Prevalence and Outcomes for Heavily Treatment-Experienced (HTE) Individuals Living with Human Immunodeficiency Virus in a European Cohort

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Running head: HTE status in people with HIV in Europe

Abstract

Background: Although antiretroviral treatments have improved survival of persons living with HIV, their long-term use may limit available drug options. We estimated the prevalence of heavily treatment-experienced (HTE) status and the potential clinical consequences of becoming HTE.

Setting: EuroSIDA, a European multicentre prospective cohort study.

Methods: A composite definition for HTE was developed, based on estimates of antiretroviral resistance and prior exposure to specific antiretroviral regimens. Risks of progressing to clinical outcomes were assessed by Poisson regression, comparing every HTE individual with three randomly-selected controls who never became HTE.

Results: Of 15,570 individuals under follow-up in 2010-2016, 1617 (10.4%, 95% CI 9.9-10.9%) were classified as HTE. 1093 individuals became HTE during prospective follow-up (HTE incidence rate 1.76, CI 1.66-1.87 per 100 person-years of follow-up). The number of HTE individuals was highest in West/Central Europe (636/4019 persons, 15.7%) and lowest in East Europe (26/2279 persons, 1.1%).

Although most HTE individuals maintained controlled viral loads (<400 copies/ml), many had low CD4 counts (≤350 cells/µl). After controlling for age, immunological parameters and pre-existing comorbidities, HTE status was not associated with the risk of new AIDS (adjusted incidence rate ratio, aIRR 1.44, CI 0.86-2.40, p = 0.16) or non-AIDS clinical events (aIRR 0.96, CI 0.74-1.25, p = 0.77).

Conclusions: HTE prevalence increased with time. After adjusting for key confounding factors, there was no evidence for an increased risk of new AIDS or non-AIDS clinical events in HTE. Additional therapeutic options and effective management of comorbidities remain important to reduce clinical complications in HTE individuals.

Keywords: HIV resistance; antiretroviral treatment; heavily treatment-experienced; AIDS; acquired immunodeficiency syndrome; non-AIDS-defining clinical conditions.

Introduction

The availability of potent antiretroviral therapy (ART) and linkage to care have resulted in improvements in life expectancy for people living with HIV,[1,2] but as treatment has to be life-long, extensive treatment experience is increasingly common. There is no standardised definition of Heavily Treatment-Experienced (HTE) status. This lack of uniformity has hampered quantification of the burden of HTE and makes it difficult to compare results across studies. A more uniform definition and a better understanding of the clinical consequences of HTE would inform patient management and treatment strategies.

Descriptions of HTE status or limited treatment options have included prolonged exposure to different antiretrovirals (ARVs) or using ≥4 ARV drugs.[3] Many definitions assess resistance to ARVs in multiple drug classes or having ≤2 classes with fully-active ARVs remaining which could be combined to form a viable new regimen.[4-7] Treatment options can also be limited by drug side-effects and drug-drug interactions, especially in an aging population of people living with HIV receiving medications for comorbidities.[8,9] Therefore alternative definitions of HTE are being explored based on ART history or use of specific ARVs indicative of HTE status.[10,11] Estimates of HTE prevalence rely heavily on how it is defined and therefore vary widely. The prevalence of triple-class resistance to nucleotide/nucleoside and non-nucleotide reverse transcriptase inhibitors (NRTIs, NNRTIs) and protease inhibitors (PIs) has been estimated to range from 2.1% to 16% (reviewed in [12]), but may be declining in recent years as the incidence of drug resistance is decreasing with the introduction of new potent ARVs and more convenient single-tablet ARV formulations.[4,13,14] Estimates of HTE prevalence based solely on an individual's ART history range from 5 to 10% of people living with HIV.[10,11]

Here we derived a composite definition for HTE based on genotypic resistance test (GRT) results, modelling to predict ARV resistance and ARV prescription history. This allowed us to estimate the

prevalence and incidence of HTE status among individuals in the EuroSIDA cohort and describe the virologic, immunologic and clinical outcomes associated with being HTE.

Methods

The EuroSIDA study

EuroSIDA is a multinational prospective observational cohort study which has systematically collected epidemiological, clinical, biological, and therapeutic data for more than 23,000 people living with HIV in 35 European countries, Israel and Argentina since 1994 (https://www.chip.dk/Studies/EuroSIDA, see also [15]). Data on HIV drug resistance as GRTs were available for a subset of participants.

All individuals gave informed consent at enrolment into the study.

Derivation of a composite definition for HTE Status

We explored three different definitions of HTE and combined them to derive a composite definition (see **Supplemental Digital Content 1**, which describes the derivation of the composite definition for HTE). About ¼ of the participants in EuroSIDA had at least one GRT available, mainly from retrospective sequencing studies before 2010. We used the Stanford HIV drug resistance database[16] to interpret any GRT data available and developed logistic regression models to identify factors associated with resistance to specific NRTIs, NNRTIs or PIs. For individuals who had no GRT, resistance to specific ARVs was predicted from the logistic regression models. For other ARVs (integrase strand-transfer inhibitors (INSTIs), CCR5- or fusion inhibitors), resistance predictions were based on virological history (high viral load (VL) while on the drug). Individuals were classified as HTE by definition 1 if they were known or predicted to have ≤2 ARV drug classes with at least one active drug (or two active NRTIs) remaining, out of NRTIs, NNRTIs, PIs or other ARVS (INSTIs,

maraviroc or enfuvirtide as fourth combined class); NRTIs and PIs were only considered if recommended in current EACS guidelines.[17]

HTE definition 2 included individuals who had undergone ≥4 combination ART (cART) anchor agent switches, and HTE definition 3 those who ever used a regimen with ≥4 ARVs.

The composite definition for HTE included everyone with GRT results and known resistance to the three original ARV classes (NRTIs, NNRTIs and PIs), or else anyone who fulfilled the criteria for at least two of the three HTE definitions. The HTE index date was defined as the earliest date at which this composite definition was satisfied.

Inclusion of study participants

All individuals aged ≥18 years, under follow-up in EuroSIDA at any time from 2010 to 2016, and on ART (≥1 ARV) were included, as shown in **Figure 1**. HTE status was assessed at pre-specified reference dates (01 January 2010, the mid-year dates (01 July) 2010 to 2016 and 31 December 2016) and also on the date of every reported ARV regimen change. Individuals also had to have at least one CD4 and VL measurement before their HTE index date.

