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TECHNICAL REPORT

Evaluating HIV treatment as prevention in the European context

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Contents

Abbreviations

AI	Anal intercourse
AIDS	Acquired immune deficiency syndrome
ART	Antiretroviral treatment
CCR5	Chemokine receptor 5
CDC	Centers for Disease Control and Prevention (United States)
CI	Confidence interval
DHHS	Department of Health and Human Services (United States)
EACS	European AIDS Clinical Society
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EU	European Union
HAART	Highly active antiretroviral treatment
HIV	Human Immunodeficiency virus
IAS	International AIDS Society
IDU	Injecting drug user
ILO	International Labor Organization
LTFU	Loss to follow-up
MAP	Medical assisted procreation
MeSH	Medical subject headings
MSM	Men who have sex with men
MTCT	Mother-to-child transmission
PEP	Post-exposure prophylaxis
pMTCT	Prevention of mother-to-child transmission
PrEP	Pre-exposure prophylaxis
PY	Person-years
RCT	Randomised controlled trial
RNA	Ribonucleic acid
sdNVP	Single dose of nevirapine
STI	Sexually transmitted infection
TB	Tuberculosis
UAI	Unprotected anal intercourse
UIAI	Unprotected insertive anal intercourse
UNAIDS	Joint United Nations Programme on HIV/AIDS
URAI	Unprotected receptive anal intercourse
VI	Vaginal intercourse
WHO	World Health Organization
ZDV	Zidovudine

Executive summary

The goal of this project is to gather evidence regarding the population-level, and to some extent, individual-level effects of the use of antiretroviral treatment (ART) to prevent HIV infection, and to relate this to current HIV treatment guidelines. To inform the project, formal literature reviews were performed for the three main areas of interest: the effect of antiretroviral therapy in adults on preventing sexual transmission of HIV, prevention of mother-to-child transmission (pMTCT) and post exposure prophylaxis (PEP).

The strongest evidence with regard to the effect of treatment of HIV positive individuals to prevent onwards sexual transmission comes from the recent randomised controlled trial (RCT), HPTN052. This study demonstrated that early versus delayed ART led to a 96% relative reduction in onwards linked transmission. Several observational studies of HIV sero-discordant heterosexual couples have also reported that transmission is rare in patients on ART, particularly in those with low HIV-RNA concentrations. However, the findings of HPTN052 and these observational studies are mainly applicable to vaginal heterosexual sex. No direct empirical evidence regarding the relationship between ART use and the risk of HIV transmission through anal intercourse is currently available. Whilst the major HIV treatment guidelines do not explicitly recommend prescribing antiretroviral treatment to prevent onwards transmission, they do not rule out individuals starting ART at a high CD4 count on a case-by-case basis. However, one must also consider the impact of earlier treatment on the HIV positive individual with regard to side effects, and development of drug resistance.

Early studies showed that pMTCT regimens containing a single antiretroviral agent (short course zidovudine or single dose nevirapine) or two antiretroviral agents (zidovudine and lamivudine with or without single dose nevirapine) led to clinically important reductions in MTCT rates. However, the most substantial reductions in MTCT rates occurred when combination antiretroviral regimens (more than three antiretroviral drugs) were introduced. These regimens involve the receipt of ART before the third trimester of pregnancy, intrapartum treatment, maternal post-partum treatment and some form of neonatal treatment. There is some evidence from RCTs and extensive evidence from observational studies of the efficacy of these combination regimens, with very low rates of transmission of around 0% to 6%, in settings with no or very little breastfeeding, and 1%-9% when breastfeeding occurs. Furthermore, in settings where avoidance of breastfeeding is not possible, there are a number of studies demonstrating that receipt of maternal and/or neonatal ART during the six months after birth can reduce the risk of perinatal transmissions. All treatment guidelines recommend that HIV-positive pregnant women should receive ART to prevent MTCT, although the exact timing of when ART should begin is not always explicit. Furthermore, where mentioned, use of neonatal ART is also recommended, regardless of whether infants are breastfed.

Much of the data supporting the use of PEP are based on animal models, which suggest that PEP is most efficacious if commenced as soon as possible after exposure. When considering occupational exposure to HIV, human studies are limited, as no RCTs exist for ethical reasons. Evidence for efficacy is based on one case control study which demonstrated an 81% reduction in transmission of HIV through the use of zidovudine. Other studies have demonstrated that PEP following occupational exposure is not always effective and there are cases of PEP failure. Similarly, there are also no RCTs assessing the efficacy of PEP for prevention of HIV transmission after sexual exposure, and limited evidence from observational data. Most treatment guidelines agree that PEP is not always effective and PEP policies need to emphasise the importance of risk prevention in the first place in all settings where there is a risk of HIV transmission. Side effects are not uncommon when using PEP, so it is important to consider carefully whether an individual should receive PEP and some studies have suggested that increase in availability of PEP may lead to an increase in risky sex behaviour.

Antiretroviral treatment has well documented benefits in reducing transmission of HIV and, in particular, has had a major population level impact on HIV acquisition in children from HIV positive mothers. Further research is needed to help us understand how we can best use ART to prevent HIV infections through other transmission routes, and to develop evidence-based policy recommendations, particularly in the European context.

1. Introduction

1.1 HIV in Europe – epidemiology

Since the first cases of AIDS were identified in 1981(1), there have been dramatic increases in the number of individuals living with HIV and AIDS worldwide. The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimate that more than 33 million HIV positive adults and young children were living worldwide at the end of 2009, of whom 820,000 were from Western and Central Europe, and 1.4 million were from Eastern Europe and Central Asia(2). New HIV infections occur most commonly through heterosexual sex, sex between men, transmission from mother to child and through exchange of blood products (e.g. through needle sharing in intravenous drug users and blood transfusions of infected blood). Despite concerted efforts to prevent new infections occurring, there were more than 27,000 newly diagnosed HIV infections reported in the European Union (EU) and the European Economic Area (EEA) in 2010. The reported number of people with diagnosed HIV is an underestimate of the number living with HIV due to delayed diagnosis, underreporting and reporting delay (3). Thus, further efforts to reduce the number of new infections occurring in the EU/EEA area are warranted.

1.2 Risk of HIV acquisition through sexual intercourse

HIV transmission involves a complex interaction between biological and behavioural factors. The risk of an individual becoming infected with HIV is dependent on many factors including the type of exposure and cofactors such as the presence of sexually transmitted infections, HIV viral load, genetic susceptibility, male circumcision and breaches in the genital or oral mucosa which may also cause local bleeding (4). Of these, the factor most strongly associated with the risk of sexual transmission of HIV is the HIV ribonucleic acid (RNA) level of the infected partner. One of the first studies to describe this was from 2000 which published data from rural Uganda in 415 sero-discordant heterosexual couples (5). Ninety transmissions occurred over follow up giving an overall incidence of 11 per 100 person-years (PY). Transmission was unusual with a serum HIV viral load below 1500 copies and no transmissions were seen in the 51 couples where the index partner had HIV viral load less than 400 who were followed for a median of 22 months. There was a significant dose response seen between risk of transmission and the serum viral load of the index case. An increased risk of HIV transmission can also be seen with levels of HIV RNA in genital secretions (6). Inter-current symptomatic and asymptomatic sexually transmitted infections can also lead to a transient increase in HIV viral load in the genital compartment which could increase HIV transmission risk, (7;8) and HSV-2 in particular is thought to contribute significantly to the on-going HIV epidemic (9;10). Certain genetic mutations can also reduce the risk for acquisition of HIV infection, even within the context of on-going high sexual risk behaviour with HIV positive partners. Chemokine receptor 5 (CCR5) is a chemokine receptor, and individuals who are homozygous (and to a lesser extent heterozygous) for a 32-base-pair deletion (delta-32 mutation) in the CCR5 reading frame are highly protected from HIV infection (11;12). Circumcision also protects HIV negative men from heterosexual transmission of HIV. Three separate RCTs in Uganda (13), Kenya (14) and South Africa (15) found a reduction in risk of acquiring HIV in the circumcised arm of the trials of 51%, 53% and 61% respectively.

Risk of transmission following exposure differs by route of exposure. In HIV negative women having unprotected vaginal sex with an HIV positive male partner, the transmission probability per exposure event is in the region of 1 in 200 to 1 in 2000 (16;17). For HIV negative men having insertive vaginal sex with an HIV positive women, the risk is 1 in 700 to 1 in 3000 (13). For men who have sex with men (MSM), the highest estimates of per contact probability of risk of HIV transmission are for receptive unprotected anal intercourse (UAI) with a range between 1 in 20 to 1 in 300 (16;18). One study looked at the impact of circumcision and ejaculation on risk and found the per-contact probability of infection for insertive UAI is 0.62% (95%CI 0.07–1.68) in uncircumcised men and 0.11% (0.02–0.24) in circumcised men. For receptive UAI it is 0.65% (95%CI 0.15–1.53) in men who withdraw and 1.43% (95%CI: 0.48–2.85) with ejaculation (19).

1.3 Risk of HIV acquisition through needle stick injury

The HIV acquisition risk for occupational exposures in terms of needle stick injury is estimated at 1 in 300 per exposure (20;21). Risk factors for HIV transmission after needle stick injury in a case control study were deep injury (odds ratio [OR] 15, 95%CI: 6.0–41), visible blood on the device (OR 6.2; 95%CI 2.2–21), needle placed in patient's artery or vein (OR 4.3 95%CI 1.7–12), and if the source had advanced HIV disease (OR 5.6; 95%CI 2.0-16) (20). For blood transfusion recipients, the transmission probability per exposure event is estimated at 90 to 100% (22).

1.4 Risk of mother-to-child transmission

From the start of the HIV epidemic, vertical transmission from mother to child appeared to be a major source of new HIV infections. Initial studies of HIV-positive pregnant women show that mother to child transmission (MTCT) rates in the absence of any interventions is around 15%–45% (23;24), with higher rates seen amongst mothers who become HIV-positive during their pregnancy (25). Although the exact mechanisms of transmission are unknown (26), researchers have identified three stages at which transmission from mother to child can occur: during pregnancy (in utero, antepartum), during labour (intra-partum) and during breastfeeding (post-partum). Transmissions in utero are thought to occur via microtransfusion of maternal blood through the placenta (26), and it is believed that most of these infections take place in the latter stages of pregnancy (27). Intra-partum transmissions are thought to occur via exposure to maternal cervico-vaginal secretions and blood by the infant through the birth canal during delivery(26). Finally, most post-partum transmissions take place as a result of breastfeeding, as HIV viraemia can be detected in breast milk (28). Mixed feeding (i.e. when both breastfeeding and formula feeding take place) potentially confers an even higher risk of transmission, perhaps because mixed feeding may compromise infant mucosal surfaces of the gastrointestinal tract and thus facilitate transmission of the virus (24).

Each transmission stage described above confers a different risk, although not all studies agree on which stage constitutes the highest risk. A modeling study by Gupte and colleagues suggested that, of babies born to HIV-positive women, 4.9% of babies are infected in utero, 2.8% are infected intra-partum, and 8.4% are infected post-partum (29). A recent study by Marinda and colleagues of in utero and intra-partum infections amongst HIV-positive women in Botswana suggested that 10% of babies are infected with HIV in utero, and 13% of babies born to HIV-positive mothers are infected intra-partum (25). Finally, Cavarelli and Scarletti estimate 5%–10%, 20%–25%, and 10%–15% of babies born to HIV-positive mothers are infected in utero, intra-partum and postpartum, respectively(24).

Clearly, as these three stages have been identified as the likely major stages at which HIV transmission can occur, it is logical that they should be the targets for interventions to prevent transmission from mother to child. Non-antiretroviral interventions, such as use of elective caesarean section to prevent intra-partum transmissions, and avoiding breastfeeding to prevent post-partum transmissions, have both been shown to be successful prevention strategies (24), and are discussed in more detail in this report. However, there are limitations to these approaches. In the developing world, avoiding breastfeeding has proved not to be a viable option in all settings due to increased infant mortality when access to formula milk or clean water is problematic. Although elective caesareans are the preferable mode of delivery for avoiding transmission, emergency caesareans and vaginal deliveries are not always avoidable. Furthermore, neither strategy will impact on antepartum transmissions. Thus, clearly, the need for further intervention is warranted. One obvious intervention is through the use of antiretroviral drugs.

1.5 Antiretroviral therapy

Since the introduction of combination antiretroviral therapy (ART) in 1997, dramatic reductions in morbidity and mortality amongst HIV positive individuals have been observed, including in the EU/EEA area, as demonstrated by the EuroSIDA study group (30). Several studies have demonstrated that the best response to ART occurs in those who achieve suppression of plasma HIV RNA levels to below the limit of detection of current assays (typically 10, 40, 50 or 400 copies/ml), and thus have successfully suppressed viral replication(31). This allows immune reconstitution to occur, which in turn leads to reductions in HIV-associated clinical disease.

The plasma HIV RNA viral load has also been shown to be a marker of ‘infectiousness’ amongst HIV positive individuals. Those with plasma viral load levels below the detectable limit are also likely to have lower levels of HIV RNA in cervix, rectum, vagina, semen and breast milk. A clear association between the level of the plasma viral load and the risk of onwards transmission has been identified (5). Therefore, the use of antiretroviral therapy as a method of preventing onwards HIV transmission is an area of current research interest.

1.6 Objective of review

The goal of this review is to gather evidence to inform prevention decision-making in EU/EEA Member States regarding the population-level, and to some extent, individual-level effects of the use of antiretroviral treatment to prevent HIV infection. The project focuses on three main areas of prevention: earlier identification and treatment of HIV positive individuals to prevent onward sexual transmission; prevention of transmission from mother to child; and post exposure prophylaxis in both the occupational setting and the sexual exposure setting. The report also considers the guidance on use of antiretroviral drugs to prevent HIV transmission offered by current treatment guidelines, synergies with non-antiretroviral based prevention strategies, and summarises the areas where further research is warranted.

2. Methods

Separate formal literature reviews were performed for the three areas of: (i) prevention of sexual HIV transmission through treatment of HIV positive individuals (ii) prevention of mother-to-child transmission through use of antiretrovirals and (iii) post exposure prophylaxis. However, all searches followed a consistent approach. For each area of interest, a computerised literature search was performed using the Web of Knowledge. This includes the databases Medline, Web of Science, BIOSIS Citation Index, BIOSIS Previews and Journal Citation Reports. Key terms were used to search article titles and abstracts and MESH terms. The search strategy and key terms used for each area to identify the relevant literature can be found in Appendix 1.

