
	Black	6505	(9.8)	3088	(8.7)	2272	(10.7)	1145	(11.5)
	Other	2354	(3.5)	936	(2.6)	1088	(5.1)	330	(3.3)
	Unknown^	20584	(30.9)	16144	(45.6)	3336	(15.7)	1104	(11.1)
Body mass index (kg/m^2)	<18.5	2762	(4.1)	1821	(5.1)	542	(2.5)	399	(4.0)
	18.5-<25	32789	(49.2)	20354	(57.4)	6573	(30.9)	5862	(59.1)
	25-<30	3102	(4.7)	1775	(5.0)	858	(4.0)	469	(4.7)
	30+	12130	(18.2)	7208	(20.3)	2827	(13.3)	2095	(21.1)
	Unknown	15853	(23.8)	4278	(12.1)	10481	(49.3)	1094	(11.0)
Geographical Region	Western Europe	25584	(38.4)	11619	(32.8)	8913	(41.9)	5052	(50.9)
	Southern Europe	12077	(18.1)	5437	(15.3)	5121	(24.1)	1519	(15.3)
	Northern Europe	20475	(30.7)	13381	(37.8)	5464	(25.7)	1630	(16.4)
	East Central Europe	2084	(3.1)	696	(2.0)	511	(2.4)	877	(8.8)
	Eastern Europe	3075	(4.6)	1349	(3.8)	1222	(5.7)	504	(5.1)
	Australia	798	(1.2)	414	(1.2)	47	(0.2)	337	(3.4)
	USA	2321	(3.5)	2321	(6.5)	0	(0.0)	0	(0.0)
HIV risk	MSM	29892	(44.9)	15763	(44.5)	9684	(45.5)	4445	(44.8)
	IDU	9247	(13.9)	5086	(14.4)	2868	(13.5)	1293	(13.0)

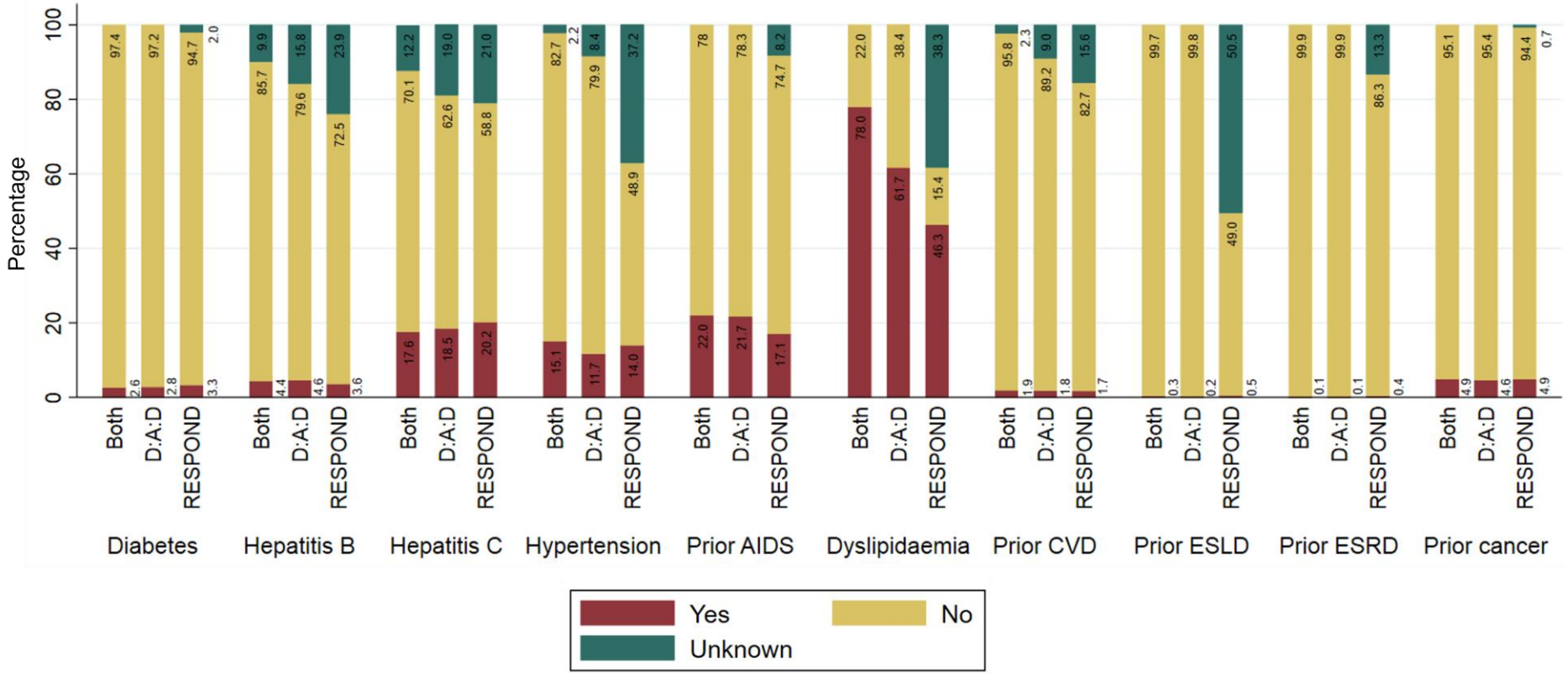
	Heterosexual	22561	(33.9)	11656	(32.9)	7311	(34.4)	3594	(36.2)
	Other	1411	(2.1)	694	(2.0)	502	(2.4)	215	(2.2)
	Unknown	3525	(5.3)	2237	(6.3)	916	(4.3)	372	(3.8)
Smoking status	Never	16211	(24.3)	8625	(24.3)	4579	(21.5)	3007	(30.3)
	Current	22487	(33.7)	13559	(38.3)	5054	(23.7)	3874	(39.1)
	Previous	8506	(12.8)	5588	(15.8)	776	(3.6)	2142	(21.6)
	Unknown	19432	(29.2)	7664	(21.6)	10872	(51.1)	896	(9.0)
ART treatment history	Naïve	22983	(34.5)	12788	(36.1)	7834	(36.8)	2361	(23.8)
	Experienced, VL<200 cps/mL	30425	(45.7)	14202	(40.1)	10773	(50.6)	5450	(54.9)
	Experienced, VL≥200 cps/mL	11995	(18.0)	7423	(20.9)	2674	(12.6)	1898	(19.1)
Prior exposure to INSTIs	Yes	73	(0.1)	71	(0.2)	1	(0.0)	1	(0.0)
Prior exposure to PIs	Yes	30820	(46.3)	15491	(43.7)	9579	(45.0)	5750	(58.0)
Prior exposure to NNRTIs	Yes	28843	(43.3)	15447	(43.6)	8812	(41.4)	4584	(46.2)
Continuous variables		**Median**	**(IQR)**	**Median**	**(IQR)**	**Median**	**(IQR)**	**Median**	**(IQR)**
Baseline date, month/year		12/05	(01/04, 01/12)	01/04	(01/04, 12/05)	01/12	(01/12, 10/14)	01/04	(01/04, 05/06)
Age, years		40.9	(34.3, 48.1)	40.5	(34.2, 47.0)	42.6	(34.3, 50.0)	40.3	(34.3, 46.8)
CD4 cell nadir, cells/mm^3		250	(116, 409)	240.0	(106, 400)	268	(132, 436)	238	(120, 375)
CD4 at baseline, cells/mm^3		455	(295, 647)	430	(272, 619)	506	(335, 698)	442	(300, 629)
Viral load at baseline, copies/mL		178	(50, 23500)	400	(50, 24700)	68	(36, 33601)	50	(50, 6540)

Total duration of previous ART, years	5.6	(2.1, 8.5)	5.6	(2.4, 7.8)	5.5	(1.7, 12.2)	5.6	(2.1, 7.8)

*Transgender was not collected in D:A:D

^Some cohorts were prohibited from reporting ethnicity.

Figure 6.4 Comorbidities experienced prior to baseline for individuals included in the analysis, split by cohort



Abbreviations: CVD-cardiovascular disease; ESLD-end stage liver disease; ESRD-end stage renal disease

When comparing baseline characteristics of participants who went on to develop a cancer during follow-up versus those who did not develop cancer, those with cancer were older at baseline (median age 46 [40-54] years cancer vs 41 [34-48] years no cancer; p<0.0001) and had a slightly lower median CD4 count at baseline (median 416 cells/mm^3 [240-620] vs 458 [299-649], p<0.0001). Additionally, a higher proportion of those who developed a cancer were current and previous smokers (42% current smokers, 17% previous smokers for those who had cancer vs 33% current smokers, 13% previous smokers for those who did not; p<0.0001), and a higher proportion had a prior AIDS event (28% vs 20%, p<0.0001) and prior comorbidities including prior cancer (8% vs 5%; p<0.0001). Baseline demographic and clinical characteristics are shown in Table 6.3.

Table 6.3 Baseline demographic and clinical characteristics, split by those who had cancer during follow-up and those who did not

		Cancer during follow-up (n=3634)		No cancer during follow-up (n=63,002)	
		n	(%)	n	(%)
Gender	Male	2910	(80.1)	46515	(73.8)
	Female	723	(19.9)	16436	(26.1)
	Transgender	1	(0.0)	44	(0.1)
Ethnicity	White	1969	(54.2)	35224	(55.9)
	Black	159	(4.4)	6346	(10.1)
	Other	51	(1.4)	2303	(3.7)
	Unknown	1455	(40.0)	19129	(30.4)
Body mass index (kg/m^2)	<18.5	219	(6.0)	2543	(4.0)
	18.5-<25	1955	(53.8)	30834	(48.9)
	25-<30	137	(3.8)	2965	(4.7)
	30+	692	(19.0)	11438	(18.2)
	Unknown	631	(17.4)	15222	(24.2)
Geographical Region	Western Europe	1513	(41.6)	24071	(38.2)
	Southern Europe	635	(17.5)	11442	(18.2)
	Northern Europe	1272	(35.0)	19203	(30.5)
	East Central Europe	115	(3.2)	1969	(3.1)
	Eastern Europe	40	(1.1)	3035	(4.8)
	Australia	46	(1.3)	752	(1.2)
	USA	12	(0.3)	2309	(3.7)
HIV risk	MSM	1780	(49.0)	28112	(44.6)
	IDU	563	(15.5)	8684	(13.8)
	Heterosexual	1039	(28.6)	21522	(34.2)
	Other	83	(2.3)	1328	(2.1)
	Unknown	169	(4.7)	3356	(5.3)
Smoking status	Never	729	(20.1)	15482	(24.6)
	Current	1515	(41.7)	20972	(33.3)
	Previous	600	(16.5)	7906	(12.5)
	Unknown	790	(21.7)	18642	(29.6)
ART treatment history	Naive	1081	(29.7)	21902	(34.8)
	Experienced, VL<200 cps/mL	1703	(46.9)	28722	(45.6)
	Experienced, VL≥200 cps/mL	773	(21.3)	11222	(17.8)
Prior exposure to INSTIs	Yes	7	(0.2)	66	(0.1)
Prior exposure to PIs	Yes	1976	(54.4)	28844	(45.8)
Prior exposure to NNRTIs	Yes	1707	(47.0)	27136	(43.1)
Prior AIDS	No	2551	(70.2)	48806	(77.5)

	Yes	1000	(27.5)	12536	(19.9)
	Unknown	83	(2.3)	1660	(2.6)
Prior cancer	No	3342	(92.0)	59986	(95.2)
	Yes	290	(8.0)	2870	(4.6)
	Unknown	2	(0.1)	146	(0.2)
Prior comorbidity	No	649	(17.9)	13101	(20.8)
	Yes	2667	(73.4)	39567	(62.8)
	Unknown	318	(8.8)	10334	(16.4)
Continuous variables		**Median**	**IQR**	**Median**	**IQR**
Baseline date, month/year		01/04	(01/04, 02/08)	01/06	(01/04, 01/12)
Age, years		46.0	(39.7, 54.4)	40.6	(34.0, 47.7)
CD4 cell nadir, cells/mm³		196	(77, 346)	252	(120, 410)
CD4 at baseline, cells/mm³		416	(240, 620)	458	(299, 649)
Viral load at baseline, copies/mL		194	(50, 34100)	177	(50, 23000)
Total duration of previous ART, years		7.0	(4.2, 10.2)	5.7	(2.4, 8.5)

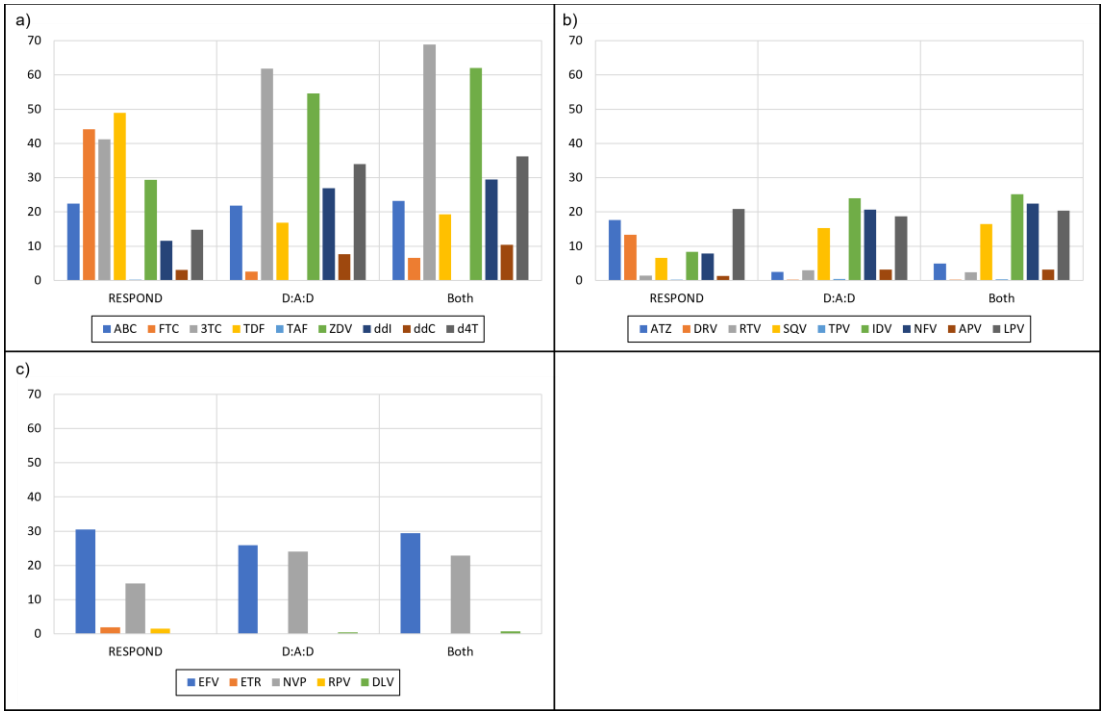
6.3.3 ART exposure

As mentioned above, approximately one third of participants were ART-naïve at baseline and this proportion was similar in D:A:D and RESPOND (36.1% D:A:D vs 36.8% RESPOND). As part of the inclusion criteria for RESPOND, participants cannot have started an INSTI prior to baseline, hence no RESPOND participants had prior INSTI exposure. Median baseline in D:A:D was January 2004 which is before any INSTIs were approved by the EMA and therefore only 0.2% of individuals in D:A:D had exposure to INSTIs prior to baseline. Just under half of participants had prior exposure to PIs and NNRTIs and this was similar in D:A:D and RESPOND (prior exposure to PIs in D:A:D 43.7% vs 45.0% in RESPOND; prior exposure to NNRTIs in D:A:D 43.6% vs 41.4% in RESPOND).

Figure 6.5 shows the proportion of individuals exposed to each NRTI, PI, and NNRTI, prior to baseline, stratified by cohort. The most common NNRTIs were efavirenz (27.9% participants exposed) and nevirapine (20.9%), and this was similar across D:A:D and RESPOND. The most common PIs prescribed prior to baseline were ritonavir-boosted lopinavir (19.7%), indinavir (19.2%), and nelfinavir (16.8%), however this differed between individuals in D:A:D and RESPOND. The same 3 PIs

were the most common in D:A:D (24.0% exposed to indinavir, 20.7% nelfinavir, and 18.7% ritonavir-boosted lopinavir); in RESPOND the most common PIs were ritonavir-boosted lopinavir (20.9%), atazanavir (17.6%), and darunavir (13.3%). The most common NRTIs prescribed were lamivudine (56.2%), zidovudine (47.6%), and stavudine (28.2%). Again, these 3 NRTIs were the most common NRTIs just amongst those enrolled in D:A:D (61.8% lamivudine, 54.6% zidovudine, and 34.0% stavudine), however in RESPOND, the most common NRTIs were tenofovir disoproxil fumarate (48.9%), emtricitabine (44.1%), and lamivudine (41.2%).

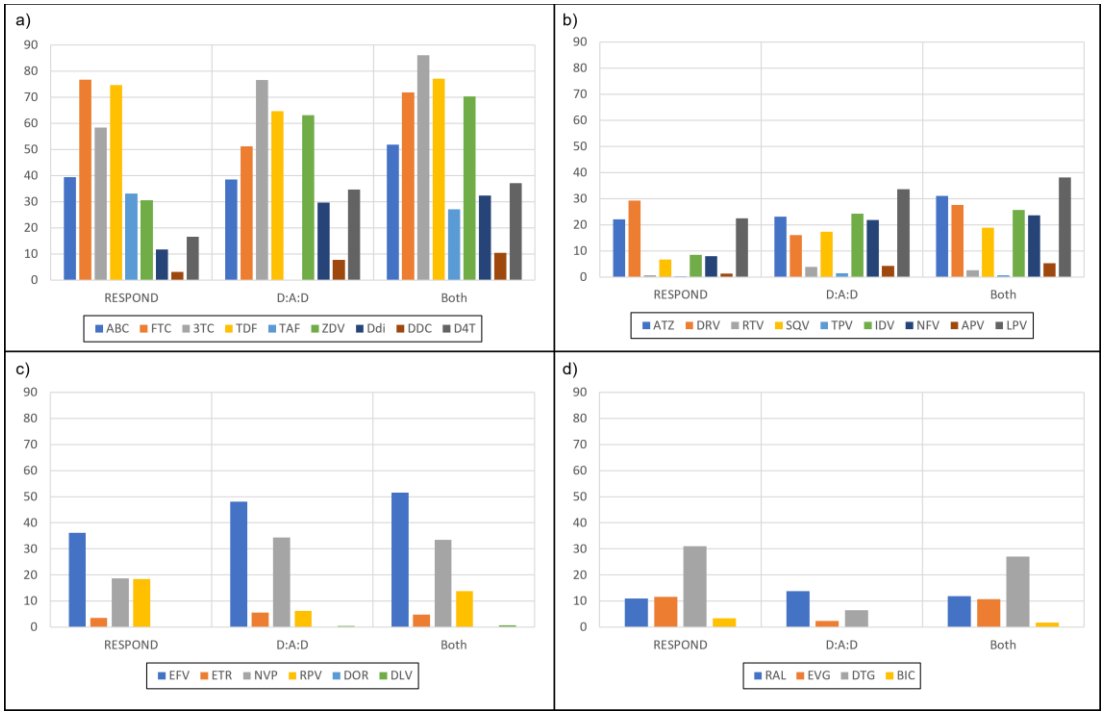
Figure 6.5 Exposure to antiretroviral therapy prior to baseline: a) nucleoside reverse transcriptase inhibitors; b) protease inhibitors; c) non-nucleoside reverse transcriptase inhibitors



Abbreviations: ABC-abacavir; FTC-emtricitabine; 3TC-lamivudine; TDF-tenofovir disoproxil fumarate; TAF-tenofovir alafenamide; ZDV-zidovudine; ddI-didanosine; ddC-zalcitabine; d4T-stavudine; ATZ-atazanavir; DRV-darunavir; RTV-ritonavir; SQV-saquinavir; TPV-tipranavir; IDV-indinavir; NFV-nelfinavir; APV-amprenavir; LPV-lopinavir; EFV-efavirenz; ETR-etravirine; NVP-nevirapine; RPV-rilpivirine; DLV-delavirdine.
RTV only recorded when used as a 3rd drug rather than a pharmacokinetic booster

Figure 6.6 shows the proportion of individuals exposed to each NRTI, PI, NNRTI, and INSTI, by the end of follow-up, split by cohort. By the end of follow-up, 68.2% of participants had been prescribed a NNRTI, 66.3% a PI, and 32.4% an INSTI. Additionally, 94.3% of participants had been prescribed an NRTI. As with exposure prior to baseline, the most common NNRTIs were efavirenz (44.8% exposed) and nevirapine (29.2%), and this was similar across the collaborations. The most common PIs were ritonavir-boosted lopinavir (30.7%), atazanavir (23.9%), and darunavir (21.9%); in D:A:D, the most common PIs were ritonavir-boosted lopinavir (33.6%), indinavir (24.3%), and atazanavir (23.1%), whereas in RESPOND, the most common PIs were darunavir (29.2%), ritonavir-boosted lopinavir (22.4%), and atazanavir (22.0%). Dolutegravir (17.4%) and raltegravir (12.7%) were the most common INSTIs and this was the same across D:A:D and RESPOND. Finally, the most common NRTIs were lamivudine (72.2%), tenofovir disoproxil fumarate (69.8%), and emtricitabine (62.5%). In D:A:D, the most common NRTIs were lamivudine (76.6%), tenofovir disoproxil fumarate (64.7%), and zidovudine (63.2%), and in RESPOND, they were emtricitabine (76.8%), tenofovir disoproxil fumarate (74.7%), and lamivudine (58.4%).

Figure 6.6 Exposure to antiretroviral therapy by the end of follow-up: a) nucleoside reverse transcriptase inhibitors; b) protease inhibitors; c) non-nucleoside reverse transcriptase inhibitors; d) integrase inhibitors



RTV only recorded when used as a 3rd drug rather than a pharmacokinetic booster

6.3.4 Cancer trends

Median follow-up for all participants was 7.5 years (IQR 3.8-11.6, total person-years of follow-up, PYFU, 489,856). As expected, follow-up was longest for participants enrolled in both D:A:D and RESPOND (median 13.7 [11.1-15.4]; total PYFU 118,914) compared to those in D:A:D only (median 8.3 [2.9-11.8]; total PYFU 264,423) and RESPOND only (5.3 [3.2-7.4]; total PYFU 106,519).

In total, 3634 individuals developed at least one cancer during follow-up (incidence rate, IR, 7.42/1000 PYFU [95% CI: 7.18-7.66]): 1078 ADCs (IR 2.21/1000 PYFU [2.07-2.34]) and 2556 NADCs (IR 5.22 [5.02-5.42]). The most common cancers were non-Hodgkin lymphoma (n=517), Kaposi's sarcoma (n=473), lung cancer (n=391), and anal cancer (n=269). Table 6.4 and Table 6.5 show the number of each cancer reported, categorised into ADCs, NADCs, infection-related cancers, smoking-related cancers,

and BMI-related cancers (groups are not mutually exclusive). A comparison of cancers between RESPOND and D:A:D is reported in Section 6.3.4.3 below.

Table 6.4 Cancers reported during follow-up, split into AIDS-defining and non-AIDS-defining cancers

AIDS-defining cancers (n=1078)		**Non-AIDS-defining cancers (n=2556)**	
Cancer	**Frequency**	**Cancer**	**Frequency**
Non-Hodgkin Lymphoma	517	Lung cancer	391
Kaposi's Sarcoma	473	Anal cancer	269
Cervical cancer	88	Unknown non-AIDS defining cancer	232
		Prostate cancer	209
		Liver cancer (HCC)	186
		Hodgkin Lymphoma	172
		Head and neck cancer	147
		Breast cancer	105
		Bladder cancer	84
		Colon cancer	83
		Other cancers*	78
		Malignant melanoma	71
		Pancreatic cancer	60
		Kidney cancer	57
		Rectum cancer	44
		Oesophageal cancer	41
		Stomach cancer	39
		Gynaecological cancer	38
		Gall bladder cancer	28
		Brain cancer	25
		Acute myeloid leukaemia	25
		Penile cancer	23
		Testicular seminoma	20
		Unknown primary cancer: metastasis of adenocarcinoma	15
		Multiple myeloma	13
		Unknown primary cancer: metastasis of squamous cell carcinoma	11
		Lip cancer	10
		Unknown primary cancer: metastasis of other cancer type	10
		Connective tissue cancer	8
		Unspecified oropharyngeal cancer	8
		Laryngeal cancer	6
		Acute lymphoid leukaemia	6

	Oral cavity cancer	6
	Chronic myeloid leukaemia	6
	Unspecified leukaemia	5
	Uterus cancer	4
	Thyroid cancer	4
	Chronic lymphoid leukaemia	4
	Saliva gland cancer	3
	Sino/nasal cavity cancer	3
	Bone cancer	3
	Unknown primary cancer: metastasis: unspecified	2
	Rhinopharyngeal cancer	1
	Hypopharyngeal cancer	1

*further detail was not provided

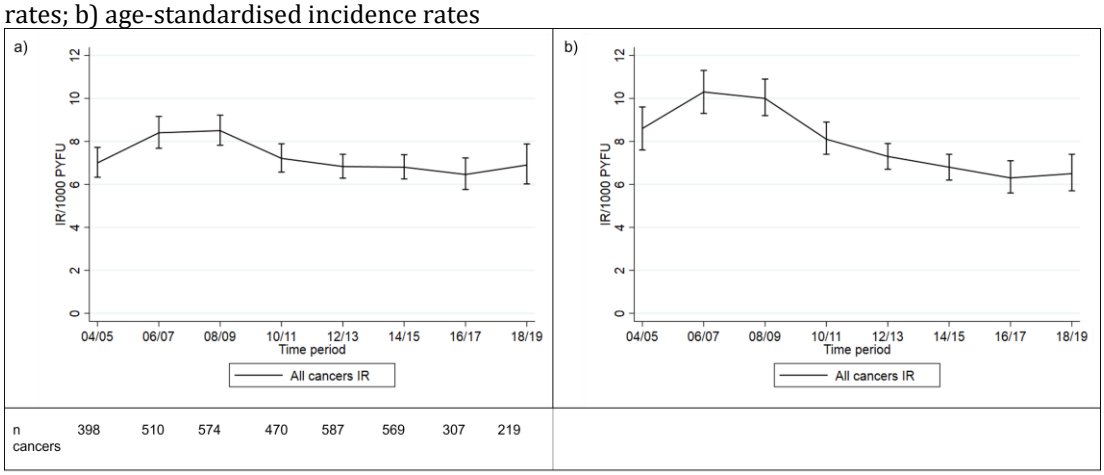
Table 6.5 Cancers reported during follow-up, split by infection-related, smoking-related, and BMI-related cancers

Infection-related cancers (n=1775)		Smoking-related cancers (n=1273)		BMI-related cancers (n=608)	
Cancer	**Frequency**	**Cancer**	**Frequency**	**Cancer**	**Frequency**
Non-Hodgkin Lymphoma	517	Lung cancer	391	Liver cancer (HCC)	186
Kaposi's Sarcoma	473	Liver cancer (HCC)	186	Breast cancer	105
Anal cancer	269	Head and neck cancer	147	Colon cancer	83
Liver cancer (HCC)	186	Cervical cancer	88	Kidney cancer	57
Hodgkin Lymphoma	172	Bladder cancer	84	Pancreatic cancer	60
Cervical cancer	88	Colon cancer	83	Rectum cancer	44
Stomach cancer	39	Pancreatic cancer	60	Oesophageal cancer	41
Penile cancer	23	Kidney cancer	57	Gall bladder cancer	28
Unspecified oropharyngeal cancer	8	Rectum cancer	44	Thyroid cancer	4
		Oesophageal cancer	41		
		Stomach cancer	39		
		Acute myeloid leukaemia	25		
		Unspecified oropharyngeal cancer	8		
		Laryngeal cancer	6		
		Oral cavity cancer	6		
		Saliva gland cancer	3		
		Sino/nasal cavity cancer	3		
		Rhinopharyngeal cancer	1		
		Hypopharyngeal cancer	1		

Figure 6.7 shows the raw and age-standardised IRs for all cancer between 2004 and 2019. The incidence of all cancer was 7.00 (95% CI: 6.33-7.72) in 2004-2005 before rising to 8.40 (7.68-9.16) in 2006-2007. The lower incidence of cancer in 2004-2005 compared to 2006 onwards may be because of delays in event reporting. In D:A:D, cancer event collection began in 2008 and events were retrospectively collected back to 2004. To investigate this further, I assessed IRs, by time period, in each cohort included in D:A:D; I found that whilst the smaller cohorts reported a lower incidence of cancer in 2004-2005, all larger cohorts did not, which suggests there may be an underlying bias in cancer reporting. Therefore, all cancer trends in this section will be described from 2006 onwards.

Between 2006 and 2019, overall raw cancer incidence decreased over time (8.40/1000 PYFU [7.68-9.16] in 2006-2007, 6.90 [6.02, 7.88] in 2018-2019), although the rate of decrease was faster before 2012, after which the incidence rate levelled out. Results were similar after standardising for age.

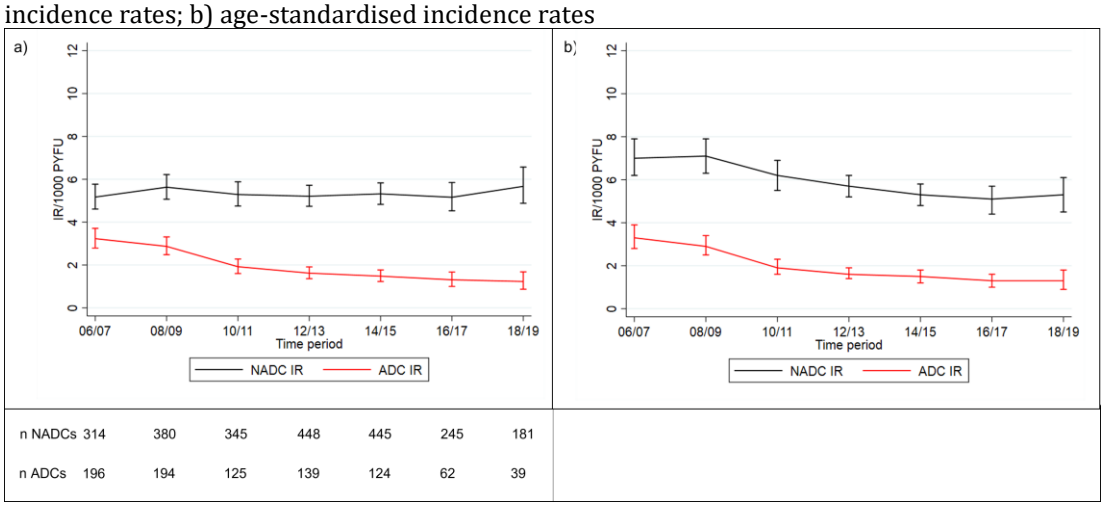
Figure 6.7 Incidence rates and 95% confidence intervals over time for all cancer: a) raw incidence rates; b) age-standardised incidence rates



Vertical bars represent 95% CIs

The raw and age-standardised incidence of cancer, split into ADCs and NADCs, is presented in Figure 6.8. The raw incidence of ADCs decreased over time from 3.23/1000 PYFU [2.79-3.71] in 2006-2007 to 1.23/1000 PYFU [0.87-1.68] in 2018-2019 whilst the incidence of NADCs remained relatively steady (5.17/1000 PYFU [4.61-5.77] in 2006-2007 to 5.67/1000 PYFU [4.88-6.57] in 2018-2019). After standardising the IRs for age, ADCs decreased substantially (3.32 [2.82-3.87] in 2006-2007, 1.29 [0.91-1.77] in 2018-2019) whilst NADCs decreased slightly (6.98 [6.18-7.85] in 2006-2007, 5.25 [4.50-6.08] in 2018-2019).

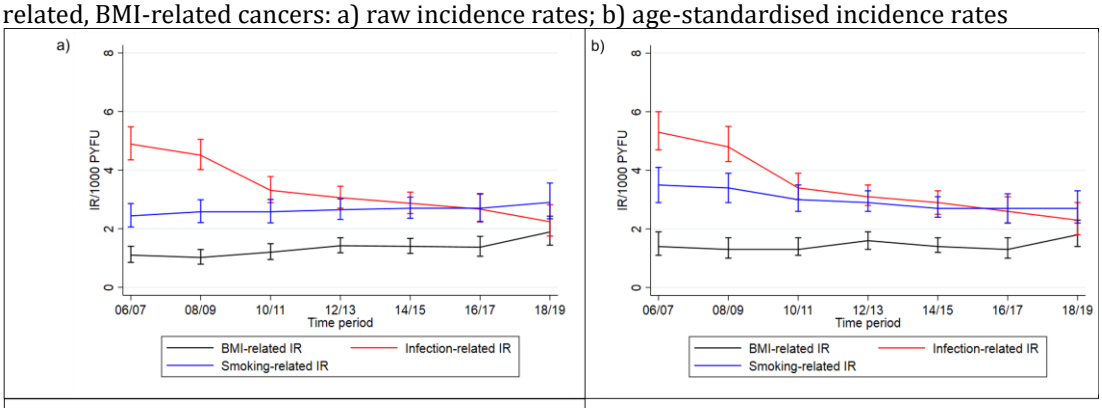
Figure 6.8 Incidence rates and 95% confidence intervals over time for ADCs and NADCs: a) raw incidence rates; b) age-standardised incidence rates



Vertical bars represent 95% CIs

Cancer incidence over time was also compared between infection-related cancers, smoking-related cancers, and BMI-related cancers. The raw incidence of infection-related cancers decreased over time (4.89 [4.35-5.48] in 2006-2007, 2.24 [1.75-2.82] in 2018-2019), whilst the incidence of smoking-related cancers (2.44 [2.06-2.86] in 2006-2007, 2.90 [2.34-3.56] in 2018-2019) and BMI-related cancer (1.10 [0.85-1.40] in 2006-2007, 1.90 [1.44-2.43] in 2018-2019) increased. Results were similar for infection-related cancers and BMI-related cancers after standardising for age, however the age-standardised incidence of smoking-related cancers remained steady over time (Figure 6.9). As liver cancer (n=186) was a major contributor to all three cancer categories, I removed liver cancer from all categories and reran the analyses, with similar results found.

Figure 6.9 Incidence rates and 95% confidence intervals over time for infection-related, smoking-related, BMI-related cancers: a) raw incidence rates; b) age-standardised incidence rates



n BMI-related cancers	67	69	79	123	118	65	61
n infection-related cancers	297	305	216	263	240	127	71
n smoking-related cancers	148	174	168	228	227	129	93

Vertical bars represent 95% CIs

Poisson regression models were then used to assess cancer trends over time after adjusting for demographic, clinical, and HIV and ART-related factors (Table 6.6). In these models, time period was fitted as a continuous variable. Results from these models showed that the adjusted incidence of overall cancer decreased slightly over time (IR ratio, IRR, 0.96 per 2-year increase in calendar year [95% CI: 0.94-0.98], p=0.001), and again, the incidence of ADCs (IRR 0.83 [0.79-0.86], p<0.0001) and infection-related cancers (0.87 [0.85-0.90], p<0.0001) decreased over time. The incidence of NADCs increased slightly over time (1.03 [1.00-1.06], p=0.038), as did the incidence of smoking-related cancers (1.05 [1.01-1.09], p=0.008) and BMI-related cancers (1.10 [1.04-1.16], p=0.001).