For calculation of HTE incidence, persons with prevalent HTE on 01 January 2010 were excluded. Individuals on ART with CD4 and VL data available were followed from the latest of 01 January 2010 or enrolment into EuroSIDA until they became HTE, their last clinic visit, or 31 December 2016, with baseline information for all variables calculated at the start of follow-up.

To assess outcomes of becoming HTE, all individuals who became HTE on or after 01 January 2010 and had ≥1 clinical follow-up visit before 31 December 2016 were included. To allow comparisons, three controls were randomly selected for every HTE participant, without matching for any characteristics, among individuals under follow-up on the index date of the HTE individual, but who

never became HTE. Baseline was set to the index date of the HTE individual, and variables and time-to-event data calculated for these matched index dates.

Clinical events and comorbidities

Clinical events included AIDS-defining conditions (opportunistic infections and malignancies[18]). Non-AIDS-defining clinical conditions were as described by Mocroft et al.[19] and comprised cardiovascular disease (CVD, including myocardial infarction, stroke, or invasive cardiovascular procedures), non-AIDS-defining malignancies (NADM, any malignancies other than Kaposi sarcoma, non-Hodgkin lymphoma or cervical cancer), liver-related events (ascites, hepatic encephalopathy grade 3-4, hepatorenal syndrome, oesophageal variceal bleeding, end-stage liver disease and hepatocellular carcinoma) or chronic kidney disease (CKD, a confirmed (two measurements >3 months apart) estimated glomerular filtration rate <60 ml/min/1.73 m^2 calculated from the CKD-EPI creatinine equation). For the analysis of new clinical event outcomes after becoming HTE (i.e. where HTE status was considered the exposure for later adverse outcomes), we included only conditions that the individual had not experienced previously (i.e. recurrence of a specific AIDS-defining condition, malignancy or cardiovascular event were not counted) and only included the first relevant event, with follow-up censored at that point. Causes of death were determined using the CoDe algorithm,[20] and deaths were included in the AIDS and non-AIDS clinical events where specified.

Statistical analysis

Prevalence of HTE by calendar year was calculated using as denominators all individuals under follow-up on the mid-year dates. Baseline characteristics, calculated at start of follow-up, are presented as proportions with Chi-squared P-values. All confidence intervals are 95%, and p-values are two-sided, with $P < 0.05$ considered significant.

Incidence rates were calculated as the number of events divided by person-years of follow-up (PYFU), assuming an underlying Poisson distribution. For multivariable modelling, factors were included as fixed-time variables calculated at baseline (the start of follow-up or the HTE index date for the incidence of HTE and for the clinical outcomes analyses, respectively). Multivariable models included all factors significant in univariable analyses (type 3 P-value <0.1) or specified *a priori* in the analysis plan. For outcomes after HTE, multivariable Poisson models were constructed by including variables that represent possible common causes of becoming HTE and the risk of outcomes (confounders); the model assumptions were described using directed acyclic graphs (DAGs) constructed with Dagitty (http://dagitty.net/, see also **Supplemental Digital Content 2**, which describes studies of the outcomes of becoming HTE, for the code).

Analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Prevalence of HTE

Of 15,570 individuals under follow-up in EuroSIDA between 01 January 2010 and 31 December 2016, 1617 (10.4%, CI 9.9, 10.9%) were ever HTE by our composite definition (see **Supplemental Digital content 1**). The majority of these had ≤2 ARV classes available based on GRT data or modelling predictions, while just 109 individuals (6.7%) were classified as HTE based solely on their previous ART prescriptions (**Figure 2A**). Overall, 503 individuals were prevalent HTE cases (i.e. already HTE by 01 January 2010), while 1114 became HTE during follow-up. Most HTE individuals resided in West/Central (15.7%), North (12.5%) and South Europe (11.6%), while just 26 of 2279 under follow-up in East Europe were HTE (1.1%, **Figure 2B**). The prevalence of HTE increased from 5.8% (CI 5.4,

6.3) in mid-2010 to 8.9% (CI 8.3, 9.4) by mid-2016 (**Figure 2C**), which represents an increase of 0.50% (CI 0.34%, 0.66%, P=0.0004) per year.

Incidence of HTE between 2010 and 2016

To assess the incidence of HTE, we followed a cohort 13,577 individuals on ART who were not already HTE on 01 January 2010 from this date or enrolment into EuroSIDA (baseline), and who had baseline CD4 counts, VL and ART information available, until 31 December 2016 or their last clinic visit (see **Figure 1**). The baseline characteristics of this cohort are shown in **Table 1**. Individuals who became HTE were older than those never HTE, more likely to be male, to have acquired HIV by sex between men (MSM) and less likely to be injecting drug users. Most HTE individuals were resident in South, West/Central or North Europe, and almost 60% had GRT information available, compared to <25% of those not HTE. HTE individuals were also more likely to have low baseline or nadir CD4 cell counts and to have been diagnosed with HIV ≥10 years earlier. As expected, HTE individuals had longer exposure to more different ARVs from all classes, and more HTE individuals than those not HTE had previously had an AIDS-defining disease. Comorbidities and clinical events were also more common in those who became HTE.

Overall 1093/13,577 individuals became HTE during 62,130 PYFU of prospective follow-up, with a crude HTE incidence rate of 1.76/100 PYFU (CI 1.66, 1.87/100 PYFU). Factors associated with becoming HTE were identified using multivariable Poisson regression modelling (**Figure 3**). After controlling for potential confounders, age was not significantly associated with the risk of becoming HTE, and women were less likely to become HTE. Compared to West/Central Europe, only individuals in East Europe had a significantly lower incidence of HTE. Individuals with a CD4 cell nadir of ≤200 cells/µl at the start of follow-up had a higher HTE incidence rate (adjusted incidence rate ratio, aIRR, 1.51, CI 1.30, 1.74, P <0.0001). Individuals who had been living with HIV for >10

years also had a higher incidence of HTE (aIRR 1.31, CI 1.01, 1.71, P=0.044 compared to those diagnosed <2 years prior), and the incidence of HTE increased 1.32x (CI 1.28, 1.36 P <0.0001) for every additional ARV drug that an individual had previously been exposed to. Individuals who had an AIDS-defining condition prior to the start of follow-up, or who had prior CVD, NADM, liver disease or CKD, all had higher incidence of HTE in univariable analyses, but after multivariable adjustment, prior comorbidities were no longer associated with HTE incidence.