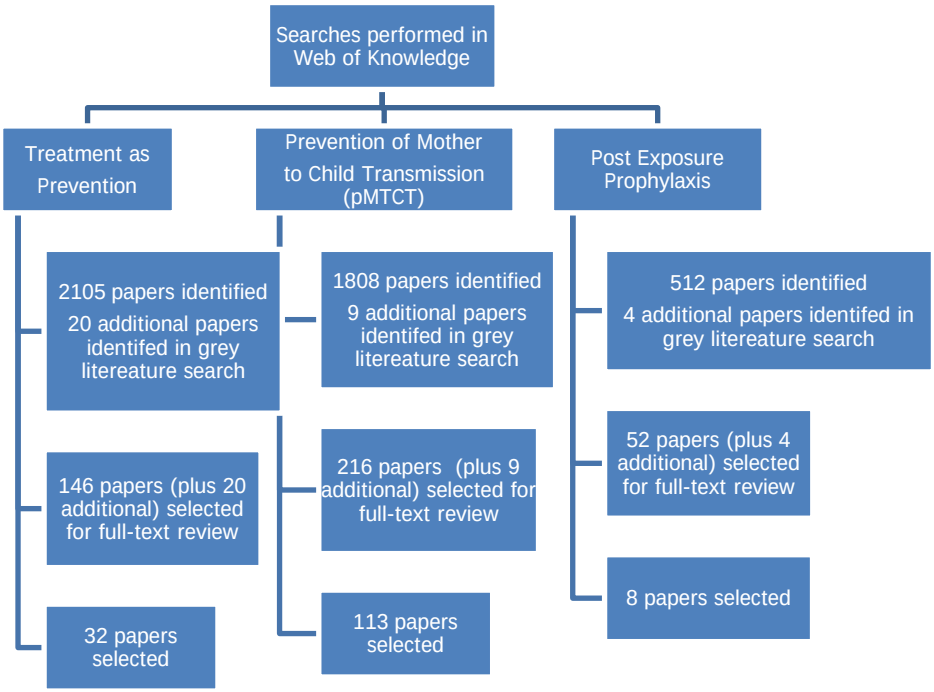
Once the potential papers for a section were identified from the literature search, the titles and abstracts of each paper were reviewed by one person (a different person for each of the three research areas). Relevant publications were then identified for full review. On the basis of this full review, relevant papers to be included were identified and included in the formal literature reviews. In addition to the manuscripts identified by the Web of Knowledge search, other potentially relevant studies were identified more informally by reviewing the references of publications already included in the literature review and in the treatment guidelines. Detailed information on the search terms used for each section is provided in Figure 1, subsections 2.1–2.3 below and in Appendix 1. The papers identified by these literature searches are summarised in the tables in Appendix 2.

2.1 Treatment as prevention

A systematic search was conducted to identify all relevant papers published in the most recent years, regarding the impact of using treatment as prevention, rather than as treatment to prevent morbidity and mortality in HIV positive individuals, focusing on the population effect. The search was conducted on all databases available on the Web of Knowledge: Web of Science, MEDLINE, BIOSIS Citation Index, BIOSIS Previews and Journal Citation Report. A search was performed for all papers (excluding case report, biography, editorial, book, correction, report, review, patent, meeting, news, bibliography, letter) written in English, in several relevant subject areas (infectious diseases, virology, social issues, behavioural sciences, social sciences other topic, mathematics, life sciences biomedicine other topipcs, biomedical social sciences, mathematical computational biology) in the last five years (2006–2011) with topic 'HIV*' and 'antiretroviral*' and ('prevent*' or 'transmi*') NOT Topic=('child*' or 'mother*' or 'vertical' or 'prophylaxis' or 'pregnan*' or 'herpes' or 'breast*' or 'tuberculosis').

The final Web of Knowledge review was performed on the 5th September 2011. 2 105 papers were found of which 146 were selected as relevant based on the title and 32 were included in the literature review. The results of this first search were compared with an extensive existing database of references on the potential use of ART in HIV positive people as prevention (the effect of ART on rate of transmission, population-effect of expanding treatment availability estimated by mathematical models) to make sure that no key references had been missed. Of 20 additional studies considered, 9 references of relevance were added to the review presented in section 3.

Figure 1. Flow chart of literature search



2.2 Prevention of mother-to-child transmission

The aim of this literature review was to identify potentially relevant literature investigating the efficacy of antiretroviral treatment to prevent HIV transmission from mother to child. We searched for all papers (excluding case report, biography, editorial, book, correction, report, review, patent, meeting, news, bibliography, letter) written in English, The search terms employed were Topic=((prevent* OR transmission) AND ("mother to child" OR "mother-to-child" OR vertical OR paediatric)) AND Topic=(HIV* AND antiretroviral*). All calendar years were searched, up until the date the search took place (24th August, 2011).

Of 1 894 studies initially identified (reduced to 1 808 after removing duplicates), 214 were selected as potentially relevant by reading the titles and abstract, and the full text was read. Of these 214 studies, 104 studies were finally selected as relevant. In addition, hand searching for grey literature was performed by checking the references included in major treatment guidelines, major review articles, and other studies already included in the literature review. This identified a further nine studies (including three conference abstracts). Therefore, 113 studies were finally included in the literature review.

2.3 Post exposure prophylaxis

The aim of the search was to identify relevant papers relating to post exposure prophylaxis in the occupational and non-occupational setting to prevent infection with HIV. Papers on animal models on which much of the data on PEP is based were also identified. Searches were performed on the online database ISI Web of Knowledge. Searches were limited to studies published in English, from January 1987 to September 2011, and excluded studies on children (< 13 years old). Search strategy combined all sets of terms under the following Medical Subject Headings (MeSH) for rates of HIV transmission following the use of PEP: “HIV” or “HIV Infections”* “transmission” and “post exposure prophylaxis”. Five hundred and twelve papers were identified of which the majority were discarded after reading the titles and the abstracts because they did not meet the inclusion criteria which were transmission outcomes after use of appropriate antiretroviral therapy as post exposure prophylaxis in animal or human studies. Only major studies were included in the review. The final Web of Knowledge review was performed on the 15th October 2011.

2.4 Review of treatment guidelines

Effective antiretroviral therapy (ART) has led to a dramatic decline in the rate of AIDS and death in those with HIV infection (30;32;33). However, financial constraints, drug availability and differing policies mean that treatment for HIV can differ greatly between countries and regions as well as between clinics. Guidelines are therefore assembled, consisting of evidence-based recommendations, to assist practicing clinicians and healthcare workers so that the best management and care can be provided for their patients. They are also a valuable source of information for patient group organisations, charities, public health boards, local authorities and policymakers.

Treatment guidelines from four major working groups and establishments (European AIDS Clinical Society, International AIDS Society, US Department of Health and Human Services and World Health Organization) have been reviewed in order to consider and compare current guidance on the matter of using treatment as prevention. Whilst several countries have their own guidelines, many are also thought to follow these international guidelines in conjunction.

The EACS (European AIDS Clinical Society) guidelines were first published in 2003 (34) when at the time, there did not exist any clinical guidelines put together specifically for patients in Europe. It has since been updated regularly (to date, the most recent guideline is version 6.0 from 2011) and has been translated into many languages spoken within the European Union (35;36). The guidelines for the clinical management and treatment of HIV-infected adults in Europe cover not only recommendations for treatment-naïve individuals, initiating ART, switching strategies and HIV/TB co-infected individuals, but also the use of treatment in HIV-infected pregnant women and post-exposure prophylaxis.

The International AIDS Society – United States of America (IAS-USA) panel first convened in 1995 to develop recommendations for the management of HIV-infected adults and use of treatment in developed country settings (37). This guideline has been updated every two years in recent years and their most recent publication is their 2010 version (38). Since the 2004 guidelines (39), the panel has been using a rating scale for the quality and strength of evidence for each recommendation.

The US Department of Health and Human Services (DHHS) also issues guidelines for using antiretrovirals in adults and adolescents to be used in the US, separately to IAS-USA (40). They have separate guidelines for different aspects of HIV care such as treatment of children, treatment of pregnant women and prevention of mother-to-child transmission (41;42). As one of the sections of the DHHS, the Centers for Disease Control and Prevention (CDC) has also issued guidelines for the management of occupational and non-occupational exposures to HIV and recommendations for post-exposure prophylaxis (43;44).

The World Health Organization (WHO) released a series of global-based guidelines in 2010. This includes guidelines for ART for HIV infection in adults and adolescents, infants and children, treating pregnant women and preventing HIV infection in infants (45-47). The guidelines for ART for adults and adolescents was first published in 2002 and the most recent update (2010 edition) is the third revision (45). The next revision is scheduled to be available in 2012. The recommendations are based on a synthesis of evidence of GRADE profiles[1], systematic reviews and consultations with people living with HIV, as well as other reports and reviews. Ratings were given to recommendations depending on the quality and strength of evidence in the same way as the IAS-USA guidelines. The WHO guidelines are primarily aimed at both resource-rich and resource-limited settings and therefore, a separate guideline outlining strategies for implementing the recommendations at national-level has also been published (48). The main changes made since the last revision include earlier initiation of ART, changes in ART regimens to drugs which are more tolerable and efficacious as well as updated recommendations to improve prevention of mother-to-child transmission (pMTCT) of HIV. The WHO Regional Office for Europe also compiles their own clinical protocols aimed at countries within the whole WHO European region(49). The choice to consider predominantly the global guidelines in this review was based on the fact these were updated more recently, whereas the European guidelines have not been revised since 2007 (although some revisions to the 2007 guidelines were made in mid-2008).

[1] A system for grading the quality of evidence and the strength of recommendations

3. HIV-positive individuals receiving treatment: the impact on sexual transmission

3.1 The population-level effects of antiretroviral treatment as prevention

3.1.1 The rationale for antiretroviral treatment as prevention

Whilst it is well documented that early detection and timely initiation of ART can substantially reduce mortality and morbidity in HIV positive individuals (32;33;50), debate continues about the role of ART for prevention of sexual transmission of HIV. The strong association found in observational studies between plasma HIV RNA viral load and risk of transmission, combined with the ability of ART to suppress HIV RNA, led some researchers (51) to suggest that earlier initiation of ART, regardless of CD4 cell count, in HIV-positive people not eligible yet for treatment according to guidelines, could prevent sexual transmission of HIV by reducing the infectiousness of HIV-positive people.

In 2008, Vernazza et al released what has been called the 'Swiss Statement' (52), stating that 'the risk of sexual transmission of HIV is negligibly low if three conditions are met: (i) the HIV-infected patient is receiving antiretroviral therapy with excellent adherence; (ii) blood viral load has consistently been undetectable (<40 copies per mL) for more than 6 months; and (iii) no sexually transmitted infections are present in either of the partners. This ignited a vigorous debate on the risk of HIV transmission in people taking combination antiretroviral therapy (cART) and on how to advise people in this situation.

The principle that ART treatment could reduce HIV infectiousness on an individual level is generally agreed. However, at a population level, the longer duration of infectiousness, the difficulty in maintaining viral suppression over time, mainly driven by adherence, the fact that transmission often occurs when people are still in primary infection, and potential increases in sexual disinhibition as a result of ART, could limit or counterbalance the potential reduction in secondary transmission, preventing the strategy from having a substantial benefit. In addition, it can be debated whether such a strategy should be implemented due to ethical difficulties and whether it is the most cost effective strategy. Therefore, the aim of this section is to review the evidence regarding the potential benefits of using antiretroviral therapy in HIV positive individuals as a strategy to reduce transmission rates at a population level. Evidence from developing as well as developed countries is considered, although the ultimate aim is to consider the implications in the European context.

To date, evidence of the effectiveness of ART in reducing transmission at a population level has been gathered from multiple sources. This includes evidence from observational studies, randomised controlled trials and mathematical models. The evidence with regard to the effectiveness of treatment as prevention from each type of study is summarised below and the key papers identified are summarised in Appendix 2.

Observational studies

Several observational studies of HIV sero-discordant heterosexual couples (53–55) have reported that transmission is rare in patients on ART, particularly in those with low HIV RNA concentrations. Among people not receiving ART, the first large epidemiological study to explore the association between HIV RNA viral load and heterosexual transmission of HIV-1 was published by Quinn et al in 2000 (5). They examined the influence of HIV RNA viral load in relation to other risk factors on heterosexual transmission of HIV-1 in a study of 415 HIV sero-discordant couples followed prospectively for up to 30 months. These couples were identified only retrospectively within the population recruited in a community-based RCT in Rakai, Uganda. They found that the mean serum HIV-1-RNA level was significantly higher among HIV-1–positive subjects whose partners seroconverted than among those whose partners did not seroconvert. A significant dose-response relationship was found between HIV RNA plasma and HIV transmission with no transmission occurring among discordant couples if the HIV-infected partner had plasma HIV RNA below 1500 copies/ml. Many other studies have subsequently confirmed this finding (56–58).

This relationship has been more accurately described in a study conducted in Southern and East Africa (59). The authors developed a predictive tool to estimate the overall decrease in HIV-1 transmissions for a given reduction in plasma HIV RNA. They found that accounting for established predictors of HIV-1 transmission, such as history of any unprotected sex, gender, HSV-2 seropositivity and male circumcision of the HIV-1 uninfected partner, did not remove the relationship between plasma HIV-1-RNA and risk of transmission.

The first evidence from observational studies of an association between use of ART and HIV prevalence came from cross-sectional studies. Castilla et al (54) observed a cohort of 393 steady heterosexual couples in Madrid, Spain, and found that the prevalence of HIV was 8.6% among partners of index cases who had not received ART, whereas no partner was infected in couples in which the index case had been on ART (P = 0.0123). Similar findings were reported by another study (60). A meta-analysis (53) of 11 observational cohort studies observed no transmissions among heterosexual HIV sero-discordant couples when the HIV positive partner was treated with ART with HIV-1-RNA levels below 400 copies/ml. The authors concluded that the data were compatible with one transmission per 79 person-years in this group. In 2010, a very large observational analysis of people recruited to the 'Partners in HSV/HIV transmission' study (55) confirmed the evidence of a reduction in HIV transmission for people on ART (the HIV positive person was co-infected with herpes simplex virus type 2 and had a CD4≥250 cells/mm^3). The primary outcome was genetically linked HIV-1 transmission within the study partnership. Of 103 genetically linked HIV-1 transmissions, only one transmission occurred from an infected participant who had started ART, corresponding to a transmission rate of 0.37 (95% CI 0.09–2.04) per 100 person-years, compared to 2.24 (1.84–2.72) per 100 person- years in those who had not initiated ART. Concordant results were found in a longitudinal study in Spain (61), where no HIV seroconversions occurred in 144 couples in which the HIV-positive partner was taking ART in over 7 000 unprotected acts of intercourse (corresponding to a risk of transmission of 0 and a 95% CI of 0 to 0.0005 per unprotected intercourse act). In contrast, there were five HIV seroconversions in 341 HIV-discordant couples and over 10 000 unprotected acts of intercourse in which the HIV-positive partner was not taking ART (a risk of 0.0004 per unprotected intercourse; 95% CI 0.0001-0.0010). Similarly, the Rakai study (62), although on a small number of couples, reported that no HIV-1 transmissions occurred during 53.6 person-years on ART. However, a word of caution comes from a Chinese study of sero-discordant couples , in which no statistical differences in sero-conversion rates were observed, regardless of whether the HIV positive partner was receiving ART or not. This may relate to the low rates of viral suppression seen in those on ART in this study (63).