Table 6.6 Change in incidence of cancer over time, calculated from a range of Poisson regression models

		All cancer			AIDS-defining cancer			Non-AIDS-defining cancer		
	n participants (PYFU) included	**IRR per two-year increase in calendar year ***	**(95% CI)**	**P**	**IRR per two-year increase in calendar year ***	**(95% CI)**	**P**	**IRR per two-year increase in calendar year ***	**(95% CI)**	**P**
Unadjusted	62,251 (442,408)	0.95	(0.93, 0.97)	<0.0001	0.83	(0.79, 0.86)	<0.0001	1.00	(0.98, 1.02)	0.91
Adjusted for age only	62,251 (442,408)	0.94	(0.92, 0.96)	<0.0001	0.83	(0.79, 0.86)	<0.0001	0.98	(0.96, 1.01)	0.17
Adjusted for a wide range of potential confounders [1]	62,251 (442,408)	0.96	(0.94, 0.98)	0.001	0.83	(0.79, 0.86)	<0.0001	1.03	(1.00, 1.06)	0.038
All confounders fixed at baseline[2]	62,251 (442,408)	0.95	(0.93, 0.98)	<0.0001	0.74	(0.70, 0.78)	<0.0001	1.03	(1.00, 1.05)	0.043
Including time updated exposure to ART[3]	62,251 (442,408)	0.99	(0.96, 1.01)	0.35	0.93	(0.88, 0.97)	<0.0001	1.02	(0.99, 1.05)	0.19
Using complete case analysis[4]	16,466 (137,418)	0.96	(0.93, 1.00)	0.067	0.74	(0.67, 0.82)	<0.0001	1.03	(0.98, 1.07)	0.23

Including validated events only[5]	61,892 (384,188)	0.96	(0.94, 0.98)	<0.0001	0.83	(0.80, 0.87)	<0.0001	1.02	(0.99, 1.04)	0.19
Excluding individuals with any cancer prior to baseline[6]	59,155 (420,590)	0.96	(0.94, 0.99)	0.002	0.83	(0.79, 0.86)	<0.0001	1.03	(1.00, 1.06)	0.027
Applying the same exclusion criteria to participants in D:A:D as in RESPOND[7]	59,503 (424,324)	0.96	(0.94, 0.98)	0.001	0.83	(0.79, 0.86)	<0.0001	1.03	(1.00, 1.05)	0.053
		Infection-related cancer			**Smoking-related cancer**			**BMI-related cancer**		
	n participants (PYFU) included	**IRR per two-year increase in calendar year ***	**(95% CI)**	**P**	**IRR per two-year increase in calendar year ***	**(95% CI)**	**P**	**IRR per two-year increase in calendar year ***	**(95% CI)**	**P**
Unadjusted	62,251 (442,408)	0.88	(0.85, 0.90)	<0.0001	1.02	(0.99, 1.05)	0.19	1.09	(1.04, 1.14)	0.001
Adjusted for age only	62,251 (442,408)	0.87	(0.85, 0.90)	<0.0001	1.01	(0.97, 1.04)	0.71	1.07	(1.02, 1.12)	0.004
Adjusted for a wide range of potential confounders[1]	62,251 (442,408)	0.87	(0.85, 0.90)	<0.0001	1.05	(1.01, 1.09)	0.008	1.10	(1.04, 1.16)	0.001

All confounders fixed at baseline[2]	62,251 (442,408)	0.84	(0.81, 0.87)	<0.0001	1.05	(1.01, 1.09)	0.007	1.10	(1.05, 1.16)	<0.0001
Including time-updated exposure to ART[3]	62,251 (442,408)	0.93	(0.90, 0.97)	<0.0001	1.05	(1.01, 1.09)	0.022	1.09	(1.03, 1.15)	0.005
Using complete case analysis[4]	16,466 (137,418)	0.85	(0.80, 0.91)	<0.0001	1.07	(1.01, 1.13)	0.033	1.10	(1.01, 1.20)	0.024
Including validated events only[5]	61,892 (384,188)	0.90	(0.86, 0.92)	<0.0001	1.04	(1.00, 1.07)	0.047	1.07	(1.02, 1.13)	0.010
Excluding individuals with any cancer prior to baseline[6]	59,155 (420,590)	0.87	(0.84, 0.90)	<0.0001	1.05	(1.01, 1.09)	0.009	1.09	(1.03, 1.16)	0.002
Applying the same exclusion criteria to participants in D:A:D as in RESPOND[7]	59,503 (424,324)	0.87	(0.84, 0.90)	<0.0001	1.05	(1.01, 1.09)	0.01	1.10	(1.04, 1.16)	0.001

*IRR, calculated from a Poisson regression model

[1]adjusted for age, gender, ethnicity, CD4 count, CD4 nadir, prior cancer, ART-experience and viral suppression status, all fixed at baseline, and smoking status, body mass index, hepatitis C, hepatitis B, hypertension, diabetes, AIDS event, cardiovascular disease, end stage liver disease, end stage renal disease, all time updated

[2]adjusted for the same variables as (1), with all variables fixed at baseline

[3]adjusted for the same variables as (1), except baseline ART-experience and viral suppressions status was removed from the model and the model is additionally

adjusted for time updated exposure to integrase inhibitors, protease inhibitors, nucleoside reverse transcriptase inhibitors, and non-nucleoside reverse transcriptase inhibitors

[4]adjusted for the same variables as (1); individuals with missing data on any variables included in the model were excluded

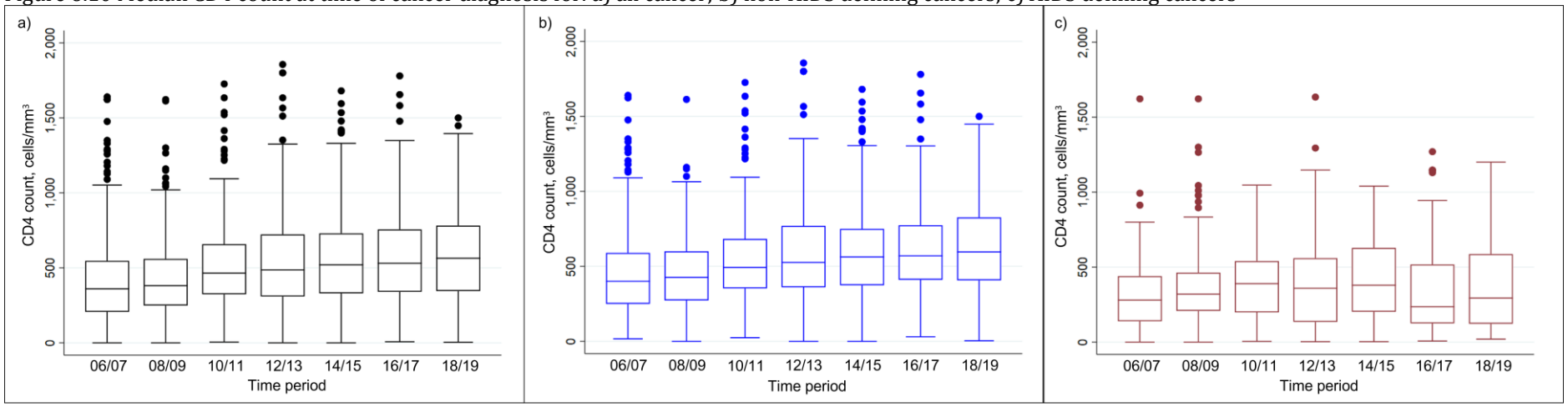
[5]adjusted for the same variables as (1); n=3346 events included

[6]adjusted for the same variables as (1); individuals with unknown cancer status prior to baseline were also excluded

[7]adjusted for the same variables as (1); exclusion criteria include missing information on gender and no CD4 count or VL measurement either 1 year prior to or 12 weeks after baseline

I also assessed CD4 count at time of cancer diagnosis, as shown in Figure 6.10. Of 3236 individuals with a cancer during follow-up from 2006 onwards, 95% had a CD4 measurement within 1 year prior to the cancer diagnosis (median [IQR] 48 days [17-95] prior to diagnosis). Of these, median CD4 count at time of cancer diagnosis was 440 cells/mm^3 (IQR 262-650) for all cancer, 316 cells/mm^3 (154-492) for ADCs, and 500 cells/mm^3 (320-709) for NADCs. CD4 count at time of diagnosis increased over time for all cancers and NADCs. For all cancer, the median increased from 360 cells/mm^3 (206-550) in 2006-07 to 564 cells/mm^3 (349-782) in 2018-19, and for NADCs, it increased from 400 cells/mm^3 (250-590) in 2006-2007 to 601 cells/mm^3 (413-828) in 2018-2019. For ADCs, median CD4 count was similar in 2006-2007 and 2018-2019 (280 cells/mm^3 [139-440] in 2006-2007 and 294 cells/mm^3 (122-587) in 2018-2019).

Figure 6.10 Median CD4 count at time of cancer diagnosis for: a) all cancer; b) non-AIDS defining cancers; c) AIDS defining cancers



6.3.4.1 Sensitivity analyses

Table 6.6 also shows the results from a range of sensitivity analyses. Results were fairly consistent when fixing all confounders at baseline, when excluding individuals with any cancer prior to baseline, when using complete case analysis to account for missing data, and when only including centrally validated events.

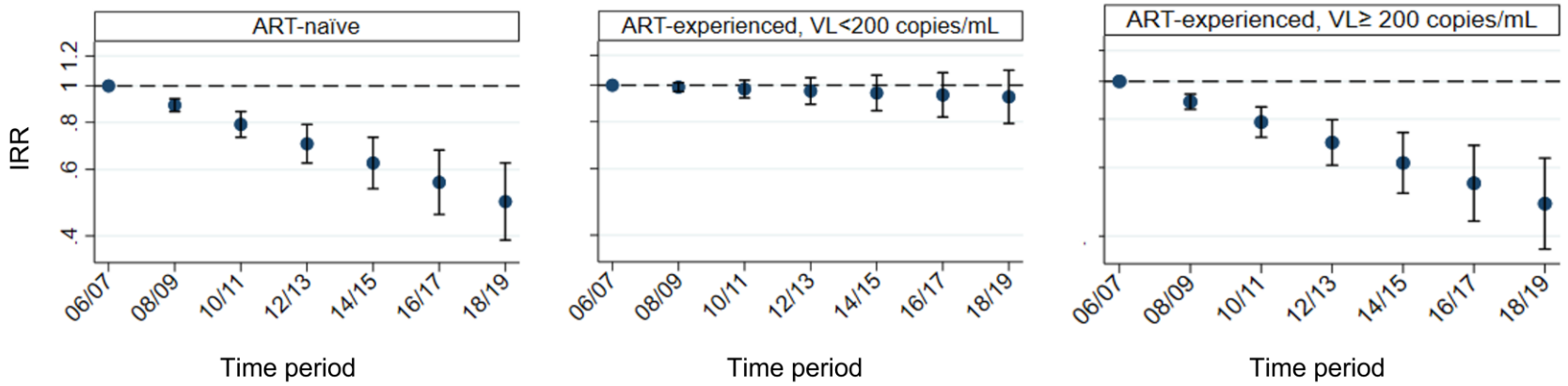
After adjusting for time-updated exposure to INSTIs, PIs, NNRTIs, and NRTIs, the incidence of all cancer no longer increased over time (IRR 0.99 [95% CI: 0.96-1.01], p=0.35). Additionally, for ADCs and infection-related cancers, the IRR per 2-year increase in calendar time shifted closer to one, although still remained significant; for ADCs, the IRR was 0.83 (0.79-0.86) in the model with ART-experience fixed at baseline and 0.93 (0.88-0.97) in the model with time-updated exposure to ART and, for infection-related cancers, these estimates were 0.87 (0.85-0.90) and 0.93 (0.90-0.97), respectively.

I repeated analyses applying the same exclusion criteria in RESPOND to D:A:D participants. The exclusion criteria were missing information on gender and no CD4 count or VL measurement either 1 year prior to or 12 weeks after baseline. A further 2748 participants were excluded from the analysis and results were similar to the overall analysis.

6.3.4.2 Subgroup analyses

There was a significant interaction between ART-experience at baseline and time period (overall interaction p<0.0001). Whilst the incidence of cancer decreased in individuals who were ART-naïve (n=22,983) or ART-experienced with uncontrolled viremia (n=30,425) at baseline, it remained constant in those who were ART-experienced with a suppressed VL (n=11,995), as shown in Figure 6.11. All other subgroup analyses were non-significant (interaction p>0.1 for all).

Figure 6.11 Change in the age-adjusted incidence of cancer, by time period compared to 2006-2007, stratified by ART-experience at baseline



n cancers	128	181	120	158	142	87	60	236	241	227	307	326	177	131	129	130	99	108	88	40	25
n NADCs	39	68	57	83	81	47	38	196	203	205	272	291	163	122	70	90	63	81	63	33	17
n ADCs	89	113	63	75	61	40	22	40	38	22	35	35	14	9	59	40	36	27	25	7	8

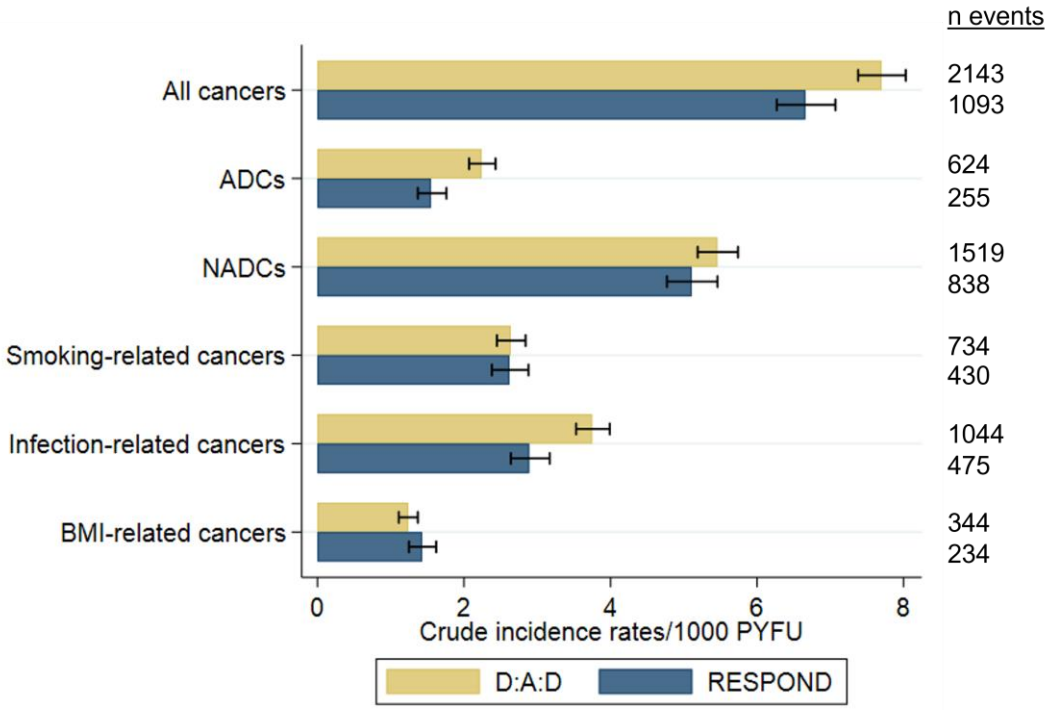
IRR calculated from a Poisson regression model, adjusted for age and including an interaction term between time period and ART-experience at baseline

6.3.4.3 Comparison of trends across ART-eras

To explore whether cancer trends differed across ART-eras, I compared cancer incidence between D:A:D, where participants were generally prescribed older ARVs, and RESPOND, where participants were prescribed more contemporary ARVs. For this analysis, for participants who were recruited into both collaborations, the events and PYFU were included in D:A:D from D:A:D baseline up until RESPOND baseline and in RESPOND thereafter (see Figure 6.2 above). I also compared cancer incidence and trends prior to 2014 versus 2014 onwards, as DTG, the first 2nd generation INSTI was approved in 2014.

The overall incidence of cancer was higher in D:A:D compared to RESPOND; of 3236 cancer events occurring during 2006-2019, 2143 occurred during 278,322 PYFU (IR 7.70/1000 PYFU [95% CI: 7.38-8.03]) in D:A:D and 1093 occurred during 164,086 PYFU in RESPOND (IR 6.66/1000 PYFU [6.27-7.07], p<0.0001). The raw incidence of each cancer type, by cohort, is shown in Figure 6.12. The incidence of ADCs was again higher in D:A:D (624 events, IR 2.24/1000 PYFU [2.07-2.43]) compared to RESPOND (255 events, IR 1.55/1000 PYFU [1.37-1/76]), as was the incidence of infection-related cancers (1044 events, IR 3.75/1000 PYFU [3.53-3.99] in D:A:D; 475 events, IR 2.89/1000 PYFU [2.64-3.17] in RESPOND). However, there was a similar incidence of NADCs in both cohorts (1519 events, IR 5.46/1000 PYFU [5.19-5.74] in D:A:D; 838 events, IR 5.11/1000 PYFU [4.77-5.46] in RESPOND) and of smoking-related cancers in both cohorts (734 events, IR 2.64/1000 PYFU [2.45-2.84] in D:A:D; 430 events, 2.62/1000 PYFU [2.38-2.88] in RESPOND). Finally, the incidence of BMI-related cancers was slightly higher in RESPOND (344 events, IR 1.24/1000 PYFU [1.11-1.37] in D:A:D; 234 events, IR 1.43/1000 PYFU [1.25-1.62] in RESPOND).

Figure 6.12 Raw incidence rates for each cancer type, by cohort



The overall incidence of cancer was higher prior to 2014; 2141 occurred during 279,471 PYFU (IR 7.66/1000 PYFU [95% CI: 7.34-7.99]) in the time period 2006-2013 and 1095 occurred during 162,937 PYFU from 2014-2019 (IR 6.72/1000 PYFU [6.32-7.13], p<0.0001). Table 6.7 shows the change in the incidence of each type of cancer over time during 2006-2013 and 2014-2019. Overall cancer incidence decreased over time during 2006-2013 (IRR per 2-year increase in calendar time 0.92 [95% CI: 0.88-0.95], p<0.0001), whilst there was no change in cancer incidence over time during 2014-2019 (IRR 0.98 [0.91-1.06], p=0.16). This was likely because, whilst ADCs decreased over time during 2006-2013 (0.78 [0.73-0.84], p<0.0001), this was no longer the case during 2014-2019 (0.90 [0.76-1.07], p=0.25), although there were substantially fewer events in this time period (n=654 ADCs in 2006-2013 vs 225 ADCs in 2014-2019). The trends in other cancer types were similar between the time periods. As follow-up was shorter in each of these time periods, results from this analysis should be interpreted with caution.

Table 6.7 Change in incidence of cancer over time

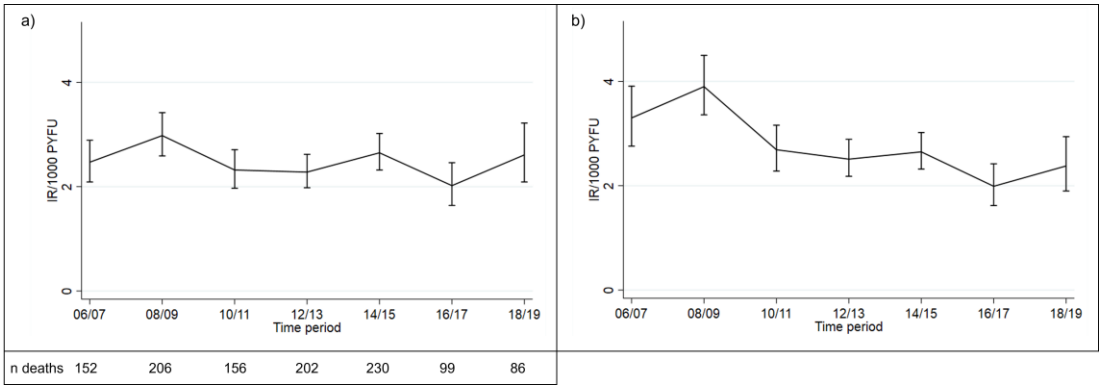
		2006-2013				2014-2019		
	N events	**IRR per two-year increase in calendar year***	**(95% CI)**	**P**	**N events**	**IRR per two-year increase in calendar year***	**(95% CI)**	**P**
All cancer	2141	0.92	(0.88, 0.95)	<0.0001	1095	0.98	(0.91, 1.06)	0.68
AIDS-defining cancer	654	0.78	(0.73, 0.84)	<0.0001	225	0.90	(0.76, 1.07)	0.25
Non-AIDS-defining cancer	1487	0.98	(0.94, 1.03)	0.46	870	1.00	(0.92, 1.09)	0.93
Infection-related cancer	1081	0.84	(0.80, 0.89)	<0.0001	438	0.89	(0.78, 1.00)	0.058
Smoking-related cancer	718	1.01	(0.95, 1.08)	0.65	446	1.01	(0.90, 1.14)	0.87
BMI-related cancer	336	1.09	(0.99, 1.20)	0.065	242	1.13	(0.96, 1.33)	0.15

*IRR, calculated from a Poisson regression model adjusted for age

6.3.5 Death due to cancer

Finally, as an exploratory analysis, trends in death due to cancer were assessed over time using raw IRs and age-standardised IRs. Overall, there were 1131 deaths due to cancer during 455,170 PYFU (IR 2.48/1000 PYFU [2.34-2.63]) and the age-standardised incidence of death due to cancer decreased over time from 3.30/1000 PYFU [2.76-3.91] in 2006-2007 to 2.38/1000 PYFU [1.90-2.94] in 2018-2019 (Figure 6.13).

Figure 6.13 Incidence rates and 95% confidence intervals of death due to cancer over time: a) raw incidence rates; b) age-standardised incidence rates



Vertical bars represent 95% CIs

6.4 Discussion

This is the first analysis to combine data from both the D:A:D and RESPOND cohort consortiums. Amongst 66,636 PLWH included in the analysis, I found that whilst the age-standardised incidence of all cancer has decreased from 2006-2019, this trend differs between different types of cancers. Results showed that the age-standardised incidence of ADCs and infection-related cancers have both decreased over time, however the incidence of NADCs and smoking-related cancers have remained steady, and the incidence of BMI-related cancers has increased. These results were fairly consistent across a range of sensitivity analyses, including restricting the analysis to individuals who had not had a cancer prior to baseline and using complete case analysis to account for missing data.

Overall, I included 3634 cancers in the analysis; the incidence of all cancer was 7.42/1000 PYFU, ADC was 2.21/1000 PYFU, and NADC was 5.22/1000 PYFU. Cancer incidence estimates vary substantially across studies with some studies reporting higher incidence rates (679,680), and others reporting similar (647,650), or lower rates (645,646,652) than those presented here. These variations are likely caused by differences between the studies in terms of event definition, time period assessed, and study design. For example, several of the studies with higher incidence rates began follow-up in the 1980s when the incidence of ADCs was substantially higher.

A declining incidence of ADCs and infection-related cancers over time has been reported by many studies (640,645–647,652) and it is reassuring that this has now also been shown in the combined D:A:D and RESPOND population. The declining incidence is likely due to improvements in CD4 counts, reduction in immune inflammation, and reductions in VL as the use and efficacy of ART has improved over time (645,668,681).

The trends of other cancers differed however, between specific groups of cancers. Whilst the incidence of smoking-related cancers remained fairly steady over time, the incidence of BMI-related cancers has increased. There are many potential reasons why the incidence of BMI-related cancers increased, including changes in lifestyle factors or toxicities associated with ART use. Some ARVs, such as DTG and tenofovir alafenamide, have been shown to be associated with weight gain (542,682,683). This could translate into an increase in the incidence of clinical outcomes, including BMI-associated cancers and more research is needed to understand the implications of this adverse event, as well as the trends in BMI-cancers better. Additionally, whilst the incidence of smoking-related cancers has not increased over time, smoking-related cancer incidence is still relatively high amongst PLWH, and further prevention strategies for smoking are needed to reduce this (684,685). As PLWH generally interact with healthcare professionals more regularly than those in the general population, there is more opportunity to provide smoking cessation interventions (686,687). On the other hand, there are several barriers to smoking cessation for PLWH. For example, smoking has been shown to be associated with other substance

use, such as drugs and alcohol use, which are more common in some subgroups of PLWH, and it has been reported that smoking is often used to reduce the psychological burden associated with living with HIV (688,689). A previous study in D:A:D showed that lung cancer incidence remained elevated more than 5 years after smoking cessation; lung cancer was the most common NADC amongst this analysis population and therefore prevention strategies for smoking should be prioritised (690). It was not possible to look further into smoking cessation in this analysis as the number of individuals who stopped smoking during follow-up was relatively low.

I repeated analyses adjusted for a wide range of potential confounders, including demographics, comorbidities and coinfections, HIV-related factors, and ART-related factors. The results from this analysis were generally similar to analyses only adjusting for age, and this was the case when factors were fit as time-updated, where appropriate, or where all factors were fixed at baseline. After adjusting for time-updated exposure to INSTIs, PIs, NNRTIs, and NRTIs, however, the incidence of all cancer no longer increased over time and whilst the incidence of ADCs still decreased, it was at a slower rate compared to when only adjusting for age. These results further suggest that ART-use is associated with the reduction in ADCs that has been seen, however other demographic and HIV-related factors are not fully explaining the cancer trends and there are likely more factors which may be playing a part. Examples of other factors which may explain the cancer trends include lifestyle factors such as alcohol use, a family history of cancer, or the presence of other viruses shown to be associated with an increased risk of infection-related cancers, such as HPV or Epstein-Barr virus, all of which are not collected in D:A:D and RESPOND (660,664,691–694). It is therefore important for further research to be done to identify causes of the trends presented in this chapter.

Subgroup analyses showed that whilst the incidence of all cancer decreased in individuals who were ART-naïve or ART-experienced with uncontrolled viremia at baseline, it remained constant in those who were ART-experienced with a suppressed VL. This was likely driven by a decreasing incidence of ADCs for ART-naïve individuals

who go on to start effective ART during follow-up, or for those with uncontrolled viremia who switch to a more effective ART-regimen (657,668).

To assess the impact of different ART-eras on cancer trends, I compared the incidence of cancer between participants in D:A:D who were treated with older ARVs and those in RESPOND who are treated with more contemporary ARVs. I also compared cancer trends pre and post 2014 as DTG was approved in 2014. I found that the overall incidence of cancer was higher in D:A:D compared to RESPOND, as were ADCs and infection-related cancers, however there was a similar incidence of NADCs and smoking-related cancers in the two cohorts and BMI-related cancers were higher in RESPOND. The higher incidence of ADCs and infection-related cancers is likely because follow-up in D:A:D began earlier than in RESPOND. When looking at cancer trends pre and post 2014, the incidence of all cancer decreased over time pre-2014, however remained fairly constant from 2014 onwards. This is likely because ADCs were decreasing at a slower rate after 2014, although this did include fewer events, and the incidence of ADCs was already relatively low by 2014. I additionally assessed the impact of ART on cancer trends by firstly adjusting for ART-experience at baseline in the Poisson regression models and then by adjusting for time-updated exposure to INSTIs, NNRTIs, PIs, and NRTIs. As mentioned before, whilst the adjusted incidence of cancer decreased over time in the former analysis, after adjusting for time-updated ART exposure, this was no longer the case; other trends were similar after adjustment, although whilst still significant, the IRR for ADCs increased from 0.83 to 0.93 for each 2-year increase in calendar time. The change in trends of all cancers may be because, after adjusting for ART, the reduction in ADCs was having a smaller impact on the overall cancer trends. Whilst many studies have compared the incidence of ADCs and NADCs before and after the introduction of ART, consistently showing a reduction in ADCs but with mixed results for NADCs (647,652,657,679), to the best of my knowledge, few have compared temporal trends in different ART-eras.

Finally, exploratory analyses showed the incidence of death due to cancer decreased slightly over time. This is a reassuring finding, although further research stratifying these trends by different subgroups, for example sex or age category, would be

valuable, as well as comparing the trends for death due to individual cancers. As RESPOND and D:A:D do not collect data on cancer treatment and staging, it was not possible to look into the trends further in this analysis, Additionally, for those who have more than one cancer, it is not possible to identify which cancer individuals died from. Results from this analysis should therefore be interpreted with caution.

6.4.1 Strengths and limitations

Results from these analyses should be considered with limitations in mind. Firstly, as explained in the results section, the incidence of cancer in D:A:D in 2004-2005 was lower than in subsequent years, likely due to bias in event reporting. To address this issue, I removed 2004-2005 from the analysis. I also modelled calendar period as a continuous variable, assuming a linear trend, rather than as a categorical variable. The median age of individuals in D:A:D is 41 years and in RESPOND is 43 years, and, given cancer is generally more prevalent in older age groups, this may be too young to be able to fully assess cancer incidence. Additionally, cancer takes many years to develop and, whilst I was able to include a longer follow-up in the analysis by combining the two cohort consortiums, median follow-up was 7.5 years which may be too short for some individuals to develop cancer. Cancer pathogenesis is multifactorial and, as mentioned previously, there are likely other factors which could explain the cancer trends seen, such as alcohol use and family history of cancer, which are not collected in D:A:D and RESPOND. The cohorts also do not provide information on the treatment given for cancer or the individual cancer staging which is important for cancer prognosis and to fully understand the trends in cancer-related deaths. As has been mentioned in previous chapters, there is also some missing data in the cohorts, including for some key variables, such as smoking status. As smoking-related cancers was a focus of the analysis, individuals with missing smoking status may have impacted these results in particular. Finally, I did not assess time trends for individual cancers, and it is likely that there is some heterogeneity amongst the groups of smoking-, BMI-, and infection-related cancers.

There are also several strengths to this analysis. This is the first study to combine data from D:A:D and RESPOND, and by doing this, I was able to assess temporal trends

over 15 years from two studies with similar designs and data collection. I was also able to include a large sample with almost half a million PYFU. Both cohort consortiums are pan-European, heterogeneous studies, with data from real-world settings, which makes these findings more generalisable to the wider population of PLWH in Europe and Australia. D:A:D and RESPOND have the same basic methodology, including rigorously collected cancer events which are centrally validated by clinicians at the D:A:D and RESPOND coordinating centres.

6.4.2 Conclusions

In conclusion, I found that the age-standardised incidence of all cancers has decreased over time from 2006 to 2019. ADCs and infection-related cancers have decreased over time, whilst NADCs and smoking-related cancers have remained constant, and BMI-related cancers have increased. These results show the need for better prevention strategies to reduce the incidence of smoking- and BMI-related cancers. Further research is also needed to better understand the causes of these cancer trends.

6.4.3 Publications

The results from this project were submitted to CROI 2022.

Chapter 7 Integrase inhibitor use and cancer incidence in a large cohort setting

7.1 Introduction

Since the introduction of combination antiretroviral therapy (ART) in 1996, HIV has been transformed from a fatal illness into a manageable, chronic condition. Several studies have shown that the life expectancy of people living with HIV (PLWH) is approaching that of the general population, although this is not the case for all subgroups of the population of PLWH, such as sex workers and transgender people (571,649,695,696). Figure 7.1 shows the life expectancy and comorbidity-free life expectancy for individuals with and without HIV using data from a matched cohort study from Kaiser Permanente in the USA from 2000 to 2016 (696).

Figure 7.1 Life expectancy and comorbidity-free life expectancy at age 21 for people living with HIV compared to those without HIV

Source: (696)

With an aging population of PLWH, however, there has been an increase in the burden of comorbidities, including cancer and cardiovascular disease (CVD) (635,648,649). As there is no cure for HIV, ART use is lifelong, and it is therefore

crucial to identify any associations between ART use and the risk of comorbidities (331,535,578).

Cancer is one of the leading causes of death amongst PLWH (80,634,635). Since the introduction of ART, the incidence of AIDS-defining cancers (ADCs) has significantly decreased. However, there has been an increase in the incidence of several non-ADCs (NADCs) reported, which may be partly attributable to the aging of PLWH (80,635,645,646,648,649). In Chapter 6, I assessed cancer trends amongst PLWH in the D:A:D and the RESPOND studies from 2004 to 2019. I found that within these cohorts, the incidence of ADCs has significantly decreased over time but the incidence of NADCs has remained fairly steady. Additionally, when categorizing cancers into infection-related, smoking-related, and BMI-related cancers, I found that whilst the incidence of infection-related cancers has decreased over time, the incidence of BMI-related cancers has increased, and smoking-related cancers has remained constant.

Several studies have assessed the association between specific antiretroviral (ARV) drugs or drug classes and the risk of groups of cancers, such as those which are infection-related, although there is limited data assessing newer ARVs, including second-generation INSTIs. INSTIs are recommended in international HIV treatment guidelines as first-line treatment for PLWH (331,535,578). Studies have shown that INSTIs are generally well tolerated and are effective in maintaining viral suppression (301,321,697,698). However, given that INSTIs are a relatively new drug class, there is limited data assessing long-term clinical outcomes associated with INSTI use and to the best of my knowledge, no studies have yet examined the association between cancer incidence and newer INSTI use more broadly by assessing cobicistat-boosted elvitegravir (EVG/c), dolutegravir (DTG), and bictegravir (BIC), as well as raltegravir (RAL).

In Chapter 2 of this thesis, I completed a literature review investigating the incidence of clinical events, including cancers, on contemporary ARVs, including the INSTIs DTG, EVG/c, and RAL, the PIs atazanavir and darunavir, and the NNRTIs efavirenz and

rilpivirine. Whilst there were very few studies identified in my review, likely due to there being too limited follow-up on these contemporary ARVs to allow an investigation into long-term clinical outcomes, the association between RAL and the incidence of any cancer has previously been investigated in two large cohort studies - one in the EuroSIDA cohort study and one at Kaiser Permanente in the USA (484,486). Both cohorts compared the risk of any cancer between a cohort of PLWH treated with RAL after 2007, a historical cohort starting ART between 2005-2007, and a concurrent cohort starting an ART-regimen after 2007 which did not contain RAL. Whilst the EuroSIDA study showed a similar incidence of all cancers in the 3 cohorts (484), the study conducted at Kaiser Permanente found an increased risk of NADCs and ADCs for those treated with RAL compared to the other 2 cohorts (486). Additionally, a meta-analysis combining 96-week data from the BENCHMRK and STARMRK clinical trials showed a similar risk of any cancer on RAL compared to the comparator (efavirenz or placebo) (556), although 96 weeks of follow-up is likely too short to capture the development of malignancies.

Previous studies have reported an increased risk of anal cancer with exposure to certain older PIs (668,669), whilst no other associations have been widely reported between NADCs and any other ARV drug classes. Whilst it is unclear why there is an increased risk of anal cancer with PI use, it has been suggested that PIs are often used as salvage therapy, possibly for individuals with poor ART adherence, and these individuals may already have poor virological control and are therefore more likely to become immunosuppressed and develop comorbidities, including cancer (669). However, this association was seen with other PIs, such as ritonavir-boosted atazanavir and ritonavir-boosted lopinavir, which have not used for salvage therapy (670). As cancers are a very heterogenous group of diseases, each with different risk factor profiles, studying individual cancers or individual ARVs requires very large studies with considerable follow-up, and there is therefore little data currently assessing this.

7.1.1 Aims

The aim of this chapter is to:

(i) assess whether there was an association between INSTI use (including RAL, EVG/c, DTG, and BIC) and the incidence of any cancer, amongst PLWH in RESPOND.

7.2 Methods

This analysis was performed on the third update (version DS2) of the RESPOND database with a data cut-off of 31st December 2019. Baseline was defined as the latest of local cohort enrolment and 1st January 2012. Individuals were followed until the earliest of first cancer event or final follow-up, with final follow-up defined as the latest of the most recent CD4 count, VL measurement, or ART start date, drop out date as defined by the local cohort, or date of death. If this date was after the data cut-off, individuals were censored at 31st December 2019.

7.2.1 Inclusion criteria

The inclusion criteria for RESPOND is detailed in Chapter 3, Section 3.1.3. For this specific analysis, individuals from RESPOND were included if they:

(i) were aged 18 years or older at baseline; and
(ii) had a CD4 count and VL measurement either 1 year prior to or within 12 weeks after baseline.

Individuals were excluded if they had missing information on gender (as there were too few to fit as an unknown category) or no follow-up data. Cohorts in RESPOND with low event reporting across all events reported in RESPOND, were excluded from this analysis. This was done by comparing the incidence of events in each cohort to the incidence in the RESPOND consortium overall. Cohorts with incidence rates less than half of the overall incidence across 4 of 7 events considered (AIDS non-cancer, ADCs, NADCs, CVD, ESLD, ESRD, and death) were excluded. This was done using the

DS1 update of the database as this was available when the project was first started. Cohorts with significantly improved data collection in DS2 were added back in to the analysis. A list of cohorts included in the analysis is included in the results section below.

7.2.2 Outcomes

The primary outcome was first incident cancer during follow-up. Pre-cancers, relapse of a primary cancer, and basal or squamous cell skin cancers were not included. Cancer events were reported in real time using a designated event form and as part of the electronic yearly data submission. Further detail on the cancer definition is provided in the RESPOND manual of operations (490). Individuals who had cancer prior to baseline were included in the main analysis. For these individuals, cancer during follow-up was only counted if the type of cancer during follow-up was different from the one which occurred prior to baseline. If the type of cancer prior to baseline was unknown, no cancers during follow-up were counted. A sensitivity analysis was performed excluding individuals with any cancer prior to baseline and another only excluding individuals with cancer prior to baseline where the type of cancer was unknown.

7.2.3 Potential confounders

All potential confounders, defined prior to or at baseline, considered in this analysis are described in Table 7.1.