Clinical outcomes of becoming heavily treatment experienced

To assess the virologic, immunologic and clinical consequences for individuals after becoming HTE we analysed data for all 1040 individuals who became HTE on or after 01 January 2010 with follow-up available after their HTE index date. The HTE individuals were compared to 3120 index date-matched controls who did not become HTE (see Methods and **Figure 1**). The main characteristics of this cohort are summarized in **Supplemental Digital Content 2**, which describes studies of the outcomes of becoming HTE.

Although more HTE individuals had an unsuppressed VL (≥400 copies/ml) on the index date compared to those not HTE (19.7% vs 8.7%, P <0.0001, **Supplemental Digital Content 2**), the majority of individuals achieved virologic control (<400 copies/ml) by 6 months, and thereafter the proportions with unsuppressed VL were similar for HTE individuals and those not HTE. In contrast, the proportion of individuals with low CD4 counts was higher among HTE compared to non-HTE individuals (13.3% vs. 5.1% with ≤200 cells/µl or 32.6% vs. 17.8% with ≤350 cells/µl, for HTE and non-HTE, respectively) and these differences in CD4 counts were maintained over >2 years of follow-up (**Supplemental Digital Content 2**).

To assess the clinical outcomes of HTE status, individuals were followed for approximately 2820 PYFU for HTE (median 2.26, IQR 0.91-4.30 years/person) and 8720 PYFU for those not HTE (median

2.33, IQR 1.02-4.37 years/person). The incidence of new AIDS events was higher among HTE individuals compared to those not HTE (incidence rate, IR, 0.90, CI 0.61, 1.34 vs. 0.35, CI 0.24, 0.49 events/100 PYFU respectively, IRR 2.61, CI 1.54, 4.44, P=0.0004, **Figure 4A and C**). There was also a higher incidence of deaths (IR 1.85, CI 1.41, 2.42 vs. 1.30, CI 1.08, 1.56 events/100 PYFU in HTE and non-HTE, respectively, IRR 1.42, CI 1.02, 1.98, P=0.035). When any deaths due to AIDS were included, the overall incidence of new fatal and non-fatal AIDS events was also higher among persons with HTE compared to those without HTE (1.09, CI 0.76, 1.55 vs. 0.45, CI 0.33, 0.62 events/100 PYFU), representing an overall 2.4-fold higher incidence of AIDS events among HTE individuals (unadjusted IRR 2.41, CI 1.50, 3.88, P=0.0003, **Figure 4B and D**). After multivariable adjustment using two sets of adjustment variables from DAGs (see **Supplemental Digital Content 2**), the multivariable fully adjusted models both indicated that HTE status was not significantly associated with the incidence of new fatal and non-fatal AIDS events during follow-up (see **Figure 4D and Supplemental Digital Content 2**).

HTE individuals also experienced more new non-AIDS clinical events during follow-up, including NADM, CKD, CVD or liver-related events (incidence rate 3.13, CI 2.53, 3.88 vs. 2.51, CI 2.19, 2.87 events/100 PYFU for HTE and non-HTE respectively, IRR 1.25, CI 0.97, 0.61, p=0.085, **Figure 4A and C**). The highest IRR was observed for liver-related events (unadjusted IRR 2.74, CI 1.37, 5.49, p=0.0044). When deaths due to non-AIDS conditions were included, the overall unadjusted IRR of fatal and non-fatal non-AIDS events was 1.27 (CI 1.00, 1.63, p=0.054). In the fully adjusted multivariable models (summarized in **Figure 4D**) no statistically significant association was found between HTE status and the risk of developing new non-AIDS clinical events.

Discussion

We developed a new definition of HTE that takes into account ARV class-resistance, based on GRT data and modelling predictions, as well as past exposures to certain ARV regimens. Within EuroSIDA, 10.4% of individuals overall were estimated to be HTE, with HTE prevalence increasing by approximately 0.5%/year. Persons with HTE were older, more likely male, with lower CD4 counts, and living with HIV for ≥10 years. Many HTE individuals previously had an AIDS-defining or non-AIDS clinical condition. Although the majority of HTE individuals seemed to maintain good virologic control during follow-up, their CD4 counts remained lower than in the non-HTE. In unadjusted analyses, HTE individuals appeared to be at higher risk of developing new AIDS or non-AIDS-defining clinical events, suggesting that new therapeutic options are required not only to suppress viraemia, but also to foster immune recovery and reduce the risk of adverse clinical outcomes in this sub-population of people living with HIV. In multivariable models, the risks of AIDS and non-AIDS events could be completely explained by aging, CD4 counts and pre-existing comorbidities.

Our definition of HTE relied mainly on estimates of ARV class resistance and less on the ARV prescription record; however, since most individuals did not have recent GRT data available, many resistance assignments relied on modelling. Although this allowed predictions of which individuals may be HTE, we cannot calculate the actual numbers of treatment options still available to any specific study participant. Our estimates of the prevalence of HTE status were broadly in line with reports for triple-class resistance,[12] but higher than some other HTE definitions.[10,11] Of note, only a small proportion of HTE individuals were identified solely based on the use of specific ARV regimens, supporting the notion that ARV resistance data, or predictions/imputations of resistance (e.g. see [21]), should be included to allow consistent monitoring and increase the accuracy of HTE prevalence estimates.

The prevalence of HTE varied strongly between European regions, with lower prevalence in Central East and East Europe, and individuals in East Europe also had a significantly lower incidence of HTE.

Identification of HTE individuals in East Europe relied strongly on resistance modelling, as few GRTs were submitted from this region, and may therefore be less reliable. However, results are in line with studies of HIV care that may indicate poorer outcomes for individuals in East Europe[15] and different approaches to initiation of ART, availability of specific ARV regimens and resistance testing.[22]

Since our definition of HTE did not require virologic failure, most HTE individuals had a controlled VL on the index date, or achieved a controlled VL during follow-up when they switched to a new ARV regimen. This is at least in part due to the availability of potent ARVs with higher genetic barriers, such as dolutegravir or darunavir, increasing the options available for individuals with multi-class ARV failure. Individualised treatment approaches including regimen simplification informed by resistance data,[3] salvage regimens (e.g. combining dolutegravir and darunavir[7,23]), adjustments of drug dosage,[24] or the introduction of new drugs from novel classes[25,26] now provide better prospects for HTE individuals. Remarkably, HTE individuals spent a higher proportion of follow-up time with lower CD4 cell counts when compared to those not HTE.