As we have seen, many observational studies have evaluated the relationship between HIV-RNA viral load and the risk of transmission among heterosexual couples (vaginal intercourse). However, no direct empirical evidence regarding the relationship between ART use and the risk of HIV transmission through anal intercourse is currently available. Baggaley et al (64) conducted a meta-analysis assessing the per-act and per-partner HIV transmission risk from anal intercourse exposure amongst both heterosexual couples and men who have sex with men (MSM). They estimated that the HIV transmission risk per-act and per-partner of unprotected receptive anal intercourse (URAI) were 1.4% (95% CI: 0.2–2.5) and 40.4% (6.0–74.9) respectively, with no significant difference between heterosexuals and MSM. The risk of HIV transmission per-partner of unprotected insertive AI (UIAI) was 21.7% (0.2–43.3). In addition, the authors assessed the potential reduction in HIV infectivity due to the effect of ART on reducing HIV RNA viral load, using two published functions of infectivity (65–67), estimated from observation data on HIV sero-discordant heterosexual couples (5;56). The predicted HIV transmission probabilities per-act for vaginal intercourse (VI) or unprotected insertive anal intercourse (UIAI) and unprotected receptive anal intercourse (URAI) with successful ART were 0.013% and 0.061%, respectively, i.e. 96% lower than without therapy. Using another function of infectivity by HIV RNA plasma viral load, the predicted per-act VI/UIAI and URAI estimates with successful ART were 0.0002 and 0.0011%, respectively, i.e. 99.9% lower than without therapy.

These estimates underline the fact that unprotected AI is a high-risk practice for HIV transmission. The practice of AI among heterosexual populations has been observed to be common in the United Kingdom, with a population based-survey finding that 7% of men and 6.5% of women reported anal intercourse in the past year in 1990; these estimates increased to 12.3% and 11.3% in 2000 (68). In the United States, a survey conducted in the general population (over 12 000 people) found that 30% of women and 34% of men have engaged in AI (69). It is likely that these are underestimates, although the rise observed in United Kingdom of AI may be attributable to reporting bias. Baggaley et al concluded that, although ART could reduce infectiousness, the high infectiousness associated with AI could mean that residual infectiousness still constitutes a high risk to partners, especially if risk compensation occurs (70).

The meta-analysis by Baggaley et al found relatively old studies where the risk of transmission was assessed in the absence of, or with very low coverage of, ART. Here there is a paucity of data, especially on HIV transmission risk at low viral loads (53;71), and almost no data on transmission and viral load in homosexual men (19;72;73). Furthermore, there is no direct empirical evidence on the reduction in anal intercourse infectiousness due to ART. Few papers estimate the risk of transmission in longitudinal observational studies (18;19;74). The first paper to compare the per-contact probability of HIV transmission in the pre-ART and ART eras was published in 2010 by Jin et al. (19). In a cohort of initially HIV-negative MSM in Sydney, the authors found that the per-contact probability of HIV transmission for receptive UAI with ejaculation was approximately twice that of receptive UAI with withdrawal or insertive UAI for uncircumcised men. The per-act probability of HIV transmission due to UAI is similar to estimates reported from developed countries in the pre-ART era (64), despite most men diagnosed with HIV in Sydney being on ART with undetectable HIV RNA viral loads.

There are several potential explanations as to why risk of transmission did not decrease despite the increased number of people on effective treatment in the Jin study. There has been an increase in the prevalence of other sexually transmitted infections (STIs) in Sydney in the post-ART compared to the pre-ART era, as happened in many other MSM populations. Therefore, there may have been risk compensation behaviour in the ART era, thus increasing the risk of HIV transmission (75). Other proposed explanations include competing exposures through other routes of transmission not reported, such as intravenous drug use, and unrepresentativeness of study participants' partners of the wider Australian homosexual population (73). Finally, given that the per-contact probability of HIV transmission through anal intercourse is more than 10-fold higher than through vaginal intercourse, the risk of HIV transmission by anal intercourse may not be as closely correlated to viral load as it is in vaginal transmission (72).

Ecological studies

The results of several ecological studies have provided evidence of a population-level association between the implementation of widescale ART and a decline in the number of new diagnoses (76–78), although a number of other studies, particularly amongst homosexuals, have not concurred (79–81). An ecological study conducted in British Columbia, Canada (78) reported a strong and significant association between increased ART coverage and a decline in the number of new HIV diagnoses per year. Between 1996 and 2009, ART coverage in British Columbia increased by 547% and the number of new diagnoses decreased by 52%.

Similar findings were reported from another study based on a cohort of all HIV-positive individuals in San Francisco (76). Community viral load (i.e. the average HIV RNA viral load among all individuals diagnosed with HIV) was calculated and analysed as a population-level marker of HIV transmission risk. A significant association was found between decreases in annual community viral load and temporal decreases in the number of new HIV diagnoses. The authors observed that HIV incidence fell by over one third in the years 2006 to 2008. Interestingly, during the same period there was an increase in the number of reported cases of rectal gonorrhoea. Although data on sexual risk behaviour were not collected, data on rates of rectal gonorrhoea were used as a surrogate marker for sexual risk behaviour. The authors argued that the reduction in the number of new infections in a period where risky sexual behaviour probably increased substantiates the hypothesis that achieving high level ART coverage is an effective and important approach towards the prevention of HIV transmission.

In Taiwan, a study was conducted using nation-wide surveillance data (77) to assess the impact of a policy to provide free ART to all HIV-positive individuals on the rate of transmission. The introduction of the policy was associated with a 53% decrease in the rate of transmission and was accredited with the effective control of the HIV epidemic in Taiwan. The incidence of syphilis was analysed in order to distinguish between the effect of ART and that of behavioural modifications. During the study period there was no statistically significant change in the incidence of syphilis in both the general population and the HIV-positive population. With thousands of new cases of syphilis reported each year, it is evident that risky sexual behaviour is prevalent and therefore, the authors argued that it is unlikely that the reduction in the HIV transmission rate was due to decreases in sexual risk behaviour. However, three studies (79–81) whose primary aim was to observe trends in recent HIV infections in MSM found that HIV incidence is increasing. These studies were conducted in a developed country which suggests that on-going HIV transmission is occurring despite access to effective ART.

The findings from ecological studies should be examined with extreme caution. Firstly, there is the possibility of ecological fallacy, whereby inferences about specific individuals are based solely upon aggregate statistics collected for the group to which those individuals belong, in which case the generalisability of the results is limited. Secondly, as with all observational studies it is difficult to rule out confounding which means that establishing causality can be problematic. Thirdly, the studies were restricted to measuring numbers of new diagnoses rather than the main aspect of interest; incidence of new infections.

The findings from a randomized controlled trial (RCT), HPTN052 (82) are in accordance with the findings from the observational studies. This RCT was designed to compare the effect of early versus delayed ART on transmission of HIV. 1 763 heterosexual sero-discordant couples in which the HIV-positive person was ART naive and had a CD4 count between 350–550 cells/mm^3 were recruited from nine countries. Couples were randomised to either the early therapy arm, in which ART was initiated at study entry, or the delayed therapy arm, in which ART was initiated after two consecutive CD4 counts ≤250. The primary endpoint was HIV infection in HIV-negative partners, with evidence based on genotyping that the infecting virus was likely to be from the partner. Three months after baseline, 89% of participants in the early therapy group had achieved viral suppression (<400 copies/mL) compared with 9% of the delayed therapy group. A total of 28 virologically linked transmissions were observed; of these 28 transmissions, only one was in the early therapy group. This represents a 96% relative reduction in linked HIV transmissions as a result of initiating ART compared with deferral. These findings provide support for the use of ART in the prevention of HIV among heterosexuals and are believed to be a result of sustained suppression of HIV RNA load in genital secretions.

Although this study provides the most definitive evidence currently available to support use of ART to prevent sexual transmission of HIV, it is not without its limitations. Trial participants were in stable HIV-sero-discordant relationships and may not be a representative sample of all heterosexual sero-discordant couples in the general

population. These couples were also receiving free condoms, couples counselling on risk-reduction, and treatment for sexually transmitted infections which may have impacted upon the low incidence of HIV transmissions in the early therapy group. Also, the findings are mainly applicable to vaginal heterosexual sex and uncertainty remains over the ability of ART to reduce infectivity through anal sex and through exchange of blood products (e.g. through needle sharing in intravenous drug users and blood transfusions of infected blood).

Mathematical Models

The effect of universal voluntary testing and increased ART coverage on HIV transmission has been analysed using several mathematical models (70;83–94). The estimated effect of such a strategy varies between models with implications as optimistic as elimination (88) ranging to exacerbation of the HIV epidemic (93). Early models of both heterosexual and homosexual transmission (70;84;86) concluded that expanded ART coverage would not be an effective transmission prevention measure. Conclusions from the Baggaley model (84), which investigated the impact of increased ART coverage in a sub-Saharan epidemic, implied that this approach would not work regardless of the degree of ART coverage, as the total number of infections prevented would be marginal. Blower (86), whose model was based on MSM in San Francisco, found that a 10% increase in sexual risk behaviour would be enough to offset the beneficial effects of wide-scale ART, and Bezemer (70), whose model was based on MSM in the Netherlands, argued that the most effective method of prevention would be to restore risk behaviour to pre-ART levels.

However, several other more recent modelling studies have suggested that expanded ART and increased testing would be effective in reducing HIV incidence (83;85;87–94) and could therefore offer public health benefits. Firstly considering the heterosexual epidemic, Wilson et al. (65) investigated the implications of the Swiss statement (52) at a population level, by means of a simple mathematical model. On the basis of Rakai study (5), they derived a mathematical relation between viral load and the risk of HIV transmission per unprotected penetrative sexual contact. By assuming that each couple had 100 acts of sexual intercourse per year they calculated the cumulative probability of transmission to the sero-discordant partner each year. The authors concluded that the risk of HIV transmission in heterosexual partnerships in the presence of effective ART is low but non-zero, and that the transmission risk in male homosexual partnerships is high over repeated exposures. Therefore, they underlined the potential danger that the claim of non-infectiousness in effectively treated patients could cause if widely accepted, and condom use subsequently reduced.

In a model by Granich, in which parameters were based on the epidemic in South Africa (88), the test and treat strategy was predicted to reduce HIV incidence to less than 1 case per 1 000 people per year by 2016. It was predicted that such a strategy would reduce the prevalence of HIV to less than 1% within 50 years of its full implementation and that elimination could be feasible by 2020 in a generalised epidemic such as that in South Africa.

A model by Bendavid (85) assessed the health benefits of four different strategies which involved combinations of test and treat, improved linkage to care and reduced loss to follow-up (LTFU). Model parameters were based on the epidemic in South Africa, where HIV transmission is predominantly heterosexual. Findings from the study showed that a comprehensive strategy which involves 90% of the population being tested, and all HIV positive individuals receiving ART within 6 months of diagnosis, perfect linkage to care and no LTFU, would result in a 73% reduction in the number of potential new infections in the South African population, over a ten year period.

El-Sadr (95) formulated a mathematical model in order to forecast the epidemic impact of treating HIV-discordant couples with ART, to prevent transmission. The model was parameterised using data from Ghana, Lesotho, Malawi and Rwanda. It was concluded from this study that although treatment of discordant couples would not be sufficient to single-handedly control the HIV epidemic, achieving high treatment coverage levels for discordant couples could significantly reduce incidence and prevent a substantial number of new infections in certain countries.

Abbas et al assessed the potential impact of ART on the heterosexual spread of HIV in a resource limited setting with a generalised epidemic. The authors used a model in which parameter values were based upon an epidemic in a sub-Saharan African nation (83). The results of this study indicate that increasing ART coverage in 2006 at a national HIV prevalence of 5% would be more effective than later implementation when the prevalence of HIV was at 40%. The predicted reduction in the number of new HIV infections was 33% at 5% prevalence and 27% at 40% prevalence.

Long (90) evaluated treatment strategies that target non-injecting drug users (non-IDUs) and IDUs in addition to untargeted strategies that implement ART irrespective of IDU status. Parameter values were based on a population of IDUs and non-IDUs from St. Petersburg, Russia. The authors concluded that expanded use of ART could dramatically reduce HIV incidence among the general population in Russia and would offer substantial population-wide health benefits. The analysis also showed that the strategy which exclusively targets non-IDUs (the current practice in Russia) offered the least health benefits and that if treatment were targeted to IDUs, over 40 000 potential infections would be averted, of which 75% would be among non-IDUs. The authors emphasised the importance of targeting expanded ART to both IDUs and non-IDUs in order to achieve the greatest reductions in the number of new HIV infections.

A second study by Long (91), aimed to understand whether the expansion of screening and treatment could substantially diminish the HIV epidemic in the United States. The investigators found that expanding HIV screening and treatment could prevent approximately 17% to 24% of potential new infections. The authors argued that even modest reductions in risk behaviours, expanded screening and treatment would produce substantial health benefits.

There are also a number of models investigating the impact of HIV treatment as prevention among MSM. The Heymer model (89) compared the impact of increasing testing rates alone, to a combination of increased testing and treatment coverage in a South Australian population where HIV transmission is predominantly confined to MSM. It was found that increasing testing rates alone would yield only marginal reductions in the expected number of new infections when compared to the current situation. However, a combination of increased testing and treatment coverage could result in a 59%–68% reduction in the number of new HIV infections over a five year period. It was predicted that this reduction could reach almost 70% if all undiagnosed individuals were tested twice a year.

The Walensky model (94) evaluated combinations of HIV testing and ART initiation for a cohort of HIV positive individuals living in Washington DC. In this study it was forecast that a test and treat strategy, which involves universal voluntary testing and immediate initiation of ART, when compared with current practice (defined as no regular screening program and administration of ART at CD4 count ≤350 cells/mm^3) would decrease the proportion of time spent with transmissible viral load over a five year period from 64% to 54%.