Table 7.1 Potential confounders considered in analyses

Variable	Categories	Comments
Calendar year	Continuous (per 1 year later)	
Age	Continuous (per 10 years later)	
Gender	Male; female	
HIV risk group	MSM; IDU; heterosexual sex; other; unknown or missing	
Ethnicity	White; Black; other; unknown or missing	
Body mass index	<18.5 kg/m^2; 18.5-<25 kg/m^2; ≥25 kg/m^2; missing	
Smoking status	Past; current; never; unknown or missing	
CD4 cell nadir prior to baseline	Continuous (per 100 cells increase)	Taken as the lowest CD4 count prior to baseline. If no CD4 count was measured, the first measurement within 12 weeks after baseline was used
CD4 count at baseline	Continuous (per 100 cells increase)	Taken as the most recent CD4 count within 12 months prior to baseline. If no CD4 count was measured, the first measurement within 12 weeks after baseline was used (median difference between CD4 count and baseline = 26 days)
Prior ART-experience and viral suppression status at baseline	ART-naïve; ART-experienced with VL <200 copies/mL; ART-experienced with VL ≥200 copies/mL (620)	VL was taken as the most recent VL within 12 months before baseline. If no VL was measured prior to baseline, the first measurement within 12 weeks after baseline was used (median difference between VL and baseline = 24 days)
Viral hepatitis C	No; yes; unknown	Defined by use of anti-HCV medication, a positive HCV antibody test, a positive HCV RNA qualitative test, HCV RNA > limit of detection, and/or a positive genotype test
Viral hepatitis B	No; yes; unknown	Defined by a positive HBV surface antigen test and/or HBV DNA >limit of detection
Hypertension	No; yes; unknown	Confirmed by use of anti-hypertensives at any time before baseline or if the most recent systolic or diastolic blood pressure measurement before baseline was

		higher than 140 or 90 mmHg, respectively
Diabetes	No; yes; unknown	Defined as reported diabetes diagnosis or use of antidiabetic medication or a random glucose measurement of 11.1 mmol/L or above, a Haemoglobin A1c measurement of 6.5% or above, or 48 mmol/mol or above (549)
Prior AIDS (non-cancer)	No; yes; unknown	Composite diagnosis as defined by the CDC list of AIDS-defining conditions (547,548)
Prior AIDS cancer	No; yes; unknown	Composite diagnosis of Kaposi's sarcoma, non-Hodgkin lymphoma, cervical cancer (549)
Prior non-AIDS defining cancer	No; yes; unknown	Any non-AIDS cancer, excluding skin cancers (expect malignant melanoma) and pre-cancers (549)
Prior end stage liver disease	No; yes; unknown	Composite diagnosis of ascites (where extrahepatic reasons are excluded), hepatic encephalopathy grade III-IV, hepatorenal syndrome, endoscopically verified variceal bleeding, spontaneous bacterial peritonitis, liver transplantation (549)
Prior end stage renal disease	No; yes; unknown	Composite diagnosis of dialysis more than three months or kidney transplant (549)
Prior cardiovascular disease	No; yes; unknown	Composite diagnosis of myocardial infarction, stroke or invasive cardiovascular procedure (549)
Prior chronic kidney disease	No; yes; unknown	Two consecutive measurements of eGFR measured at least 3 months apart $\leq$60 mL/min if the first eGFR was >60 mL/min or a 25% decline if first eGFR was <60 mL/min. eGFR was calculated using the CKD-EPI creatinine equation (550)
Prior dyslipidaemia	No; yes; unknown	Defined as total cholesterol>239.4mg/dL or HDL cholesterol<34.7mg/dL or triglyceride >203.55mg/dL or use of lipid lowering treatments (621)
Geographical region	Western Europe; Northern Europe/Australia; Southern Europe; Eastern/East Central Europe	Due to low numbers, Australia was combined with Northern Europe in the analysis models, and Eastern Central Europe was combined with Eastern Europe. For further details, see Chapter 3, Table 3.1 footnote

Abbreviations: MSM – men who have sex with men; IDU – injecting drug use; HCV – hepatitis C; RNA - ribonucleic acid; HBV – hepatitis B; CKD – chronic kidney disease;

eGFR - estimated glomerular filtration rate; CKD-EPI - Chronic Kidney Disease Epidemiology Collaboration; HDL - high-density lipoproteins
Continuous variables were checked to see if there was a linear relationship with the outcome before fitting as continuous
Note, all variables are defined at baseline unless stated otherwise

7.2.4 Statistical methods

I summarised the baseline characteristics of all participants included in the analysis. To calculate exposure to ARVs, I divided participant follow-up into consecutive monthly periods. Cumulative exposure to each ARV was calculated at the start of each month, following a similar method to that used in previous D:A:D analyses (25,26). ARV exposure prior to baseline was included, although to be included in RESPOND, individuals on INSTIs could not have started the INSTI prior to baseline, and therefore there was no INSTI exposure prior to baseline. Time updated confounders, as detailed below, were also calculated for each participant-month using last observation carried forward.

I calculated the crude incidence of any cancer overall and by INSTI exposure. INSTI exposure was grouped as no exposure, ≤6 months exposure, >6 months-1-year exposure, >1-2 years exposure, >2-3 years exposure and >3 years of exposure. Those with no exposure were either ART-naïve or on ART containing other non-INSTI 3rd drugs. INSTI exposure was lagged by 6 months in all analyses for the following reasons. Firstly, as cancer is a slow developing event, it is unlikely that the current cancer risk can be attributable to the current level of exposure of any ARV. Further, this approach reduces any potential confounding by indication, where individuals at higher risk of cancer or with underlying symptoms suspected to be cancer, but without a clinical diagnosis, may be preferentially given INSTIs, either due to their presumed favourable safety profile, better efficacy, or fewer interactions with chemotherapy (8,27).

The association between the incidence of any cancer and lagged cumulative exposure was estimated from a negative binomial regression model using generalised estimating equations (GEEs) with an unstructured working correlation structure and robust standard errors. The model was adjusted for potential confounders, as listed

above. As detailed in Chapter 3, Section 3.3.3, GEEs are used when data is correlated. Observations in this analysis represent participant months and therefore, observations from the same participants are likely to be correlated. Negative binomial regression is an alternative regression model to Poisson regression, which accounts for overdispersion in the outcome. Poisson regression assumes the mean and variance of the outcome is the same and overdispersion occurs when the variance of the outcome is greater than the mean of the outcome. An alternative method to account for overdispersion is to use a Poisson regression model with robust standard errors, which I did in a sensitivity analysis.

Each potential confounder was added to a univariable model and those with p-value <0.1 or those defined to be a confounder a priori were included simultaneously in a multivariable model. To ensure I did not include variables which may lie on the causal pathway between INSTI exposure and cancer risk, all variables were fixed at baseline, apart from smoking status which was included as time-updated. In Chapter 3, Section 3.3.2.1, I outline the advantages of including time-updated confounders compared to confounders fixed at baseline.

All prospectively collected events in RESPOND which occur during the validation period (from 12 months prior to the last local cohort visit before RESPOND enrolment onwards) are submitted using a case report form and these events are then centrally validated by a clinician at the RESPOND coordinating centre. Analyses in this chapter were repeated only including validated cancer events.

I also repeated analyses separately for ADCs and NADCs to investigate whether the association between INSTIs and cancer differs for ADCs and NADCs.

As mentioned above, participants in RESPOND were INSTI-naïve at enrolment and therefore those on INSTIs started the INSTIs during prospective follow-up. Thus, I performed a sensitivity analysis including only participants who started any new ART after baseline (defined as started a new 3rd drug), regardless of whether INSTIs were included, and redefined baseline as the date of regimen start. Participants did not

need to be naïve to the ARVs when starting the regimen, however they did need to start a regimen during follow-up. I then repeated this analysis restricted to individuals who were naïve to the regimen that they started.

I performed several subgroup analyses to investigate whether the association between INSTI exposure and cancer risk differed between those who were ART-naïve at baseline compared to those who were ART-experienced with a VL <200 copies/mL or VL ≥200 copies/mL, between different age groups, between smokers and non-smokers at baseline, and by prior CD4 nadir. These were all performed by including an interaction term in the multivariable regression model between INSTI exposure and the subgroup of interest.

Finally, to investigate whether individuals with cancer were preferentially being prescribed INSTIs, I calculated the proportion of those with cancer who switched their ART regimen within 1-year post cancer diagnosis and compared this between drug classes.

In all analyses, missing data for categorical variables was accounted for by including an unknown category in the regression models. The primary analysis was repeated using complete case analysis where individuals with missing data on any variables included in the multivariable model were excluded.

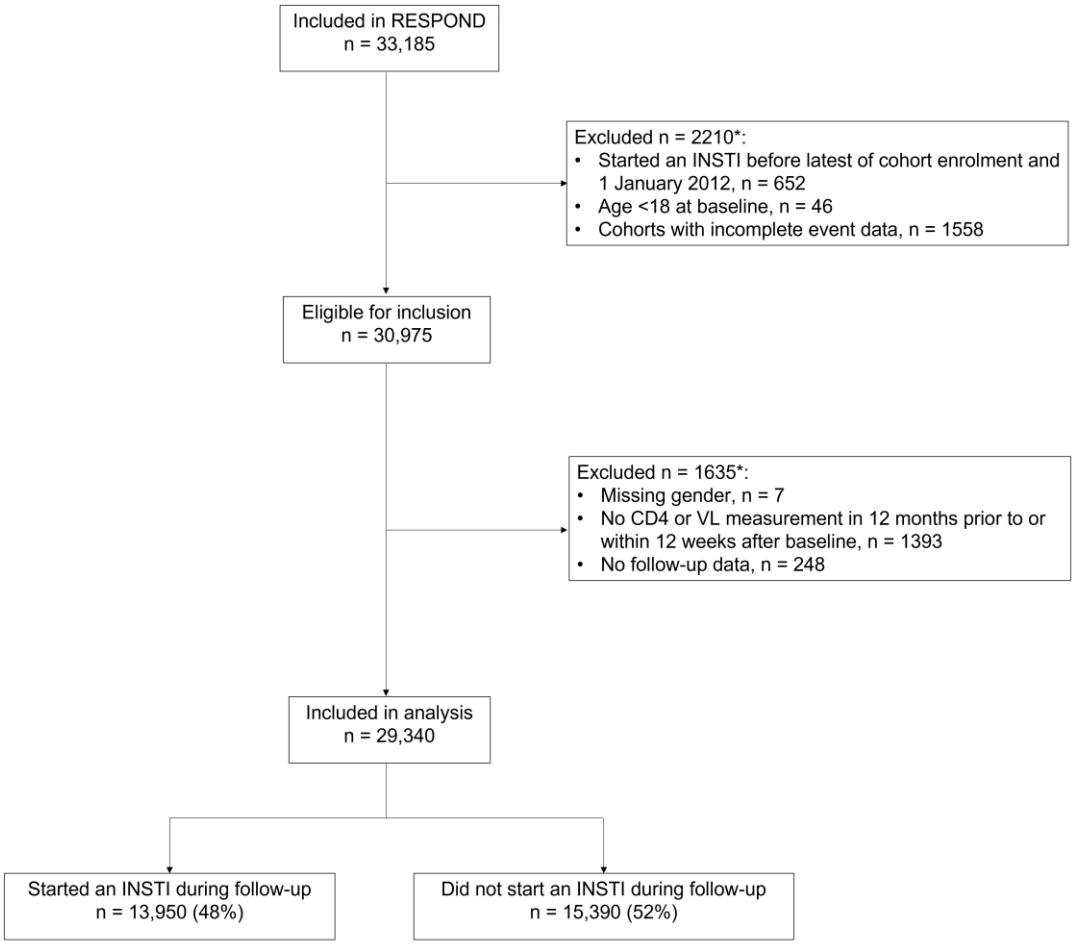
Analyses were performed using Stata/SE 15.0 (StataCorp LLC) and SAS version 9.4 (Statistical Analysis Software, Cary, NC, USA). All p-values are two sided with a p-value <0.05 defined as statistically significant.

7.3 Results

7.3.1 Participants included

There were 33,185 participants from 17 cohorts included in version DS2 of the RESPOND database. In total, 30,975 individuals were eligible for analysis and of these, 29,340 (94.7%) were included. The reasons for exclusion from the analysis were as follows (more than one reason could apply): 1393 did not have a CD4 count or VL measured in the 12 months prior to or within 12 weeks after baseline, 248 had no follow-up data, and 7 were missing information on gender. The study flow for this chapter is shown in Figure 7.2. A higher proportion of those excluded were ART-naïve (41.8% excluded vs 24.4% included, p<0.0001). Additionally, a lower proportion of those excluded had a prior CD4 nadir <200 cells/mm^3 (17.6% excluded vs 40.6% included, p<0.0001) and a lower proportion had prior comorbidities (53.6% excluded vs 71.3% included, p<0.0001).

Figure 7.2 Study flow



*More than one reason can apply

Of the 17 cohorts in RESPOND, 4 were excluded for low event reporting. The cohorts included and the number of participants in each cohort are listed in Table 7.2.

Table 7.2 Cohorts from the RESPOND collaboration included in the analysis

Cohort	**Number of participants included**
Austrian HIV Cohort Study (AHIVCOS)	4024
AIDS Therapy Evaluation in the Netherlands (ATHENA)	1395
Centre Hospitalier Universitaire (CHU) Saint-Pierre	1441
EuroSIDA Study	9545
Italian Cohort Naive Antiretrovirals (ICONA)	1265
Modena HIV Cohort	1340
Nice HIV Cohort	855
PISCIS Cohort Study	605
Royal Free HIV Cohort Study	3256
San Raffaele Scientific Institute	990
Swiss HIV Cohort Study (SHCS)	3197
Swedish InfCare HIV Cohort Study	610
University Hospital Cologne	817

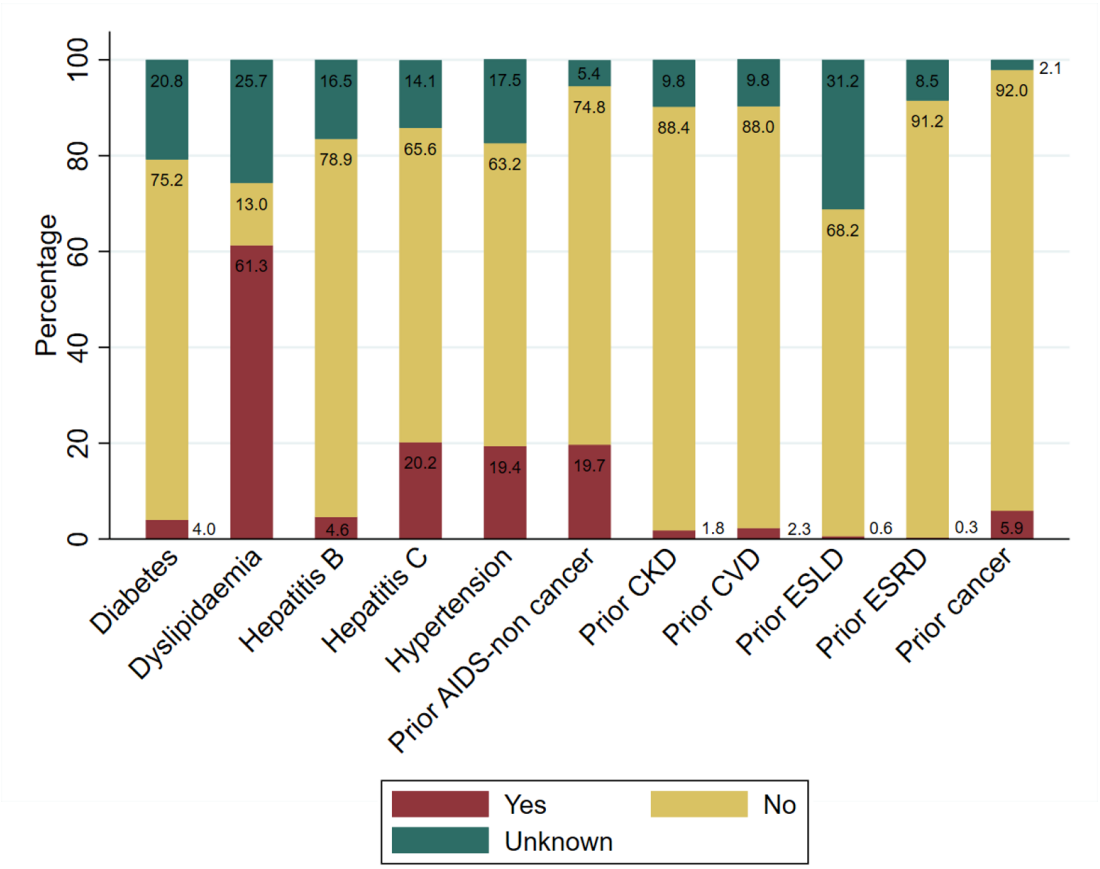
7.3.2 Baseline characteristics

Baseline characteristics of individuals included in the analysis are shown in Table 7.3. Of 29,340 individuals included, 74% were male and 70% were of white ethnicity. The majority of individuals were ART-experienced with a VL<200 copies/mL (68%) and just under a quarter (24%) were ART-naïve. A similar proportion of individuals were never smokers and current smokers (28% never smoked, 28% current smokers, 8% previous smokers). Median age was 44 years (interquartile range [IQR] 36-51), median CD4 count was 524 cells/mm^3 (357-715), and for those with prior ART experience, the median time on ART was 8 years (3-14). Overall, 20% of individuals had a prior AIDS defining event (not including AIDS cancers) and there was a high proportion of prior clinical events including prior cancer (6%), hypertension (19%), and diabetes (4%), as shown in Figure 7.3.

Table 7.3 Characteristics of participants at baseline

		Overall	
		n	**(%)**
	Total	29340	(100)
Gender	Male	21818	(74.4)
	Female	7478	(25.5)
	Transgender	44	(0.1)
Ethnicity	White	20419	(69.6)
	Black	2983	(10.2)
	Other	1267	(4.3)
	Unknown	4671	(15.9)
Body mass index (kg/m^2)	<18.5	873	(3.0)
	18.5-<25	11321	(38.6)
	25-<30	1547	(5.3)
	30+	5159	(17.6)
	Unknown	10440	(35.6)
Geographical Region	Western Europe	12810	(43.7)
	Southern Europe	6626	(22.6)
	Northern Europe	7069	(24.1)
	Eastern Europe	1466	(5.0)
	East Central Europe	1366	(4.7)
HIV risk	MSM	13229	(45.1)
	IDU	3993	(13.6)
	Heterosexual	10253	(34.9)
	Other	654	(2.2)
	Unknown	1211	(4.1)
ART history	Naive	7172	(24.4)
	Experienced, VL<200 copies/mL	19951	(68.0)
	Experienced, VL≥200 copies/mL	2217	(7.6)
Smoking status	Never	8207	(28.0)
	Current	8196	(27.9)
	Previous	2261	(7.7)
	Unknown	10676	(36.4)
Continuous variables		**Median**	**(IQR)**
Baseline date, month/year		01/12	(01/12, 02/13)
Age, years		44.3	(36.2, 51.3)
CD4 cell nadir, $cells/mm^3$		241	(120, 384)
CD4 at baseline, $cells/mm^3$		524	(357, 715)
Viral load at baseline, copies/mL		39.0	(19.0, 2228.5)
Total duration of previous ART, years		7.7	(3.0-13.9)

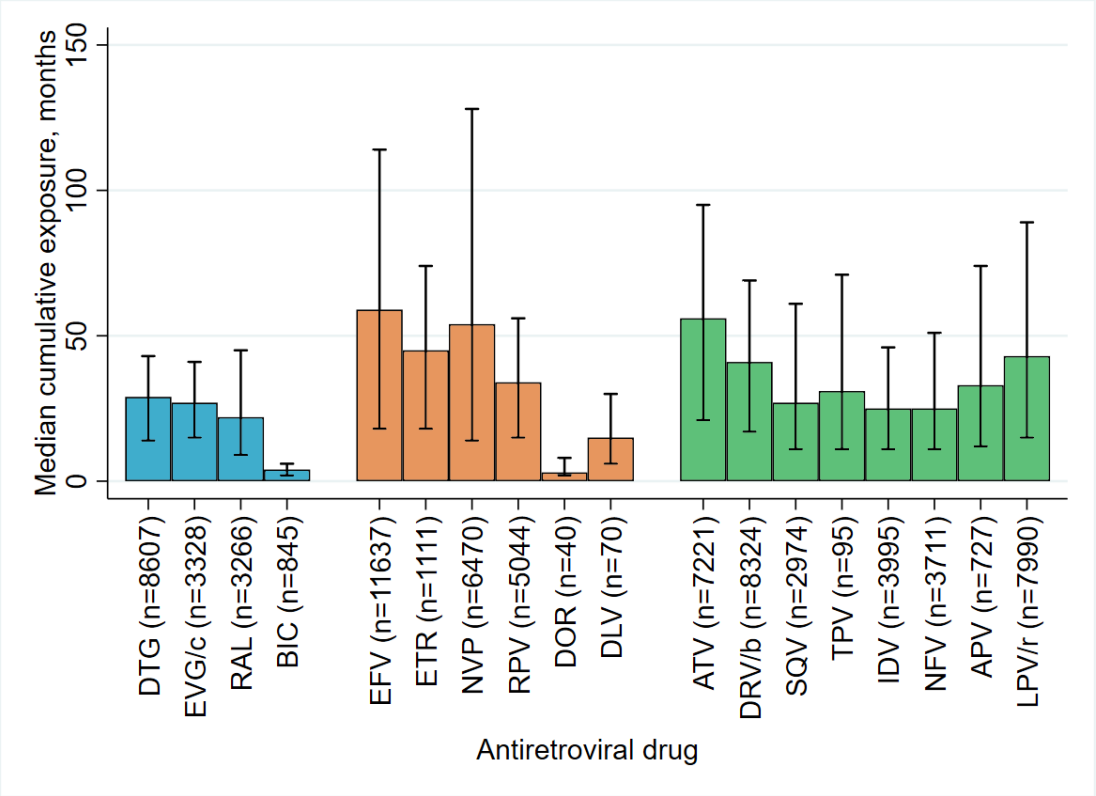
Figure 7.3 Prior comorbidities of individuals included in the analysis



7.3.3 ART exposure

By the end of follow-up, 13,950 (48%) individuals had been exposed to one or more INSTIs: 8607 to DTG, 3328 to EVG/c, 3266 to RAL, and 845 to BIC. For those exposed to INSTIs, median cumulative exposure was 32 months (IQR 16-47) and highest on DTG compared to the other INSTIs (DTG 29 months [14-43], EVG/c 27 [15-41], RAL 22 [9-45], BIC 4 [2-6]). Median cumulative exposure to all 3rd drugs are shown in Figure 7.4. The most common non-INSTI 3rd drugs prescribed were efavirenz (n=11637; median cumulative exposure 59 [18,114] months), boosted darunavir (8324; 41 [17-49] months), ritonavir boosted lopinavir (7990; 43 [15-89] months), and boosted or unboosted atazanavir (7221, 56 [21-95] months). Amongst all participants, the most common NRTIs prescribed were tenofovir disoproxil fumarate (n=21748, 74%), emtricitabine (n=21616, 74%), and lamivudine (n=19733, 67%).

Figure 7.4 Median (interquartile range) cumulative exposure to 3rd drug antiretrovirals



Abbreviations: EFV-efavirenz; ETR-etravirine; NVP-nevirapine; RPV-rilpivirine; DOR-doravirine; DLV-delavirdine; ATV-boosted or unboosted atazanavir; DRV/b-cobicistat or ritonavir boosted darunavir; SQV-saquinavir; TPV-tipranavir; IDV-indinavir; NFV-nelfinavir; APV-amprenavir; LPV/r-ritonavir boosted lopinavir
n represents the number of participants prescribed each antiretroviral drug.
Integrase inhibitors shown in blue bars, non-nucleoside reverse transcriptase inhibitors shown in orange bars, protease inhibitors shown in green bars

7.3.4 Cancer incidence

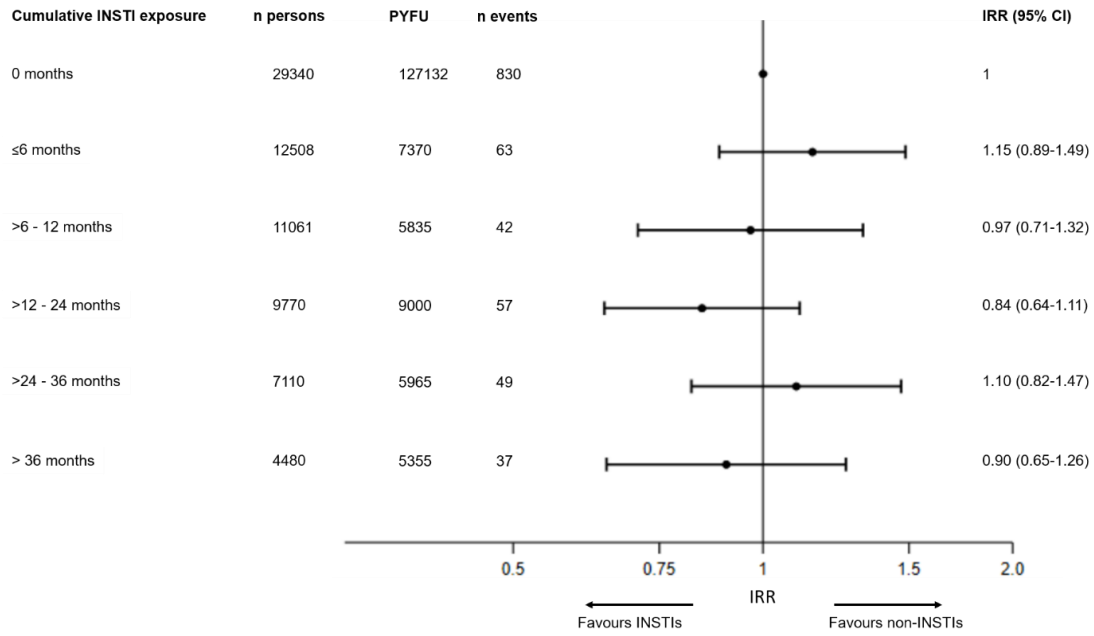
During 160,657 person-years of follow-up (PYFU, median 6.2 years [IQR 3.9-7.5]), there were 1078 cancer events (incidence rate [IR] 6.7/1000 PYFU [95% CI: 6.3-7.1]): 243 ADCs and 835 NADCs. Table 7.4 shows the individual cancer types included in the analysis. The most common individual cancers were non-Hodgkin lymphoma (n=113, 10.5%), lung cancer (112, 10.4%), Kaposi's sarcoma (106, 9.8%), and anal cancer (103, 9.6%). There were 631 cancer events which occurred during the validation period and were validated. Of these, the most common cancers were lung cancer (n=71, 14.1%), Kaposi's sarcoma (50, 10.0%), and non-Hodgkin lymphoma (47, 9.4%).

Table 7.4 Individual cancer types for all cancer events and only validated cancer events

All cancers (n=1078)			Validated cancers (n=502)		
Cancer type	**n**	**%**	**Cancer type**	**n**	**%**
Non-Hodgkin Lymphoma	113	10.48	Lung cancer	71	14.14
Lung cancer	112	10.39	Kaposi's Sarcoma	50	9.96
Kaposi's Sarcoma	106	9.83	Non-Hodgkin Lymphoma	47	9.36
Anal cancer	103	9.55	Prostate cancer	37	7.37
Prostate cancer	81	7.51	Anal cancer	34	6.77
Hepatocellular carcinoma	56	5.19	Liver cancer	27	5.38
Bladder cancer	44	4.08	Head and neck cancer	26	5.18
Head and neck cancer	41	3.80	Bladder cancer	21	4.18
Hodgkin lymphoma	39	3.62	Hodgkin lymphoma	20	3.98
Colon cancer	38	3.53	Pancreas cancer	19	3.78
Breast cancer	34	3.15	Colon cancer	18	3.59
Unknown	34	3.15	Breast cancer	15	2.99
Pancreas cancer	33	3.06	Other	11	2.19
Other	32	2.97	Malignant melanoma	11	2.19
Kidney cancer	28	2.60	Kidney cancer	11	2.19
Cervical cancer	24	2.23	Cervical cancer	10	1.99
Malignant melanoma	23	2.13	Oesophagus cancer	10	1.99
Other gynaecologic cancer	14	1.30	Gallbladder cancer	9	1.79
Oesophagus cancer	14	1.30	Stomach cancer	8	1.59
Stomach cancer	14	1.30	Leukaemia: Acute myeloid	7	1.39
Rectum cancer	13	1.21	Other gynaecologic cancer	6	1.20
Gallbladder cancer	12	1.11	Metastasis of adenocarcinoma, unknown primary tumour	6	1.20
Metastasis of adenocarcinoma, unknown primary tumour	9	0.83			
Leukemia: Acute myeloid	8	0.74	Rectum cancer	5	1.00
Brain cancer	7	0.65	Penile cancer	5	1.00
Penile cancer	7	0.65	Brain cancer	3	0.60
Testicular seminoma	6	0.56	Connective tissue cancer	3	0.60
Lip cancer	6	0.56	Multiple myeloma	3	0.60
Multiple myeloma	5	0.46	Testicular seminoma	2	0.40
Connective tissue cancer	5	0.46	Lip cancer	2	0.40
Metastasis of other cancer type, unknown primary tumour	4	0.37	Metastasis of other cancer type, unknown primary tumour	2	0.40
Metastasis of squamous cell carcinoma, unknown primary tumour	4	0.37	Metastasis of squamous cell carcinoma, unknown primary tumour	2	0.40
Uterus cancer	2	0.19	Leukaemia: chronic myeloid	1	0.20
Leukemia: unspecified	2	0.19			
Leukemia: acute lymphoid	2	0.19			
Leukemia: chronic myeloid	1	0.09			
Leukemia: chronic lymphoid	1	0.09			
Bone cancer	1	0.09			

The crude incidence of any cancer was similar for those with no exposure to INSTIs compared to those with any exposure to INSTIs and this remained the case after adjusting for potential confounders (≤6 months exposure vs no exposure adjusted IRR (aIRR): 1.15 [0.89-1.49], >6-12 months: 0.97 [0.71-1.32], >12-24 months: 0.84 [0.64-1.11], >24-36 months: 1.10 [0.82-1.47], >36 months: 0.90 [0.65-1.26], p=0.60, Figure 7.5).

Figure 7.5 Association between any cancer risk and cumulative exposure to INSTIs, adjusted for potential confounders



IRR adjusted for age, sex, ethnicity, HIV risk group, antiretroviral treatment experience, CD4 count, CD4 nadir, BMI, geographical region, hepatitis B, prior diabetes, prior AIDS, prior cancer, prior chronic kidney disease, prior cardiovascular disease, prior end stage liver disease (all fixed at baseline), smoking status (time updated)
Note, INSTI exposure is lagged by 6 months.

7.3.4.1 Sensitivity analyses

Analyses were repeated separately for ADCs and NADCs; results are presented in Table 7.5. Results were similar for NADCs showing no association between INSTI exposure and the incidence of NADCs (≤6 months exposure vs no exposure aIRR: 1.22 [0.90-1.65], >6-12 months: 1.25 [0.89-1.74], >12-24 months: 1.11 [0.84-1.48], >24-36 months: 1.31 [0.95-1.80], >36 months: 1.16 [0.82-1.65], p=0.32).

However, the incidence of ADCs decreased as exposure to INSTIs increased, compared to those with no exposure to INSTIs (≤6 months exposure vs no exposure aIRR: 0.86 [0.52-1.43], >6-12 months: 0.31 [0.13-0.77], >12-24: 0.22 [0.09-0.53], >24-36: 0.56 [0.28-1.15], >36: 0.25 [0.08-0.78], p=0.0002).

Table 7.5 Association between INSTI exposure and NADCs and ADCs

	All NADCs		**All ADCs**	
INSTI exposure, months	**n events (PYFU)**	**Adjusted IRR* (95% CI)**	**n events (PYFU)**	**Adjusted IRR* (95% CI)**
0	625 (127132)	1	205 (127132)	1
≤6	46 (7370)	1.22 (0.90, 1.65)	17 (7370)	0.86 (0.52, 1.43)
>6-12	37 (5835)	1.25 (0.89, 1.74)	5 (5835)	0.31 (0.13, 0.77)
>12-24	52 (9000)	1.11 (0.84, 1.48)	5 (9000)	0.22 (0.09, 0.53)
>24-36	41 (5965)	1.31 (0.95,1.80)	8 (5965)	0.56 (0.28, 1.15)
>36	34 (5355)	1.16 (0.82, 1.65)	3 (5355)	0.25 (0.08, 0.78)
Global p-value		0.32		0.0002

*Adjusted IRR adjusted for age, sex, ethnicity, HIV risk group, antiretroviral treatment experience, CD4 count, CD4 nadir, BMI, geographical region, hepatitis B, prior diabetes, prior AIDS, prior cancer, prior chronic kidney disease, prior cardiovascular disease, prior end stage liver disease (all fixed at baseline), smoking status (time updated)

Results from other sensitivity analyses are presented in Table 7.6. Analyses were rerun only including centrally validated cancer events. As the study validation period started after 1 January 2015 for 86% of participants and INSTIs were not widely used before this date, this analysis was left censored at the latest of 1 January 2015 and the start of the validation period. Additionally, those participants with a validation period before 1 January 2015 had a much higher incidence of cancer compared to those with a validation period starting after this date, and this was driven by very few cancer events. The analysis included 502 events during 65,073 PYFU (IR 7.7/1000 PYFU [95% CI: 7.1-8.4]): 395 NADCs, 107 ADCs. Results were similar to the overall analysis (p=0.06).

Analyses were also repeated only including individuals who started a new ART during follow-up, with baseline here defined as the date of regimen start. This analysis included 20,782 individuals, 574 events during 75,566 PYFU (IR 7.6/1000 PYFU [95% CI: 7.0-8.2]; 431 NADCs and 143 ADCs) and again showed no association between cancer incidence and INSTI exposure. For this analysis, individuals did not have to be naïve to the regimen they started during follow-up. The analysis was then repeated restricted to those starting a regimen they were naïve to, and again this showed similar results.

Further sensitivity analyses excluding individuals with any cancer prior to baseline, only excluding individuals with cancer prior to baseline where the type of cancer was unknown, using complete case analysis to account for missing data, and using Poisson regression with robust standard errors for the main analysis, all showed similar results to the overall analysis.

Table 7.6 Adjusted incidence of cancer, by increasing cumulative exposure to INSTIs, calculated from a range of sensitivity analyses

	n individ-uals included	n cancers include-ed		0 months	≤6 months	>6-12	>12-24	>24-36	>36	Global P-value
Primary analysis	29340	1078	Adjusted IRR (95% CI)	1	1.15 (0.89, 1.49)	0.97 (0.71, 1.32)	0.84 (0.64, 1.11)	1.10 (0.82, 1.47)	0.90 (0.65, 1.26)	0.60
			n cancers (PYFU)	830 (127132)	63 (7370)	42 (5835)	57 (9000)	49 (5965)	37 (5355)	
All validated cancers	25118	502	Adjusted IRR (95% CI)	1	1.25 (0.88, 1.78)	0.98 (0.65, 1.47)	0.65 (0.45, 0.93)	0.80 (0.56, 1.14)	0.77 (0.54, 1.10)	0.06
			n cancers (PYFU)	336 (43381)	36 (3300)	26 (3061)	34 (5795)	34 (4656)	36 (4880)	
Excluding individuals with cancer prior to baseline	27958	983	Adjusted IRR (95% CI)	1	1.12 (0.85, 1.47)	0.94 (0.68, 1.31)	0.81 (0.61, 1.08)	1.08 (0.80, 1.46)	0.87 (0.61, 1.23)	0.56
			N events (PYFU)	759 (119581)	57 (6910)	38 (5499)	51 (8470)	45 (5614)	33 (5023)	
Excluding individuals with cancer prior to baseline, where the cancer type is unspecified	29040	1078	Adjusted IRR (95% CI)	1	1.15 (0.88, 1.49)	0.96 (0.70, 1.32)	0.84 (0.64, 1.09)	1.09 (0.81, 1.47)	0.90 (0.64, 1.26)	0.60
			N events (PYFU)	830 (12692)	63 (7357)	42 (5830)	57 (8994)	49 (5963)	37 (5353)	

Only including individuals who started a new ART	20782	574	Adjusted IRR (95% CI)	1	0.92 (0.71, 1.22)	0.84 (0.62, 1.51)	0.75 (0.57, 0.99)	0.75 (0.64, 1.18)	0.77 (0.55, 1.08)	0.28
			N events (PYFU)	312 (40821)	64 (7801)	46 (6171)	64 (9535)	49 (6325)	39 (5647)	
Only including individuals who started a new ART to which they were naïve	9983	274	Adjusted IRR (95% CI)	1	0.83 (0.56, 1.24)	0.71 (0.45, 1.14)	0.57 (0.37, 0.88)	0.74 (0.46, 1.19)	0.62 (0.36, 1.07)	0.08
			N events (PYFU)	171 (21005)	28 (3559)	19 (2854)	23 (4311)	19 (2767)	14 (2414)	
Using complete case analysis to account for missing data	7071	298	Adjusted IRR (95% CI)	1	1.02 (0.58, 1.78)	1.72 (1.05, 2.84)	1.19 (0.74, 1.91)	1.50 (0.91, 2.47)	1.25 (0.72, 2.15)	0.21
			N events (PYFU)	218 (33507)	13 (1933)	17 (1571)	19 (2536)	17 (1794)	14 (1756)	
Using Poisson regression with robust standard errors	29340	1078	Adjusted IRR (95% CI)	1	1.15 (0.88, 1.49)	0.97 (0.70, 1.33)	0.84 (0.64, 1.11)	1.10 (0.82, 1.47)	0.90 (0.65, 1.26)	0.60
			N events (PYFU)	830 (127132)	63 (7370)	42 (5835)	57 (9000)	49 (5965)	37 (5355)	

IRR adjusted for age, sex, ethnicity, HIV risk group, antiretroviral experience, CD4 count, CD4 nadir, BMI, geographical region, hepatitis B, prior diabetes, prior AIDS, prior cancer, prior chronic kidney disease, prior cardiovascular disease, prior end stage liver disease (all fixed at baseline), smoking status (time updated

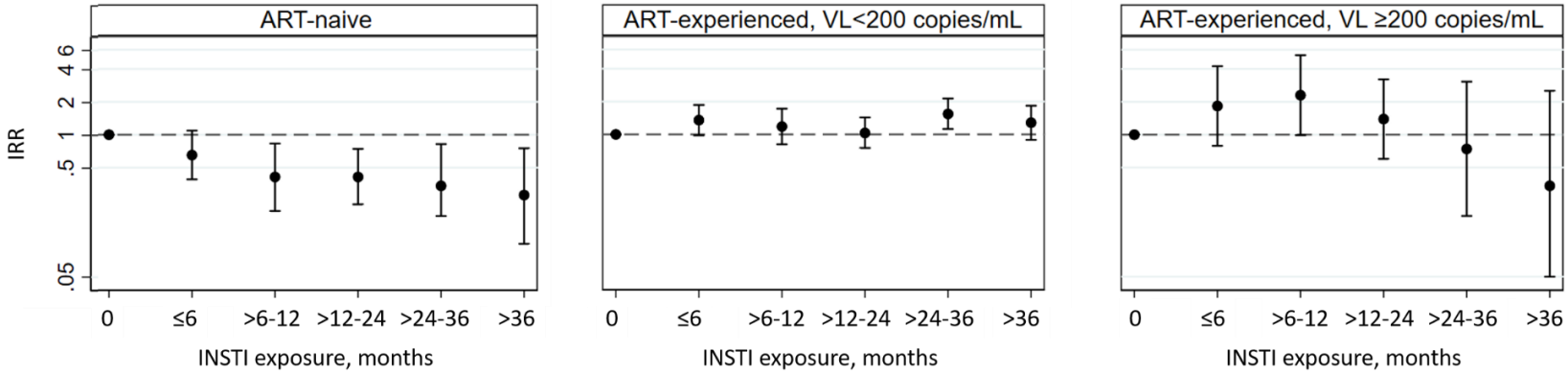
As mentioned above, there is the possibility that confounding by indication is present in this analysis as individuals with cancer may be preferentially given INSTIs, either because of their presumed favourable safety profile or the fewer number of interactions between INSTIs and chemotherapy compared to other drug classes (331,578). Therefore, to explore whether individuals with cancer are preferentially given INSTIs, I calculated the proportion of individuals who switched ART within 1-year post cancer diagnosis. Of 1078 individuals with cancer, 337 (31.3%) switched ART within 1-year. The majority of these switched to an INSTI (62% switched to INSTIs, 14% non-NRTIs, 14% PIs, 10% other), suggesting those with cancer are more likely to be prescribed INSTIs and therefore confounding by indication is likely to be present. This bias could make it seem as though the incidence of cancer is higher on INSTIs, however by lagging INSTI exposure by 6 months, I have tried to minimise this bias.