Analysis of the clinical outcomes after becoming HTE showed that, in unadjusted analyses, HTE individuals experienced a significantly higher rate of new AIDS-related clinical events or deaths compared to controls. Increases in AIDS and mortality in individuals with drug resistance have also been reported in other cohorts.[6,27] The excess risk was mostly explained by differences in baseline CD4 counts, indicating that the HTE group may include a significant proportion of immuno-virologically discordant individuals or immunological non-responders (INRs, see[28,29]). Indeed other studies have indicated increased mortality and increased rates of AIDS and non-AIDS events in INRs.[30-33] The observation that CD4 count trajectories in the HTE group were less favourable, despite a similar virological response, support the hypothesis that CD4 count was an important mediator of the effect seen in the unadjusted analysis, highlighting the need for treatment strategies that support immune reconstitution. Similarly there was a higher incidence of new non-AIDS clinical

events in HTE individuals, mainly due to higher incidence of liver-related events; this may reflect previous exposures to certain NRTIs (didanosine, stavudine) that have been linked to liver conditions.[34] After controlling for potential confounders, the higher risk of non-AIDS events during follow-up reflected older age, longer time since HIV diagnosis, and pre-existing non-AIDS comorbidities.

Strengths of this study include the large number of persons recruited across all European regions, with complete ARV prescription data as well as some GRT results reported. The availability of a range of clinical events across the population allowed us to estimate the impact of HTE status on clinical outcomes. The analysis also has limitations. One major limitation is that most GRTs were from samples taken before 2010; therefore modelled predictions of resistance were extrapolated to later years, which may have underestimated the reduction in drug resistance that has been reported in other settings[13,14] or the improved treatment options available after introduction of new ARVs. We did not have treatment adherence data available, and current virologic failure was not included in the HTE definition, reflecting modern practice where many people maintain controlled VL even with limited options remaining[4]. To evaluate clinical consequences of being HTE, a control group was required. We used a randomly-selected sample of three controls from those who were never HTE, but without matching. Although the characteristics of those included in this cohort were similar to the general population in EuroSIDA, there may be some selection bias. While we used current knowledge and published evidence to inform the design of the DAGs, some assumptions might not be correct. Furthermore, as the analyses were conducted in an observational setting, unmeasured confounding in the association between HTE and the evaluated outcomes cannot be ruled out.

In conclusion, we derived a novel comprehensive definition for HTE and estimated that about 10% of individuals in EuroSIDA were HTE between 2010 and 2016. We found that individuals with HTE had a higher risk of developing AIDS-related and unrelated complications. However, the higher risk of

AIDS was largely explained by differences in CD4 counts between HTE and non-HTE individuals, which highlights persisting missed opportunities to optimise cART regimens among HTE persons. Initiation or extension of prophylaxis against opportunistic diseases should be further assessed in this population. The fact that the risk of non-AIDS-complications in those with HTE was related to a higher prevalence of comorbidities suggests that HIV guidelines should single out HTE persons as a priority group to screen and manage non-AIDS-defining comorbidities, such as cancer and cardiovascular disease. Our study sets a path towards a standardized definition of HTE, which should help to identify individuals with limited therapeutic options available and guide individualised approaches to ensure viral suppression and immune recovery.

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List of Supplemental Digital Content:

Supplemental Digital Content 1: Text, which describes the derivation of the composite definition for Heavily Treatment-Experienced (HTE) status**.**

Supplemental Digital Content 2: Text, which describes further studies of outcomes of becoming heavily treatment experienced (HTE).

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Table 1: Baseline characteristics at start of follow-up (01 January 2010 or enrolment) for individuals who became HTE or not

	HTE	Not HTE		Proportion HTE
	N (%) [a]	N (%) [a]	P-value [b]	% of Total
Number included	**1093**	**12484**		**8.1**
Age group (years)				
<40	112 (10.2)	3730 (29.9)	<0.0001	2.9
40 to <50	538 (49.2)	4727 (37.9)		10.2
50 to <60	321 (29.4)	2865 (22.9)		10.1
≥60	122 (11.2)	1162 (9.3)		9.5
Sex				
Male	826 (75.6)	9013 (72.2)	0.0166	8.4
Female	267 (24.4)	3471 (27.8)		7.1
Ethnic group				
White/Caucasian	877 (80.2)	10648 (85.3)	<0.0001	7.6
Other/Unknown	216 (19.8)	1836 (14.7)		10.5
Risk group				
MSM	444 (40.6)	4579 (36.7)	0.0002	8.8
IDU	231 (21.1)	3273 (26.2)		6.6
Heterosexual	315 (28.8)	3711 (29.7)		7.8
Other/Unknown	103 (9.4)	921 (7.4)		10.1
Region of Europe [c]				
South	308 (28.2)	3309 (26.5)	<0.0001	8.5
West/Central	435 (39.8)	3209 (25.7)		11.9
North	267 (24.4)	2507 (20.1)		9.6
Central East	71 (6.5)	1761 (14.1)		3.9
East	12 (1.1)	1698 (13.6)		0.7
Genotypic resistance test				
Never tested	449 (41.1)	9533 (76.4)		4.5
≥1 GRT available	644 (58.9)	2951 (23.6)		17.9
CD4 counts (cells/µl)				
≤200	128 (11.7)	949 (7.6)	<0.0001	11.9
201 – 350	226 (20.7)	2036 (16.3)		10.0
351 – 500	235 (21.5)	2791 (22.4)		7.8
>500	504 (46.1)	6708 (53.7)		7.0
CD4 nadir (cells/µl)				
≤200	821 (75.1)	5516 (44.2)	<0.0001	13.0