Lou et al. (92) modelled the effect of ART in the presence of increased sexual disinhibition in a cohort of MSM in China. The simulations conducted in this study demonstrated that ART for MSM in China would have both individual and public health benefits on transmission, even in the presence of increased sexual risk behaviour.

Charlebois (87) modelled the impact of offering ART to all HIV positive MSM in San Francisco. Projections from the model demonstrated that ART expansion to all HIV positive MSM in care could significantly reduce the incidence of HIV infection. The authors concluded that ART expansion alone could offer a 59% reduction in HIV incidence at 5 years which could increase to a 76% reduction if ART expansion was combined with annual HIV testing.

The McCormick model (93) evaluated the effectiveness of ART expansion on the incidence of HIV infection, using two cohorts of MSM: a cohort not receiving ART and a cohort treated according to United States guidelines. Findings from the McCormick model indicate that ART could reduce transmissions from 1.9 to 1.4 per person during the first ten years since infection, assuming no increase in risk behaviour. However, simulations showed that over longer time periods, the benefit of ART decreases due to there being a longer time of infectiousness. The total number of infections for the treated cohort began to exceed the number of infections for the untreated cohort at 33 years since infection. In view of this, the authors concluded that ART alone will not be sufficient to significantly reduce the spread of HIV.

Law et al. (96) formulated a model based on the HIV epidemic in Australian MSM, in which the aim was to assess the competing effects on HIV incidence of effective combination ART and MSM engaging in unprotected anal intercourse (UAI) with an increased number of partners. In this study it was found that decreases in infectiousness as a result of ART would be counterbalanced by even modest increases in the levels of unsafe sex. In fact, several authors of mathematical modelling studies have argued that the benefits of wide scale ART could be offset by increases in unsafe sexual practices, and conclude that expanded ART should be part of a comprehensive strategy for prevention, which should include behavioural interventions that target the reduction of sexual risk behaviour (70;84;86;93;94;96).

As with all research methods, mathematical modelling studies are subject to limitations. As mentioned above, the findings from several mathematical studies are inconsistent. The validity of conclusions drawn from models depends upon the reliability and completeness of the assumptions, on which the model parameters are based upon. Therefore, the findings from mathematical modelling studies should be interpreted with this caveat in mind.

3.1.2 HIV RNA levels, infection stage and transmission

Correlation of HIV RNA in plasma and in genital and rectal compartments

The concentration of HIV-1 in semen and in the genital and rectal compartments is likely to be the most important determinant of sexual HIV transmission. However, evidence on the relationship between HIV RNA and risk of transmission mainly considers HIV RNA levels in the plasma (pVL) rather than in genital secretions. Correlations between plasma and genital HIV RNA levels have been consistently reported (97105), but the strength of this association differs across studies and between genders. Most individuals who did not achieve HIV-1 RNA suppression in plasma on treatment also had detectable HIV RNA in their (male or female) genital samples (9;101–103).

When considering men with undetectable pVL on ART, the proportion with detectable HIV RNA in semen (sVL) varies considerably. One of the first studies to explore the relationship between antiretroviral treatment, pVL and sVL was published by Vernazza et al (106), who found that only 1.8% of those with a plasma HIV RNA below 400 copies/ml had detectable HIV RNA in semen. More recent studies among individuals who have been on ART with pVL below 50 copies/mL for at least one year found that the proportion with sVL >700 copies/mL varies from 0% in a study conducted in Australia (98), (none above 200 copies/ml) to 6% (n=2) in a small study (n=33) conducted in Canada (107). Furthermore, low proportions with genital shedding, varying from 3% to 5%, have been found in studies of participants in medical assisted procreation (MAP) (108–110).

A contrasting result comes from a small study in people starting first-line antiretroviral treatment, where shedding of HIV RNA in semen was detected at more than one visit (conducted at 2, 4, 8, 12, 16, 20 and 24 weeks) in 48% of the participants, despite suppressed plasma HIV RNA. In fact, seminal HIV RNA was above 5000 copies/ml in 16% of study visits (111). Therefore one must be cautious before concluding that a man on ART, even with undetectable pVL, is non-infectious. HIV-shedding in semen occurs frequently, particularly in the first months of treatment, but the degree to which HIV RNA in semen is associated with risk of HIV-1 transmission is still unclear (112).

A moderate correlation has also been found between HIV RNA in plasma and in the rectum (rVL) (100;113;114). Early studies have been cross-sectional, which does not allow exploration of how the relationship between HIV RNA in plasma and the genital compartments varies during the course of infection and over time.

At present, there seems to be no evidence of an effect of disease progression on the association between HIV RNA in plasma and seminal fluids, whereas an effect of calendar year has been observed, presumably due to changes in ART efficacy. Dulioust and colleagues (108) found a decreasing prevalence over time of discordant cases of men with detectable HIV RNA in semen and undetectable HIV RNA in plasma: in this study all cases occurred between 2002 and 2005, and none between 2005 and 2008, potentially suggesting an improved efficacy of recent ART regimens in the genital compartments.

Among women, treatment seems to have an equal effect on HIV RNA levels in cervical secretions and in the plasma, as no association between HIV RNA levels in cervical secretions and use of treatment have been observed after adjustment for plasma HIV RNA and CD4 count (102). Plasma levels have been consistently identified as the most important predictor of genital HIV-1 shedding, even among women on ART (102;115). Nonetheless, shedding does occur among women who achieve plasma HIV RNA below 500 copies/mL: the observed proportion of women with detectable HIV-1 RNA in cervical specimens, despite HIV RNA below detectable levels (500 or 400 copies/ml) varies from 3% to 33% (10;102;115–119).

HIV transmission rates may depend not only on HIV RNA level in plasma, but also on whether the individual is receiving ART and on the class of drugs being used. Different ART regimens have different tissue penetration of genital fluids. Therefore, some drugs could be sufficient to maintain an undetectable plasma viral load, but insufficient to suppress HIV in the genital compartments. The correlation between plasma HIV RNA and HIV RNA in semen, cervicovaginal, or rectal fluids varies by drug class and regimen (106;120;121). In addition, although ART reduces HIV RNA both in plasma and in genital tracts, it is plausible that other biological or methodological factors contribute to the variability of the genital shedding of HIV (122). The presence of sexually transmitted infections, as well as genital inflammation, increases HIV RNA in genital secretions (102;123–125). A recent meta-analysis of 39 studies assessing the effect of genital tracts infections on male and female genital tract shedding found that the odds of detecting HIV in the genital tract were significantly higher in the presence of either *Neisseria gonorrhoeae* or Chlamydia trachomatis. However, many studies of women, exploring the relationship between pVL and HIV RNA in genital compartments have excluded women with other STIs. In contrast, a recent study evaluating the relationship between rectal STIs and rectal HIV-1 shedding in men (100) found that presence of a rectal STI did not increase the likelihood of detecting HIV in the rectal secretions in MSM, including those with low HIV RNA in plasma. Therefore if this latter finding is confirmed, it is plausible that suppressing HIV RNA in plasma, regardless of whether an STI is present or not, reduces the risk of HIV transmission to the insertive partner. This may not be true for heterosexual couples and the receptive partner in a homosexual couple.

In conclusion, although most people on ART have undetectable HIV RNA in plasma, this does not guarantee an undetectable viral load in genital compartments, partly because of low antiretroviral drug penetration into the genital tracts. A randomised controlled trial, HPTN 052 (82), showed a dramatic effect on the rate of HIV transmission in people on treatment. However, there is at least a theoretical concern that transmission might still be possible in people with undetectable HIV RNA in plasma, as HIV has been detected in the genital tract secretions of men and women with undetectable plasma viral loads.

Role of stages of infection

Since the early days of HIV research, models and longitudinal studies have suggested that the rate of heterosexual HIV-1 transmission per coital act was higher during primary infection, lower during the asymptomatic/latent period and higher again in the late stages of HIV infection. This is likely due to the high viral loads observed in the earliest and latest period (126–128). The first data on the variation in HIV transmission by stage of infection came from the Rakai study (129), described above. In this study Wawer estimated that the rate of HIV transmission per coital-act during the first five months since seroconversion is 0.0082/coital act (95% CI: 0.0039–0.0150), 8-10 times higher than during the asymptomatic infection (between 6–15 months rate of transmission per coital-act= 0.0015 (95% CI, 0.0002–0.0055), and then it increases again during the two years before death of the HIV-infected partner: 0.0028/coital act (95% CI, 0.0015–0.0041). The data on the primary and asymptomatic phase were based on a small number of sero-discordant incidence couples (n=23), where individuals were tested every ten months. Therefore the date of sero-conversion and death were assumed halfway through the interval.

In 2008, Hollingsworth (130) re-analysed the data from the Rakai Study to estimate the transmission rates and the duration of each stage of HIV infection. The authors attempted to discount coital acts that happened after transmission occurred and assessed the rate of transmission as a function of time since the partnership was first observed, after assuming incident infection and death had an equal probability of occurring at each possible time under study rather than at the interval mid-point. They estimated that the primary infection lasts for 2.9 months, in agreement with previous findings (131), during which the transmission rate per 100 person-years is 276 (95% CI: 131–509). The asymptomatic phase was characterised by a much lower transmission rate: 10.6 (95% CI: 7.61–13.3) per 100 person-years. The late stage of the disease was assumed to consist of two parts, one with a high transmission risk and one, just preceding death characterised by limited sexual contact due to the unhealthy condition of the infected partner. They estimated that the very last phase lasts for ten months (95% CI: 6.97–12.7), while the preceding lasts for nine months (4.81–14.0) and is characterised by a transmission rate of 76 (95% CI: 41.3–128) per 100 person-years. In addition, they estimated how much each of this stage contributed to the HIV epidemic, in two opposite extreme scenarios by means of a mathematical model: serial monogamy and random mixing. The authors found that the acute infection contributed between 9 to 31% of HIV infections, while the late stage contributed between 20% to 27% of HIV infections.

A recent study by Powers (132) also suggested that early infection plays an important part in HIV transmission. They used a mathematical model describing heterosexual HIV transmission, informed by detailed information on behaviour and viral-load collected in Lilongwe in Malawi. They estimated that 38.4% (95% credible interval 18.6–52.3) of HIV transmissions in that setting were attributable to sexual contact with individuals in primary infection. Evidence of the crucial role of the acute infection also comes from phylogenetic studies. For example, a large study on over 2 000 patients in London estimated that 25% of infections occurred within six month from infection (133).

At present there is no clear evidence of an individual health benefit of treating individuals during primary infection. The short pulse anti retroviral therapy at HIV seroconversion (SPARTAC) trial evaluated the effect of short course ART in individuals identified in primary HIV infection on HIV disease progression, viral set point and inflammatory biomarkers. Individuals were randomised to ART for 48 weeks (ART-48), 12 weeks (ART-12) or no therapy (standard of care). They found that the ART- 48 arm experienced delayed disease progression (time to reach CD4<350 cells/mm^3), although not by significantly longer than the time already spent on treatment. The potential effect on HIV transmissibility of treating people in primary infection has not been directly investigated (134).

It seems that HIV RNA viral load may not explain all of the increased risk of transmission seen during the first months since seroconversion (129;130;135). Additional factors are the presence of other sexually transmitted infections and potentially higher susceptibility in newly exposed HIV-negative partners. This latter phenomenon is due to the high variability in susceptibility across individuals: the most susceptible individuals are likely to get infected during the first exposure period. This could be a reason why a high rate of transmission is observed in the early phase of infection, while other less susceptible partners are less likely to get infected at all. In addition to the highest rate of HIV transmission per sex act, there is also the fact during primary infection people are unlikely to know their HIV status and are therefore less likely to use condoms. This partly explains why a large proportion of infections are attributable to this stage, despite its short duration. The important role that acute infection plays is generally agreed, although the relative contribution of primary infection varies considerably according to the stage of the epidemic and the structure of sexual contact networks.

The advanced stage of the disease is also characterised by a high rate of transmission per sexual contact, but the contribution of this phase is believed to be smaller. This is likely because individuals in the late stage of HIV infection report less sexual intercourse and have fewer partners, and only a minority of HIV-infected partners

remain discordant by this stage. It is not clear that the advanced stage is a risk factor for transmission independent of HIV RNA level. Therefore despite the dramatic effect on HIV transmission of ART seen among sero-discordant couples in a RCT (96% reduction in incidence), the potential roll-out of this intervention is unlikely to have the same effect at a population level, given the extreme difficulty in identifying people very shortly after infection and starting them on treatment.

Risk of increase in condom-less sexual behaviour with antiretroviral treatment

Although, as reviewed above, there is evidence that ART can prevent HIV transmission through reduced infectivity, this could be offset by increases in risky sexual behaviour. The first studies have found contrasting results: in the US higher risky sexual behaviour (136–138) and a higher STI incidence (139) was found among people on ART, whereas other studies, including several from Europe, have shown significantly lower rates of risky sex among those on ART (140–143). A meta-analysis in 2004 from 16 studies in industrialised countries found that the prevalence of unprotected sex was not higher among people on ART compared to those not on ART (144). The first study to assess the effect of ART on risky sexual behaviour in a prospective cohort study was conducted in Uganda (145). They found that ART provision, prevention counselling, and partner counselling and testing were associated with reduced sexual risk behaviour during the first six months of ART. Finally, a recent meta-analysis of studies conducted among HIV-diagnosed MSM in the United States (146) observed that being on ART, having undetectable HIV RNA, and reporting higher than 90% medication adherence were not associated with unprotected anal intercourse (UAI). In addition they found that the prevalence of UAI was considerably higher with HIV-seropositive partners than with partners of unknown or negative serostatus (so-called "sero-sorting"). There may also be limited impact of use of ART for HIV prevention amongst individuals in settings where there is a fast-spreading HIV epidemic, for example amongst injecting drug users, such as those seen in Eastern Europe and Central Asia (147).

Implications for the individuals receiving treatment

When antiretroviral drugs were first introduced in the mid-1990s, there was limited availability and drugs were expensive and toxic. However, this past decade has seen the development of more potent and tolerable antiretrovirals and the advent of combination therapy meant that resistance mutation development became rarer. Individuals infected with HIV are now living much longer and healthier lives; one modelling study has shown that a near-normal life expectancy may be achieved providing the individual is diagnosed early and have good adherence to therapy (148).