7.3.4.2 Subgroup analyses

I found a significant interaction between INSTI exposure and baseline ART-experience (interaction $p<0.0001$) showing that the association between INSTI exposure and cancer incidence differed between those ART-naïve and those ART-experienced at baseline. The adjusted IRRs for cancer for each INSTI exposure category, stratified by baseline ART-experience are presented in Figure 7.6. For individuals who were ART-naïve at baseline (n=7172), there were 228 cancers: 104 NADCs and 124 ADCs. The adjusted incidence of cancer decreased as cumulative INSTI exposure increased, and this was mainly driven by a decreasing incidence of ADCs (Figure 7.6). Conversely, for those ART-experienced with a suppressed VL (n=19951, 770 cancers: 680 NADCs and 90 ADCs) or with uncontrolled viremia (n=2217, 80 cancers: 51 NADCs and 29 ADCs) at baseline, the incidence of cancer was similar across all INSTI exposure categories.

There was no interaction between INSTI exposure and age group, CD4 cell nadir, or baseline smoking status (interaction $p>0.1$ for all). This means the association between INSTI exposure and cancer incidence was the same regardless of an individual's age group, CD4 cell nadir, or baseline smoking status.

Figure 7.6 Adjusted incidence of cancer, by INSTI exposure compared to no exposure, stratified by ART-experience at baseline



n individuals at risk	7172	3796	3318	2867	1998	1167	19951	7936	7068	6309	4694	3040	2217	776	675	594	418	273
n cancers	181	16	8	12	7	4	590	41	28	39	40	32	59	6	6	6	2	1
n NADCs	68	6	7	12	7	4	518	37	26	37	32	30	39	3	4	3	2	0
n ADCs	113	10	1	0	0	0	72	4	2	2	8	2	20	3	2	3	0	1

IRR calculated from a negative binomial regression model, adjusted for the same confounders as the main analysis, and including an interaction term between INSTI exposure and ART-experience at baseline

7.4 Discussion

In this chapter, I assessed the association between exposure to INSTIs and the incidence of any cancer. I included just under 30,000 PLWH from RESPOND and over 1000 cancer events. I found no association between cumulative INSTI exposure and the risk of any cancer overall. Additionally, when analysing NADCs and ADCs separately, I found that whilst there was no association between INSTI exposure and NADCs, the incidence of ADCs decreased significantly with increasing exposure to INSTIs.

This is one of the first studies assessing the association between INSTI use and cancer in real-life settings and using centrally validated events. INSTI use is becoming increasingly widespread as INSTIs are recommended as first-line treatment for PLWH (331,578) and, as cancer incidence is increasing amongst the aging population of PWLH, it is of vital importance to identify potential risk factors for cancer, including the impact of different ARVs. Such analyses require substantial power and follow-up time, limiting the availability of high-quality data. Additionally, studies have shown that other risk factors for cancer, such as smoking, a low CD4 count, and co-infections, are more prevalent in PLWH (657). For these reasons, the results in this chapter showing no increased risk of NADCs and a lowered risk of ADCs on INSTIs are reassuring for PLWH and clinicians. It is possible that cancer risk differs amongst individual INSTIs or between individual cancers, which I was not able to look at, due to limited power. My findings are, however, in line with early animal trials of INSTIs which showed that none of the individual INSTIs showed signs of displaying any type of carcinogenic effects (699–702).

Median follow-up in the analysis was 6.2 years and median exposure to INSTIs was 2.7 years. This may have been too short to detect a signal, given cancers can take many years to develop. Studies which have shown a carcinogenic effect of other drugs have included a wide range of follow-up times. For example a meta-analysis showing the effect of azathioprine on lymphoma risk included studies with median follow-up ranging from 2.8 years to 9 years (703) and a meta-analysis including 54

studies found an increased risk of breast cancer up to 10 years after stopping hormonal contraceptive use (704). Studies with longer follow-up time are therefore needed to confirm these findings.

As individuals in RESPOND are only able to start an INSTI during follow-up, I performed sensitivity analyses only including individuals who started any new treatment during follow-up, either from ART-naïve or ART-experienced status. The aim of this analysis was to make the non-INSTI group more comparable to the INSTI group and exclude individuals on long-term stable ART. I included 20,782 individuals and results were similar to the main analysis. As INSTIs are recommended in most treatment guidelines as first-line treatment for PLWH (331,535,578), it is possible this analysis introduced other bias as those starting PIs are likely to be younger, using less co-medication, and have fewer comorbidities compared to those starting INSTIs. Nonetheless, it is reassuring to show that the results were consistent in this analysis compared to the overall analysis.

Subgroup analysis showed that for individuals who were ART-experienced at baseline, there was no association between INSTI exposure and cancer incidence, however for those ART-naïve at baseline, the incidence of cancer decreased with increasing INSTI exposure, and this was mainly driven by a decreasing incidence of ADCs. Whilst in the overall analysis, 77% of cancers were NADCs, amongst those who were ART-naïve at baseline, just over half of cancers (54%) were ADCs. Many studies have previously shown that initiating ART for PLWH who are ART-naïve can lead to a drastic reduction in the incidence of AIDS events, including ADCs, due to improvements in immune function and viral suppression (644,705,706). These results are likely showing the impact of starting an effective ART-regimen for those who were ART-naïve, rather than being specific to INSTIs, although INSTIs have been shown to be particularly effective at quickly improving immune function and lowering viremia (301,321,697,698).

7.4.1 Strengths and limitations

Results from this analysis should be considered with limitations in mind. Firstly, whilst I was able to include over 1000 cancers, there were still too few events to assess the association between the risk of individual cancers and INSTI exposure, or as mentioned above, to assess individual INSTIs. As has been seen with the increased risk of anal cancer with long-term use of PIs, associations between ARVs and cancers may differ between specific types of cancers (668,669).

As mentioned throughout this thesis, cohorts in RESPOND who provide data from a sample of their participants are requested to include at least half using INSTIs, and this may not be representative of the general population of PLWH in Europe and Australia, although INSTIs are becoming increasingly used.

Additionally, the date of cancer diagnosis in RESPOND is reported as the date the cancer is confirmed through a biopsy, if available. Whilst most clinicians would wait for a formal diagnosis and disease stage before switching an individual's ART regimen, it is possible that on first suspicion of cancer a clinician may switch an individual's ART to ensure there are few interactions with chemotherapy. This may appear as the individual was on INSTIs before cancer diagnosis. Analyses were lagged to address this potential bias. As mentioned above, it is also possible that follow-up in the study was too short to detect a signal given cancer can take many years to develop. There is also some missing data in RESPOND for key variables, such as smoking status, and whilst I have adjusted for key confounders in the analysis, there is still the possibility of residual confounding or confounding by indication. I have explored the possibility of confounding by indication through a range of methods, such as lagging INSTI exposure, assessing which treatments individuals are switched to post cancer diagnosis, and only including individuals who switched their treatment during follow-up to exclude those on long-term stable ART, all with consistent results. There may also be other potential confounders which were not collected in RESPOND, such as alcohol use or human papillomavirus co-infection, both of which could increase the risk of cancer.

There are also several strengths to this analysis. RESPOND is a large cohort with routinely collected data from real-life settings across Europe and Australia. I was therefore able to include many cancer events and many individuals exposed to INSTIs in the analysis. Events in RESPOND are rigorously collected and a subset are centrally validated by clinicians at the RESPOND coordinating centre using pre-specified algorithms.

7.4.2 Conclusions

In conclusion, there was no association between the risk of cancer and cumulative exposure to INSTIs amongst ART-experienced PLWH. The risk of cancer decreased with increasing exposure to INSTIs amongst ART-naïve individuals, and this was mainly driven by a decreasing incidence of ADCs.

7.4.3 Publications

The results from this project were presented at the International AIDS Society (IAS) conference 2021 as a virtual poster (appendix X) and the manuscript has been submitted for publication.

Chapter 8 Discussion

With over 30 ARVs now approved by the EMA, the choice of treatment for PLWH is constantly improving, in settings where these treatments are readily available. It is therefore possible to take a more individual-centred approach when choosing treatment regimens, taking into account the efficacy of the drugs and the individual's history of drug resistance, whilst attempting to minimise toxicities associated with the drugs and simplify treatment regimens. To do this, however, long-term data on the safety and efficacy of contemporary ARVs is needed.

In this thesis I aimed to assess the use and outcomes of contemporary ART in PLWH in Europe and Australia using data from RESPOND. The main focus was on use and outcomes of INSTIs, including the association between INSTI use and incident cancer, and on the use and outcomes of 2DRs. I also assessed temporal trends in cancer incidence across different ART-eras. As INSTIs and the treatment strategy of using 2DRs are relatively new, long-term follow-up of these ARVs in real-life settings is missing.

8.1 My role in RESPOND

RESPOND was initiated in 2017, and therefore when I started my PhD in 2018, it was still a relatively new collaboration. Throughout my PhD, I had several roles within the collaboration. For each project presented in this thesis, I was the lead researcher on the project, and with help from my supervisors, other clinicians working at CHIP in Copenhagen, and other members of the RESPOND collaboration, I worked on the projects from design until publication. I was also part of the RESPOND secretariat, which allowed me to be involved in the day to day running of RESPOND. Additionally, I was centrally involved in cleaning the data and helping to improve the data quality, by monitoring the completeness of the data over time and providing feedback on this to the cohorts. Being involved in several different aspects of RESPOND, and from an early stage, gave me an insight into how a large cohort collaboration is set-up and run, the advantages of such a collaboration, for example the benefit of sharing

research ideas amongst many different researchers, and the challenges, such as the difficulty collecting specific types of data from all cohorts. It was also helpful to understand from members of the collaboration what the important research questions were for HIV treatment and how to interpret analysis results in a way which was useful for PLWH and their clinicians.

8.2 Summary of the main findings of the PhD

To explore the literature available on contemporary ART up to 2020, I completed two literature reviews in Chapter 2. One review focused on the incidence of, reasons for, and factors associated with discontinuation of INSTIs in real-life settings from 2007, when the first INSTI was approved by the EMA, until 2020. I found that discontinuation of RAL was reported to be higher than for EVG/c or DTG, and reasons for discontinuation differed between INSTIs; the most common reason for discontinuation of RAL was treatment simplification, whilst the most common reason for discontinuation of DTG and EVG/c was toxicity, with the proportion discontinuing for toxicity generally ranging from 5%-10% across the INSTIs. Additionally, the risk of discontinuation was higher for females, older individuals and those taking abacavir at the same time as the INSTI. There were some gaps in the literature, however, as no studies included in the review were performed in international settings and therefore there was no comparison of discontinuation between countries or geographical regions.

The second review focused on the incidence of clinical outcomes including cancer, CVD, ESLD, and ESRD, with use of contemporary 3rd drugs, from 1998, when ATV was first approved by the EMA, until 2020. For this review, I included the INSTIs DTG, EVG/c, and RAL, as well as the PIs ATV and DRV/r and the NNRTIs EFV and RPV. The majority of studies included in the review focused on CVD incidence. The review I conducted showed no association between CVD incidence and the use of INSTIs. There were mixed results reported on the use of other 3rd drug ARVs, such as ATV and DRV/r, and the risk of CVD, and this was likely due to differences between the studies included, in terms of study design, length of follow-up, sample size, and the

definition of CVD used. Similarly, two studies assessing the risk of cancer with use of RAL also reported mixed results, with one showing no association and another reporting a higher risk of cancer with use of RAL. No studies reported an association between contemporary ARVs and ESLD and, for ESRD, one study reported a higher incidence with use of ATV. Again, I identified several gaps in the literature; no studies focused specifically on DTG or EVG/c, likely due to a lack of follow-up for newer ARVs. Additionally, more contemporary regimen types such as dual therapy were not included, and the studies included were relatively small so may not have been powered to look at rarer clinical endpoints.

In Chapter 3, I provided an overview of the structure of and data collection in RESPOND, as well as an overview of D:A:D, and the statistical methods used to analyse the RESPOND and D:A:D data.

Chapter 4 of the thesis focused on the choice of and discontinuation of INSTIs. The aims of the chapter were to identify baseline characteristics associated with initiating DTG, EVG/c, and RAL, compare rates of discontinuation and reasons for discontinuation of the INSTIs, and identify baseline characteristics associated with INSTI discontinuation. Overall, I included 9702 individuals in the analysis with follow-up from 1st January 2012 to 1st October 2017: 5051 (52.1%) on DTG, 1933 (19.9%) on EVG/c and 2718 (28.0%) on RAL. I found that as the year of INSTI start increased, the likelihood of starting RAL or EVG/c decreased compared to DTG, with a greater decline for RAL, and uptake of DTG compared to the other INSTIs was higher in Western Europe compared to other European regions. Discontinuation was highest on RAL, primarily due to treatment simplification, and the main reason for discontinuation of DTG and EVG/c was toxicity, with discontinuation due to nervous system toxicities being highest on DTG. Whilst the proportion discontinuing due to toxicity was highest on DTG, this proportion was low across all INSTIs (<5%). Females were more likely to discontinue an INSTI, as were those with hepatitis C or a prior non-AIDS defining cancer, whilst those in Southern and Eastern Europe were less likely to discontinue an INSTI.

In Chapter 5, I analysed the use and virological, immunological, and clinical outcomes of 2DRs compared to 3DRs. As more contemporary ARVs have a higher barrier to resistance and are more effective, the use of regimens with fewer ARVs is becoming more common. I included 9791 individuals in this analysis from 1st January 2012 to 1st October 2018: 1088 (11.1%) on 2DRs and 8703 (88.9%) on 3DRs. The most common 2DRs included were DTG plus 3TC (n=248), RAL plus DRV/b (n=215), and DTG plus DRV/b (n=200). I found that a similar proportion of individuals on 2DRs and 3DRs achieved CD4 cell count recovery (defined as a CD4 count increase from baseline of greater than 100 cells/mm^3 or greater than 25%), VL<200 copies/mL, and composite treatment outcome success (with failure defined as at least one of: VL ≥ 200 copies/mL, missing VL, any ART-regimen change, AIDS event, or death), at 6- and 12-months follow-up. I also found that during a median follow-up of 2.6 years, there was a similar incidence of severe clinical events on 2DRs and 3DRs, after adjusting for baseline characteristics, primarily age.

Chapters 6 and 7 of this thesis focused specifically on cancer as a clinical endpoint. In Chapter 6, I combined data from D:A:D and RESPOND to assess cancer trends across different ART-eras from 1st January 2004 to 31st December 2019. I included 66,636 individuals and 3634 incident cancers. I found that overall cancer incidence decreased over time, as did the incidence of ADCs and infection-related cancers. However, BMI-related cancers increased, whilst NADCs and smoking-related cancers remained steady. Finally, I looked at trends in the incidence of death due to any cancer over time and found that the incidence was decreasing.

In the final results chapter, I investigated whether increasing exposure to INSTIs as a class was associated with an increased risk of cancer, with follow-up from 1st January 2012 to 31 December 2019. I included 29,340 individuals, 13,950 of which had exposure to INSTIs during follow-up. Overall, there were 1078 cancer events. I found that there was no association between the risk of cancer and cumulative exposure to INSTIs, however this differed between those ART-naïve at baseline and those ART-experienced at baseline. In those ART-experienced, there was no association between cancer incidence and INSTI exposure, however the risk of cancer decreased

with increasing exposure to INSTIs amongst ART-naïve individuals, and this was mainly driven by a decreasing incidence of ADCs.

8.3 Limitations of main findings

Specific limitations of each analysis are detailed in the corresponding chapters. As the data used for all analyses in this thesis are from observational cohorts, there are some general limitations which I discuss here. Firstly, whilst RESPOND collects data from real life settings, there are some inclusion criteria which cohorts must satisfy to be included in the collaboration, such as having a dedicated data manager and carrying out regular quality assurances on the data provided. Whilst this ensures that the data in RESPOND is of a better quality, it may limit the generalisability of the results when compared to the wider population of PLWH, as smaller centres with less resources are less likely to be included in the collaboration. Individuals attending these centres, and the treatments available at these centres, may differ from other, larger centres which were included. Other characteristics of individuals in RESPOND differ from the wider population of PLWH, for example in RESPOND, 75% of participants are male and 72% are of white ethnicity compared to 17% Black ethnicity. Globally, almost half of PLWH are female and at the end of 2018, 41% of adults living with HIV in the USA were Black or African American (707–709). Therefore, findings from RESPOND may be less generalisable to other regions where the demographics of PLWH differ.

As mentioned in previous chapters, RESPOND was originally set up to focus on INSTIs, and therefore one of the inclusion criteria into RESPOND is that cohorts providing data on a sample of individuals at their clinics, should ensure at least half of those included are taking INSTIs. Again, this may limit generalisability as more individuals in RESPOND may be taking INSTIs compared to the general population of PLWH. However, many cohorts did provide data on all individuals at the clinics, rather than a sample, and some individuals who were not initially included in RESPOND were subsequently included in later versions of the data; therefore this limitation may be of less importance.

As this is a cohort study, there will inevitably be unmeasured confounding and unknown confounding present. For example, in analyses focused on use of INSTIs or 2DRs, it is likely that the cost of treatment or an individual's history of drug-resistance or adherence to treatment could influence the decision to prescribe a specific ARV. Similarly, for analyses of clinical events, it may be that an individual's level of exercise or family history of the events, may affect the likelihood of the event occurring; this data is unfortunately not collected in RESPOND. Whilst RCTs are generally considered the gold standard for answering many research questions, as these would not be subject to confounding, many of the questions I address in this thesis are unlikely to be answered in a RCT. Studies looking at relatively rare clinical outcomes, such as cancer, require large samples with long follow-up, and it is often not feasible or too expensive to conduct a large enough RCT. Additionally RCTs often have strict inclusion criteria which can limit the generalisability of the results. Hence, the use of cohort studies, such as RESPOND and D:A:D, are of vital importance when addressing these clinical questions, and results from RCTs and observational studies should be interpreted together.

Missing data is another limitation which is often more likely to occur when using observational data. In RESPOND, there is some missing data on key variables, for example in the most recent version of the database, 36% of participants were missing data on smoking status. Additionally, the completeness of the data varies between the cohorts included. It is also possible that not all clinical events experienced by participants are fully reported by cohorts, which is difficult to verify. Data quality in RESPOND has improved over time and the later chapters of this thesis use more recent versions of the database with better quality data. I also used multiple methods to account for missing data to try to address this issue, all showing similar results to the primary analyses. To try to ensure that clinical events were not underreported, I compared the incidence of each type of clinical event in each cohort to the overall incidence in RESPOND. This was fed back to the cohorts and decisions were made on whether to include specific cohorts in each analysis; details of these are included in the appropriate chapters. Whilst these strategies were used to minimise the effects

of missing data, results from this thesis should be interpreted with this limitation, as well as the others outlined above, in mind.

8.4 Strengths of main findings

There are several strengths to the analyses presented in this thesis. RESPOND is a large, multicentre and heterogeneous study based in real-world settings across Europe and Australia. The findings in this thesis are therefore more generalisable to the wider population of adults living with HIV in Europe and Australia. The methodology in RESPOND is built on that of existing cohort collaborations, such as EuroSIDA and D:A:D, which have contributed research findings to the field of HIV for many years.

RESPOND includes approximately 30,000 PLWH and it was therefore possible to perform analyses that individual, smaller cohorts are not necessarily able to do, for example assessing the incidence of relatively uncommon clinical endpoints such as cancer, performing intraclass comparisons of INSTIs in Chapter 4, and assessing 2DRs which are currently less commonly used in Chapter 5.

Finally, clinical events in RESPOND are rigorously collected and a subset are centrally validated by clinicians at the RESPOND coordinating centre using pre-specified algorithms. To improve the event data quality further, a subset of these events are reviewed by an expert from the relevant medical specialty, external to RESPOND.

8.5 Clinical relevance of main findings and future research

I believe the findings in this thesis are of key importance for PLWH and their clinicians. INSTIs are one of the latest ARV drug classes to be approved and are recommended as first-line and switch treatment in all international treatment guidelines, however systematic post-marketing surveillance data and assessment of long-term follow-up in real-life settings was missing from the literature when this thesis was started. My findings in Chapter 4 showing that discontinuation overall and discontinuation due to toxicity is relatively low on INSTIs compared to other 3rd drug ARVs is a reassuring

finding as it suggests that INSTIs have a good overall safety profile. I did however find that nervous system toxicities are higher on DTG, and it is therefore important to consider this as a potential adverse event and monitor this for individuals taking DTG. Additionally, I have identified characteristics associated with INSTI discontinuation and again, this may help inform caretakers about which groups of individuals one may consider monitoring more closely when taking INSTIs, such as females and those with hepatitis C coinfection. Since the analysis was done, another INSTI, cabotegravir, has been approved for use by the EMA. I was also not able to include bictegravir in the analysis as there is currently limited follow-up on this INSTI. Therefore, further large-scale research is needed including these INSTIs, once there is sufficient follow-up available. Additionally, it is important to investigate the specific nervous system toxicities associated with DTG use more closely, to understand whether switching to another INSTI would cause the same adverse event, and to understand why specific groups in the population, such as females, are more likely to discontinue INSTIs.

To the best of my knowledge, the analyses in Chapter 5 are one of the first to compare clinical outcomes of contemporary 2DRs to 3DRs. As the prevalence of several non-AIDS comorbidities, and therefore the need for concomitant medication, is increasing amongst the aging population of PLWH, it is becoming increasingly important to be able to simplify ART regimens and minimise the potential for toxicities and drug-drug interactions. The results from this chapter show that 2DRs are a viable treatment option with regards to virological, immunological, and clinical outcomes. However, further research is needed on the long-term durability of 2DRs and, whilst short term data from RCTs show that drug resistance on 2DRs is relatively low (626,710), further research including longer follow-up on this is needed. Additionally, due to low numbers in the analysis, I grouped 2DRs together and I analysed severe clinical events as a composite endpoint. Once more data becomes available, research on individual 2DRs and individual clinical events is needed.

Chapter 6 assessing cancer trends across different ART-eras provides an overview of how cancer incidence has changed amongst PLWH. Whilst overall cancer incidence slightly decreased over time, this differed between different types of cancers. As

expected, the incidence of ADCs and infection-related cancers have decreased over time, likely due to the use of more effective ART and immune restitution. However, the incidence of BMI-related cancers has increased over time and smoking-related cancers remained constant. It is important to understand the causes of these trends, whether it be changes in lifestyle factors or toxicities associated with ART use, for example some ARVs have been shown to be associated with weight gain which could translate into an increase in the incidence of clinical outcomes, including BMI-associated cancers. These results provide important insight into the types of cancers which need closer monitoring and highlights the need for closer focus on prevention strategies for smoking and BMI-related cancers. Further research on temporal trends of individual cancers is needed, as it is likely that there is some heterogeneity in the groups of smoking, BMI, and infection-related cancers, as well as more research on the causes of these trends. It would also be valuable to use the population attributable fraction (PAF) method to estimate the proportion of different cancers that could be prevented if exposure to specific risk factors were reduced, for example the proportion of smoking-related cancers that could be prevented by reducing the number of PLWH who smoke.

The final results chapter showing that cumulative exposure to INSTIs is not associated with an increased risk of cancer suggests that use of INSTIs as a group should not be a safety concern for cancer risk. Additionally, for individuals who started INSTIs from ART-naïve, the incidence of cancer decreased with increasing exposure to INSTIs. As cancer is a relatively rare outcome, large studies, such as RESPOND, are needed to detect associations between cancer incidence and ART use. However, as has been seen with the association between older PIs and anal cancer, future research is needed to assess the association between individual INSTIs and the risk of individual cancers. Additionally, the 95% confidence intervals for the adjusted incidence rate ratio of cancer for each INSTI exposure group were relatively wide and therefore an increased risk of cancer could not be completely ruled out, and so longer follow-up is needed to confirm this finding.

8.6 Lessons learnt from the PhD

I have learnt many lessons from working on RESPOND and completing my PhD. As detailed in previous chapters, one limitation of my analyses is the impact of missing data and potential confounders which were not collected in RESPOND. Whilst it is extremely hard to ensure consistent data quality amongst all of the cohorts in a large collaboration, I have learnt the importance of dedicating time to improving data quality, understanding the key variables which need to be collected for each analysis, and understanding the advantages and disadvantages of different methods of handling missing data. As a statistician, it is also important to work with clinicians to better understand the clinical side of the analyses. This is helpful for designing the analysis projects, determining how to analyse them, interpreting the results, and explaining the results to a multi-disciplinary audience. In future, I hope to be able to spend some time shadowing a clinician in a HIV clinic to better understand the full process that takes place from a clinician seeing an individual in clinic to their data being uploaded for analysis. Whilst this was planned for the final year of my PhD, it was unfortunately not possible to do this due to travel restrictions during the coronavirus pandemic. Finally, I have developed skills in public speaking through presenting my work at RESPOND meetings and at international conferences. In future, I hope to use all of these skills and experiences to further develop my career as a medical researcher.

8.7 Concluding remarks

The number of options, effectiveness, and tolerability of contemporary ART has significantly improved over the past 30 years, and the use of these ARVs has transformed HIV from a fatal illness into a manageable, chronic condition, with the life expectancy of PLWH now approaching that of the general population. With an aging population of PLWH, however, there has been an increase in the burden of comorbidities, including cancer. As there is no cure for HIV, ART use is lifelong, and it is therefore crucial to identify any adverse events associated with ART use and any associations between ART use and the risk of comorbidities. In this thesis, I assessed

pertinent clinical questions related to different aspects of the use and outcomes of contemporary ART, with a specific focus on INSTIs and 2DRs. The results from my analyses provide evidence from large, real-life and heterogenous settings that INSTIs and 2DRs are safe and effective options for PLWH in Europe and Australia. My findings also contribute to further develop principles of personalised HIV care by highlighting key subgroups who would benefit from closer monitoring whilst on these ARVs. However, as follow-up accrues in RESPOND, further research on individual ARVs and individual cancers is needed.

Appendices

Appendix I: Search strategy for INSTI discontinuation literature review

Final search was done on 12th February 2020

Pubmed (n=703 articles identified)

("HIV"[MeSH Terms] OR "HIV"[All Fields] or “human immunodeficiency virus”[All Fields] or “human immuno deficiency virus”[All Fields]) AND (("hiv integrase inhibitors"[MeSH Terms]) OR (“integrase inhibitor*”[All Fields] or “INSTI*”[All Fields] or “integrase strand transfer inhibitor*”[All Fields]) OR ("raltegravir potassium"[MeSH Terms] OR "raltegravir"[All Fields] OR "Isentress"[All Fields] OR “dutrebis” [All Fields]) OR ("dolutegravir"[All Fields] OR "triumeq"[All Fields] OR "tivicay"[All Fields]) OR (“Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination”[All Fields] or "elvitegravir"[All Fields] OR "vitekta"[All Fields] OR "stribild"[All Fields] OR “Genvoya”[All Fields])) AND (discontinu*[All Fields] OR withdraw*[All Fields] or deprescrib*[All Fields] or cessation*[All Fields] or stop*[All Fields] or switch*[All Fields]) AND ("2007/01/01"[Publication Date] : "3000"[Publication Date])

Embase (n=3057 articles identified)

1. Human immunodeficiency virus/

2. (human immunodeficiency virus or human immuno deficiency virus or hiv).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

3. 1 or 2

4. integrase inhibitor/

5. (integrase inhibitor* or insti* or integrase strand transfer inhibitor*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

6. raltegravir/ or lamivudine plus raltegravir/

7. dolutegravir/ or abacavir plus dolutegravir plus lamivudine/ or dolutegravir plus lamivudine plus tenofovir disoproxil/ or dolutegravir plus emtricitabine plus tenofovir alafenamide/ or dolutegravir plus rilpivirine/

8. cobicistat plus elvitegravir plus emtricitabine plus tenofovir disoproxil/ or cobicistat plus elvitegravir plus emtricitabine plus tenofovir alafenamide/ or elvitegravir/

9. (raltegravir or Isentress or dutrebis).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

10. (elvitegravir or vitekta or stribild or genvoya).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

11. (dolutegravir or tivicay or Triumeq).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

12. drug withdrawal/

13. (discontinu* or withdraw* or deprescrib* or cessation* or switch* or stop*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

14. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11

15. 12 or 13

16. 3 and 14 and 15

17. limit 16 to (human and yr="2007 -Current")

MEDLINE (n=662 articles identified)

1. HIV/

2. (human immunodeficiency virus or human immuno deficiency virus or hiv).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

3. 1 or 2

4. integrase inhibitors/ or hiv integrase inhibitors/

5. (integrase inhibitor* or insti* or integrase strand transfer inhibitor*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

6. Raltegravir Potassium/

7. Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination/

8. (raltegravir or Isentress or dutrebis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

9. (elvitegravir or vitekta or stribild or genvoya).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

10. (dolutegravir or tivicay or Triumeq).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

11. 4 or 5 or 6 or 7 or 8 or 9 or 10

12. (discontinu* or withdraw* or deprescrib* or cessation* or switch* or stop*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

13. 3 and 11 and 12

14. limit 13 to (humans and yr="2007 -Current")

Appendix II: Search strategy for clinical outcomes on contemporary antiretrovirals literature review

Final search was done on 13th February 2020

Pubmed (n=419 articles identified)

((((("HIV"[MeSH Terms] OR "HIV"[All Fields] or “human immunodeficiency virus”[All Fields] or “human immuno deficiency virus”[All Fields])))) AND ((("hiv integrase inhibitors"[MeSH Terms]) OR (“integrase inhibitor*”[All Fields] or “INSTI*”[All Fields] or “integrase strand transfer inhibitor*”[All Fields]) OR ("raltegravir potassium"[MeSH Terms] OR "raltegravir"[All Fields] OR "Isentress"[All Fields]) OR (“dutrebis” [All Fields] OR "dolutegravir"[All Fields] OR "triumeq"[All Fields] OR "tivicay"[All Fields] or “juluca”[All Fields] or “dovato”[All Fields]) OR (“Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination”[MESH Terms] or "elvitegravir"[All Fields] OR "vitekta"[All Fields] OR "stribild"[All Fields] OR “Genvoya”[All Fields]) OR (“Atazanavir Sulfate”[MESH Terms] or “atazanavir"[All Fields] or “Reyataz"[All Fields] or “Evotaz"[All Fields]) Or (“Rilpivirine”[MESH Terms] or “Emtricitabine, Rilpivirine, Tenofovir Drug Combination”[MESH Terms] or “rilpivirine"[All Fields] or “Edurant"[All Fields] or “Complera"[All Fields] or “Eviplera"[All Fields] or “Odefsey"[All Fields]) OR (“Darunavir”[MESH Terms] or “darunavir"[All Fields] or “Prezista"[All Fields] or “Prezcobix"[All Fields] or “Symtuza"[All Fields]) OR (“Efavirenz, Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination”[MESH Terms] or “efavirenz"[All Fields] or “Sustiva"[All Fields] or “Telura"[All Fields] or “atripla"[All Fields] or “viraday"[All Fields] or “Symfi"[All Fields]))))) AND (((“neoplasms”[MESH Terms] or (“aids defining cancer*”[All Fields] or “aids cancer*"[All Fields] or “aids defining malignanc*"[All Fields] or “aids malignanc*"[All Fields] or “non aids defining cancer*"[All Fields] or “non aids cancer*"[All Fields] or “non aids defining malignanc*"[All Fields] or “non aids malignanc*"[All Fields]) OR (“Cardiovascular Diseases”[MESH Terms] or “Myocardial Infarction”[MESH Terms] or “Inferior Wall Myocardial Infarction”[MESH Terms] or “Anterior Wall Myocardial Infarction”[MESH Terms] or “Non-ST Elevated Myocardial

Infarction”[MESH Terms] or “ST Elevation Myocardial Infarction”[MESH Terms] or “coronary artery bypass”[MESH Terms] or “Death, Sudden, Cardiac”[MESH Terms] or “Myocardial Ischemia”[MESH Terms] or “Stroke”[MESH Terms] or “Coronary Artery Disease”[MESH Terms] or “Acute Coronary Syndrome”[MESH Terms] or “Cardiovascular Surgical Procedures”[MESH Terms] or “Cardiac Surgical Procedures”[MESH Terms] or “Angioplasty”[MESH Terms] or “Angioplasty, Balloon, Laser-Assisted”[MESH Terms] or “Angioplasty, Laser”[MESH Terms] or “Angioplasty, Balloon, Coronary”[MESH Terms] or “Angioplasty, Balloon”[MESH Terms] or “Acute Coronary Syndrome”[MESH Terms] or “Endarterectomy, Carotid”[MESH Terms] or “Atherosclerosis”[MESH Terms] or “Cardiovascular Disease"[All Fields] or “sudden cardiovascular mortality"[All Fields] or “sudden cardiovascular death"[All Fields] or “sudden cardiac death"[All Fields] or “sudden cardiac mortality"[All Fields] or “myocardial Infarction"[All Fields] or “cerebrovascular accident"[All Fields] or “stroke"[All Fields] or “myocardial ischemia"[All Fields] or “acute coronary syndrome"[All Fields] or “invasive cardiovascular surg*"[All Fields] or “invasive cardiovascular procedure*"[All Fields] or “coronary artery bypass"[All Fields] or “coronary angioplasty"[All Fields] or “carotid endarterectomy"[All Fields] or “atherosclerosis"[All Fields]) OR (“End Stage Liver Disease”[MESH Terms] or “Liver Transplantation”[MESH Terms] or “hepatic encephalopathy”[MESH Terms] or “ascites”[MESH Terms] or “hepatorenal syndrome”[MESH Terms] or “Carcinoma, Hepatocellular”[MESH Terms] or “End Stage Liver Disease"[All Fields] or “Liver Transplant*"[All Fields] or “Hepatic Encephalopathy"[All Fields] or “Ascites or Hepatorenal Syndrome"[All Fields] or “oesophag* varices bleed*"[All Fields] or “esophag* varices bleed*"[All Fields] or “Hepatocellular Carcinoma"[All Fields]) OR (“Kidney Failure, Chronic”[MESH Terms] or “Kidney transplantation”[MESH Terms] or “end stage renal disease"[All Fields] or “end stage kidney disease"[All Fields] or “terminal renal disease"[All Fields] or “terminal kidney disease"[All Fields] or “chronic Kidney Failure"[All Fields] or “Kidney Transplant*"[All Fields] or “chronic dialysis"[All Fields] or “chronic kidney disease stage 5"[All Fields] or “ckd stage 5"[All Fields] or “ckd stage five"[All Fields] or “chronic kidney disease stage five"[All Fields]))) AND ("1998/01/01"[Publication Date] : "3000"[Publication Date])