	HTE	Not HTE		Proportion HTE
	N (%) [a]	N (%) [a]	P-value [b]	% of Total
Number included	**1093**	**12484**		**8.1**
Viral load				
Controlled (<400 copies/ml)	950 (86.9)	11004 (88.1)	0.2301	7.9
Time since HIV diagnosis (years)				
<2	77 (7.0)	1781 (14.3)	<0.0001	4.1
2 to <10	67 (6.1)	4027 (32.3)		1.6
≥10	949 (86.8)	6676 (53.5)		12.4
Time on ART (years)				
<2	7 (0.6)	1790 (14.3)	<0.0001	0.4
2 to <10	95 (8.7)	4984 (39.9)		1.9
≥10	991 (90.7)	5710 (45.7)		14.8
ARV regimen at start of FU				
2-Drug regimen	26 (2.4)	627 (5.0)	<0.0001	4.0
cART (2 NRTIs + anchor) [d]	516 (47.2)	9960 (79.8)		4.9
≥4 ARVs	459 (42.0)	988 (7.9)		31.7
Other regimens	92 (8.4)	909 (7.3)		9.2
Previously exposed to:				
NRTI	1093 (100)	12423 (99.5)	0.0205	8.1
NNRTI	991 (90.7)	8389 (67.2)	<0.0001	10.6
Protease inhibitor	1080 (98.8)	9140 (73.2)	<0.0001	10.6
Boosted Protease inhibitor	1005 (91.9)	7503 (60.1)	<0.0001	11.8
INSTI	278 (25.4)	1154 (9.2)	<0.0001	19.4
Fusion inhibitor (ENF)	127 (11.6)	55 (0.4)	<0.0001	69.8
CCR5 inhibitor (MVC)	43 (3.9)	109 (0.9)	<0.0001	28.3
Clinical conditions				
Prior AIDS	459 (42.0)	3335 (26.7)	<0.0001	12.1
HCV positive [e]	376 (34.4)	5440 (43.6)	<0.0001	6.5
HCV status unknown	548 (50.1)	4778 (38.3)		10.3
Cardiovascular disease	68 (6.2)	420 (3.4)	<0.0001	13.9
Non-AIDS-defining malignancy	61 (5.6)	372 (3.0)	<0.0001	14.1
Liver-related clinical events	37 (3.4)	315 (2.5)	0.0855	10.5
Chronic kidney disease (CKD)	67 (6.1)	475 (3.8)	<0.0001	12.4
CKD Unknown [f]	98 (9.0)	2563 (20.5)		3.7
Continuous variables	**Median (IQR)**	**Median (IQR)**	**P-value [b]**	
Age at start of FU (years)	48.5 (44.1, 54.5)	45.5 (38.3, 52.3)	<0.0001	
CD4 counts (cells/µl)	483 (307, 665)	524 (359, 721)	<0.0001	
CD4 nadir (cells/µl)	110 (46, 200)	223 (117, 349)	<0.0001	

	HTE N (%) [a]	Not HTE N (%) [a]	P-value [b]	Proportion HTE % of Total
Number included	**1093**	**12484**		**8.1**
Time since HIV diagnosis	17.2 (13.7, 20.5)	11.0 (4.7, 17.1)	<0.0001	
Time previously on ART	14.6 (12.8, 16.9)	8.9 (3.6, 13.5)	<0.0001	
Number of ARVs previously exposed to	12 (10, 14)	6 (4, 9)	<0.0001	

[a] Column percentages.
[b] Chi-squared P-values for proportions, or Wilcoxon signed rank test P-values for the continuous variables.
[c] Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal and Spain; West/Central Europe: Austria, Belgium, France, Germany, Luxembourg and Switzerland; North Europe: Denmark, Finland, Iceland, Ireland, the Netherlands, Norway, Sweden and the United Kingdom; Central East Europe: Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia, Slovakia and Slovenia; and East Europe: Belarus, Estonia, Georgia, Latvia, Lithuania, Russia and the Ukraine.
[d] cART defined as exactly three ARVs, including two NRTIs plus an anchor drug from a different class.
[e] HCV positive if ever had a positive HCV antibody test, HCV RNA test, an HCV genotype assay or received HCV treatment.
[f] Individuals where no blood creatinine/estimated glomerular filtration rate was available.
Abbreviations: ART, anti-retroviral therapy; ARV, anti-retroviral; ENF, enfuvirtide; FU, follow-up; GRT, genotypic resistance test; HCV, Hepatitis C virus; HTE, heavily treatment-experienced; IDU, intravenous drug user; INSTI, Integrase strand-transfer inhibitor; MSM, men who have sex with men; MVC, maraviroc; NNRTI, non-nucleotide reverse transcriptase inhibitor; NRTI, nucleotide/nucleoside reverse transcriptase inhibitor.

Figure Legends

Figure 1. Selection of study participants. Flow diagram showing the number of individuals included for the analysis of HTE prevalence (**A**), for HTE incidence during prospective follow-up from 01 January 2010 (**B**), or included in the clinical outcomes cohort after individuals became HTE (**C**). Individuals were identified as HTE from the composite definition.

* Excluded 204 individuals with missing data on the HTE index date, or last visit for those who were never HTE (187 individuals without CD4 cell counts or a VL measurement available, and 17 not on ART).

** Excluded 1490 individuals with missing data at baseline, 01 January 2010 or the date of enrolment into EuroSIDA. (6 individuals had no follow-up after baseline, 647 had no CD4 cell counts or a VL measurement available, and 837 were ART naïve or not on ART at baseline)

ART, anti-retroviral therapy; FU, follow-up; HTE, heavily treatment-experienced; VL, viral load;

Figure 2. Prevalence of HTE in Europe, 2010-2016. A Contributions to the composite definition for HTE. Altogether 1617 individuals were HTE, either because they had GRT results available and were known to have resistance to the three main ARV classes (NRTIs, NNRTIs and PIs, 'from GRT', black shading), or else who fulfilled the criteria of at least two of the three HTE definitions (definition 1: predicted resistance with ≤2 ARV classes remaining; definition 2: multiple cART regimens with ≥4 anchor agent switches; definition 3: ART regimen with ≥4 ARVs). **B** Proportion of HTE individuals by region of Europe, defined as South and Argentina: Argentina, Greece, Israel, Italy, Portugal and Spain; West/Central Europe: Austria, Belgium, France, Germany, Luxembourg and Switzerland; North Europe: Denmark, Finland, Iceland, Ireland, the Netherlands, Norway, Sweden and the United Kingdom; Central East Europe: Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia, Slovakia and Slovenia; and East Europe: Belarus, Estonia, Georgia, Latvia, Lithuania, Russia and the Ukraine**. C** The Prevalence of HTE on 01. January 2010 (start) or on mid-year (01. July) 2010 to 2016, by different regions of Europe. Bars in (b) and (c) indicate 95% confidence intervals for the proportions.

GRT, genotypic resistance test;

Figure 3. Factors associated with HTE incidence, 2010-2016. Incidence rate ratios (IRR) were modelled assuming a Poisson distribution, and adjusted for age, sex, ethnic group, mode of infection, region of Europe, CD4 nadir, time since HIV diagnosis, the total number of ARV drugs previously exposed to, the length of time on ART, the number of NRTIs previously exposed to, prior exposure to NNRTIs, boosted protease inhibitors or fusion inhibitor (ENF), and prior AIDS-defining event, cardiovascular disease, non-AIDS-defining malignancy, liver-related clinical event or chronic kidney disease. bPI, boosted protease inhibitor; ENF, enfuvirtide; NNRTI, non-nucleotide reverse transcriptase inhibitor; NRTI, nucleotide/nucleoside reverse transcriptase inhibitor.