A recent study which looked into the incubation time from seroconversion to CD4 count <500, <350 and <200 cells/mm^3 found that the median times for people to reach those CD4 counts were 1.2, 4.2 and 7.9 years respectively (149). This implies that, if a threshold of 500 CD4 cells/mm^3 is used to decide whether to start ART, approximately half of HIV-infected individuals would require ART initiation within a year of seroconverting. If ‘test and treat’ was implemented in the United States, the time period from diagnosis to treatment may not be much shorter than the average one year which it takes for someone’s CD4 to decline to 500 cells/mm^3. In reality however, there are a substantial number of people who present with conditions such as hepatitis co-infection or with a viral load >100,000 copies/ml or who has a high cardiovascular risk, in which case they would be considered for ART regardless of their CD4 count. Therefore, the likely impact of treating individuals at a higher CD4 count on person-years spent infectious may also be small. Measuring the success in implementing this guideline may provide an indication to whether ‘test and treat’ is actually feasible and effective if or when it is put into practice. A modelling study, based on an epidemic concentrated around MSM and IDUs, which looked at the impact of changing the CD4 eligibility criteria from <200 to <350 cells/mm^3, reported gains in healthy life years and a decline in premature mortality and incidence of new HIV infections (150). This shows the potential impact of changes to guidelines both on an individual and population level.

3.2 Treatment guidelines for timing of when HIV-positive individuals should receive treatment

Guidelines on the optimal time for a treatment-naïve person to start ART has thus far been driven by the clinical prognosis of the HIV-positive individual, rather than by the desire to reduce transmission to a specific partner, or to reduce transmission more generally as a public health policy. However, the implications with respect to the impact on HIV incidence rates of those clinically-driven recommendations can be considered once this decision is made.

The issue of the timing of ART initiation has been controversial and much debated, due to the lack of randomised controlled trials designed specifically to answer this question. Despite reliable, published findings from large multi-cohort analyses, observational studies have an inherent drawback wherein unmeasured confounders may lead to bias in results. The START (Strategic Timing of AntiRetroviral Treatment) trial was therefore designed and set up to explicitly answer the question of whether ART-naïve people with CD4 count >500 cells/mm^3 would do better to initiate ART immediately, or defer until a CD4 count of 350 cells/mm^3 or when clinical AIDS develops (151). The follow-up period is not anticipated to finish until the end of 2015. Until the results of this trial are analysed, experts predominantly only have findings from observational studies to inform their recommendations. A randomised controlled trial has been conducted in Haiti, in which it was found that starting ART immediately in people with CD4<350 cells/mm^3 resulted in greater survival benefits over starting when the CD4 dropped to <200 cells/mm^3 or if the individual developed severe AIDS (152). The HPTN 052 trial, which randomised the positive partner (all of whom had CD4 count 350-550 cells/mm^3) in serodiscordant couples to immediate ART or deferral to CD4 count <250 cells/mm^3 also compared clinical outcomes, although power was low. There was a significantly reduced risk of clinical disease in the intervention group, mainly driven by a reduction in extrapulmonary TB (82). In a subset of participants in the SMART trial with CD4 count >350 cells/mm^3 who were ART naive at baseline, there was a reduced risk of clinical disease in those initiating ART compared to those who deferred (153). All these trials were based on a comparison involving deferral to CD4 count 200 or 250 cells/mm^3, which is now no longer standard of care. Here, the focus is on what the guidelines say about the criteria for when treatment-naïve individuals are recommended to start antiretroviral therapy (without addressing the choices for first line regimen), as observed to the recommendations given by EACS, IAS-USA and WHO (35;38;45) and with respect to the implications of treatment as prevention.

3.2.1 When to start treatment according to current guidelines

All three guidelines agree that treatment should be initiated without delay in patients with HIV-related symptoms or AIDS regardless of CD4 count. The WHO guidelines recommend starting ART in asymptomatic patients with CD4 count <350 cells/mm^3, whereas the IAS-USA guidelines recommend starting if CD4 count ≤500 cells/mm^3. The EACS guidelines suggest that treatment should be considered if CD4 count is between 350 and 500 cells/mm^3 for asymptomatic patients, but recognise that not all experts will agree with this recommendation; some would recommend starting when the CD4 declines to those levels whilst others would recommend deferral. There are several differences in the recommendations if patients present with comorbidities or other HIV-associated conditions (Table 1).

The EACS recommendation for asymptomatic individuals reflects the uncertain risk-to-benefit ratio for the use of ART in those with moderately high CD4 counts. Although there is some evidence supporting ART initiation at 350< CD4 count <500 cells/mm^3, there are also risks inherent in using antiretroviral drugs (which are not all known). The IAS-USA recommendation to start treatment where CD4 count ≤500 cells/mm^3, is based on the evidence from large observational studies (154;155). However, the panel states that there is better quality evidence, i.e. data from clinical trials as well as observational studies, to support starting ART if CD4 ≤350 cells/mm^3 (38). Both the EACS and IAS-USA guidelines advise that the decision for someone to start ART should depend heavily on whether the patient himself/herself is ready to start. This is to ensure that adherence can be optimised. However, the same does not apply to late presenters (generally defined as people with CD4 <200 cells/mm^3) who should be started immediately. Support should be given to these patients as needed.

The previous version of the WHO guidelines recommended patients should start ART once their CD4 count was <200 cells/mm^3 (156). This was revised based on pooled clinical evidence from two studies suggesting a reduction in mortality in ART-naïve people starting ART with CD4 >200 or >250 cells/mm^3 (153;157). The fact that the two trials, which demonstrated the reduction in mortality in people with CD4 >200 cells/mm^3, took place in different settings (one was in resource-rich countries whereas the other was in a resource-limited setting), impacted largely on the decision to change the CD4 eligibility threshold due to the extensive applicability of the results. Note that the pooled clinical evidence is disputable as it is based on two studies only, one of which is a post-hoc analysis nested in an RCT (153). However, the results from these two studies are consistent with other observational studies (158;159). Late presenters are still considered to be a priority and those with CD4 <200 cells/mm^3 are advised to start immediately. The guideline also recommends patients with WHO clinical stage three or four to start treatment irrespective of CD4 count and also calls for increased access to CD4 testing for those with WHO clinical stage one or two to decide when to start treatment. Although the supporting evidence for the use of clinical

staging to determine ART initiation is of low quality, resource-limited settings often do not have access to CD4 measurement assays and are thus limited to using WHO clinical staging.

Despite the WHO Europe guidelines from 2007 (and not revised since) (49) recommending initiation of ART for asymptomatic patients if CD4 <200 cells/mm^3, it is thought that in many countries, the implementation of the new CD4 count cut-off of 350 cells/mm^3 is already in practice. For patients with higher CD4 counts (between 350 and 500 cells/mm^3), the viral load measurement is considered as an additional measure to decide whether treatment should be started.

There is no doubt that all guidelines agree on the fact that that the strength of evidence which supports ART initiation increases as the individual's CD4 cell count declines. Without compelling data from randomised controlled trials, recommendations will inevitably differ to some extent, resulting from differences in panel opinions on the public health approach to take, given the current available evidence. One key aspect, which none of the guidelines address in detail, is cost-effectiveness. It is fast becoming an increasingly important issue and may become more crucial to consider this in the future. One recent example where cost-effectiveness has been a major factor in influencing recommendations is the case with the London HIV Consortium earlier in 2011, which has restricted use of specific drugs in order to control costs. It is expected that the new recommendations will be incorporated into the revised British HIV Association guidelines.

Guidelines on the treatment of HIV-positive individuals have also been issued by individual countries. Of those issued in Europe, these include the United Kingdom, France, Spain, Netherlands, Sweden, Germany, Austria and Italy (160–166).

3.2.2 The use of 'treatment as prevention'

Perhaps due to the advent of new drugs which are more effective and have better drug profiles, as well as increasing evidence of the safety and advantages of starting therapy earlier, the EACS guidelines state that ART can be started on a case-by-case basis, irrespective of the patient's CD4 count or viral load, particularly 'if a patient is requesting therapy and ready to start, and/or for any other personal reasons.' This also includes the use in serodiscordant couples where ART may be initiated earlier than in other situations, suggesting that using treatment as a method of preventing HIV transmission is advocated by EACS and should at least be discussed between the physician and patient. Similar to the EACS guidelines, the IAS-USA guidelines note that 'there is no CD4 cell count threshold at which initiating therapy is contraindicated'. Further, the panel recommends that treatment should be considered in situations where there is an increased risk for secondary HIV transmission, such as in HIV-serodiscordant couples. Although there was only moderate evidence to support this at the time the recommendations were published, the results from the HPTN 052 trial now provides strong evidence (82). In these situations however, the guidelines state that ART should not replace traditional methods of prevention and recommend that clinicians carry out risk-reduction counselling regularly.

WHO have looked into the possibility of using treatment as prevention in much detail, having done a mathematical modelling study to investigate the impact of voluntary HIV testing and immediate ART on transmission (88), which was then followed by a three-day consultation in 2009. Currently, there seems to be inadequate evidence for WHO to recommend the use of ART as a method to prevent further HIV transmission in general. However, use in serodiscordant couples should now be offered to the HIV-positive partner to reduce transmission to uninfected partners as per the most recent guidance on couples HIV testing and counselling, including antiretroviral therapy for treatment and prevention in serodiscordant couples . Although scientific evidence exists suggesting that ART reduces HIV transmission, mainly seen in the decrease in risk of transmission in mother to child, and between serodiscordant couples, not much is known about the consequences of starting ART earlier, including issues surrounding adherence, drug toxicity, required coverage and cost-effectiveness (23;53;145;167;168). Community randomised trials are being considered in order to strengthen the evidence base for increased testing and immediate ART initiation as a prevention approach. WHO emphasise that people who are in need of immediate treatment should not be overlooked, nor should condom use be neglected, in expanding access to ART for the purpose of preventing further transmission.

Table 1. Recommendations by guidelines for ART initiation in treatment-naïve HIV patients

Guidelines	Condition	CD4 count, cells/mm^3	Recommendation
EACS (2011)	Symptomatic (including TB)	Any value	ART initiated without delay
	Primary HIV infection	Any value	ART should be considered
	-	<350	ART recommended
	Asymptomatic	350-500	ART should be considered
	Asymptomatic	>500	ART should be deferred
	Conditions (likely or possibly) associated with HIV: HIV-associated kidney disease or neurocognitive impairment, Hodgkin's lymphoma, HPV-associated cancers	>350	ART recommended
	Conditions (likely or possibly) associated with HIV: Other non-AIDS defining cancers requiring chemo- and/or radiotherapy, Autoimmune disease (otherwise unexplained), high risk or history of CVD	>350	ART should be considered
	Chronic viral hepatitis	350-500	ART generally recommended (but also depends on whether individual is HBeAg-positive)
	On an individual basis, especially if patient is seeking and ready for ART and/or for any personal reasoning including being part of a serodiscordant relationship as one aspect of the overall strategy to reduce HIV transmission	Any value	ART can be offered irrespective of CD4 count or viral load
ISA-USA (2010)	Symptomatic	Any value	ART recommended
	Asymptomatic	≤500	ART recommended
	Asymptomatic	>500	ART should be considered
	Rapid CD4 count decline (>100 cells/mm^3/year)	Any value	ART recommended
	Viral load >100,000 copies/mL	Any value	ART recommended
	Age >60 years, Pregnancy (at least by second trimester), chronic HBV or HCV co-infection[1], HIV-associated kidney disease[2], high cardiovascular risk[3], opportunistic infections[4], symptomatic primary HIV infection.	Any value	ART recommended
	An increased risk for HIV transmission, such as in HIV-serodiscordant couples	Any value	ART should be considered
WHO (2011)	-	<200	ART initiated without delay
	WHO clinical stage 3 or 4[5]	Any value	ART initiated without delay
	-	≤350	ART should be started irrespective of WHO clinical stage

[1] *'although for patients with HCV genotype 2 or 3 and high CD4 cell counts, an attempt to eradicate HCV may be undertaken before ART is initiated'*

[2] *'avoiding drugs with potential adverse effects on the kidney (TDF, IND, ATZ), if possible'*

[3] *'modifiable risk factors for cardiovascular disease should be aggressively managed'*

[4] *'including tuberculosis, with attention to drug interactions and the potential for immune reconstitution inflammatory syndromes'*

[5] *'WHO clinical staging of HIV disease in adults and adolescents' (45). The use of clinical staging is suggested once HIV serostatus has been confirmed. Individuals are classified to one of four stages. Loosely speaking, clinical stage 1 is associated with asymptomatics, 2 with mild disease, 3 with advanced disease and 4 with severe disease.*

3.3 Current practices in Europe – evidence from observational and surveillance studies

As discussed above, definitions of ART eligibility in terms of CD4 count have changed several times since the introduction of potent combination therapy in the mid 1990s. At the beginning of the highly active ART era, the majority of countries generally felt the consensus was to start when the CD4 count declined to 500 cells/mm^3, although some experts at the time preferred to defer therapy in patients with stable CD4 counts and viral loads(37). After around the year 2000, treatment was rarely started unless CD4 declined to 350 or 200 cells/mm^3 (34;39). Some of the most recent guidelines, as summarised in the previous sections, now advocate initiation of treatment in patients irrespective of their CD4 counts, if the patient is willing and/or in situations where the risk of HIV transmission is high, which applies particularly to serodiscordant couples (35;38).

It is useful to consider data from cohort studies on how the CD4 count at ART initiation has changed over time, although this is largely influenced by patterns of testing and diagnosis rates, rather than the decision on when to start in identified patients. Some cohorts have observed ART being initiated on average at lower CD4 counts than the recommended CD4 count at initiation of therapy in treatment naïve patients (169;170), whilst, many other cohorts have observed CD4 counts >350 cells/mm^3 at start of therapy (171-173). Differences between areas in initial CD4 count at start of therapy have also been documented (174) highlighting the variation in the treatment and management of HIV-infected people or perhaps diagnosis rates'

European surveillance data from 2009 show that amongst the countries which report CD4 at diagnosis, approximately half of these countries report that over 50% of individuals are diagnosed with CD4 <350 cells/mm^3 (175). Therefore, many people should have already started antiretroviral therapy in line with current treatment guidelines by the time that they are diagnosed.

4. Pregnant HIV-positive women and their children in utero/post-delivery

4.1 The use of antiretroviral treatment as prevention

The aim of this section is to review the literature regarding the efficacy of antiretroviral treatment to prevent HIV transmission from mother to child. Results of the studies are included in the formal literature review (summarised in Appendix 2), and are described, as well as supporting literature of related studies where applicable. The review is structured chronologically, starting with a discussion of the early antiretroviral regimens considered to prevent MTCT, through to the highly effective combination antiretroviral regimens used at present. A summary of the main findings of the review is presented in Table 2. Next, a discussion of the relative importance of providing ante-partum, intrapartum and post-partum antiretrovirals is conducted. Finally, the known and potential limitations of pMTCT are described.