Embase (n=3551 articles identified)

1. Human immunodeficiency virus/

2. (human immunodeficiency virus or human immuno deficiency virus or hiv).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

3. 1 or 2

4. integrase inhibitor/

5. (integrase inhibitor* or insti* or integrase strand transfer inhibitors).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

6. atazanavir plus cobicistat/ or atazanavir/ or atazanavir plus ritonavir/

7. efavirenz plus emtricitabine plus tenofovir disoproxil/ or efavirenz/ or efavirenz plus lamivudine plus zidovudine/ or efavirenz plus lamivudine plus tenofovir disoproxil/

8. emtricitabine plus rilpivirine plus tenofovir alafenamide/ or dolutegravir plus rilpivirine/ or rilpivirine/ or emtricitabine plus rilpivirine plus tenofovir disoproxil/

9. cobicistat plus darunavir plus emtricitabine plus tenofovir alafenamide/ or cobicistat plus darunavir/ or darunavir plus ritonavir/ or darunavir/

10. raltegravir/ or lamivudine plus raltegravir/

11. dolutegravir/ or abacavir plus dolutegravir plus lamivudine/ or dolutegravir plus lamivudine plus tenofovir disoproxil/ or dolutegravir plus emtricitabine plus tenofovir alafenamide/

12. cobicistat plus elvitegravir plus emtricitabine plus tenofovir disoproxil/ or cobicistat plus elvitegravir plus emtricitabine plus tenofovir alafenamide/ or elvitegravir/

13. (raltegravir or Isentress or dutrebis).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

14. (elvitegravir or vitekta or stribild or genvoya).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

15. (dolutegravir or tivicay or Triumeq or Dovato or juluca).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

16. (efavirenz or Sustiva or Telura or atripla or viraday or Symfi).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

17. (darunavir or Prezista or Prezcobix or Symtuza).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

18. (rilpivirine or Edurant or Complera or Eviplera or Odefsey).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

19. (atazanavir or Reyataz or Evotaz).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

20. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19

21. malignant neoplasm/

22. (aids defining cancer* or aids cancer* or aids defining malignanc* or aids malignanc* or non aids defining cancer* or non aids cancer* or non aids defining malignanc* or non aids malignanc*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

23. cardiovascular disease/

24. heart infarction/ or acute heart infarction/ or anterior myocardial infarction/ or heart atrium infarction/ or heart infarction size/ or heart muscle necrosis/ or heart reinfarction/ or heart ventricle infarction/ or inferior myocardial infarction/ or non st segment elevation myocardial infarction/ or posterior myocardial infarction/ or silent myocardial infarction/ or st segment elevation myocardial infarction/

25. coronary artery bypass graft/

26. sudden cardiac death/

27. heart muscle ischemia/

28. cerebrovascular accident/

29. cardiovascular mortality/

30. coronary artery disease/ or acute coronary syndrome/

31. cardiovascular surgery/ or heart surgery/

32. angioplasty/ or carotid angioplasty/ or carotid artery stenting/ or coronary stenting/ or laser angioplasty/ or patch angioplasty/ or percutaneous transluminal angioplasty/ or transluminal coronary angioplasty/

33. acute coronary syndrome/ or coronary artery disease/ or ischemic heart disease/

34. carotid endarterectomy/ or atherosclerosis/

35. (Cardiovascular Disease or sudden cardiovascular mortality or sudden cardiovascular death or sudden cardiac death or sudden cardiac mortality or myocardial Infarction or cerebrovascular accident or stroke or myocardial ischemia or acute coronary syndrome or invasive cardiovascular surg* or invasive cardiovascular procedure* or coronary artery bypass or coronary angioplasty or carotid endarterectomy or atherosclerosis).mp. [mp=title, abstract, heading word,

drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

36. liver transplantation/ or end stage liver disease/

37. hepatic encephalopathy/

38. ascites/

39. hepatorenal syndrome/

40. liver cell carcinoma/

41. esophagus varices bleeding/

42. (End Stage Liver Disease or Liver Transplant* or Hepatic Encephalopathy or Ascites or Hepatorenal Syndrome or oesophag* varices bleed* or esophag* varices bleed* or Hepatocellular Carcinoma).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

43. kidney failure/ or end stage renal disease/

44. kidney transplantation/

45. (end stage renal disease or end stage kidney disease or terminal renal disease or terminal kidney disease or chronic Kidney Failure or Kidney Transplant* or chronic dialysis or chronic kidney disease stage 5 or ckd stage 5 or ckd stage five or chronic kidney disease stage five).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

46. 36 or 37 or 38 or 39 or 40 or 41 or 42

47. 43 or 44 or 45

48. 21 or 22

49. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35

50. 46 or 47 or 48 or 49

51. 3 and 20 and 50

52. limit 51 to (human and yr="1998 -Current")

MEDLINE (n=506 articles identified)

1. HIV/

2. (human immunodeficiency virus or human immuno deficiency virus or hiv).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

3. 1 or 2

4. hiv integrase inhibitors/ or integrase inhibitors/

5. (integrase inhibitor* or insti* or integrase strand transfer inhibitor*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

6. Efavirenz, Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination/

7. Rilpivirine/ or Emtricitabine, Rilpivirine, Tenofovir Drug Combination/

8. Darunavir/

9. Raltegravir potassium/

10. Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination/

11. (raltegravir or Isentress or dutrebis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

12. (elvitegravir or vitekta or stribild or genvoya).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

13. (dolutegravir or tivicay or Triumeq or Dovato or juluca).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

14. (efavirenz or Sustiva or Telura or atripla or viraday or Symfi).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

15. (darunavir or Prezista or Prezcobix or Symtuza).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word,

keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

16. (rilpivirine or Edurant or Complera or Eviplera or Odefsey).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

17. (atazanavir or Reyataz or Evotaz).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

18. neoplasms/

19. (aids defining cancer* or aids cancer* or aids defining malignanc* or aids malignanc* or non aids defining cancer* or non aids cancer* or non aids defining malignanc* or non aids malignanc*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

20. Cardiovascular Diseases/

21. myocardial infarction/ or anterior wall myocardial infarction/ or inferior wall myocardial infarction/ or non-st elevated myocardial infarction/ or shock, cardiogenic/ or st elevation myocardial infarction/

22. coronary artery bypass/

23. Death, Sudden, Cardiac/

24. Stroke/

25. coronary artery disease/ or acute coronary syndrome/

26. cardiovascular surgical procedures/ or cardiac surgical procedures/

27. angioplasty/ or angioplasty, balloon/ or angioplasty, laser/

28. acute coronary syndrome/ or coronary artery disease/ or Myocardial Ischemia/

29. Endarterectomy, Carotid/ or Atherosclerosis/

30. (Cardiovascular Disease or sudden cardiovascular mortality or sudden cardiovascular death or sudden cardiac death or sudden cardiac mortality or myocardial Infarction or cerebrovascular accident or stroke or myocardial ischemia or acute coronary syndrome or invasive cardiovascular surg* or invasive cardiovascular procedure* or coronary artery bypass or coronary angioplasty or carotid endarterectomy or atherosclerosis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

31. liver transplantation/ or end stage liver disease/

32. hepatic encephalopathy/

33. ascites/

34. hepatorenal syndrome/

35. Carcinoma, Hepatocellular/

36. (End Stage Liver Disease or Liver Transplant* or Hepatic Encephalopathy or Ascites or Hepatorenal Syndrome or oesophag* varices bleed* or esophag* varices bleed* or Hepatocellular Carcinoma).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

37. Kidney Failure, Chronic/

38. kidney transplantation/

39. (end stage renal disease or end stage kidney disease or terminal renal disease or terminal kidney disease or chronic Kidney Failure or Kidney Transplant* or chronic dialysis or chronic kidney disease stage 5 or ckd stage 5 or ckd stage five or chronic kidney disease stage five).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

40. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

41. 18 or 19

42. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30

43. 31 or 32 or 33 or 34 or 35 or 36

44. 37 or 38 or 39

45. 41 or 42 or 43 or 44

46. 3 and 40 and 45

47. limit 46 to (humans and yr="1998 -Current")

Appendix III: RESPOND study group

AIDS Therapy Evaluation in the Netherlands Cohort (ATHENA): F Wit, P Reiss, M Hillebregt, Stichting HIV Monitoring (SHM), Amsterdam, Netherlands

The Australian HIV Observational Database (AHOD): M Law, K Petoumenos, N Rose, UNSW, Sydney, Australia

Austrian HIV Cohort Study (AHIVCOS): R Zangerle, H Appoyer, Medizinische Universität Innsbruck, Innsbruch, Austria

CHU Saint-Pierre: S De Wit, M Delforge, Centre de Recherche en Maladies Infectieuses a.s.b.l., Brussels, Belgium

EuroSIDA Cohort: G Wandeler, CHIP, Rigshospitalet, RegionH, Copenhagen, Denmark

Frankfurt HIV Cohort Study: C Stephan, M Bucht, Johann Wolfgang Goethe-University Hospital, Frankfurt, Germany

Infectious Diseases, AIDS and Clinical Immunology Research Center (IDACIRC): N Chkhartishvili, O Chokoshvili, Infectious Diseases, AIDS and Clinical Immunology Research Center, Tbilisi, Georgia

Italian Cohort Naive Antiretrovirals (ICONA): A d'Arminio Monforte, A Rodano, A Tavelli, ASST Santi Paolo e Carlo, Milan, Italy; I Fanti, Icona Foundation, Milan, Italy.

Modena HIV Cohort: C Mussini, V Borghi, Università degli Studi di Modena, Modena, Italy

Nice HIV Cohort: C Pradier, E Fontas, K Dollet, C Caissotti, Université Côte d'Azur et Centre Hospitalier Universitaire, Nice, France.

PISCIS Cohort Study: J Casabona, JM Miro, JM Llibre, A. Riera, J. Reyes- Urueña, Centre Estudis Epidemiologics de ITS i VIH de Catalunya (CEEISCAT), Badalona, Spain

Royal Free Hospital Cohort: C Smith, F Lampe, Royal Free Hospital, University College London, London, United Kingdom

San Raffaele Scientific Institute: A Castagna, A Lazzarin, A Poli, Università Vita-Salute San Raffaele, Milano, Italy

Swedish InfCare HIV Cohort: A Sönnerborg, K Falconer, V Svedhem, Karolinska University Hospital, Stockholm, Sweden

Swiss HIV Cohort Study (SHCS): H Günthard, B Ledergerber, H Bucher, K Kusejko, University of Zurich, Zurich, Switzerland

University Hospital Bonn: JC Wasmuth, J Rockstroh, Bonn, Germany

University Hospital Cologne: JJ Vehreschild, G. Fätkenheuer, Cologne, Germany

RESPOND Executive Committee:

A Mocroft*, J Rooney, F Rogatto, V Vannappagari, H Garges, G Wandeler, M Law, R Zangerle, C Smith, S De Wit, J Lundgren, H Günthard (*Chair)

RESPOND Scientific Steering Committee:

J Lundgren*, H Günthard*, J Kowalska, D Raben, L Ryom, A Mocroft, J Rockstroh, L Peters, A Volny Anne, N Dedes, ED Williams, N Chkhartishvili, R Zangerle, M Law, F Wit, C Necsoi, G Wandeler, C Stephan, C Pradier, A D'Arminio Monforte, C Mussini, A Bruguera, H Bucher, A Sönnerborg, JJ Vehreschild, JC Wasmuth, C Smith, A Castagna, F Rogatto, R Haubrich, V Vannappagari, H Garges

*Chairs

RESPOND Outcomes Scientific Interest Group:

L Ryom, A Mocroft, B Neesgaard, L Greenberg, L Bansi-Matharu, V Svedhem-Johansson, F Wit, K Grabmeier-Pfistershammer, R Zangerle, J Hoy, M Bloch, D Braun, A Calmy, G Schüttfort, M Youle, S De Wit, C Mussini, S Zona, A Castagna, A Antinori, N Chkhartishvili, N Bolokadze, E Fontas, K Dollet, C Pradier, JM Miro, JM Llibre, JJ Vehreschild, C Schwarze-Zander, JC Wasmuth, J Rockstroh, K Petoumenos, M Law, C Duvivier, G Dragovic, R Radoi, C Oprea, M Vasylyev, J Kowalska, R Matulionyte, V Mulabdic, G Marchetti, E Kuzovatova, N Coppola, J Begovac, I Aho, S Martini, H Bucher, A Harxhi, T Wæhre, A Pharris, A Vassilenko, G Fätkenheuer, J Bogner, A Maagaard, E Jablonowska, D Elbirt, G Marrone, C Leen, C Wyen, M Kundro, N Dedes, E Dixon Williams, J Gallant, D Thorpe, H Diaz Cuervo, V Vannappagari, H Garges.

Community Representatives:

A Volny-Anne, N Dedes, L Mendao (European AIDS Treatment Group), E Dixon Williams (UK)

RESPOND Staff:

D Raben, L Peters, L Ryom, B Neesgaard, JF Larsen, ML Jakobsen, T Bruun, A Bojesen, EV Hansen, TW Elsing, D Kristensen, S Thomsen, T Weide, A Mocroft, L Greenberg.

Statistical Staff:

A Mocroft, L Greenberg, L Bansi-Matharu, A Pelchen-Matthews, K Petoumenos, N Rose, D Byonanebye.

Appendix IV: RESPOND research proposal form

RESPOND International Cohort Consortium of Infectious Diseases

Project proposal for consideration by the RESPOND Scientific Steering Committee

(1-2 pages)

Name:
Phone:
Email:
Affiliation:

1. **Project Title**
2. **Writing Group (lead author on manuscript)**
2. **Background/Scientific Rationale**
3. **Hypothesis**
4. **Objectives**
5. **Significance**
6. **Feasibility**
7. **Possible Limitations**
8. **Study design/data required**
9. **Statistical Analysis**
10. **Timelines (including potential conference)**
11. **Budget (itemised)**
12. **COI (All potential conflicts of interest (COI), from an individual, cohort or pharma, must be clearly stated and acknowledged. Please refer to the RESPOND governance document for more information)**

Appendix V: IWHOD 2019 poster entitled "Uptake and Discontinuation of Integrase Inhibitors (INSTIs) in a Large Cohort Setting"

Poster No. 46

23rd International Workshop on HIV Observational Databases

Lauren Greenberg
Institute for Global Health,
Rowland Hill St,
London, UK, NW3 2PF
Tel: 0207 794 0500 34604
Email: l.greenberg@ucl.ac.uk

RESPOND International Cohort Consortium of Infectious Diseases

Uptake and Discontinuation of Integrase Inhibitors (INSTIs) in a Large Cohort Setting

L. Greenberg[1], L. Ryom[2], G. Wandeler[3], K. Grabmeier-Pfistershammer[4], A. Öllinger[4], B. Neesgaard[2], C. Stephan[5], A. Calmy[6], A. Rauch[3], A. Castagna[7], V. Spagnuolo[7], M. Johnson[8], C. Stingone[9], C. Mussini[10], S. De wit[11], C. Necsoi[12], M. Riera[13], C. Pradier[14], M. Stecher[13], J.C. Wasmuth[14], A. d'Arminio Monforte[15], M. Law[16], R. Puhr[16], N. Chkhartishvili[17], T. Tsertsvadze[17], H. Garges[18], D. Thorpe[19], J.D. Lundgren[2], L. Peters[2], L. Bansi-Matharu[1] and A. Mocroft[1]
on behalf of the RESPOND study group

[1]Centre for Clinical Research, Epidemiology, Modelling and Evaluation (CREME), Institute for Global Health, University College London, UK; [2]CHIP, Department of Infectious Diseases, Rigshospitalet, University of Copenhagen, Denmark; [3]Department of Infectious Diseases, Bern University Hospital, University of Bern, Switzerland; [4]Wiener Medizinische Universität, Austria; [5]Johann Wolfgang Goethe-University Hospital, Germany; [6]University of Zurich, Switzerland; [7]Università Vita-Salute San Raffaele, Italy; [8]Royal Free Hospital, University College London, United Kingdom; [9]Università degli Studi di Modena, Italy; [10]Centre de Recherche en Maladies Infectieuses a.s.b.l., Belgium; [11]Hospital Son Espases de Mallorca - Department of Internal Medicine, HIV Unit; [12]Université Côte d'Azur et Centre Hospitalier Universitaire, France; [13]University Hospital Cologne, Germany; [14]University Hospital Bonn, Germany; [15]ASST Sierti Paolo e Carlo, Italy; [16]UNSW, Australia; [17]Infectious Diseases, AIDS and Clinical Immunology Research Center, Georgia; [18]ViiV Healthcare, RTP, USA; [19]Gilead science, Foster City, USA

BACKGROUND

- Despite increasing evidence of the safety and efficacy of INSTIs to control HIV [1-4], limited data exists on the choice and discontinuation of INSTIs in large real-life settings.

METHODS

- RESPOND is a collaboration of 17 observational HIV cohorts from Europe and Australia with >27,000 individuals under follow-up (FU).
- Participants first starting dolutegravir (DTG), elvitegravir (EVG) or raltegravir (RAL) after 1/1/2012 were included.
- Predictors of choice of INSTI uptake were compared using multinomial logistic regression.
- Kaplan Meier (KM) and Cox proportional hazards models describe time to and factors associated with discontinuation.

RESULTS

- 10,642 persons were included; the majority were male (75.6%) with median age 48 (IQR 39-54) years and median CD4 553 (IQR 352-763) cells/mm^3 (**Table 1**).

Table 1: Baseline characteristics

		DTG		RAL		EVG	
		n	(%)	n	(%)	n	(%)
		5511	(51.8)	3006	(28.2)	2125	(20.0)
Gender	Male	4126	(74.9)	2201	(73.2)	1720	(80.9)
Ethnicity	White	3736	(67.8)	1919	(63.8)	1275	(60.0)
Mode of transmission	MSM	3443	(44.3)	1230	(40.9)	1070	(50.7)
Prior ARV treatment	No (naive)	1585	(28.8)	791	(26.3)	761	(35.8)
	Yes (HIV-VL <400 cp/mL	3578	(64.9)	1851	(61.6)	1231	(57.9)
Hepatitis B	Positive	190	(3.4)	150	(5.0)	136	(6.4)
Hepatitis C	Positive	1224	(22.2)	771	(25.6)	322	(15.2)
Comorbidity	Yes	1935	(35.1)	953	(31.7)	538	(25.3)
		Median	(IQR)	Median	(IQR)	Median	(IQR)
INSTI start date (mm/yy)		12/15	(05/15, 09/18)	01/14	(01/13, 03/15)	12/15	(10/14, 10/16)
Age(yr)		48	(39, 55)	48	(40, 55)	45	(36, 52)
CD4 (cells/µL)		575	(370, 788)	510	(334, 720)	580	(381, 796)

Percentage of unknown variables (all): Ethnicity 21.3; Mode of transmission 8.5; Hepatitis B 23.3; Hepatitis C 20.6; Comorbidity 32.7. Comorbidities: diabetes, hypertension, chronic kidney disease, end stage liver disease, non-AIDS defining malignancy, cardiovascular disease, fracture.

- Factors associated with specific INSTI used included year of INSTI start, age, concomitant comorbidities, and region (**Fig. 1**).
- During 20.7 months median FU (IQR 10.3-33.3), 2356 (22.1%) persons discontinued an INSTI.
- The KM estimate of discontinuation at 6 months was 8.9% (95% CI 8.4-9.5); 6.7% DTG, 14.0% RAL, 7.1% EVG (p<0.001).
- Main reasons for discontinuation were patient/physician choice, toxicity and treatment simplification (**Fig. 2**).
- The most common individual toxicity leading to discontinuation ≤6 months was nervous system related and more common on DTG and EVG (18.9% DTG,13.3% EVG, 2.7% RAL).

Figure 1: Baseline characteristics associated with choice of INSTI

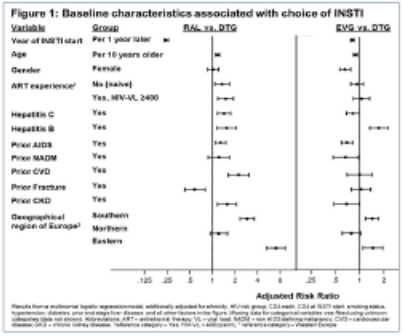
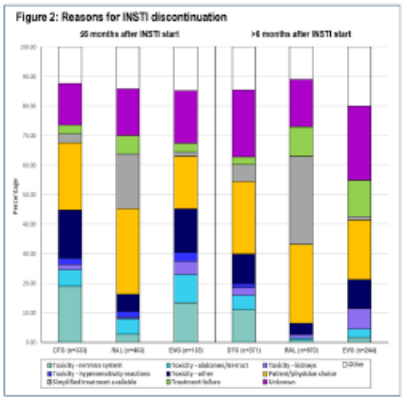
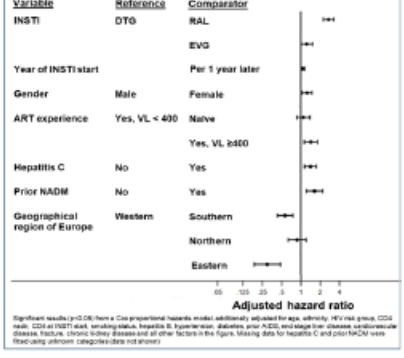


Figure 2: Reasons for INSTI discontinuation



- The adjusted risk of discontinuation increased with year of INSTI start, was higher for those on RAL or EVG vs. DTG, and for females, antiretroviral therapy (ART) experienced with uncontrolled viremia, and those with hepatitis C (HCV), or prior non-AIDS defining malignancy (NADM) (**Fig. 3**).
- Individuals in Southern and Eastern Europe were less likely to discontinue compared to those in Western Europe.
- Results were similar for discontinuations >6 months and for ART naïve and experienced persons (p=0.79; interaction between ART experience and INSTI type).

Figure 3: Baseline characteristics associated with INSTI discontinuation in the first 6 months after INSTI start



CONCLUSION

- Uptake of DTG vs. EVG or RAL increased over time.
- Overall, discontinuation was highest for RAL, and mainly due to treatment simplification.
- Discontinuation was mainly due to toxicity in the first 6 months and discontinuation due to nervous system toxicity was highest on DTG.
- Females, those with HCV or prior NADM were more likely to discontinue an INSTI.

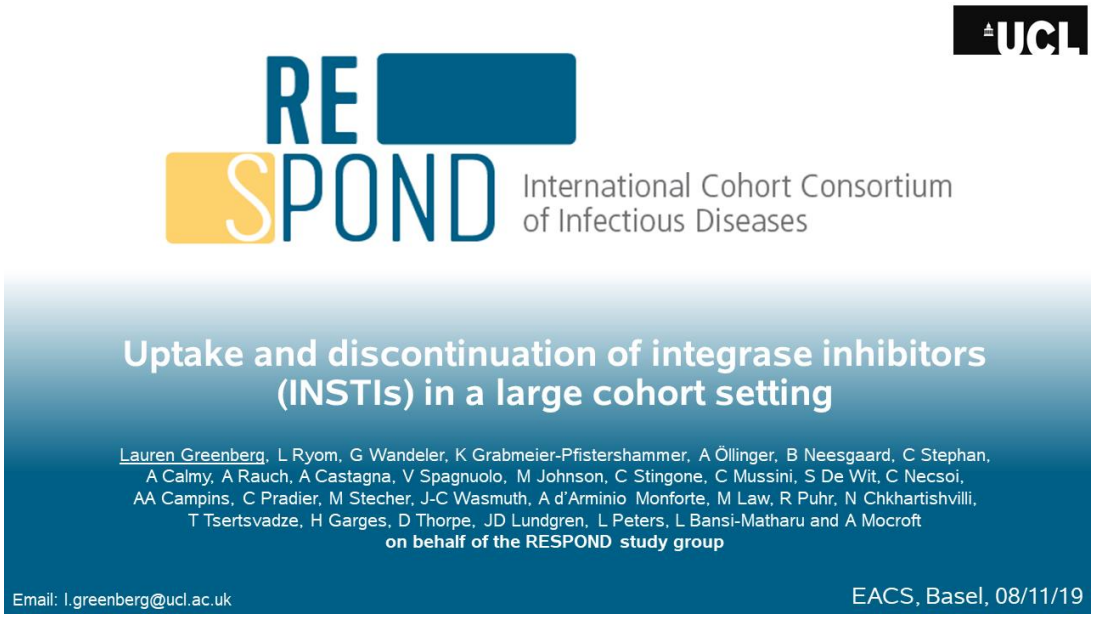
Download poster at: www.chip.dk

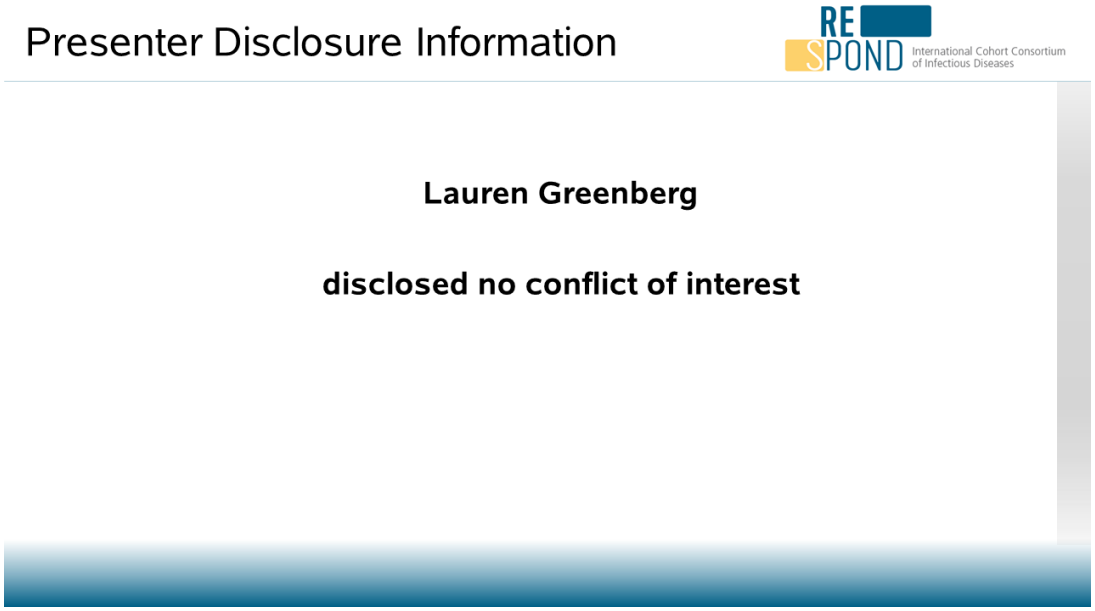
UCL

REFERENCES
[1] Steigbigel RT, et al. N Engl J Med 2008
[2] Sax PE, et al. Lancet 2012
[3] Raffi F, et al. Lancet 2013
[4] Pellafel J, et al. J Antimicrob Chemother 2017

The RESPOND Study Group:
https://www.chip.dk/Studies/RESPOND/Study-Group

Appendix VI: EACS 2019 presentation entitled "Uptake and discontinuation of integrase inhibitors (INSTIs) in a large cohort setting





Background

- INSTIs are recommended as part of initial antiretroviral therapy (ART) regimens for adults living with HIV [1]
- Clinical trials and small observational studies have shown:
  - good virological efficacy
  - fewer adverse events
  - lower rates of discontinuation

  with INSTIs vs non-nucleoside reverse transcriptase inhibitors and boosted protease inhibitors [2-5]
- However, limited data exists on the choice of INSTIs and discontinuation of INSTIs in large, heterogeneous real-world settings

[1] EACS Guidelines version 9.1, October 2018; [2] Steigbigel RT, et al. N Engl J Med 2008;
[3] Sax PE, et al. Lancet 2012; [4] Raffi F, et al. Lancet 2013; [5] Peñafiel J, et al. J Antimicrob Chemother 2017

Aims

1. Identify characteristics associated with initiating:
   - dolutegravir (DTG)
   - cobicistat boosted elvitegravir (EVG/c)
   - raltegravir (RAL)
2. Describe time to and reasons for discontinuation of initial INSTI regimens
3. Identify characteristics associated with discontinuing INSTIs

RESPOND

- The International Cohort Consortium of Infectious Diseases (RESPOND):
  - collaboration of 17 observational cohort studies
  - across Europe and Australia
  - including >28,000 individuals living with HIV-1
- Enrolment into RESPOND began in 2017:
  - data was retrospectively collected back to 2012
  - data is prospectively collected annually from enrolment

Inclusion criteria

- Started DTG, EVG/c or RAL for the first time after the latest of:
  - date enrolled into local cohort, or
  - 1/1/2012
- Age ≥ 16
- CD4 cell count and viral load (VL) measured prior to or within 6 months after starting an INSTI

Outcomes/statistical methods

1. Uptake of DTG, EVG/c, or RAL

Outcomes/statistical methods

1. Uptake of DTG, EVG/c, or RAL

Multinomial logistic regression was used to assess associations between baseline* characteristics and the likelihood of starting:

RAL vs DTG

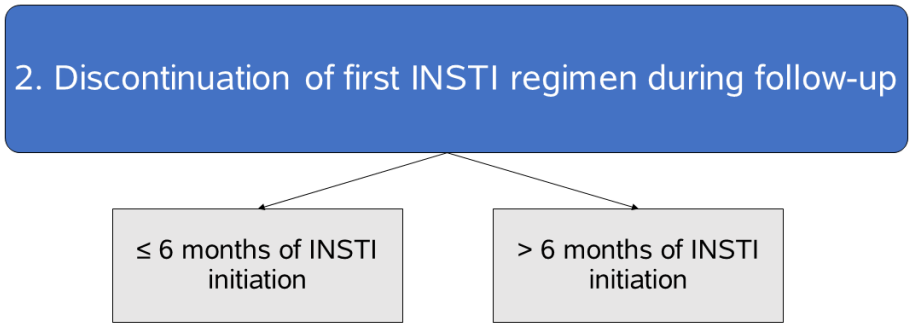
EVG/c vs DTG

*baseline - date of INSTI start

Outcomes/statistical methods

2. Discontinuation of first INSTI regimen during follow-up

Outcomes/statistical methods



Outcomes/statistical methods

2. Discontinuation of first INSTI regimen during follow-up

Cox proportional hazards models were used to assess factors associated with time to discontinuation within the first 6 months

Baseline characteristics

Demographics	HIV related	Comorbidities
Age	Year of starting INSTI	Viral hepatitis B and C status (HBV/HCV)
Gender	HIV risk category	Hypertension
Ethnicity	CD4 cell count nadir	Diabetes
Smoking status	CD4 cell count at INSTI initiation	AIDS defining event (ADE)
Geographical region	ART experience and viral suppression status	Non-AIDS defining malignancy (NADM)
Cohort	For discontinuation models, INSTI type was also included	End stage liver disease
		Cardiovascular disease (CVD)
		Fracture
		Chronic kidney disease

Characteristics at INSTI start (**N=9702**)

INSTI, n (%)		DTG 5051 (52.1)	RAL 2718 (28.0)	EVG/c 1933 (19.9)
		%		
Gender	Male	74.5	73.5	80.7
Ethnicity*	White	84.1	81.2	80.6
ART experience	Naïve	23.5	20.5	30.4
	Experienced, VL<400 cps/mL	69.9	66.2	62.8
HIV risk*	MSM	47.0	43.3	54.7
Geographical region of Europe	Western	59.9	38.5	55.6
	Southern	26.1	26.8	32.7
	Northern & Australia	10.0	27.0	7.9
	Eastern/Eastern Central	5.1	9.1	5.2
Any prior/current comorbidity		37.6	33.1	27.7
INSTI start date (median (IQR))		Jan16 (May15, Oct16)	Feb14 (Jan13, Apr15)	Dec15 (Oct14, Nov16)
Age, years (median (IQR))		48 (39, 55)	48 (41, 54)	45 (36, 53)
CD4 at INSTI start, cells/mm³ (median (IQR))		578 (369, 788)	507 (297, 714)	560 (386, 756)

*Denominator for percentages is all participants with non-missing data. Total unknown %: ethnicity 14.8, HIV risk 5.4

Characteristics at INSTI start (**N=9702**)

INSTI, n (%)		DTG 5051 (52.1)	RAL 2718 (28.0)	EVG/c 1933 (19.9)
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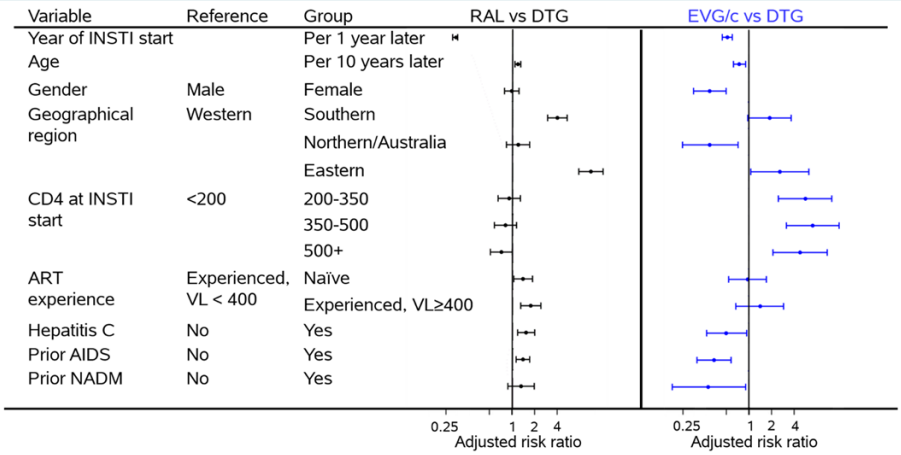
ART experience	Naïve	23.5	20.5	30.4
	Experienced, VL<400 cps/mL	69.9	66.2	62.8
HIV risk*	MSM	47.0	43.3	54.7
Geographical region of Europe	Western	59.9	38.5	55.6
	Southern	26.1	26.8	32.7
	Northern & Australia	10.0	27.0	7.9
	Eastern/Eastern Central	5.1	9.1	5.2
Any prior/current comorbidity		37.6	33.1	27.7
INSTI start date (median (IQR))		Jan16 (May15, Oct16)	Feb14 (Jan13, Apr15)	Dec15 (Oct14, Nov16)
Age, years (median (IQR))		48 (39, 55)	48 (41, 54)	45 (36, 53)
CD4 at INSTI start, cells/mm³ (median (IQR))		578 (369, 788)	507 (297, 714)	560 (386, 756)

*Denominator for percentages is all participants with non-missing data. Total unknown %: ethnicity 14.8, HIV risk 5.4

INSTI Uptake

Choice of INSTI



Results from a multinomial logistic regression model, additionally adjusted for ethnicity, HIV risk group, CD4 nadir, smoking status, hepatitis B, hypertension, diabetes, end stage liver disease, cardiovascular disease, fracture, chronic kidney disease and all other factors in the figure. Missing data was fitted using unknown categories (data not shown)

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Discontinuation of INSTIs

Discontinuation

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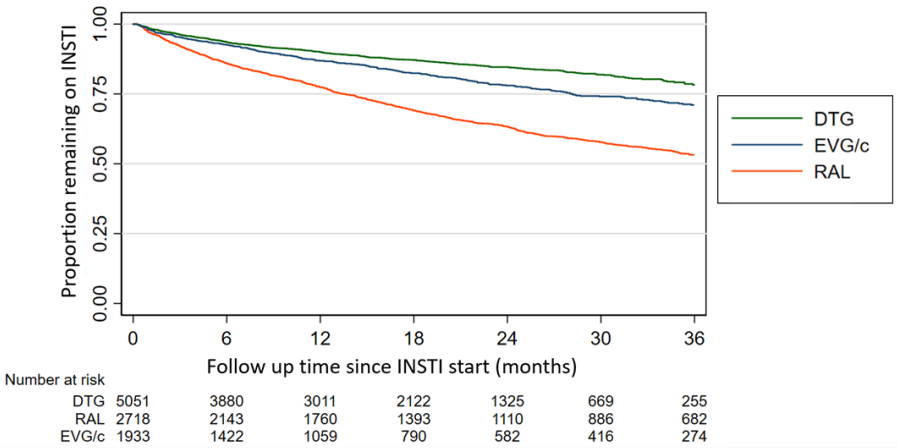
	Overall (n=9702)	DTG (n=5051)	RAL (n=2718)	EVG/c (n=1933)
Median (IQR) follow-up, months	20.0 (9.9-32.4)	17.1 (8.5-26.2)	33.4 (16.7-48.3)	17.7 (7.6-31.7)