Figure 4. Incidence of new clinical events after becoming HTE. A, B Incidence rates of new AIDS or non-AIDS clinical events or deaths (**A**), or pooled fatal and non-fatal AIDS or non-AIDS events (**B**) are shown for HTE individuals (dark grey) or those not HTE (light grey). Error bars indicate 95% confidence intervals. Data for approximately 2820 PYFU for HTE individuals and 8720 PYFU for those not HTE. The numbers events are shown above the bars. Note that some individuals experienced more than one event. **C** Unadjusted incidence rate ratios (IRR) for all new clinical outcomes during follow-up after the HTE index date. **D** Unadjusted and adjusted IRR of pooled fatal and non-fatal new AIDS or non-AIDS clinical events. Multivariable adjustments were for new AIDS events: Model 1: Age, baseline CD4 counts and Prior AIDS; Model 2: baseline and nadir CD4 counts, baseline viral load, the number of ARVs previously exposed, time since HIV diagnosis, prior AIDS and prior non-AIDS clinical conditions, and region of Europe. and for new non-AIDS clinical events: Model 1: Age, baseline and nadir CD4 counts, prior non-AIDS comorbidities and region; Model 2: Age, baseline CD4 counts, Ethnicity, Sex, HCV infection status, prior non-AIDS comorbidities and region; Model 3: Baseline and nadir CD4 counts, baseline viral load, the number of ARVs previously exposed to, time since HIV diagnosis, prior non-AIDS clinical events and region. See also **Supplemental Digital Content 2**, describing studies of outcomes of becoming heavily treatment experienced (HTE)

CKD, chronic kidney disease; CVD, cardiovascular disease; HCV, Hepatitis C-virus co-infected; LRE, liver-related events; NADM, non-AIDS-defining malignancy.

Figure 1. Selection of study participants.

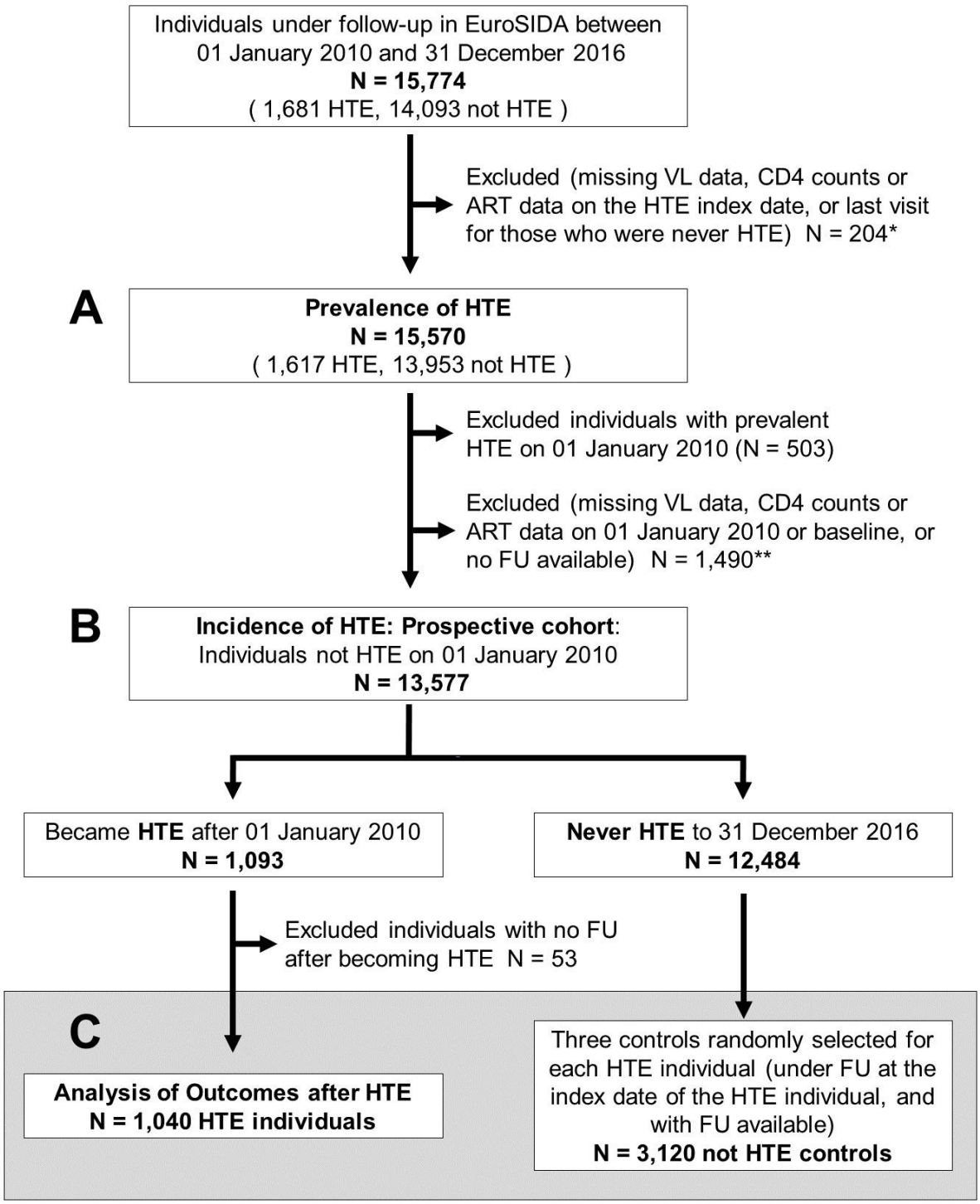


Figure 1. Selection of study participants. Flow diagram showing the number of individuals included for the analysis of HTE prevalence (**A**), for HTE incidence during prospective follow-up from 01 January 2010 (**B**), or included in the clinical outcomes cohort after individuals became HTE (**C**). Individuals were identified as HTE from the composite definition.

* Excluded 204 individuals with missing data on the HTE index date, or last visit for those who were never HTE (187 individuals without CD4 cell counts or a VL measurement available, and 17 not on ART).
** Excluded 1490 individuals with missing data at baseline, 01 January 2010 or the date of enrolment into EuroSIDA. (6 individuals had no follow-up after baseline, 647 had no CD4 cell counts or a VL measurement available, and 837 were ART naïve or not on ART at baseline)
ART, anti-retroviral therapy; FU, follow-up; HTE, heavily treatment-experienced; VL, viral load.

Figure 2. Prevalence of HTE in Europe, 2010-2016.