Table 2. Summary of rates of mother-to-child transmission using different antiretroviral drug strategies

Antiretroviral regimen type	Observed mother to child transmission rates in predominantly breast-fed populations (or not stated)	Observed mother to child transmission rates in predominantly formula-fed populations
None	15%–48%	-
ZDV regimen One or more of: - Short-course ZDV during pregnancy (typically from 36 weeks gestation) - Intrapartum ZDV - Neonatal ZDV - Maternal post-partum ZDV	4%–26%	-
sdNVP regimen One or more of: - maternal single dose nevirapine - neonatal single dose nevirapine	12%–22%	-
Dual therapy (ZDV+3TC) regimen One or more of: - Short-course ZDV+3TC during pregnancy (typically from 36 weeks gestation) - Intrapartum ZDV+3TC - Neonatal ZDV+3TC - Maternal post-partum ZDV+3TC	5%	-
Combination of mono/dual therapy and sdNVP regimen	5%–15%	0.5%–6%
Triple therapy One or more of: - 1 or more PI or NNRTI with 2 or more NRTIs during pregnancy - Neonatal antiretrovirals - Intrapartum maternal antiretroviral therapy	1%–9%	0%–6%

4.1.1 Antiretrovirals to prevent mother to child transmission

Use of single antiretrovirals (mono-therapy)

The first major randomised controlled trial studying the use of antiretrovirals to prevent mother-to-child transmission (pMTCT), was the Pediatric AIDS Clinical Trials Group 076 (PACTG076) study, published by Connor and colleagues in 1994 (23). HIV-positive mothers from the United States of America and France were recruited for the study. Here, even in the early days of pMTCT, the strategy employed by the investigators targeted preventing new infections occurring at more than one stage of infection. In this study, pregnant women in the active treatment arm received ZDV antepartum from study enrollment (14–34 weeks' gestation) onwards. The women then received intrapartum intravenous zidovudine (ZDV) during labour, after which the newborn was given six weeks of ZDV. The control arm received equivalent placebos. The study was stopped early at a planned interim analysis, as the results at that point clearly demonstrated that this treatment strategy for pMTCT was effective. At 18 months, the estimated proportion of HIV-positive infants was 8.3% (3.9%–25.5%) in the ZDV arm, and 25.5% (18.4%–32.5%) in the placebo arm, corresponding to a 67.5% reduction in the risk of transmission (95% confidence interval [CI] 40.7%–82.1%). Similarly, Jamieson and colleagues compared short-course ZDV from 36 weeks gestation and intrapartum ZDV to placebo in an RCT in the Cote d'Ivoire in the RETRO-CI trials (176).

Here, the rate of transmission at 24 months was 29.2% in the placebo arm, compared to 22.1% in the active treatment arm.

As a result of this finding, the '076 regimen' became an often utilised strategy in clinical care. Therefore, a number of observational studies corroborated the findings of the PACTG 076 study. Outside of the clinical trial setting, in clinical practice, not all mothers necessarily received all three components of the 076 regimen even though it was considered as the standard of care in most studies,The reasons for this included late diagnosis and babies being delivered outside of the hospital setting. Thus, several observational studies compare the rates of transmission according to whether the mother and infant pair received a 'complete 076 regimen', 'incomplete 076 regimen' or no antiretroviral therapy. All showed that both complete and incomplete strategies were more effective than no ART, with complete regimens in turn being more effective than incomplete regimens (177-180). For example, the European Collaborative Study (177), which includes centres from across Europe, found an adjusted odds ratio of 0.41 (95% CI 0.25, 0.67) for those receiving an incomplete 076 regimen, and 0.34 (0.18, 0.63) for those receiving a complete 076 regimen compared to those receiving no ART. Therefore, this study suggests that women receiving a complete 076 regimen have a 66% reduction in the odds of transmission compared to a woman receiving no ART.

Other ZDV-based prevention regimens that do not explicitly follow the 076 regimen, such as short-course ZDV for the mother, or short-course ZDV with intrapartum ZDV, have also been shown to be effective (168;176;177;181–199). For example, an RCT, conducted in Burkina Faso and Ivory Coast compared placebo to ZDV from pregnancy until seven days post-delivery, and found the rate of transmission fell from 27.5% to 18.0% (182).

A commonly used alternative monotherapy regimen consists of a single dose of oral nevirapine (sdNVP) taken by the mother during labour. A second dose of sdNVP is also frequently given to the newborn. Clearly, this regimen is useful in resource-limited settings, as just one or two doses of NVP are required, and can be taken by mothers during delivery even if they have a home birth. The relative efficacy of a maternal and neonatal sdNVP regimen was compared to a ZDV monotherapy maternal and neonatal regimen in the HIVNET-012 RCT published in 2003(200). This study of a breastfed population found that the transmission rate at 18 months was 25.8% in the ZDV monotherapy arm, compared to 15.7% in the sdNVP arm, suggesting that sdNVP is a more efficacious approach. However, Kiarie and colleagues compared these two types of regimens in a relatively small RCT (201). The authors found a transmission rate of 9% in 55 mother-child pairs receiving a ZDV-based short course regimen with intrapartum ZDV, compared to a rate of 22% in 55 mother-child pairs receiving maternal and neonatal sdNVP. Although there was a trend towards a lower transmission rate in the ZDV-based arm (p=0.07), the RCT was too small to make any firm conclusions, although the authors comment on the fact that high adherence to the regimen is very important. Similarly, surveillance data by Hillis and colleagues suggested a higher rate of transmission with maternal and neonatal sdNVP at 12.2%, compared to full course ZDV at 4.1% (202). A further observational study in 2004 found similar rates of HIV transmission with either a regimen of short-course ZDV monotherapy to both mother and infant or using a regimen of maternal and infant sdNVP, with transmission rates of 16.7% and 16.4%, respectively. This was in a setting in which 66% of the mothers breastfed their children: in the absence of any treatment, the rate of transmission was very high at 47.8%. This suggests that intervening with mono-therapy more than halved the rate of transmission, despite limited exposure to ART during the breastfeeding phase. However, addition of seven days of ZDV post-partum to a regimen of maternal andneonatal sdNVP is unlikely to add much extra benefit in terms of HIV transmission rates, as shown in two RCTs carried out in Malawi (203;204). This regimen may of course confer a benefit in terms of avoidance of antiretroviral drug resistance, as discussed later on.

There is also evidence that prompt administration of sdNVP as close to the time of delivery as possible is vital. Chi and colleagues (205) performed an observational analysis of RCT data from HIVNET024. The authors reported that the rate of transmission was 6.3% if the time from maternal dose until delivery was <2hours, rising to 10.5% amongst mothers for whom more than 48 hours had elapsed between maternal dose and delivery. In contrast, timing of the neonatal dose appeared less important; the rate of transmission was around 8%, regardless of when the neonatal sdNVP dose was administered.

Thus, it is likely that regimens containing a single antiretroviral agent in the form of ZDV monotherapy or sdNVP more than halve the risk of mother-to-child transmission. However, the remaining risk is non-negligible at around 20% when using this strategy. Clearly further reductions in MTCT rates remain desirable.

Use of two antiretrovirals (dual-therapy)

After the success of the use of single antiretroviral agents to reduce the risk of mother-to child-transmission, the use of treatment strategies consisting of two antiretrovirals were investigated in a number of RCTs and observational studies in the mid to late 1990s.

Several observational studies have shown that rates of HIV transmission are lower amongst those receiving dual regimens (usually ZDV+3TC) compared to ZDV monotherapy regimens. In this situation, the dual regimens are usually administered similarly to the 076 regimen strategy. Therefore, these regimens typically consist of short-course treatment with ZDV+3TC during pregnancy, an additional intrapartum dose for the mother, followed by ZDV+3TC for the neonate, usually for 7 days (206–217). These studies demonstrated the superiority of dual therapy regimens over a ZDV monotherapy strategy. For example, the Mitra study investigated the use of dual therapy (ZDV+3TC) with antenatal, intrapartum and neonatal components and observed a low transmission level of 4.9% despite breastfeeding (206). Panburana observed a similar rate in a non-breastfeeding population in Thailand (207). Finally, a pilot study by Lolekha in Thailand of short-course ZDV+3TC, intrapartum ZDV+3TC and neonatal ZDV in a population with no breastfeeding led to a low transmission rate of 4.7% (208).

Furthermore, there is also evidence that combining a sdNVP strategy (maternal exposure, with or without neonatal sdNVP) with either ZDV monotherapy or ZDV+3TC dual regimens from 28 weeks of pregnancy leads to a reduced transmission rate (218–223). The studies suggest that these regimens reduce transmission rates to around 0.5% to 6% in formula-feeding settings and 5–8% in settings where at least the majority of mothers breastfed. Furthermore, a study by Shapiro suggests that the maternal dose of sdNVP could be removed from the regimen (provided ZDV antepartum, intrapartum ZDV and neonatal sdNVP with one week of ZDV is included) to prevent NVP resistance occurring in the mother (224). However, regimens without a short course antepartum antiretroviral regimen may not be so efficacious, even with the addition of sdNVP to the regimen. This was demonstrated by Thistle and colleagues (225), who conducted an RCT of over 600 individuals in Zimbabwe. Here, a regimen of intrapartum ZDV with sdNVP, along with neonatal sdNVP plus ZDV for three days led to a relatively high transmission rate at six weeks of 14.4%. A similar rate of 16.5% was seen in the same regimen without the maternal and neonatal sdNVP element included. However, this was conducted in a population with 91% breast-fed, which may also partly explain the higher observed rates of transmission, as well as the omission of antenatal ZDV.

Therefore, the use of two antiretrovirals is a more effective pMTCT treatment strategy than no treatment, or ART consisting of only one antiretroviral. However, the risk of transmission is still likely to be non-zero. Furthermore, the vast superiority of triple combination regimens over dual therapy regimens for the care of HIV-positive individuals with respect to their individual health has clearly been demonstrated. Thus, treatment with combination antiretroviral therapy to prevent pMTCT transmission could potentially be equally as effective compared to dual therapy regimens, and further reductions in pMTCT rates may be possible.

Use of three or more antiretrovirals (combination therapy)

As with treatment for HIV-positive individuals' clinical wellbeing, the real reductions in pMTCT occurred when combination antiretroviral regimens were introduced in the late 1990s and early 2000s. These cART regimens typically consist of three or more antiretrovirals including a protease inhibitor (PI) or non-nucleotide reverse transcriptase inhibitor (NNRTI) plus two or more nucleotide reverse transcriptase inhibitors (NRTIs). Similarly to the single and two antiretroviral agent regimens, use of combination therapy regimens to prevent MTCT include starting a combination ART regimen before the third trimester of pregnancy, intrapartum treatment, postpartum maternal treatment, and some form of neonatal treatment (either short-term ZDV monotherapy, sdNVP or combination treatment).

There is some evidence from RCTs as to the efficacy of combination regimens to prevent mother to child transmission (226;227). For example De Vincenzi and colleagues considered perinatal HIV transmission in the Kesho Bora RCT in Burkina Faso and South Africa (226). The study investigators compared a combination regimen of ZDV+3TC+LPV/r from 34 weeks gestation until the cessation of breastfeeding, to a simplified regimen of ZDV from 34 weeks until delivery, with intrapartum sdNVP and seven days of maternal ZDV+3TC post-partum. All infants received neonatal sdNVP plus seven days of ZDV. There was a transmission rate of 5.4% in the combination therapy arm compared to 9.5% in the simplified regimen arm.

The most compelling evidence of the substantial benefits of combination therapy has been demonstrated in observational studies. A vast number of studies have demonstrated dramatic reductions in mother-to-child transmission with the use of combination therapy (168;178;181;183;202;209;212–214;222;228–254). These studies show very low rates of transmission of around 0% to 6%, usually in settings with none or very little breastfeeding. For example, the European Collaborative study following HIV positive pregnant mothers throughout Europe reported a group of individuals who had received combination therapy (255–257). They found a rate of transmission of 1.2% amongst women receiving ART, with 61% caesarean section births, and very low levels of breastfeeding, compared to a rate of transmission of 11.5% among untreated women. Although higher rates of transmission are observed in settings where breastfeeding occurred and no ART was given during the breastfeeding phase, these rates are none the less a dramatic improvement on those seen in the no ART or monotherapy ART setting and have been observed to be in the region of 1%–9% (258–265).

Finally, Siegfried and colleagues have recently performed a systematic review for the Cochrane Library of data from randomised controlled trials investigating the use of antiretrovirals to reduce the risk of MTCT(266). The authors identified all relevant randomised trials up until the end of 2009, investigating the impact of any regimen aimed at decreasing the risk of MTCT. The authors identified 25 relevant studies (all included here). However, the authors could not perform a meta-analysis as no studies assessed identical drug regimens. They conclude that triple antiretroviral regimens are most effective for pMTCT, and that the risk of adverse events appears low in the short term, although further long-term data are needed. The authors also conclude that short course antiretrovirals are also effective to reduce MTCT, recommending that short-course ZDV during pregnancy, with ZDV+3TC intrapartum and for one week post-partum, also with neonatal sdNVP and neonatal ZDV for seven days post-delivery may be the most effective regimen. They also recommend neonatal sdNVP plus six weeks of neonatal ZDV for those who present late for delivery. However, the authors caution that further research into the emergence of resistance is required.

4.1.2 Importance of antiretrovirals at different stages of transmission

Even the very first studies of antiretrovirals to prevent MTCT combined antiretroviral use in the antepartum, intrapartum, post-partum and neonatal stages of pregnancy and post-pregnancy. The relative efficacy and importance of using ART at each of these points is therefore difficult to disentangle from these studies. It follows that it is difficult to ascertain whether omitting certain antiretroviral doses is likely to be possible. Nonetheless, there exists some research investigating whether omission of certain elements of the pMTCT regimen is possible without detracting from the overall efficacy of the regimen. However, the other elements of the regimen must also be considered carefully in these studies, as the ability to omit certain elements of a pMTCT regimen may depend on the potency of the other components.