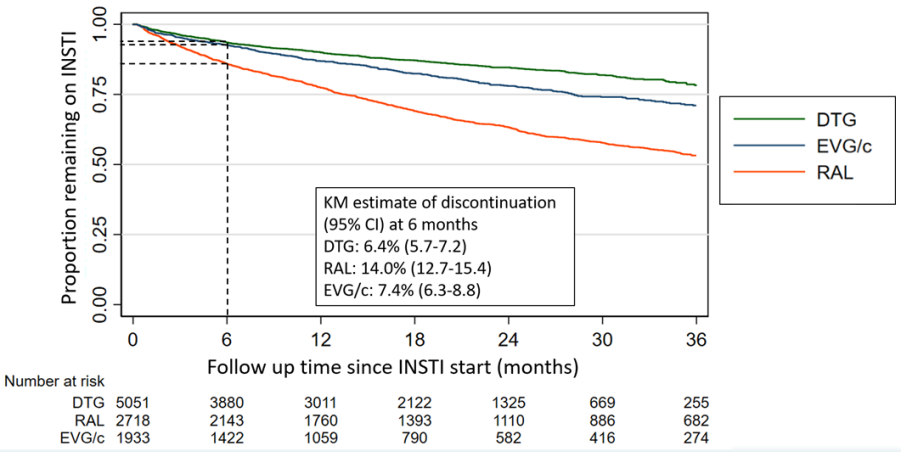
Discontinuation

	Overall (n=9702)	DTG (n=5051)	RAL (n=2718)	EVG/c (n=1933)
Median (IQR) follow-up, months	20.0 (9.9-32.4)	17.1 (8.5-26.2)	33.4 (16.7-48.3)	17.7 (7.6-31.7)
Number (%) who discontinued during follow-up	2105 (21.7%)	619 (12.3%)	1145 (42.1%)	341 (17.6%)

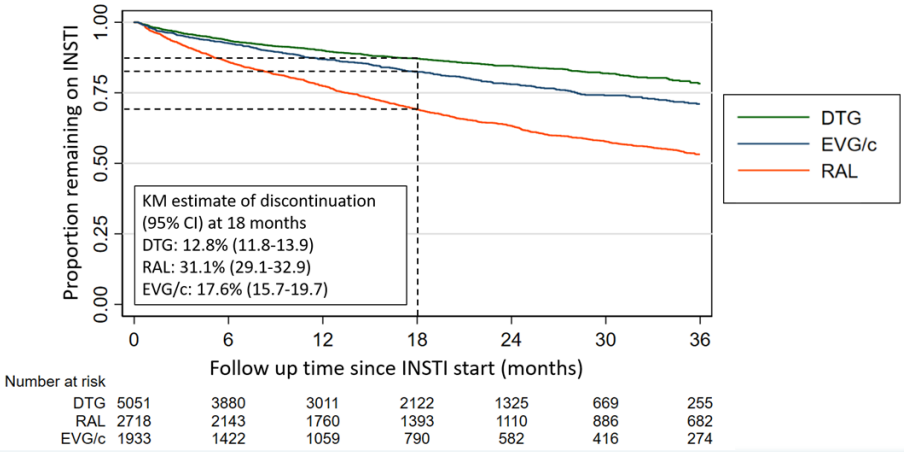
Discontinuation



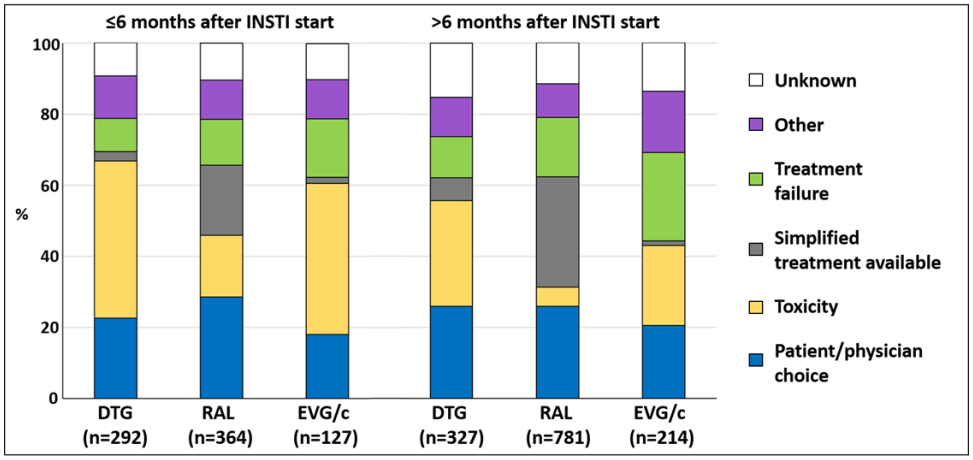
Discontinuation



Discontinuation

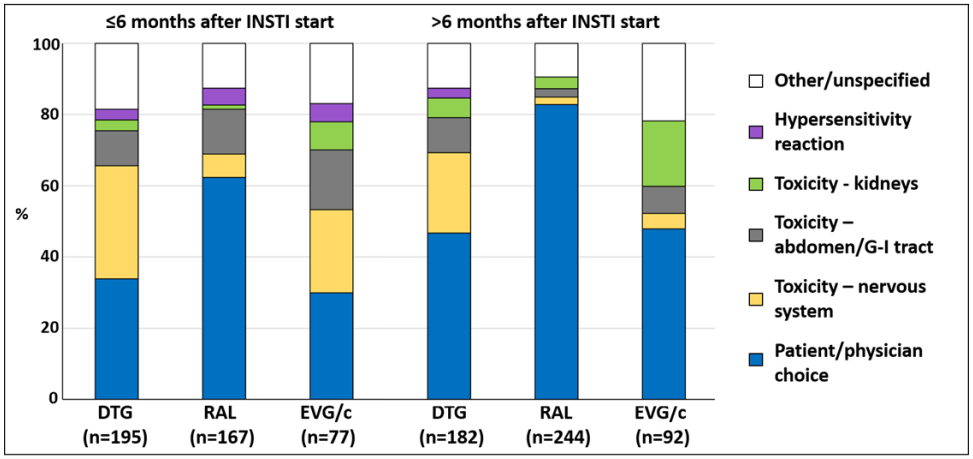


Reasons for discontinuation (n=2105)



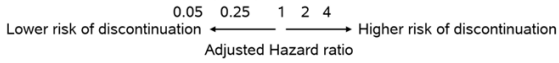
Toxicity includes abnormal fat redistribution, concern of cardiovascular disease, hypersensitivity reaction, abdomen/gastrointestinal tract, nervous system, kidney, or endocrine system toxicities, unspecified side effects

Reasons for discontinuation due to toxicity (n=957)



Factors associated with INSTI discontinuation within 6 months

Variable	Reference	Group	aHR (95% CI)
INSTI type	DTG	RAL	3.03 (2.47, 3.71)
		EVG	1.37 (1.10, 1.70)
Year of INSTI start		Per 1 year later	1.11 (1.04, 1.18)
Gender	Male	Female	1.28 (1.06, 1.56)
ART experience	Experienced, VL < 400	Naïve	1.10 (0.87, 1.39)
		Experienced, VL≥400	1.36 (1.07, 1.73)
Hepatitis C	No	Yes	1.32 (1.06, 1.66)
Prior NADM	No	Yes	1.55 (1.13, 2.12)
Geographical region	Western	Southern	0.58 (0.43, 0.78)
		Northern/Australia	0.90 (0.64, 1.25)
		Eastern	0.31 (0.20, 0.50)



Plot includes variables with p<0.05 from a Cox proportional hazards model, additionally adjusted for age, ethnicity, HIV risk group, CD4 nadir, CD4 at INSTI start, smoking status, hepatitis B, hypertension, diabetes, prior AIDS, end stage liver disease, cardiovascular disease, fracture, chronic kidney disease. Missing data for hepatitis C and prior NADM were fitted using unknown categories (data not shown)

Limitations

- Individuals in RESPOND were not randomly selected as we pre-specified the minimum number on INSTIs to be included
- Not possible to rule out residual confounding
- Completeness of data varies between cohorts
- Only one reason for discontinuation per antiretroviral was collected, without further detail

Conclusion (I)

- This is one of the first large, multi-national studies investigating the choice of INSTIs and discontinuation of INSTIs in real life settings
- Uptake of DTG vs EVG/c or RAL has increased:
  - over calendar time
  - more in Western Europe compared to other European regions

Conclusion (II)

- INSTI discontinuation was mainly due to toxicity in the first 6 months and patient/physician choice thereafter, but was low overall
- Discontinuation was significantly higher for RAL, mainly due to treatment simplification
- Discontinuation was lowest on DTG
- However discontinuation due to nervous system toxicities was highest on DTG
- Our findings highlight the need for further research to better understand adverse effects on INSTIs

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Cohort principal investigators:.

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Members of the scientific interest group:

Hepatis, Public Health, Outcomes with antiretroviral treatment, PrEP, Resistance. Details at: https://www.chip.dk/Studies/RESPOND/Scientific-Interest-Groups

Statisticians:

A. Mocroft and L. Greenberg

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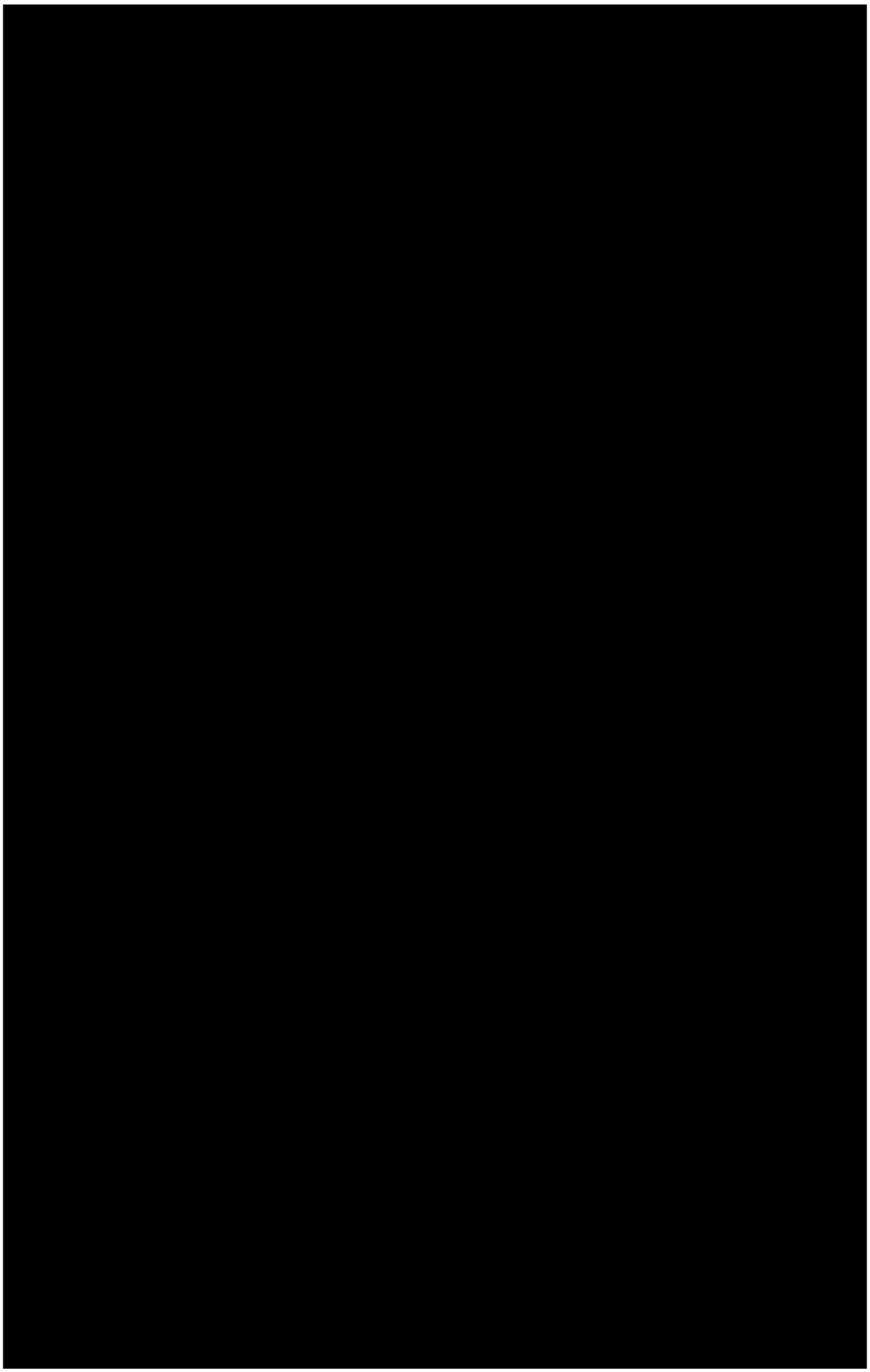
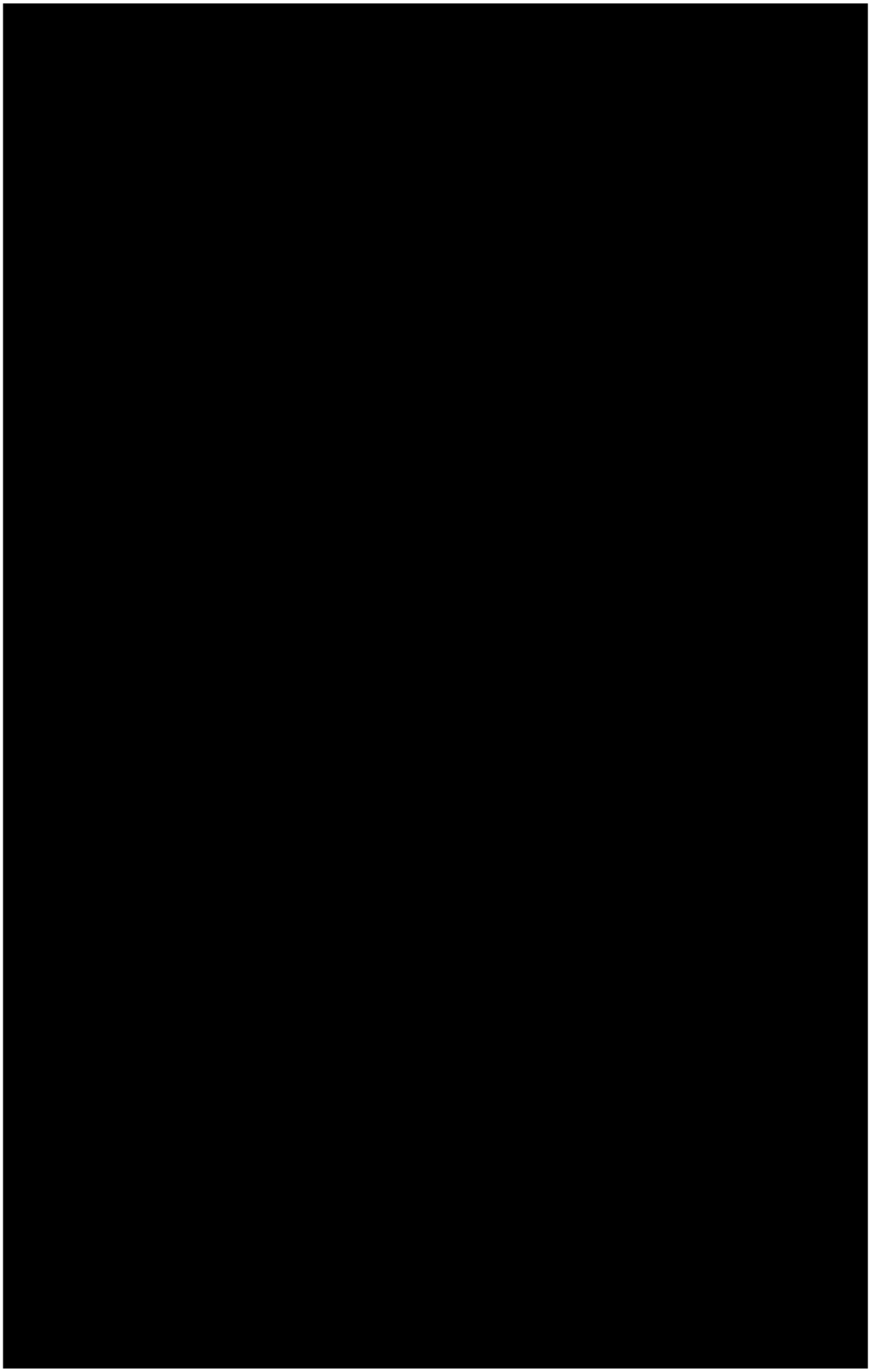
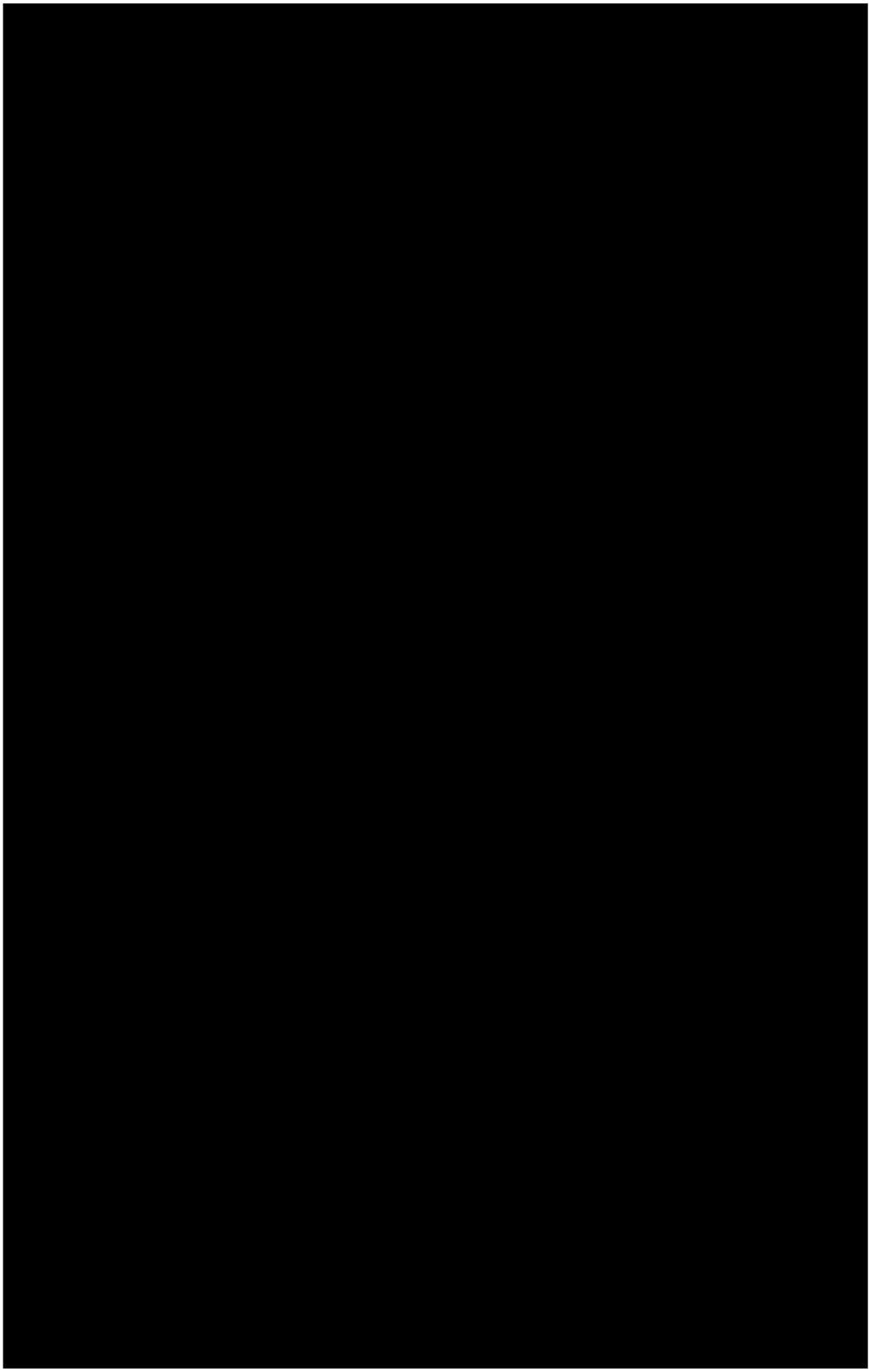
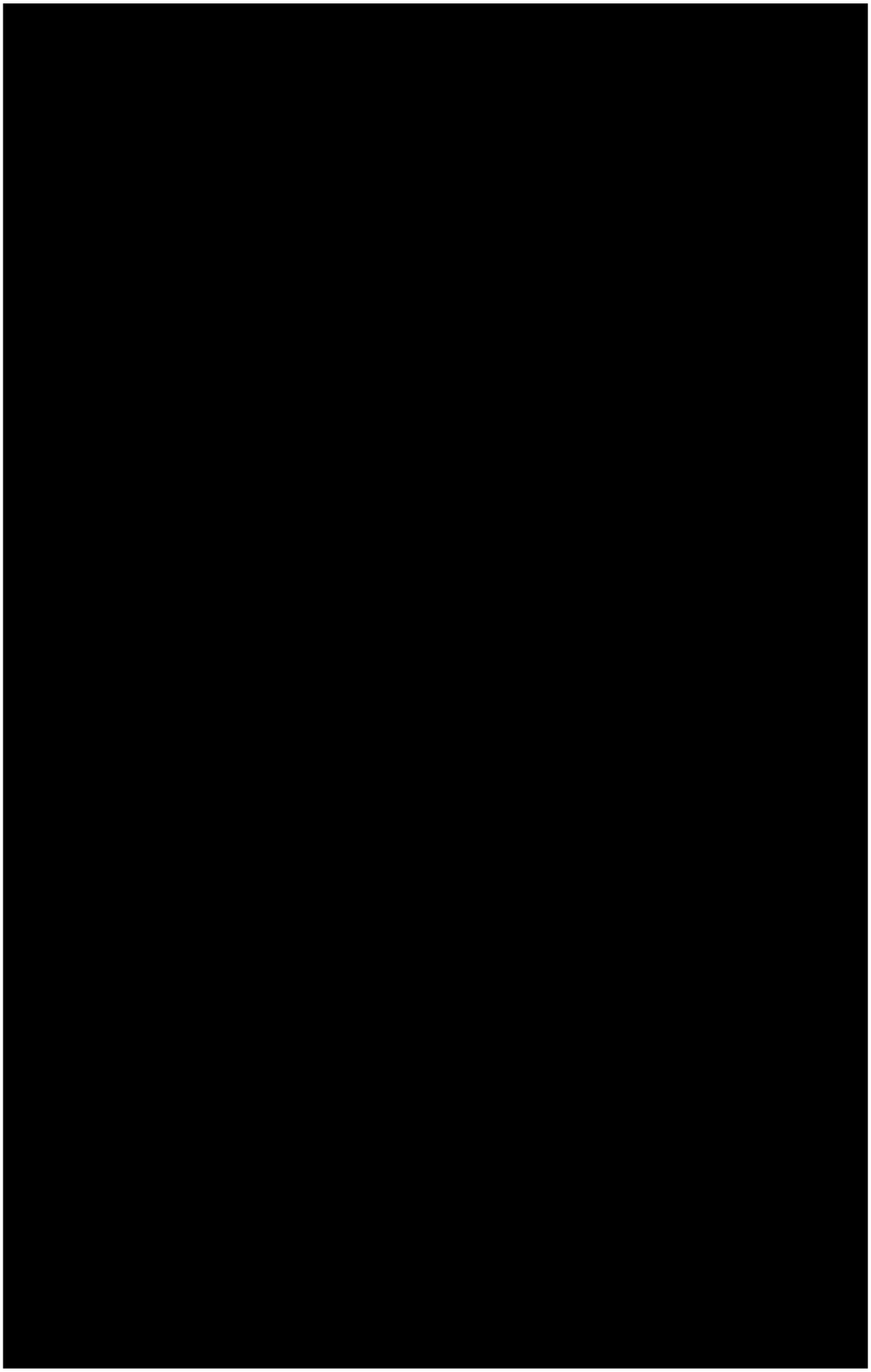
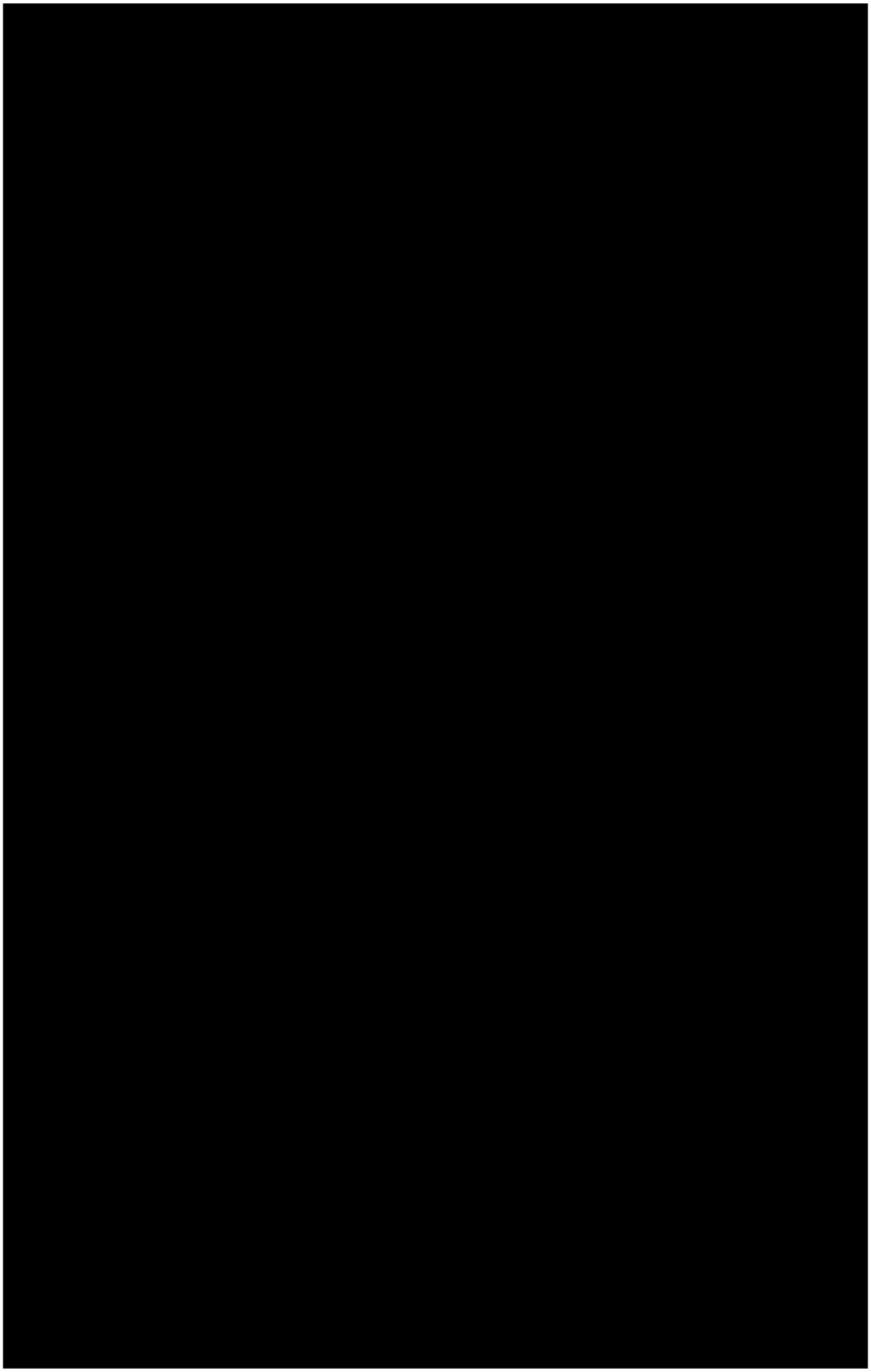
Appendix VII: Published manuscript JAIDS 2020 entitled "Uptake and Discontinuation of Integrase Inhibitors (INSTIs) in a Large Cohort Setting"