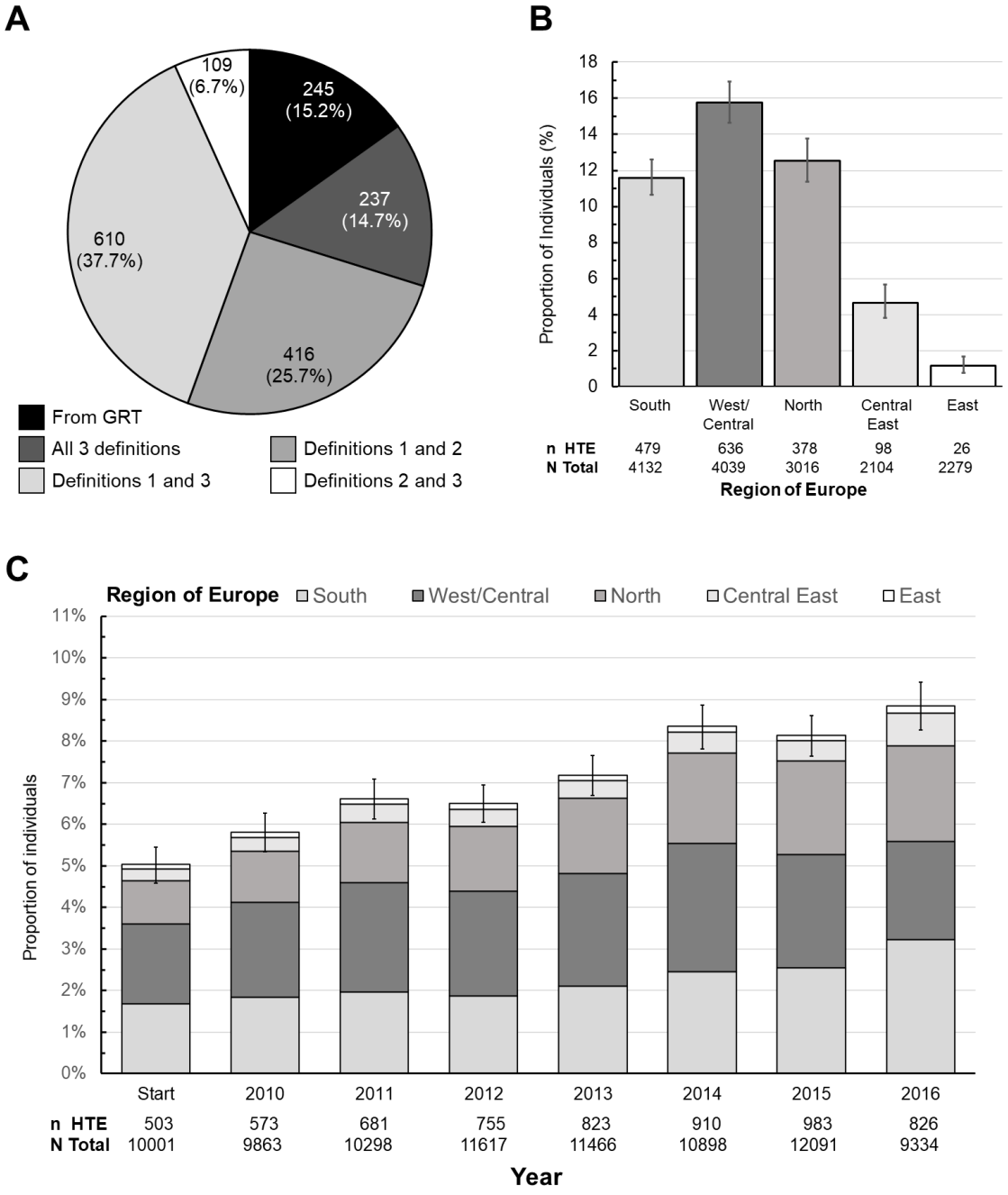
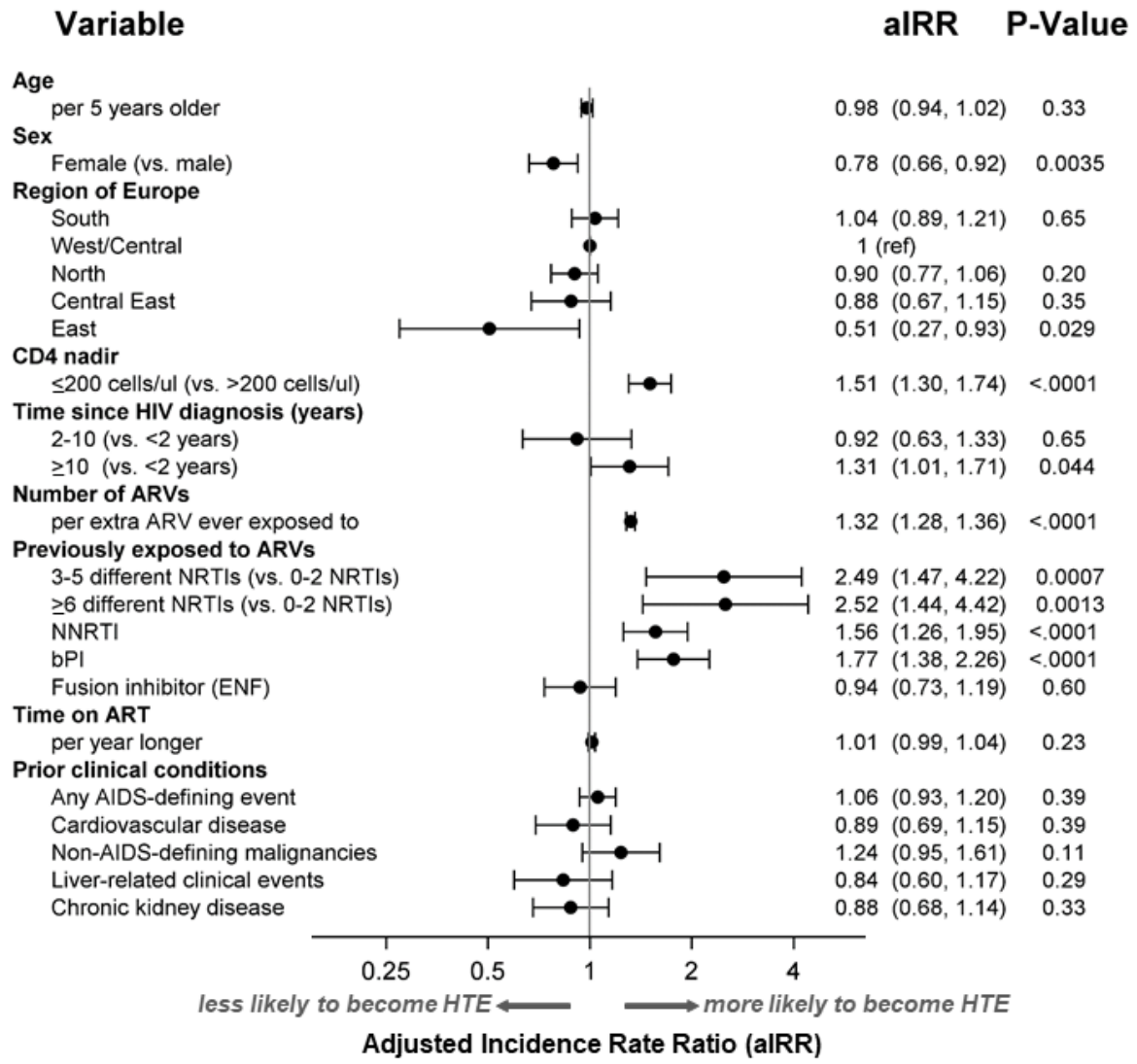