There are a few studies investigating whether antiretroviral therapy is required at one, two, or all three stages (i.e. antepartum, intrapartum and immediately postpartum; ART use during the breast-feeding phase, is considered separately in subsection 4.1.3). The PETRA RCT in Southern Africa showed that the lowest transmission rates occurred when ART was included at all three stages (antepartum, intrapartum and immediately post-partum), although the transmission rate was still high at 14.9%, as 74% of mothers breastfed (267). The international perinatal HIV group, a worldwide collaboration, found that there was a transmission rate of 15.6% amongst mothers and infants who received ART during one or two periods, whereas the rate was more than halved to 6.6% amongst those who received ART in all three periods, a result that has been corroborated by others (268–270). However, the perinatal HIV group study was carried out in 1999, and the other studies in the earlier years of treatment, when ART was in general mono or dual therapy, rather than the more effective combination antiretroviral regimens.

There are a few studies investigating whether antiretrovirals during the antenatal phase are necessary. As shown in section 1.4, most studies suggest that the risk of HIV transmission during this stage is lower than at the intrapartum and the post-partum stages. Chung and colleagues performed a RCT directly comparing a sdNVP intrapartum prevention regimen to an antenatal short-course ZDV regimen (271). The risk of HIV transmission was a secondary endpoint in this study. The study was small with 56 participants, but the authors observed a much lower transmission rate (6.8%) for those receiving a regimen of maternal sdNVP with neonatal sdNVP compared to a short-course ZDV regimen from 34 weeks onwards (30.3%). This suggests that, where monotherapy is administered, intrapartum ART plays a larger role in preventing transmission than antenatal ART, in line with the higher risk of transmission observed during the intrapartum phase. However, as we have seen in sub-section 3.1.2, this finding has not been corroborated by all (201;202). Birkhead and colleagues also observed an odds ratio for transmission of 8.44 for those who received no antenatal ART compared to those who received at least some antenatal ART (228).

Intrapartum ART, frequently through the use of sdNVP, is clearly an important tool in preventing MTCT. Birkhead and colleagues observed an odds ratio for transmission of 6.00 for those who received no intrapartum ART compared to those who received some (228). However, in the setting of triple therapy, the benefits of addition of sdNVP during labour and to the neonate is not clear cut. The PACTG316 study showed that the addition of maternal and neonatal sdNVP to standard ART regimens (approximately half of which were triple therapy regimens) did not confer any additional benefit over standard ART regimens alone (272).

Neonatal ART is also an important component of pMTCT regimens. Birkhead and colleagues observed an odds ratio for transmission of 7.73 for those who received no neonatal ART compared to those who received some (228). Furthermore, use of neonatal ART without intrapartum and antepartum ART is a vital strategy for mothers who are diagnosed immediately after delivery (273). Gray and colleagues performed an RCT in women who were diagnosed post-delivery (274). Neonates were randomised to either receive sdNVP, or six weeks of ZDV monotherapy. The majority of babies (82%) were formula fed. The sdNVP option resulted in reduction in infections which was of borderline statistical significance ($p=0.06$), but rates were high in both treatment arms as a result of no maternal or intrapartum prophylaxis treatment at 14.3% for sdNVP and 18.1% for six weeks of neonatal ZDV.

4.1.3 Antiretrovirals during breastfeeding

Although breastfeeding by HIV positive mothers is best avoided, there are situations in which this is not possible. In this setting, there are a number of studies investigating whether receipt of ART during the breast-feeding period up until six months after birth can prevent perinatal transmissions occurring. Antiretroviral therapy can be given either to the mother in order to aim to lower levels of HIV viraemia present in the breast milk, and/or to the infant as prophylaxis.

The SWEN study (275;276) was an RCT comparing infant prophylaxis for 42 days post-birth with NVP in addition to maternal sdNVP during delivery and neonatal sdNVP. At 12 months, the rates of transmission were 8.9% and 10.4% in the two arms respectively, suggesting a modest, non-significant benefit. Thus, this may not be an effective treatment strategy for breastfeeding mothers, although it must be noted that the treatment period of 42 days is likely to be much shorter that the breastfeeding period (typically around six months). Furthermore, a regimen of 6m of neonatal ZDV during breastfeeding was not as effective as formula feeding with one month of neonatal ZDV in an RCT (219), suggesting this regimen is not potent enough. However, other studies have demonstrated low transmission rates when combination antiretroviral treatment during the breastfeeding phase occurs, in some cases comparable to formula feeding (245;277–281). One such example is the BAN RCT, which was conducted in Malawi (278). In this study, all mother received sdNVP with one week of ZDV+3TC, and all neonates received ZDV+3TC for one week. All mothers breastfed their babies for 24–28 weeks. Compared to no antiretrovirals (transmission rate: 2.4%), neonatal NVP throughout the breastfeeding phase led to a transmission rate of 0.1%, and combination therapy for the mothers throughout the breastfeeding phase led to a rate of 1.2%, suggesting that ART for infant or mother was equally effective. The PEPI RCT (279;280) also compared strategies for antiretroviral therapy amongst babies born to HIV positive mothers that were HIV negative at birth. ART was provided for up to 14 weeks of age to the infant, although breastfeeding took place for six months. In the control group which did not receive ART in the first 14 weeks of infant life, neonatal sdNVP with one week of ZDV led to an infection rate of 15.6%. Addition of 14 weeks of NVP led to a significantly lower 10.8% transmission rate; addition of ZDV for 14 weeks also led to a significantly lower transmission rate compared to the control arm of 11.2%.

4.1.4 Surrogate markers of successful treatment – maternal HIV RNA viral load

Similarly to the use of ART as prevention of sexual transmission, it is clear that pregnant women with lower plasma viral loads are at a reduced risk of onwards transmission to their infants (282;283). This includes reduction in viral load as a result of receipt of antiretroviral therapy. Ioannidis and colleagues considered those with viral loads<1000 copies/ml, and found an overall transmission rate of 3.7%. However, they found that those on ART had a transmission rate of 1.0% compared to 9.8% for those not on HAART, suggesting a beneficial effect of ART over and above the viral load level (284). This could perhaps reflect the fact that those on ART had even lower levels below the 1,000 copies/ml cut-off compared to those not on ART. Thomas and colleagues have shown that amongst women on ART, those with a maternal viral load <10,000 copies/ml at study entry, had almost a three-fold reduction in risk of transmission compared to those with a higher viral load (265). Warszawski and colleagues investigated a French cohort of HIV positive pregnant women who were all receiving ART. They demonstrated that, compared to mothers with a viral load<400 copies/ml at delivery, the odds ratio (95% CI) of transmission for those with viral loads of 400–999, 1 000–9 999 and ≥10 000 copies/ml were 1.14 (0.33–3.90), 2.52 (1.25–5.11) and 9.82 (5.24–18.37) respectively (285). Therefore, successful pMTCT is most likely to occur when the maternal viral load is at undetectable levels. Thus, the importance of selecting potent antiretroviral regimens and maintaining high levels of adherence to ensure the best chance of pMTCT success should be a cornerstone of pMTCT strategies.

4.1.5 Limitations to successful treatment

Despite the huge success story of antiretroviral treatment in reducing HIV infections amongst neonates, some potential negative consequences must also be considered. For example, several observational studies have suggested that there is a higher risk of prematurity. Rudin and colleagues investigated this issue in the Swiss Mother and Child HIV Cohort Study and found that the odds ratio (95% CI) for prematurity (<37 weeks) for women receiving mono/dual therapy and cART were 1.8 (0.85–3.6) and 2.5 (95% CI 1.4–4.3) compared with women not receiving ART during pregnancy (286). Similarly, Townsend and colleagues discovered that HAART was associated with a 1.4-fold increased odds of preterm delivery (adjusted odds ratio 1.43, 95% CI 1.10–1.86) and twofold increased odds of severe preterm delivery (<32 weeks; adjusted odds ratio 2.06, 95% CI 1.09–3.88) in data from the United Kingdom and Ireland (287). The authors estimated that for every 100 HIV transmissions prevented through the use of HAART (rather than monotherapy), 63 additional preterm deliveries would occur, including 23 at <32 weeks gestation. The authors stated that interpretation of these ratios is context-dependent and requires additional information about morbidity, mortality and costs associated with the outcomes. The effects appear stronger amongst PI-containing regimens. A RCT conducted by Powis and colleagues in the United States found that women receiving LPV/r+ZDV+3TC had twice the odds of premature delivery compared to women

receiving ABA+3TC+ZDV (288), although this association with PIs was not seen in Townsend's observational analysis.

Antiretroviral use must also be monitored for potential teratogenetic effects. A study by the Women and Infants Transmission Study (WITS) in the USA found a reassuringly low rate of birth defects in a study of 2 353 live births (289). However, it is important to consider the potential side effects of each individual antiretroviral separately to assess whether it is appropriate for use in HIV positive pregnant women. For example, there have been suggestions of an association between efavirenz use in the first 14 days of pregnancy and potential neural tube defects. The Antiretroviral Pregnancy Registry (http://www.apregistry.com/) has been established to monitor this issue. This international collaboration is a voluntary prospective, exposure-registration observational study intended to provide an early signal of any major teratogenetic effect associated with prenatal exposure to antiretrovirals (290).

Any potential long-term effects for HIV-uninfected children who were exposed to ART antenatally and neonatally must also be considered. A recent review of the issue by Heidari and colleagues concluded that there are currently limited data on this issue, particularly as a large number of potential confounding factors are present (291). The authors conclude that further large observational studies are required.

Finally, the future treatment options for the mother after birth should also be considered. A high proportion of women who receive sdNVP develop resistance to the drug, which can hinder future treatment options, particularly if NVP is included as part of the first line treatment regimen (292). Furthermore, infants who become HIV-positive despite receipt of sdNVP can also acquire drug resistance, even in the context of triple ART (293). Nevirapine resistance could also impact on the efficacy of sdNVP as a pMTCT strategy when being used in subsequent pregnancies. However, Martinson and colleagues have shown that pMTCT efficacy rates in second pregnancies that include sdNVP are lower compared to first pregnancies (294;295). Similarly, resistance rates were lower at second pregnancies. This implies that a sdNVP pMTCT regimen can be effective on more than one occasion. These results were corroborated by McConnell and colleagues in Uganda from 1997–2006 (296). Furthermore, steps to reduce the chance of acquiring NVP resistance can be taken. Maternal receipt of seven days of dual NRTIs after receipt of the sdNVP has been shown to reduce the risk of acquiring resistance (210;297). Furthermore, use of HAART as the pMTCT regimen leads to much reduced risks of HIV resistance, with levels comparable to those seen amongst individuals receiving ART for their own health (298).

4.2. Treatment of pregnant HIV-positive women and infants according to treatment guidelines

The use of ART in pregnant women and in newborns has helped to significantly reduce mother-to-child transmission in both resource-rich settings (168;249;250) and resource-limited settings (299;300). Prevention of mother-to-child transmission has advanced substantially over the last two decades in Europe and worldwide, with the advent of universal HIV testing in all pregnant women as well as use of ART during and after pregnancy and in labour. Other non-antiretroviral prevention methods include caesarean sections and refrainment from breastfeeding where possible.

Guidelines for the treatment of HIV-infected pregnant women and infants are prepared separately to those for adults and adolescents by many panels and organisations (42;46;301). Most guidelines focus on two key objectives in pMTCT: management of the health of the pregnant women; and use of antiretroviral prophylaxis to reduce perinatal transmission. Both components are fundamental to benefit the health of the mother but also to reduce the risk of HIV transmission from mother to child during pregnancy, delivery and the breastfeeding period.

The IAS-USA panel does not publish separate recommendations for the treatment of pregnant women and infants, but in the main treatment guidelines (38) suggests that pregnant women should initiate treatment regardless of CD4 count at least by the second trimester and for treatment to be continued after delivery. However, it refers to the EACS and DHHS guidelines for complete recommendations for the use of ART in pregnant women. For this reason, guidelines from EACS, DHHS and WHO are considered (35;42;46).

In all three guidelines, the criteria for treatment-naïve pregnant women to start ART are similar, with all in agreement over starting treatment midway through pregnancy and definitely before delivery where possible. The suggested choice of antiretroviral regimen during the pregnancy is also basically the same as for non-pregnant women, although some drugs are best avoided due to potential harmful effects on the unborn baby, such as efavirenz.

In the case where the pregnant woman does not need ART for her own health, antiretroviral prophylaxis is still required to prevent transmission from mother-to-child. Recommendations on the timing of initiating prophylaxis differ by guideline. However, all are in agreement in suggesting that if a pregnant woman presents late or even during labour, that as much of the full prophylaxis regimen should be administered where possible (Table 2). The World Health Organization suggests starting prophylaxis from as early as 14 weeks into the pregnancy, based on results from observational studies showing that an earlier start to prophylaxis during pregnancy may be more effective in reducing MTCT (23;249). This is an updated recommendation since the previous guidelines to further decrease the possibility of in utero transmission. In contrast, DHHS advise that the benefits of early therapy must be weighed against potential difficulties of ART regimens including adherence, side-effects and risk of developing resistance mutations, and hence suggest for women to consider deferring initiating if needs be. The EACS guidelines additionally recommend for pregnant women to be monitored on a monthly basis and as close as possible to the due date.

The WHO guidelines present two prophylaxis options for pregnant women who do not need ART for themselves; option A and option B (see Table 3 for details). However, it states that there is no preference for either option because current evidence does not suggest that one is better than the other. They suggest that the decision should be made at a national or more local level taking into account all circumstances such as cost and feasibility. Both prophylaxis options A and B take into account the results from many recent trials and cohort studies which showed that the interventions are effective in reducing HIV transmission (as well as infant mortality in some studies).

Although caesarian sections (C-sections) are known to reduce the risk of MTCT (302;303), guidelines differ in their recommendations. The EACS guidelines mention that the benefit of carrying out a caesarean section is uncertain if the woman's viral load is <50 copies/ml at weeks 34 to 36. The United States Department for Health and Human Studies guidelines recommend for the scheduling of C-sections at 38 weeks if viral load >1000 copies/ml near the time of delivery. The global WHO guidelines only deal with use of antiretrovirals (in any case, this intervention is not available in the majority of resource-limited settings). The decision to opt for a C-section at 38 weeks is guided by the viral load at 36–38 weeks, adherence to ART regimen in the European WHO guidelines.

The recommendations for infant prophylaxis differ considerably between guidelines. The EACS guidelines do not cover any aspect of infant prophylaxis or treatment management of the mother postpartum. Both the DHHS and WHO guidelines recommend treatment from birth with zidovudine as a minimum. WHO guidelines note that despite evidence that a shorter infant prophylaxis regimen may be sufficient if the mother has had more than 4 weeks of therapy prior to the birth, a simple, single recommendation is easier to implement and will also compensate for any periods of low adherence to therapy by the mother.