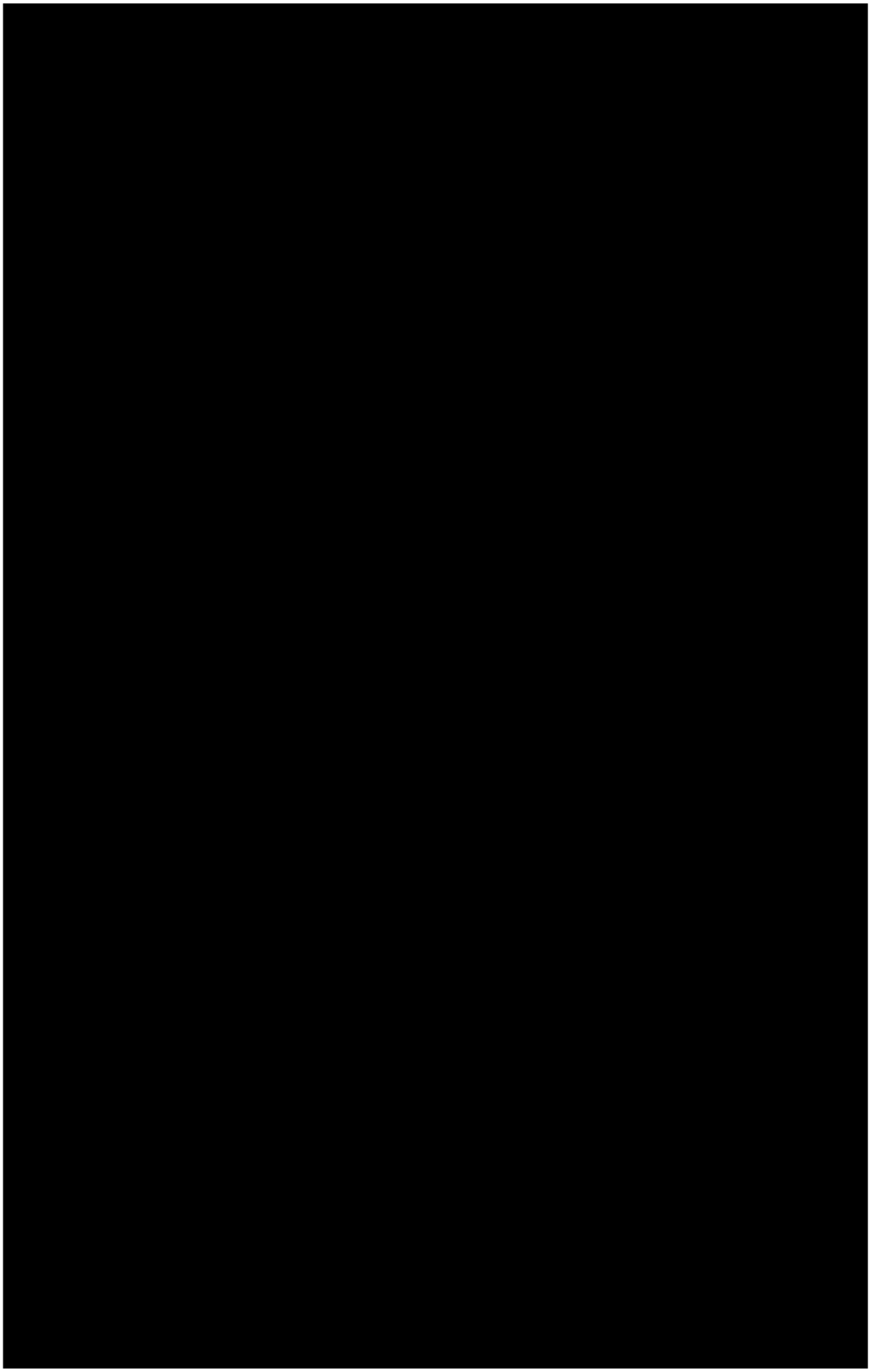


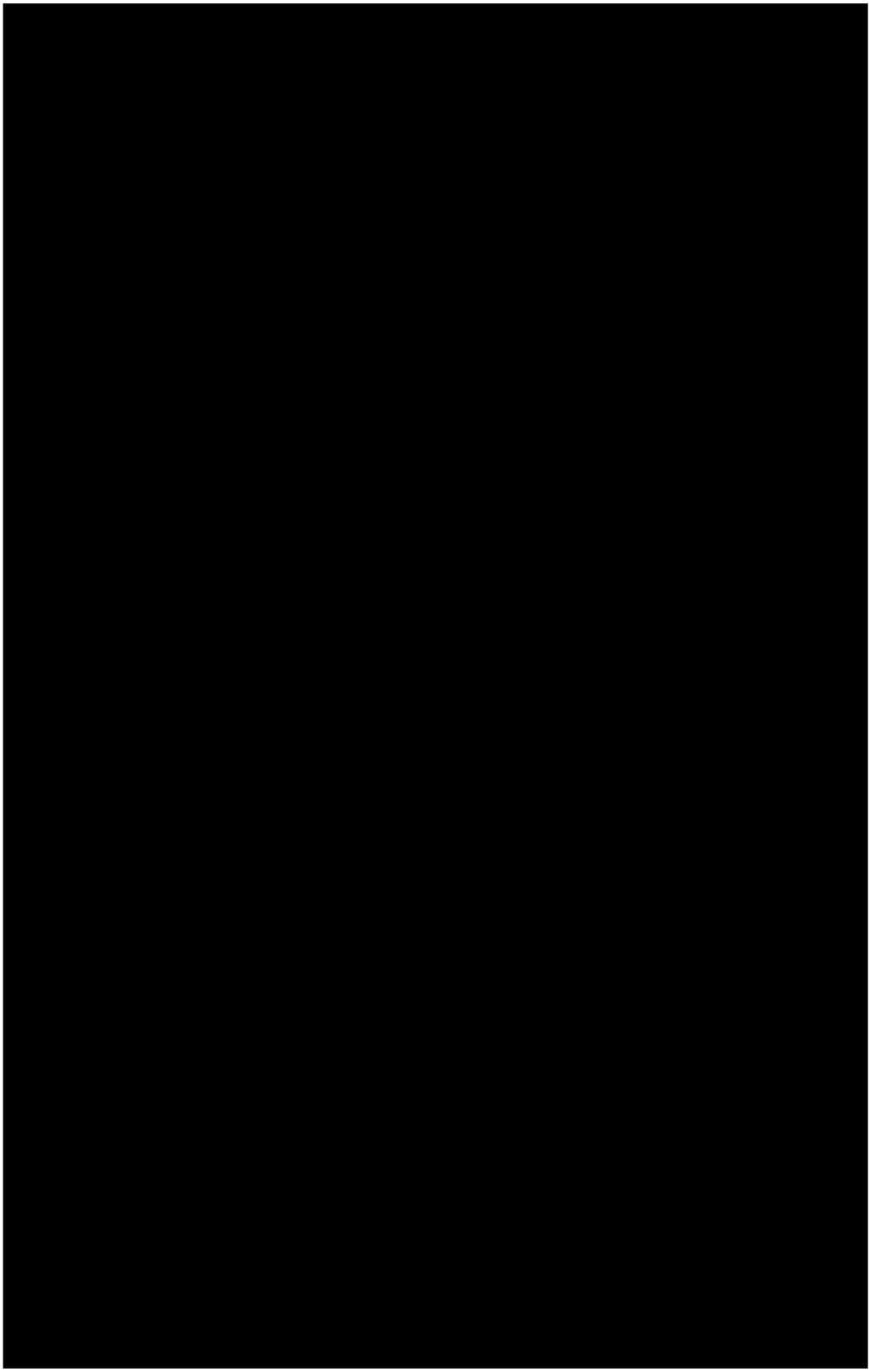


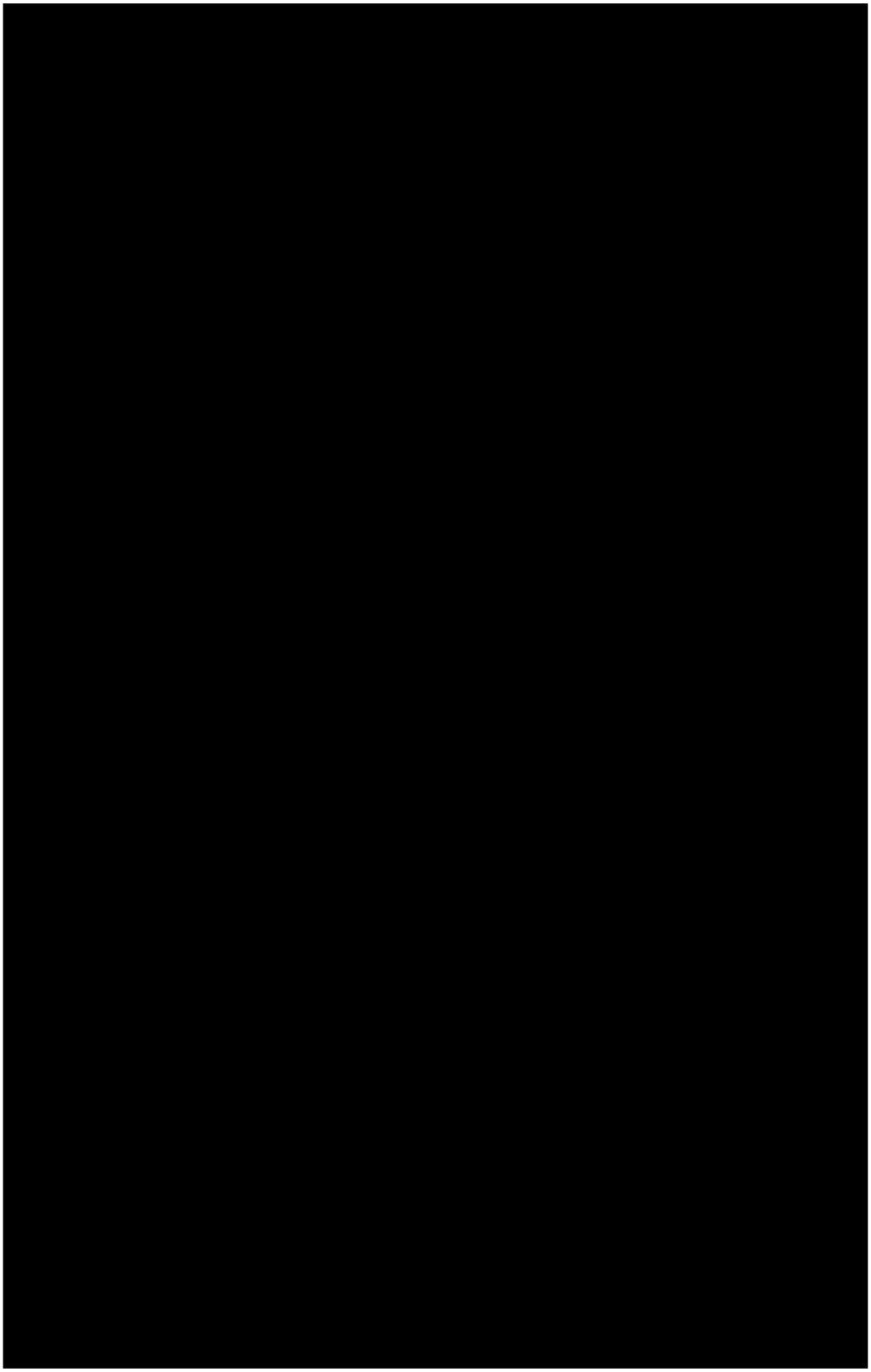


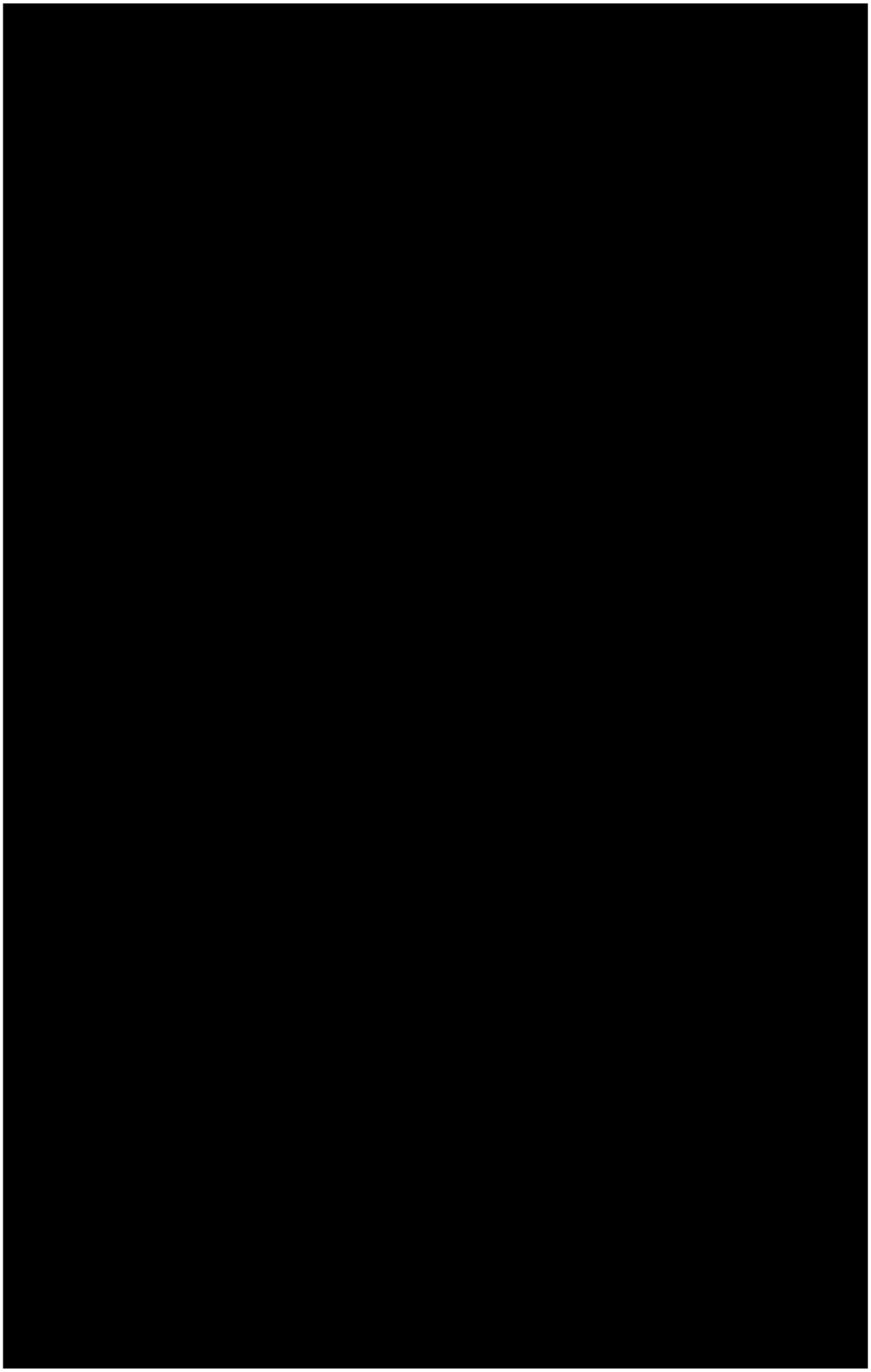


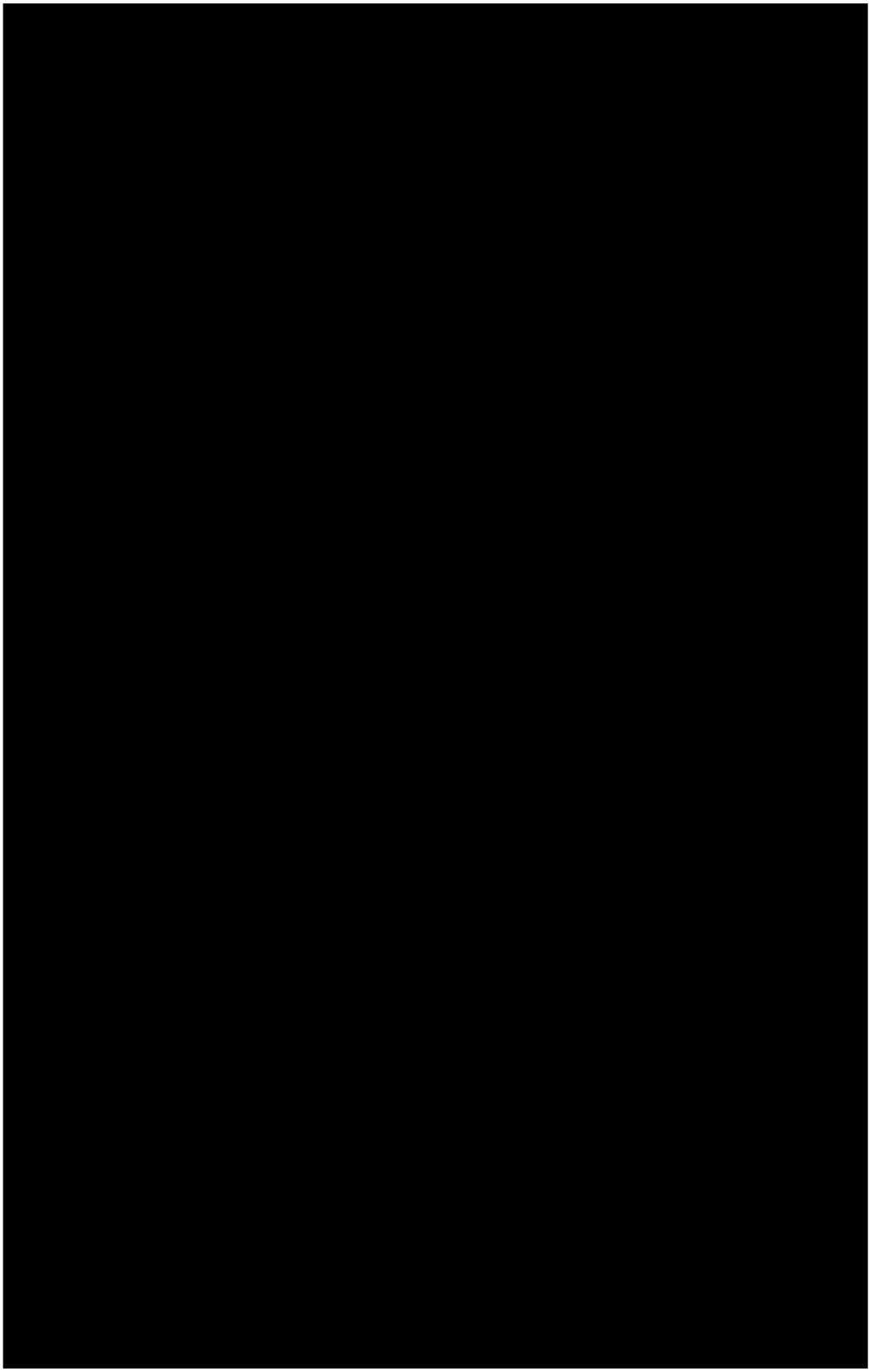


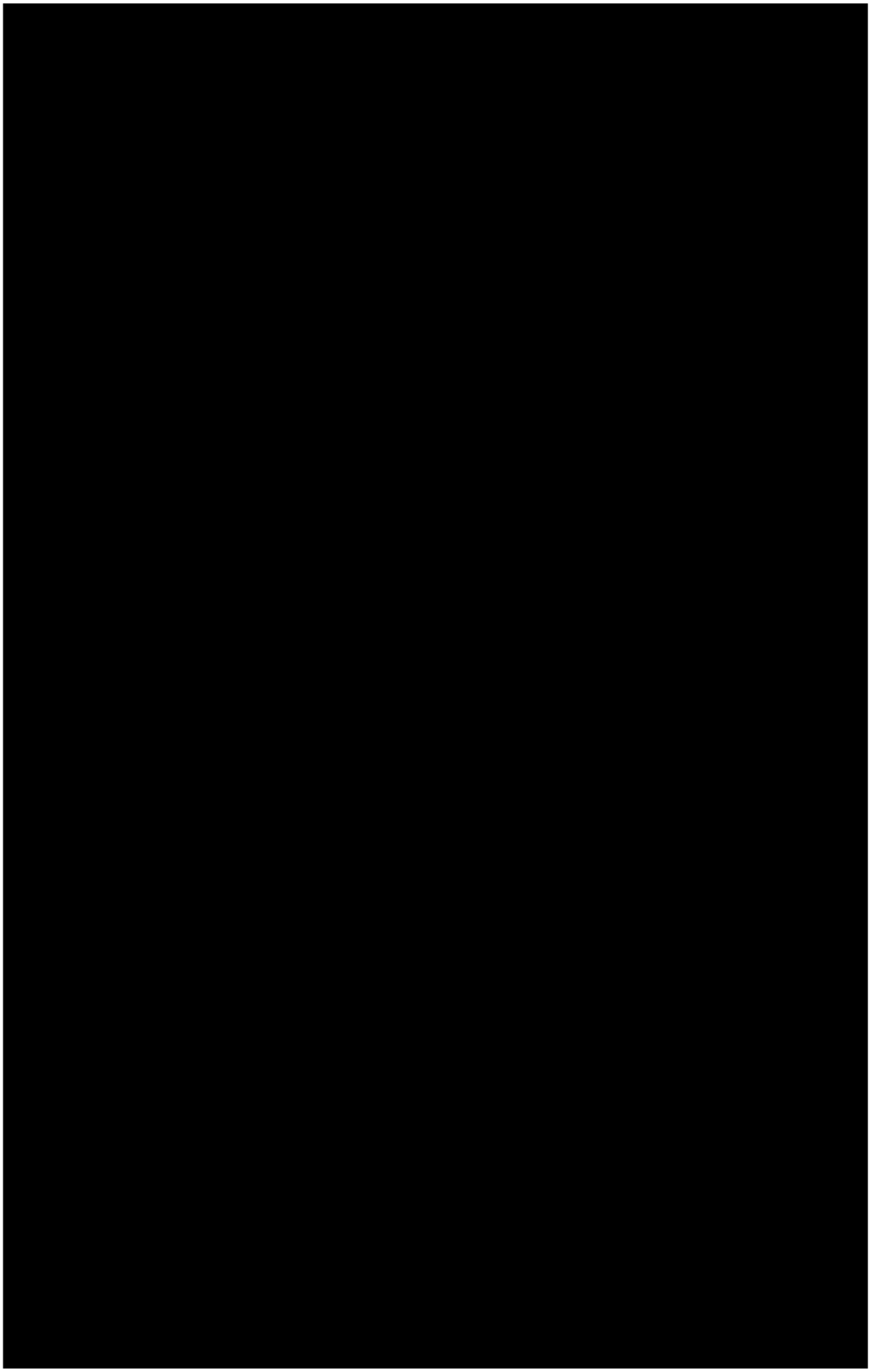












Appendix VIII: CROI 2020 poster entitled “Clinical outcomes of two-drug regimens (2DRs) vs. three-drug regimens (3DRs) in HIV”

CROI 2020

Poster No. 0487

CLINICAL OUTCOMES OF TWO DRUG REGIMENS (2DRs) VS. THREE DRUG REGIMENS (3DRs) IN HIV

RESPOND International Cohort Consortium of Infectious Diseases

L Greenberg[1], L Ryom[2], B Neesgaard[2], G Wandeler[3], T Staub[3], M Gisinger[4], M Skoll[5], H Günthard[6], A Scherrer[6], C Mussini[7], C Smith[8], M Johnson[8], S De Wit[9], C Necsoi[9], C Pradier[10], F Wit[11], C Lehmann[12], A d'Arminio Monforte[13], JM Miró[14], A Castagna[15], V Spagnuolo[15], A Sönnerborg[16], M Law[17], J Hutchinson[17], N Chkhartishvili[18], N Bolokadze[18], J-C Wasmuth[19], C Stephan[20], V Vannappagari[21], F Rogatto[22], J Llibre[23], C Duvivier[24], J Hoy[17], M Bloch[17], HC Bucher[6], A Calmy[25], A Volny Anne[26], A Pelchen-Matthews[1], JD Lundgren[2], L Peters[2], L Bansi-Matharu[1], A Mocroft[1] *on behalf of the RESPOND study group*

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BACKGROUND

- Several clinical trials and small observational studies have shown good short term virological efficacy and tolerability of 2DRs (1-6)
- Reasons for switching to 2DRs are multifactorial and include concerns about long-term toxicities and drug-drug interactions (7-8)
- Little is known from large studies regarding clinical outcomes of 2DRs

METHODS

- Antiretroviral treatment experienced participants in the RESPOND consortium starting an eligible regimen during follow-up (FU) were included (**Table 1**)
- Baseline was defined as date of starting the first regimen of interest after cohort enrolment or 1/1/2012, whichever occurred the latest
- If a participant started a 2DR and 3DR of interest, they were included in the 2DR group
- Reasons for discontinuing the previous regimen were compared. Reasons were only counted if the previous regimen was discontinued ≤7 days before starting an eligible regimen
- This analysis focused on severe clinical events including: AIDS (cancer and non-cancer), non-AIDS defining cancer (NADC), cardiovascular disease (CVD; invasive cardiovascular procedures, myocardial infarction, or stroke), end stage liver disease (ESLD), end stage renal disease (ESRD), and death
- Individuals were followed until the first severe event of any type or until last clinical visit or 1/10/2018, whichever occurred first
- Incidence rates (IR) of clinical events between those starting a 2DR vs. 3DR were compared using Poisson regression with adjustment for baseline characteristics
- Sensitivity analyses were performed including centrally validated events only and only including approved 2DRs

Table 1: Number of individuals on each treatment regimen

3DR			2DR		
Regimen	n	(%)	Regimen	n	(%)
Total	8703	(88.9)	Total	1088	(11.1)
2 NRTIs + DTG	4081	(46.9)	DTG + 3TC*	248	(22.8)
2 NRTIs + RPV	1726	(19.8)	RAL + DRV/b	215	(19.8)
2 NRTIs + RAL	1228	(14.1)	DTG + DRV/b	200	(18.4)
2 NRTIs + DRV/b	923	(10.6)	DTG + RPV*	146	(13.4)
2 NRTIs + NVP	388	(4.5)	3TC + DRV/b	107	(9.8)
2 NRTIs + ATV or ATV/b	277	(3.2)	RAL + ETV	79	(7.3)
2 NRTIs + ETV	80	(0.9)	RAL + NVP	36	(3.3)
			RPV + DRV/b	31	(2.9)
			3TC + ATV/b	26	(2.4)

Abbreviations: NRTI – nucleoside reverse transcriptase inhibitor; 3TC – lamivudine; ATV – atazanavir; DRV – darunavir; DTG – dolutegravir; ETV – etravirine; RAL – raltegravir; RPV – rilpivirine; NVP – nevirapine; /b – boosted with cobicistat or ritonavir; Eligible 3DRs were chosen so that the 3rd antiretrovirals were the same antiretrovirals as used in the 2DRs; *approved 2DRs

Download poster at: www.chip.dk

RESULTS

- Overall, 9791 individuals were included; 1088 (11.1%) on 2DRs and 8703 (88.9%) on 3DRs
- Individuals on 2DRs were older and a higher proportion had a prior AIDS defining event or prevalent comorbidity (**Table 2**)
- The most common 2DRs were DTG plus 3TC (22.8%) and RAL plus DRV/b (19.8%) (**Table 1**)
- The most common 3DR was 2 NRTIs plus DTG (46.9%). The most common NRTI backbones were TDF plus FTC (45.0%) and ABC plus 3TC (40.5%)
- The main reason for discontinuing the previous regimen before starting a 2DR or 3DR was toxicity (30.9% 2DRs vs. 31.1% 3DRs; p=0.87); renal toxicity was most common for switches to 2DRs (37.9%) and toxicity from the nervous system was most common for switches to 3DRs (28.3%)

Table 2: Baseline clinical characteristics

		All		3DR		2DR	
		n	(%)	n	(%)	n	(%)
		9791	(100)	8703	(88.9)	1088	(11.1)
Gender	Male	7048	(72.0)	6253	(71.9)	795	(73.1)
Ethnicity	White	6976	(71.2)	6147	(70.6)	829	(76.2)
BMI (kg/m²)	<18.5	363	(3.7)	310	(3.6)	53	(4.9)
	≥25	2923	(29.9)	2666	(30.6)	257	(23.6)
Current smoking		2836	(29.0)	2599	(29.9)	237	(21.8)
Risk of acquisition	MSM	4037	(41.2)	3631	(41.7)	406	(37.3)
HIV VL	<200 Cp/mL	8588	(87.7)	7648	(87.9)	940	(86.4)
Viral hepatitis B	Positive	488	(5.0)	445	(5.1)	43	(4.0)
Viral hepatitis C	Positive	2568	(26.2)	2268	(26.1)	300	(27.6)
AIDS defining event	Yes	2021	(20.6)	1731	(19.9)	290	(26.7)
Comorbidity	Yes	7321	(74.8)	6433	(73.9)	888	(81.6)
		Median	(IQR)	Median	(IQR)	Median	(IQR)
Regimen start date (mm/yy)		08/15	(05/14, 09/16)	07/15	(04/14, 08/16)	12/15	(12/14, 01/17)
Age (years)		48	(40, 55)	48	(40, 54)	53	(47, 59)
CD4 count (cells/uL)		608	(423, 810)	605	(424, 809)	622	(409, 814)
Number of previous antiretrovirals exposed to		6	(4-9)	6	(4-8)	8	(5-11)

Percentage of unknown variable (all): Ethnicity 13.0; BMI 23.7; Smoking 30.9; Risk of acquisition 4.2; Hepatitis B 9.2; Hepatitis C 6.4; AIDS defining event 5.8;Comorbidity 16.3. Comorbidities included: diabetes, hypertension, non AIDS defining cancer, cardiovascular disease, chronic kidney disease, end stage liver disease, end stage renal disease, fracture, dyslipidaemia. Differences between 3DRs and 2DRs are significant (p≤0.05), except for gender, hepatitis C, and CD4 count

- Median FU was 2.6 (IQR 1.4-3.8) years and was similar on 2DRs and 3DRs (2.2 (1.2-3.2) on 2DRs and 2.7 (1.4-3.8) on 3DRs)
- Overall, there were 619 clinical events during 27159 person years of FU [PYFU] (IR/1000 PYFU [95% CI] 23.3 [21.6-25.2])
- The most common events were death (IR 7.5/1000 PYFU [6.5-8.6]), and NADC (IR 5.8/1000 PYFU [4.9-6.8]) (**Figure 1**)
- There were 79 events on 2DRs during 2642 PYFU (IR 30.9 [24.8-38.5]) and 540 events on 3DRs during 24516 PYFU (IR 22.5/1000 PYFU [20.7-24.5])
- In unadjusted analyses, there was a higher IR of events on 2DRs (IR ratio 1.37 [1.08-1.73], p=0.009). However, after adjustment for potential confounders (age and number of drugs previously exposed to in particular) there was no significant difference between 2DRs and 3DRs (IR ratio 0.92 [0.72-1.19], p=0.53) (**Figure 2**)
- Sensitivity analyses including only centrally validated events and only including approved 2DRs showed similar results

Figure 1: Crude IR/1000 PYFU and 95% CI for 2DR vs 3DR

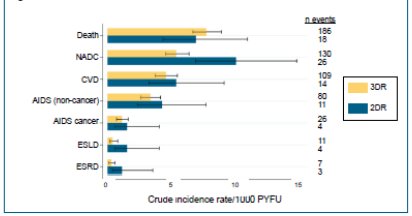
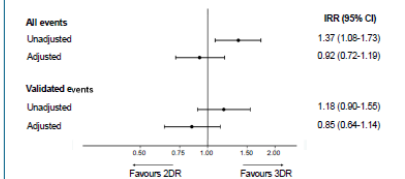


Figure 2: Incidence rate ratio comparing events on 2DR vs 3DR



Adjusted analyses adjusted for age, gender, ethnic origin, BMI, smoking status, HIV risk group, HIV viral load at regimen start, CD4 cell nadir, CD4 cell count at regimen start, viral hepatitis C, viral hepatitis B, prior hypertension, prior diabetes, prior AIDS defining event (excluding cancer), prior AIDS cancer, prior non-AIDS cancer, prior end stage liver disease, prior cardiovascular disease, prior fracture, prior chronic kidney disease, prior dyslipidaemia, number of drugs previously exposed to, prior treatment duration

LIMITATIONS

- Residual confounding cannot be ruled out
- This analysis focuses on a composite endpoint, rather than individual events
- Due to limited numbers, we were unable to include treatment naïve individuals in the analysis

CONCLUSIONS

- This is the first large, international cohort to assess rigorously defined severe clinical outcomes on 2DRs
- After accounting for demographic and clinical characteristics, there was a similar incidence of events on 2DRs and 3DRs
- 2DRs appear to be a viable treatment option with regard to clinical outcomes. Further research on long-term durability of 2DRs is needed

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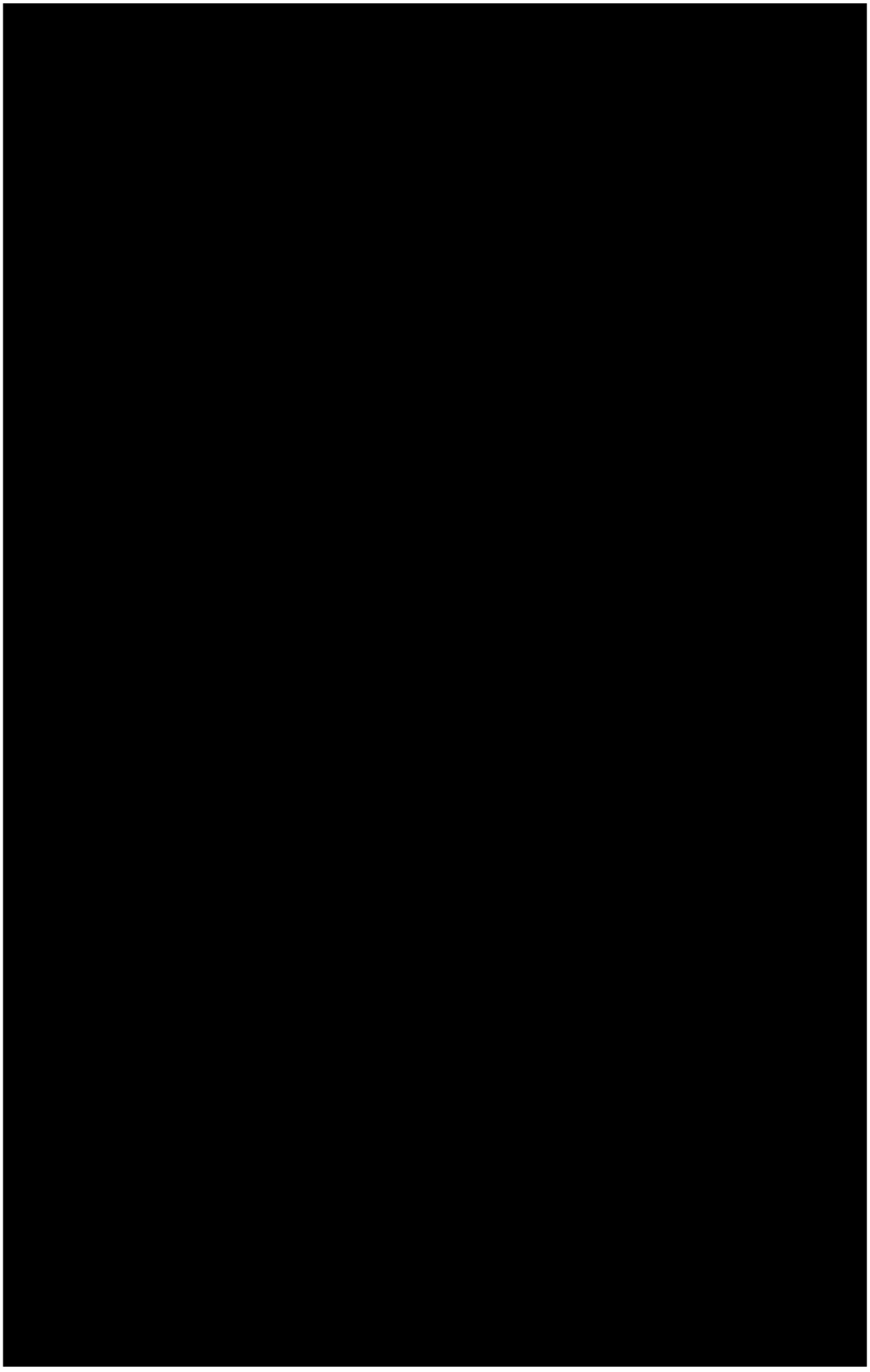
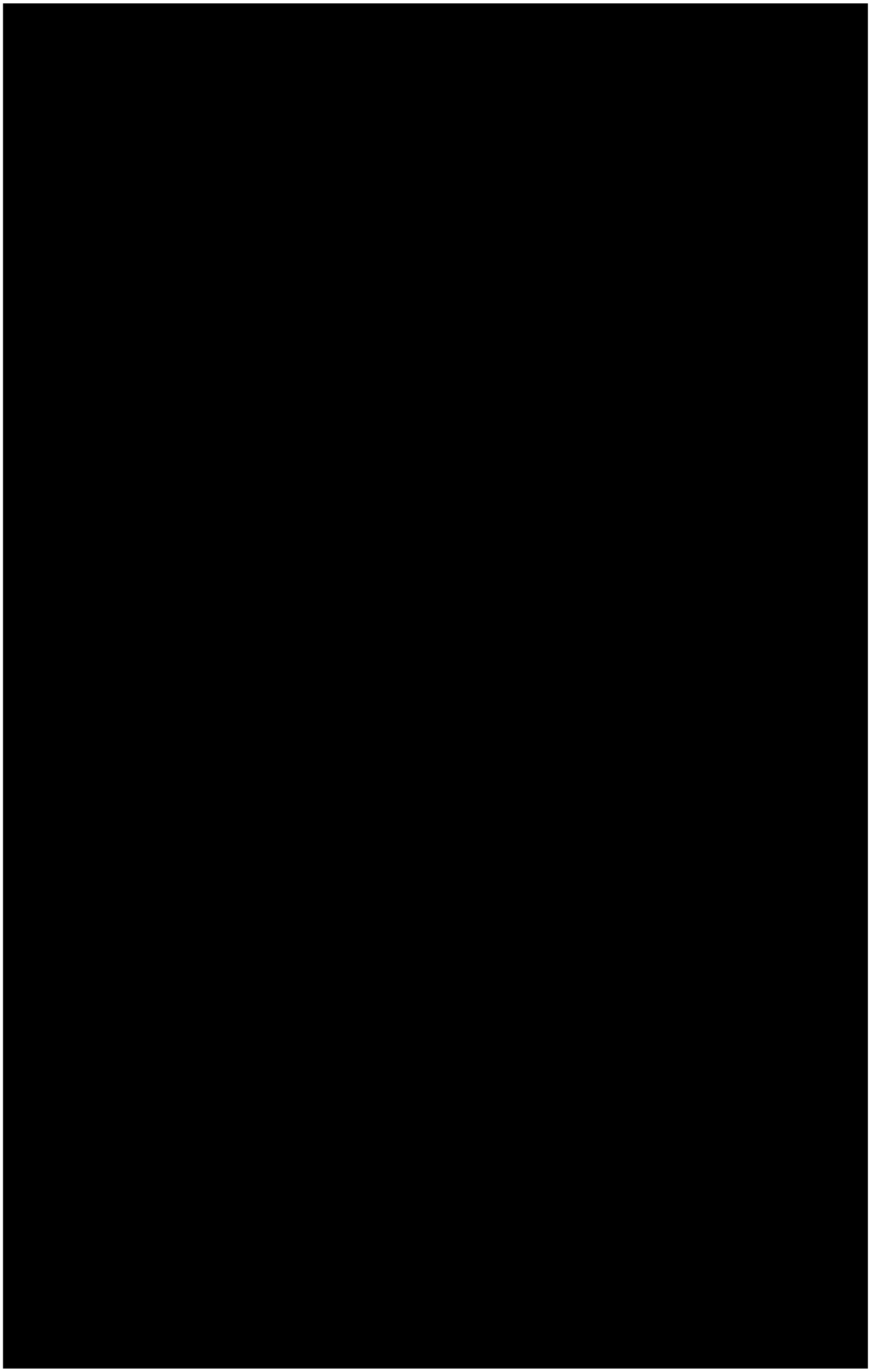
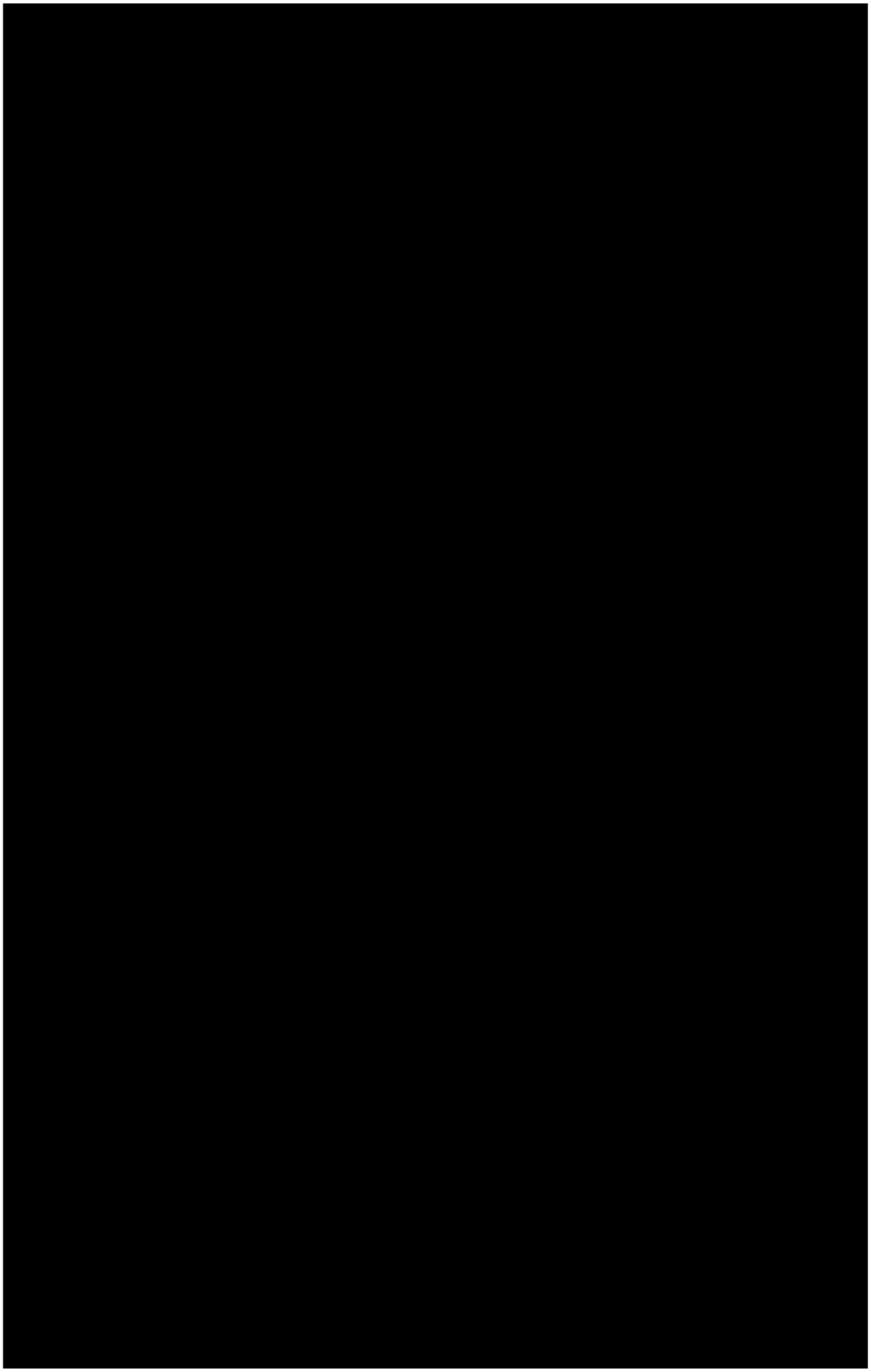
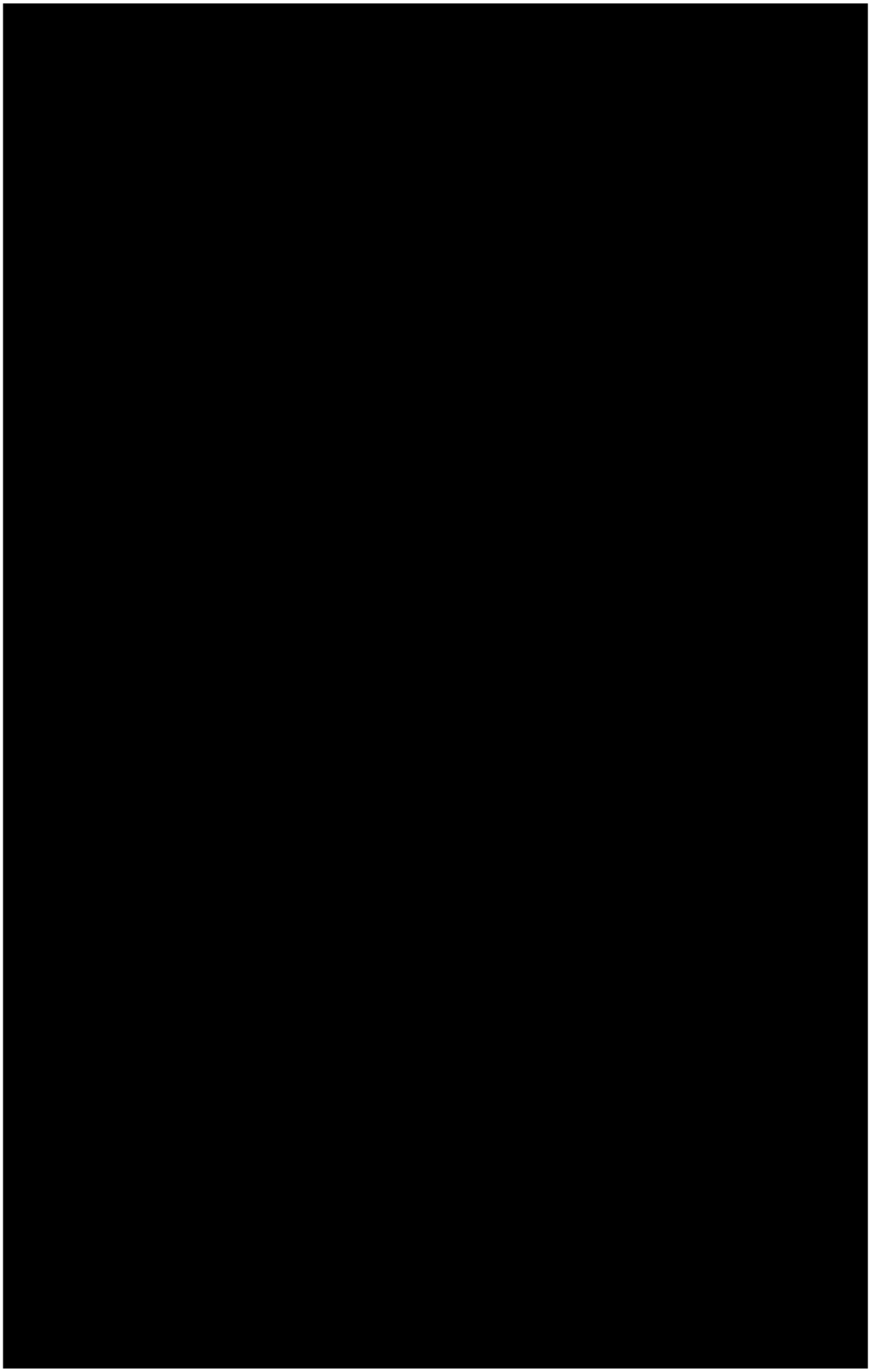
The RESPOND Study Group: https://www.chip.dk/Studies/RESPOND/Study-Group