Figure 2. Prevalence of HTE in Europe, 2010-2016. A Contributions to the composite definition for HTE. Altogether 1617 individuals were HTE, either because they had GRT results available and were known to have resistance to the three main ARV classes (NRTIs, NNRTIs and PIs, 'from GRT', black shading), or else who fulfilled the criteria of at least two of the three HTE definitions (definition 1: predicted resistance with ≤2 ARV classes remaining; definition 2: multiple cART regimens with ≥4 anchor agent switches; definition 3: ART regimen with ≥4 ARVs). **B** Proportion of HTE individuals by region of Europe, defined as South and Argentina: Argentina, Greece, Israel, Italy, Portugal and Spain; West/Central Europe: Austria, Belgium, France, Germany, Luxembourg and Switzerland; North Europe: Denmark, Finland, Iceland, Ireland, the Netherlands, Norway, Sweden and the United

Kingdom; Central East Europe: Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia, Slovakia and Slovenia; and East Europe: Belarus, Estonia, Georgia, Latvia, Lithuania, Russia and the Ukraine**. C** The Prevalence of HTE on 01. January 2010 (start) or on mid-year (01. July) 2010 to 2016, by different regions of Europe. Bars in (b) and (c) indicate 95% confidence intervals for the proportions.
GRT, genotypic resistance test;

Figure 3. Factors associated with HTE incidence, 2010-2016



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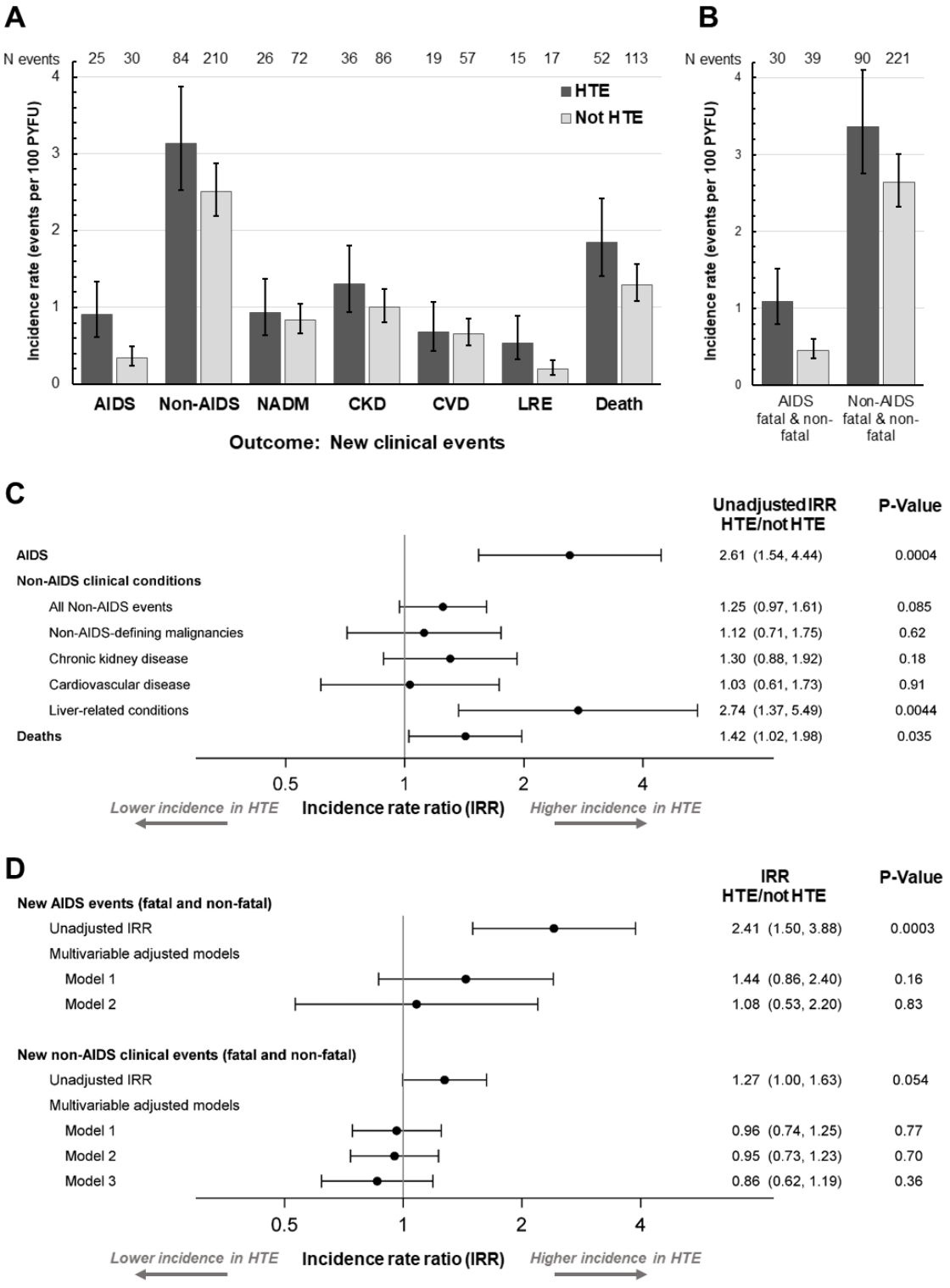

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