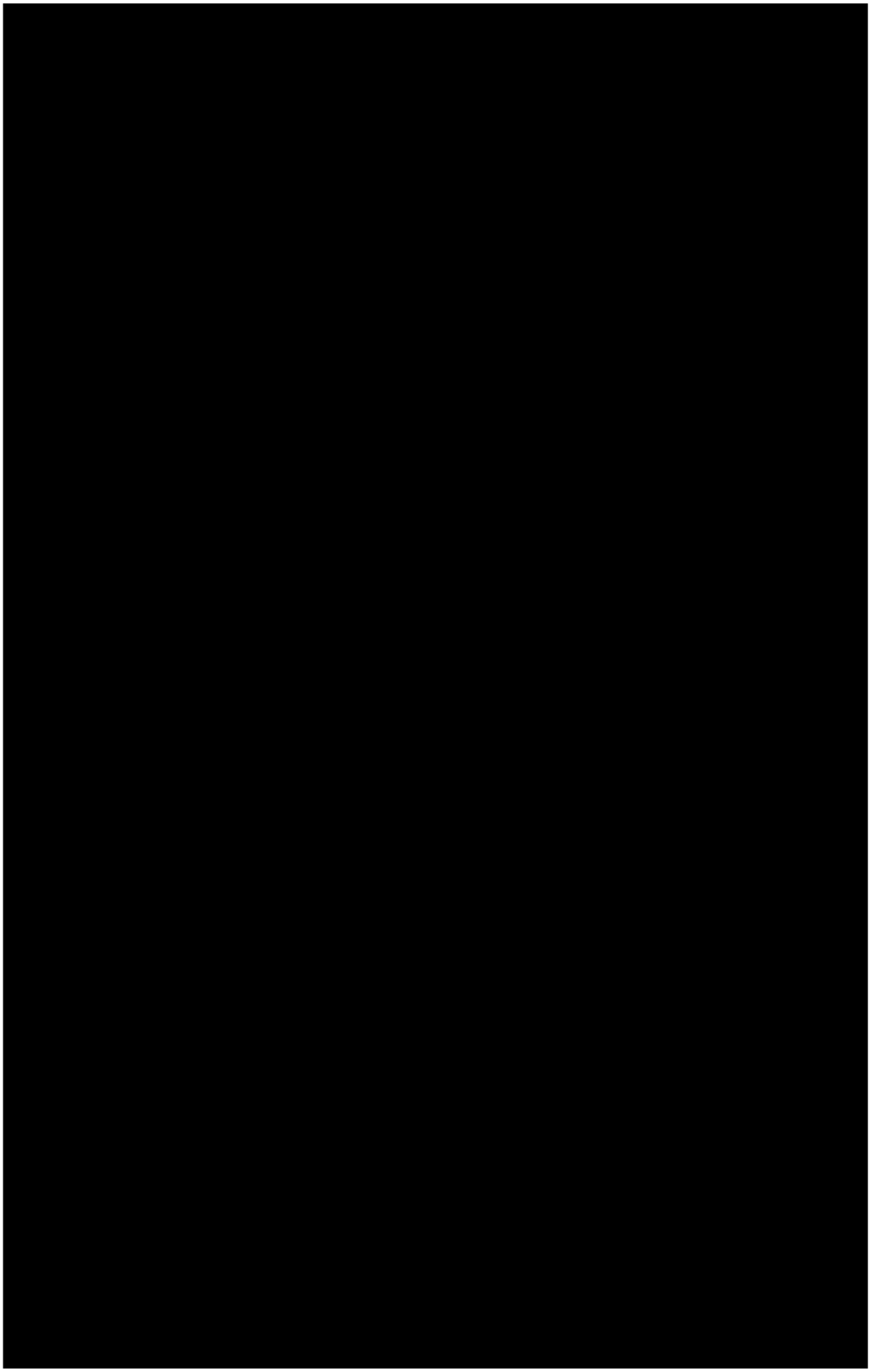
Appendix IX: Published manuscript CID 2021 entitled "Clinical Outcomes of 2-Drug Regimens vs 3-Drug Regimens in Antiretroviral Treatment–Experienced People Living With Human Immunodeficiency Virus"

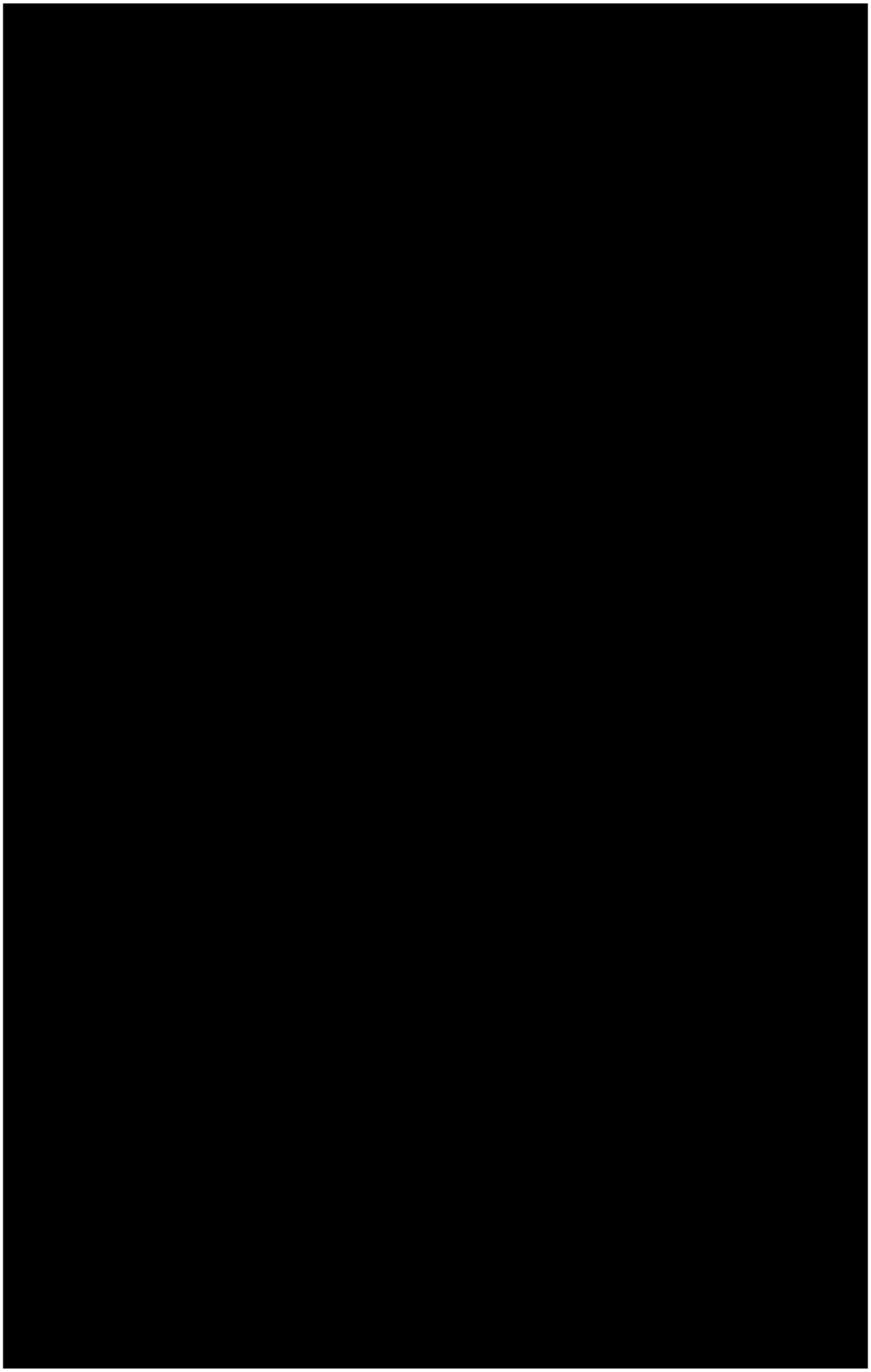


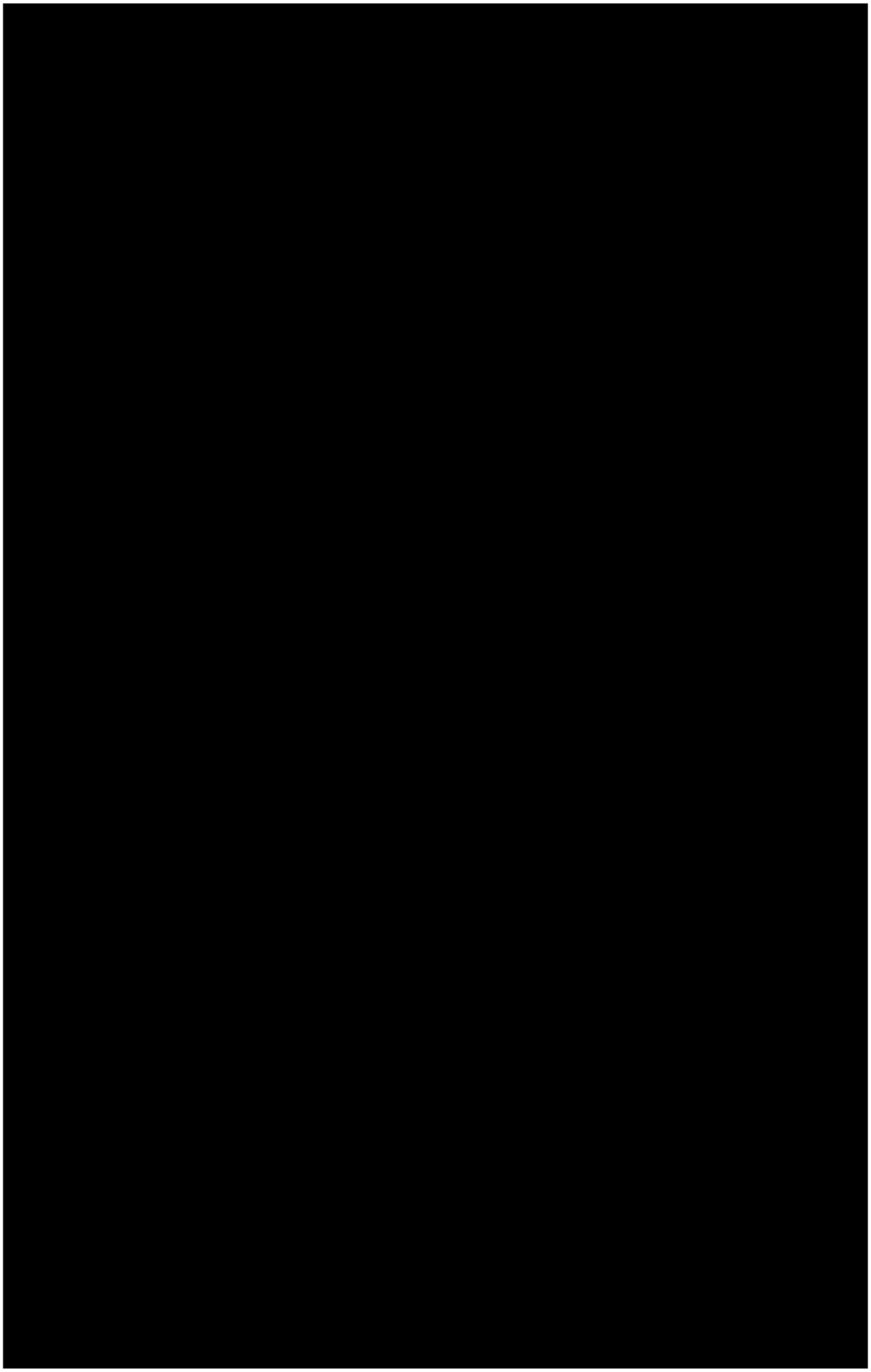


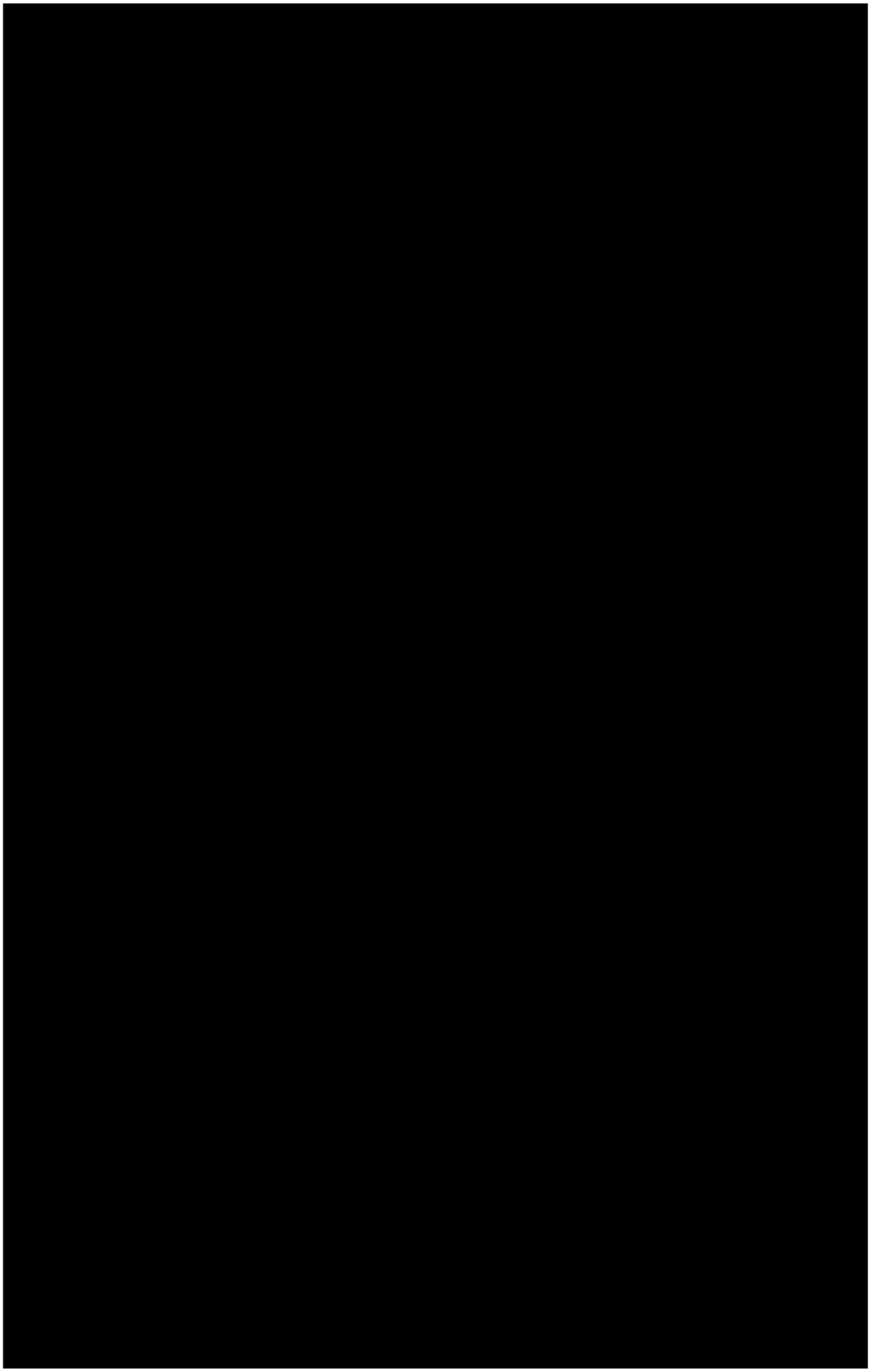


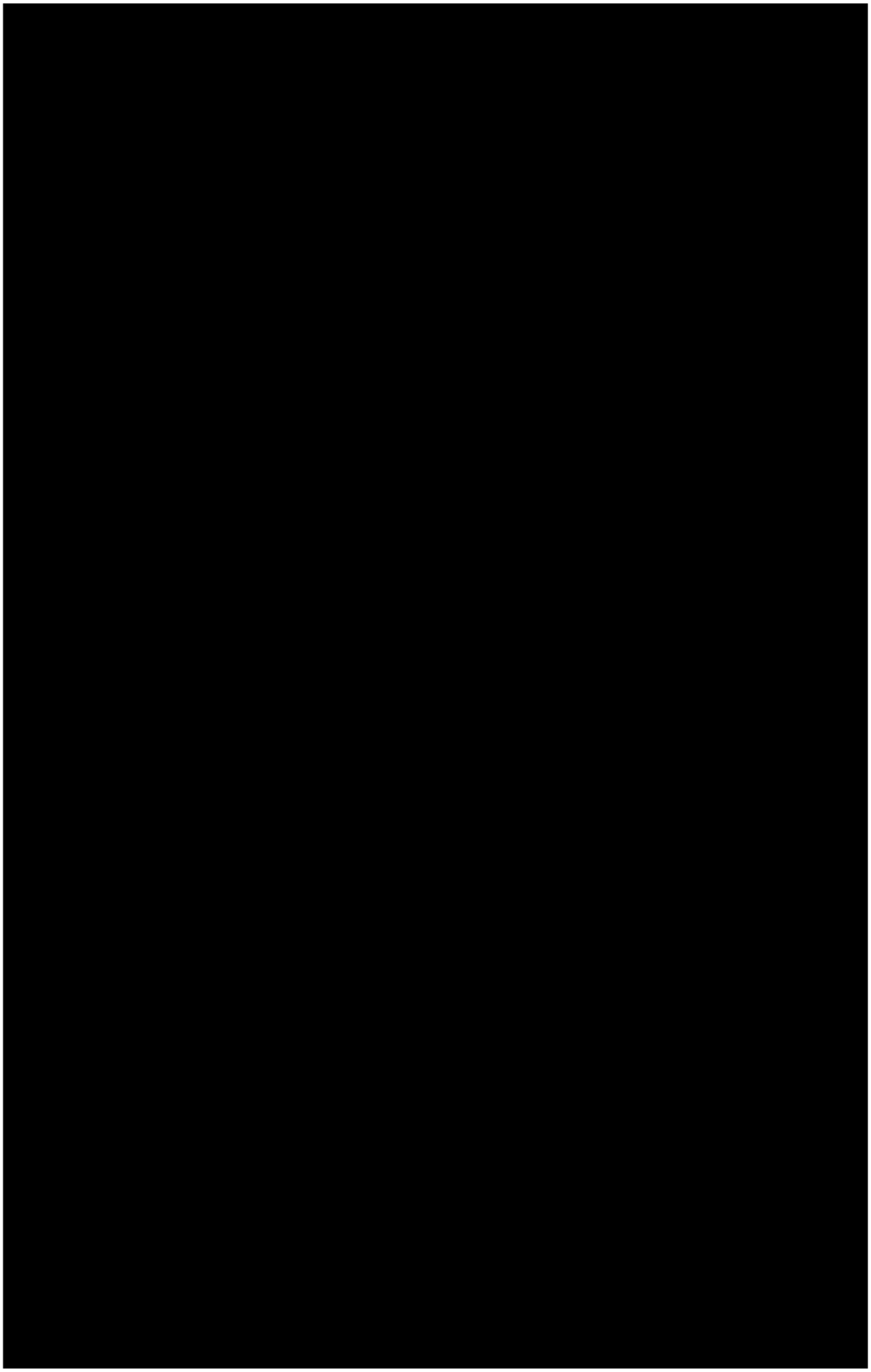


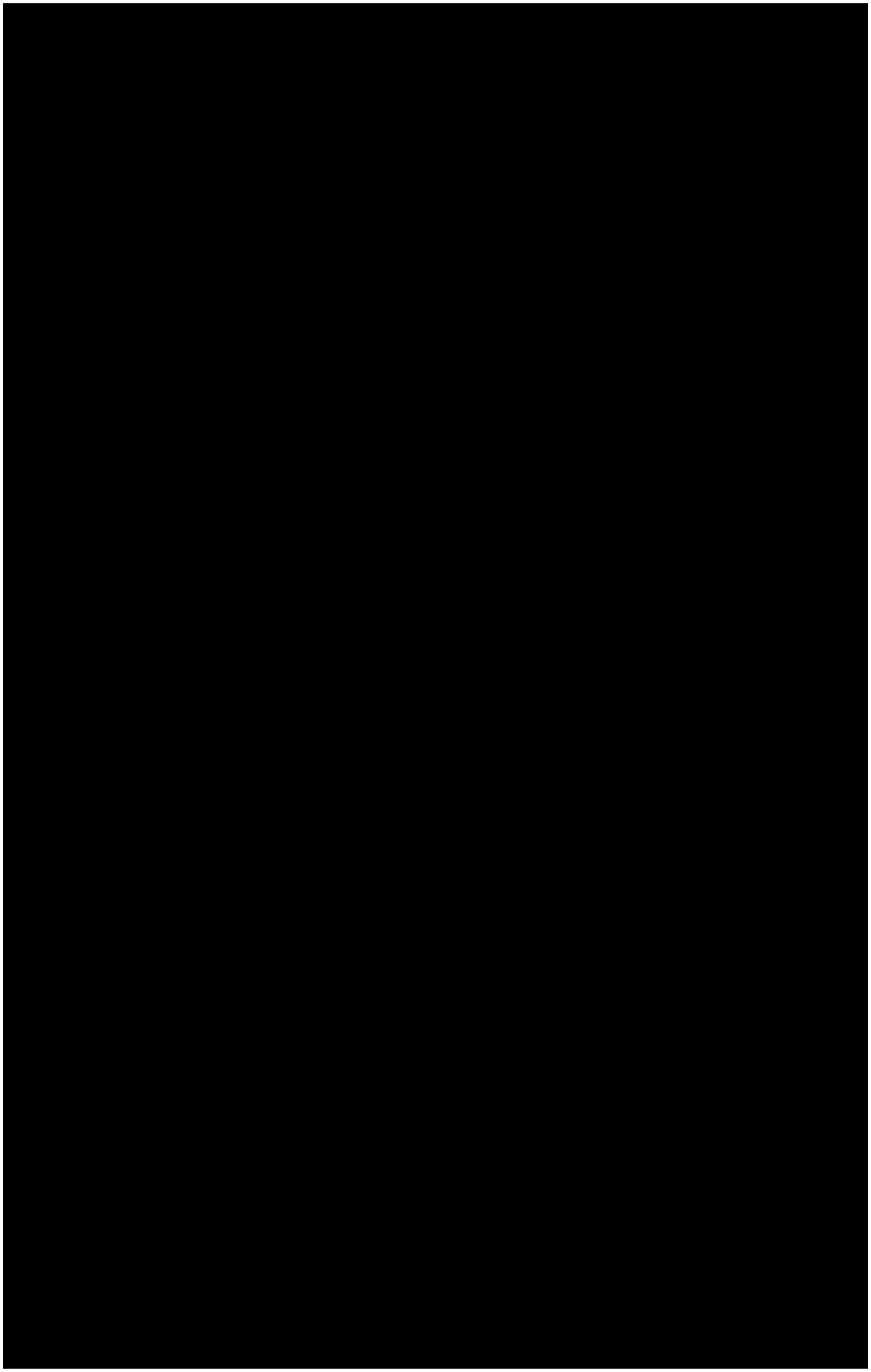


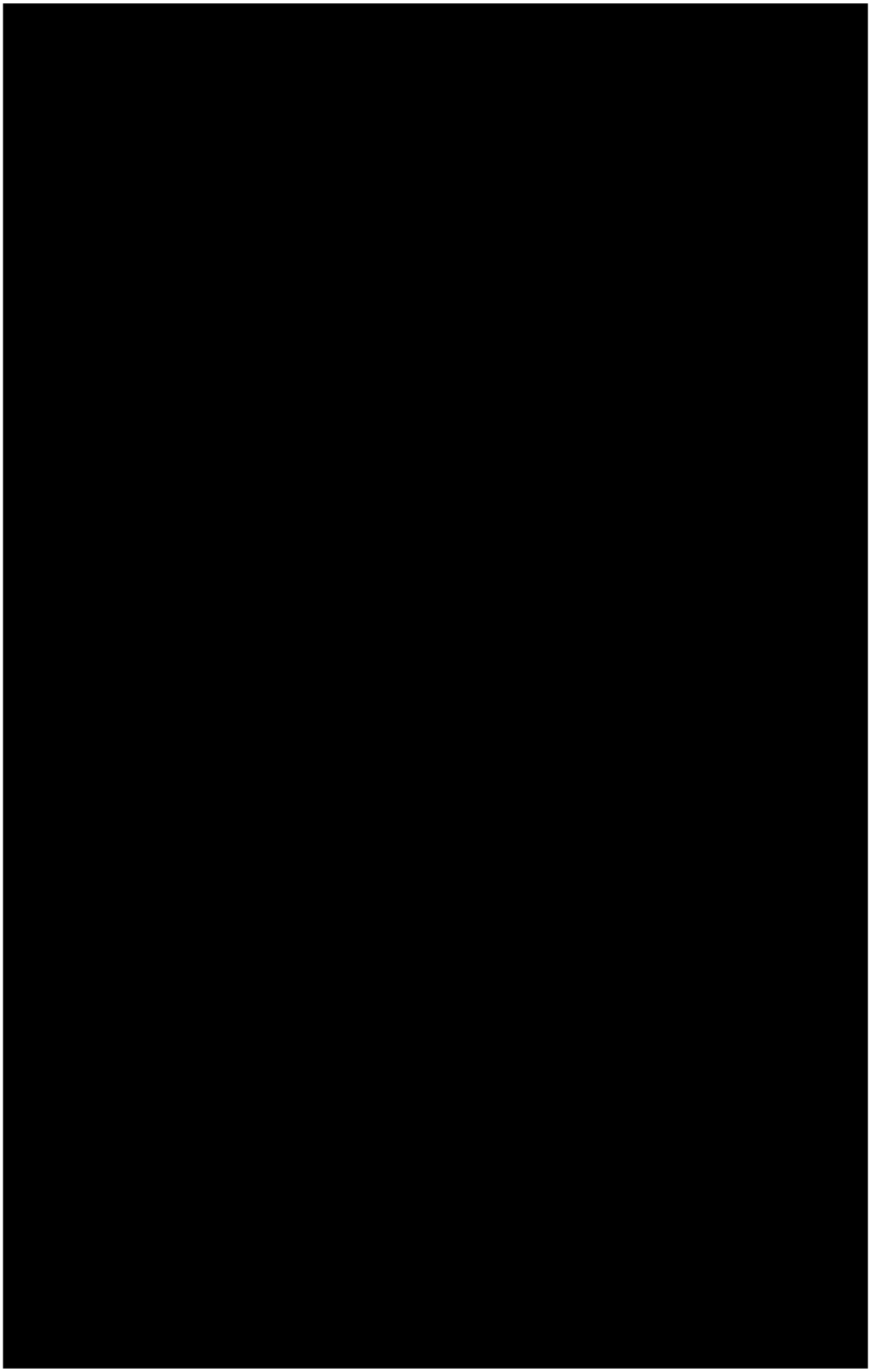












Appendix X: IAS 2021 poster entitled "Integrase strand transfer inhibitor (INSTI) use and cancer incidence in a large cohort setting"

Integrase strand transfer inhibitor (INSTI) use and cancer incidence in a large cohort setting

L Greenberg[1], L Ryom[2], B Neesgaard[3], JM Miro[4], LD Rasmussen[5], R Zangerle[6], K Grabmeier-Pfistershammer[7], H Günthard[7,8], K Kusejko[7,8], C Smith[9], C Mussini[10], M Mancuso[10], F Wit[11], M Van Der Valk[11], A d'Arminio Monforte[12], S De Wit[13], C Necsoi[13], A Falcon-Matthews[1], J Lundgren[2], L Peters[2], A Castagna[14], C Mussini[15], JJ Vehreschild[16,17], C Prasse[17], A Bruguera Riera[18], A Sönnerborg[19], K Petoumenos[20], H Garges[21], F Rogatto[22], N Dedes[23], L Serra-Mestres[1], A Mocroft[1,2], for the RESPOND study group

Background

- Since the introduction of highly effective antiretroviral therapy (ART), the life expectancy of people living with HIV is approaching that of the general population [1,2].
- With an aging population there has also been an increase in the burden of comorbidities, such as non-AIDS-defining cancer (NADC) [3,4].
- As ART use is lifelong, it is crucial to identify any associations between ART use and the risk of comorbidities.
- INSTIs are a relatively new drug class, and so there is limited data assessing long-term clinical outcomes associated with INSTI use, such as cancers.

Methods

- Participants from RESPOND were followed from baseline (latest of local cohort enrolment and 1 Jan 2012) until earliest of first cancer event (excluding pre cancers, relapse of a primary cancer, non-melanoma skin cancers), final follow-up, or 31 Dec 2019.
- INSTI exposure was lagged by 6 months to:
  - reduce potential confounding by indication where individuals at higher cancer risk or with symptoms indicative of cancer but no clinical diagnosis, may be preferentially prescribed INSTIs;
  - account for the fact that cancer development is a slow process, and so current cancer risk is unlikely to be attributable to recent ART-exposure.
- Generalised estimating equations with negative binomial regression was used to assess the association between cancer incidence and lagged cumulative INSTI exposure, adjusting for potential confounders (Figure 1 footnote).
- Analyses were repeated for NADCs and AIDS-defining cancers (ADCs) separately.

Table 1: Baseline characteristics

		Overall n	Overall (%)
		29340	(100)
Gender	Male	21818	(74.4)
Ethnicity	White	20419	(69.6)
	Black	2983	(10.2)
BMI (kg/m²)	<18.5	873	(3.0)
	≥25	6706	(22.9)
HIV risk group	MSM	13229	(45.1)
ART history at baseline	ART Naive	7172	(24.4)
	ART Experienced, VL<200 cps/mL	19951	(68.0)
Smoking status	Current	8196	(27.9)
	Previous	2261	(7.7)
Prior AIDS event		5785	(19.7)
Prior cancer		1742	(5.9)
Prior comorbidity		19172	(65.3)
		Median	Interquartile Range
Baseline date, month/year		01/12	(01/12, 02/13)
Age, years		44	(36, 51)
CD4 cell count at baseline, cells/mm³		524	(357, 715)
CD4 cell nadir, cells/mm³		241	(120, 384)
Total duration of previous ART, years		7.7	(3.0-13.9)

Abbreviations: BMI-body mass index; MSM-men who have sex with men; ART-antiretroviral; VL-viral load. Comorbidities include hypertension, diabetes, non-AIDS defining cancer, end-stage liver and renal disease, cardiovascular disease, chronic kidney disease, and dyslipidemia. Percentage of unknown variable: Ethnicity 15.9, body mass index 35.6, HIV risk 4.1, smoking status 36.4, prior AIDS 5.4, prior cancer 2.1, prior comorbidity 25.7

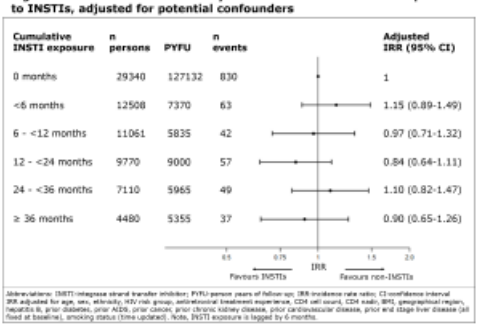
Table 2: Association between INSTI exposure and NADCs and ADCs

INSTI exposure, months	All NADCs N events (PYFU)	All NADCs Adjusted IRR (95% CI)	All ADCs N events (PYFU)	All ADCs Adjusted IRR (95% CI)
0	625 (127132)	1	205 (127132)	1
<6	46 (7370)	1.22 (0.90, 1.65)	17 (7370)	0.86 (0.52, 1.43)
6-<12	37 (5835)	1.25 (0.89, 1.74)	5 (5835)	0.31 (0.13, 0.77)
12-<24	52 (9000)	1.11 (0.84, 1.48)	5 (9000)	0.22 (0.09, 0.53)
24-<36	41 (5965)	1.31 (0.95,1.80)	8 (5965)	0.56 (0.28, 1.15)
36+	34 (5355)	1.16 (0.82, 1.65)	3 (5355)	0.25 (0.08, 0.78)
Global P-value		0.32		0.0002

Results

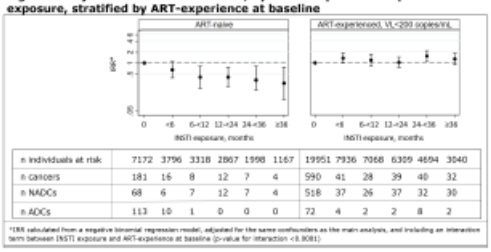
- Overall, 29,340 individuals were included in the analysis (Table 1).
- By the end of follow-up (FU), 13,950 (48%) individuals had been exposed to ≥1 INSTI: 8607 dolutegravir, 3328 cobicistat-boosted elvitegravir, 3266 raltegravir, and 845 bictegravir.
- For those exposed to INSTIs, median cumulative exposure was 32 months (IQR 16-47).
- During 160,657 person-years of FU (PYFU, median 6.18 years [IQR 3.86-7.52]), there were 1078 cancer events (incidence rate [IR] 6.7/1000 PYFU [95% CI: 6.3-7.1]): 243 ADCs and 835 NADCs.
- The most common incident cancers were non-Hodgkin lymphoma (n=113, 10.5%), lung cancer (112, 10.4%), Kaposi's sarcoma (106, 9.8%), and anal cancer (103, 9.6%).
- After adjustment for potential confounders, the incidence of any cancer was similar for those with and without exposure to INSTIs (Figure 1).

Figure 1: Association between any cancer risk and cumulative exposure to INSTIs, adjusted for potential confounders



- There was a significant interaction between INSTI exposure and baseline ART-experience (interaction p<0.0001; Figure 2). For ART-naïve participants, cancer incidence decreased with increasing INSTI exposure, mainly driven by a decreasing incidence of ADCs. For ART-experienced, cancer incidence was similar across all INSTI exposure categories.
- There was no interaction between INSTI exposure and other subgroups (age group, smoking status, CD4 nadir; interaction p>0.1 for all).
- There was no association between INSTI exposure and NADCs, while the incidence of ADCs decreased as exposure to INSTIs increased (Table 2).

Figure 2: Adjusted incidence of cancer, by INSTI exposure compared to no exposure, stratified by ART-experience at baseline



n individuals at risk	7172	3796	3318	2867	1998	1167	19951	7936	7068	6309	4694	3040
n cancers	181	16	8	12	7	4	590	41	28	39	40	32
n NADCs	68	6	7	12	7	4	518	37	26	37	32	30
n ADCs	113	10	1	0	0	0	72	4	2	2	8	2

*IRR calculated from a negative binomial regression model, adjusted for the same confounders as the main analysis, and including an interaction term between INSTI exposure and ART-experience at baseline (p-value for interaction <0.0001)

Limitations

- Despite the large study size, we had too few events to reliably assess associations between cancer risk and individual INSTIs or to assess individual cancers.
- Median exposure to INSTIs may have been too short to detect an association with cancer risk, given cancers can take years to develop.
- We cannot exclude the possibility of unmeasured confounding or confounding by indication.

Conclusion

- There was no association between INSTI exposure and cancer risk in ART-experienced individuals.
- There was a decreasing cancer incidence with increasing exposure in those starting INSTIs from ART-naïve, driven by a fast decline in ADCs, likely due to improvements in immune function.

The RESPOND Study Group: https://www.chip.dk/Studies/RESPOND/Study-Group

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