Guidelines on the treatment of pregnant women and infants have also been issued by individual countries. Of those issued in Europe, these include the United Kingdom, France, Spain, Netherlands, Germany, Austria and Italy (160-162;166;301;304).

Table 3. Recommendations for the treatment of HIV pregnant women and their infants, by guidelines

Guidelines	Scenario	When to start	Women		Infants
			Regimen during pregnancy	During labour or delivery or postpartum	
EACS (2011)	Women already on ART becoming pregnant	Continue current ART	Maintain ART but switch potentially teratogenic drugs	IV ZDV (benefit uncertain if viral load <50 copies/ml). During labour, the use of single-dose NVP is advised against.	-
	Women who are ART-naïve and who fulfil the CD4 criteria for starting ART becoming pregnant (i.e. <350 cells/mm^3)	Starting ART at beginning of 2nd trimester is optimal	Same as for non-pregnant women[1] Among PI/r, prefer LPV/r or SQV/r or ATV/r. ZDV should be part of the regimen if possible.		
	Women becoming pregnant while ART-naïve and who do not fulfil the CD4 criteria for starting ART (i.e. ≥350 cells/mm^3)	Start ART at beginning of week 28 of pregnancy (by 12 weeks before delivery at least); start earlier if high viral load or prematurity risk			
	Women whose follow-up starts after week 28 of pregnancy	Start ART immediately			
DHHS (2011)	Women already on ART becoming pregnant	Continue current ART if viral load suppressed	Continue ART but switch drugs that are potentially teratogenic or harmful.	Continue ART (IV ZDV during labour, other antiretrovirals orally) intra- and postpartum.	Start ZDV as soon as possible after birth and administer for 6 weeks
	Women who are ART-naïve and who have indications for ART becoming pregnant	Start as soon as possible, including in 1st trimester	Avoid potentially teratogenic drugs in 1st trimester and drugs with known adverse potential for mother[2]	Continue ART (IV ZDV during labour, other antiretrovirals orally) intra- and postpartum.	Start ZDV as soon as possible after birth and administer for 6 weeks
	Pregnant women who are ART-naïve and who do not require ART for their own health	Delayed initiation until after 1st trimester can be considered[3]	Avoid potentially teratogenic drugs in 1st trimester and drugs with known adverse potential for mother[2]	Continue ART (IV ZDV during labour, other antiretroviral orally) intrapartum. Continue ART postpartum if mother requires it for her own health.	Start ZDV as soon as possible after birth and administer for 6 weeks
	Pregnant women who are ART-experienced but currently not receiving ART	Start as soon as possible, (even in 1st trimester) if mother requires it for her own health. Delayed initiation until after 1st trimester can be considered if treatment is not needed for mother's health.	Avoid potentially teratogenic drugs in 1st trimester and drugs with known adverse potential for mother[2]	Continue ART (IV ZDV during labour, other antiretroviral orally) intrapartum. Continue ART postpartum if mother requires it for her own health.	Start ZDV as soon as possible after birth and administer for 6 weeks
	Women who have received no ART before labour	-	-	IV ZDV during labour	Start ART as soon as possible from birth. ZDV given for 6 weeks combined with 3 doses of NVP (at birth, 48 hours later, 96 hours after second dose)

Guidelines	Scenario	When to start	Women		Infants
			Regimen during pregnancy	During labour or delivery or postpartum	
WHO (2011)	Pregnant women who need ART for their own health	Start ART if CD4 cell count <350 cells/mm^3, irrespective of WHO clinical staging; if WHO clinical stage 3 or 4, irrespective of CD4 cell count. Irrespective of gestational age.	Same as for non-pregnant women* ZDV + 3TC + NVP or ZDV + 3TC + EFV. Alternatively, TDF can be used instead of ZDV and FTC instead of 3TC.	Continue ART throughout labour, delivery, in the case of breastfeeding and afterwards	Daily NVP or twice-daily ZDV from birth (or as soon as possible) until 4 to 6 weeks of age. This applies to all infants, regardless of whether breastfeeding or not.
	Pregnant women who do not need ART for their own health	Start antiretroviral prophylaxis from as early as 14 weeks gestation, or as soon as possible when women present later in pregnancy or in labour or in delivery	Option A: antepartum twice-daily ZDV for the mother, single-dose NVP at the onset of labour, twice-daily ZDV + 3TC during labour, delivery and continued for 7 days postpartum[4]		If breastfed: NVP from birth until 1 week after all exposure to breast milk has ended, or 4 to 6 weeks if they stop breastfeeding before 6 weeks (but at least 1 week after it is stopped). If not breastfed: NVP from birth or single-dose NVP at birth plus twice-daily ZDV from birth until 4 to 6 weeks of age
			Option B: triple therapy starting from as early as 14 weeks of gestation until delivery. Recommended regimen: ZDV + 3TC + (LPV/r or ABC or EFV). Alternative: TDF + 3TC (or FTC) + EFV.	If infant is breastfed, continue ART until 1 week after all exposure to breast milk has ended.	Daily ZDV or NVP to be administered to the infant from birth until 4 to 6 weeks of age, irrespective of whether the infant is breastfed or not.
	Women who have received no ART before labour	-	-	Should receive antiretroviral prophylaxis but then start ART as soon as feasible after birth.	

[1] except for contra-indicated drugs

[2] Avoid use of EFV or other potentially teratogenic drugs in 1st trimester and drugs with known adverse potential for mother (e.g. combination D4T/DDI) throughout pregnancy. When feasible, include ≥1 NRTIs with good placental passage. Use NVP only in mothers with CD4 ≤250 cells/mm^3 (otherwise use NVP only if benefit clearly outweighs risk).

[3] but earlier initiation may be more effective in reducing pMTCT

[4] If the mother receives more than 4 weeks of ZDV during pregnancy, the single-dose NVP and ZDV + 3TC intra- and post-partum can be omitted. If this is the case, they recommend that the ZDV is continued twice daily during labour but to stop at deliver.

4.3 Current practices in Europe – evidence from observational and surveillance studies

Rates of mother-to-child transmission of HIV are now incredibly low in resource-rich countries (249;250;256). This results from the lack of breastfeeding, use and provision of potent ART during and after the period of pregnancy and availability of good quality care and support to both mother and child. Globally, only about half of HIV-infected pregnant women receive ART, the majority of whom will be based in resource-rich settings. Although resource-limited countries have also seen reduced rates of mother-to-child transmission (299;300), there is still room for improvement.

Much of the success in Europe and America in pMTCT results from good access to antenatal and postnatal facilities. In particular, these countries have a wide selection of antiretroviral drugs and individuals are usually prescribed combination therapy which is more effective than single or double drug regimens. Recent data showed that the use of a nevirapine-based regimen intrapartum in mothers, who have had prior perinatal single-dose nevirapine exposure, was not as efficacious as a regimen containing ritonavir-boosted lopinavir (305). The EACS and DHHS guidelines both do not recommend the use of single-dose nevirapine during labour. This is now also supported by the most recent WHO guidelines and in future, may make a significant improvement in a reduction of resistance mutations resulting from monotherapy nevirapine which will in turn reduce rates of virological failure and ultimately early mortality.

The use of antiretroviral prophylaxis in infants is crucial and provides further protection from transmission of HIV from mother to child. Infant prophylaxis is recommended irrespective of whether or not the infant is breastfed. It is especially important in situations where the mother presents late and is not able to have the recommended full course of treatment. Together with effective ART and good provision of maternity services, it has been shown that virtual elimination of new infections via vertical transmission is possible (306). There should be no reason why this would not be the case in Western Europe where healthcare facilities are excellent. Prescribing patterns of ART in HIV-positive pregnant women and their infants have changed over time in Western Europe (307). Data from the European Collaborative Study documented that the use of antenatal ART has increased over time whereas the use of infant prophylaxis has decreased over time, particularly if the mother received antenatal ART. The duration of infant prophylaxis use also declined over time. Note that current guidelines recommend the use of infant prophylaxis (42;46;46;308). The use of ART in women also increased over time in Denmark and New York (228;250) and in addition, the use of ZDV-sparing combination therapy in pregnant women increased between 2000 and 2009 in Europe (247).

The European Collaborative Study also found large differences between treatment regimens and delivery methods in Western Europe and in Ukraine (256). Between 2000 and 2004, only 2% of pregnant women in Ukraine received combination ART whereas this figure was 72% for pregnant women in Western Europe (however, the study notes that in Ukraine, the national policy is for mothers and infants to use short-course ZDV and/or single-dose NVP). During the same period, delivery was by elective caesarean section in 33% and 66% of women in Ukraine and Western Europe respectively. The use of elective Caesarean section in Western Europe has since declined to 51% in 2005–2007 alongside a concomitant increase in vaginal deliveries (309). The same study also found that there were regional differences within Western Europe over the rates of elective caesarean sections (women in Italy and Spain were more likely to deliver by elective caesarean section than those in Belgium, UK and Netherlands). After a policy was implemented in Spain to offer vaginal deliveries in HIV-infected pregnant women who fulfilled certain criteria (such as viral load <1000 copies/ml, on combination ART), an analysis found that of the women encouraged to deliver vaginally, many still opted for elective Caesarean sections (310).

5. Individuals exposed to HIV and treated with post-exposure prophylaxis

5.1 Evidence for the effectiveness of post-exposure prophylaxis

5.1.1 Post-exposure prophylaxis

Post-exposure prophylaxis (PEP) is the use of antiretroviral therapy following exposure to HIV infection to try to prevent the establishment of infection. As discussed in Section 1.3, the risk of HIV transmission is determined by the type of exposure and host and source co-factors. There is a lack of data for both the timing of initiation of post-exposure prophylaxis within which it remains potentially effective, and the length of treatment required. Current guidelines are based on a combination of data from animal models (macaques), mother-to-child transmission (MTCT) studies, and the natural history of very early HIV infection from pathogenesis studies. Data from HIV pathogenesis studies indicate that there is a brief period after exposure to HIV infection when it may be possible to prevent the HIV infection being established through inhibition of viral replication. After successful transmission of HIV across a mucosal barrier, HIV replicates within dendritic cells before spreading through lymphatic vessels to regional lymph nodes where it can be detected within the first 48 hours of exposure, and then proceeding into a systemic infection by 72 hours, when HIV RNA can be detected in the plasma (311–313). This suggests that there is a brief period between exposure to HIV and development of systemic infection during which time HIV seroconversion can be interrupted. This period is thought to last between 48 and 72 hours.

5.1.2 Animal studies

Data supporting the use of post-exposure prophylaxis are based on animal models (Appendix 2 Table A.2.4). For these experiments, different viruses, modes of transmission and size of inoculum were used and these may affect interpretation of results. In one study all macaques (n=4) treated with tenofovir for 28 days initiated at less than 24 hours after intravenous exposure to inoculums of simian immunodeficiency virus (SIV) remained uninfected at the end of treatment. However initiation of treatment at 48 or 72 h post exposure reduced effectiveness in preventing establishment of persistent infection with two out of four Macaques in both the 48 hour and 72h groups becoming persistently infected with SIV. In addition, only half of the macaques (two out of four) treated for ten days, and none of the four treated for three days, were completely protected when treatment was initiated at 24 hours (314). This study suggested that both time of initiation of PEP and duration of treatment are crucial factors for prevention of acute SIV infection in the macaque model. A further animal study demonstrated that anti-viral treatment for three days blocked infection with intravenous and rectally administered SIV in four out of four monkeys if given at one, three or eight hours after exposure. Infection was prevented in one out of two monkeys when initiated at 24 hours after virus inoculation and in monkeys where treatment was initiated at three or six days after virus inoculation, infection was not prevented (315). This study appeared to confirm that administration of PEP conferred no benefit if given later than 72 hours post exposure, and that greatest benefit was seen if given within the first 8 hours. A further animal study attempted to replicate conditions of transmission in humans by inoculating with HIV-2 vaginally and then giving PEP with tenofovir. In this study, when tenofovir PEP was initiated, 12 to 36h following HIV-2 exposure and given for 28 days, HIV-2 infection was prevented. However in those who did not have PEP initiated till 72 hours following exposure, infection was detected at week 16 post exposure, indicating that PEP was effective if given at 12 and 36 hours post intra vaginal exposure to HIV-2, but not if given at 72 hours (316). Data from animal studies therefore suggests that PEP is most efficacious if commenced as soon as possible after exposure.

5.1.3 Human studies

Human studies on occupational exposure to HIV are limited. For ethical reasons no RCTs to determine the efficacy of PEP have been conducted. Evidence for efficacy is based on one case control study which demonstrated a 81% reduction in transmission of HIV through the use of zidovudine (20). The case control study recruited health care workers from France, Italy, the UK and the USA with documented occupational percutaneous exposure to HIV infected blood, cases (n=33) were health care workers who HIV seroconverted and controls (n=665) were those who did not. In this study 27% cases and 36% controls took ZDV, with two thirds of controls and almost all cases taking the first dose of ZDV less than 24 hours after exposure. Two thirds of controls and just under half of cases took ZDV for at least 28 days. On multivariate analyses, cases had significantly lower odds of taking ZDV than controls (OR 0.19, 95% CI 0.06–0.53%), a reduction of 81%. Although this study demonstrated a beneficial effect of taking ZDV as PEP there were limitations to study design which demand a cautious interpretation of results, including the retrospective collection of exposure data and the inclusion of cases from several different countries.

However the fact that ZDV may have preferentially been given to those who had more significant exposures may have led to an underestimate of the efficacy of ZDV as PEP. Other studies have demonstrated that PEP following occupational exposure is not always effective and there are cases of PEP failure, with one study reporting 11 cases of ZDV PEP failure to prevent HIV infection between 1990 and 1997 in HCWs. In these cases, ZDV was begun 30 minutes to eight days (median 1.5 hours) post-exposure, at doses of 600–1,200 mg/day (median 1,000 mg/day) for 8–54 days (median 21 days) indicating that while use of ZDV is protective as PEP, protection is not absolute (317). Transmission of drug resistant virus also occurs despite the use of PEP (318).

There are also no randomised studies assessing the efficacy of PEP for prevention of HIV transmission after sexual exposure. One observational cohort study reported outcomes in 200 high-risk HIV negative MSM in Rio de Janeiro, Brazil, who were given a four-day supply of zidovudine and lamivudine, and instructed to begin PEP immediately after an eligible exposure. In this study PEP was initiated 109 times by 68 participants (34%) after a high risk exposure and not initiated by at least 86 participants (43%) (319). There were eleven HIV seroconversions during follow up, ten among non-PEP users and one in the group that took PEP. This study gave an overall incidence of HIV seroconversion of 2.9 per 100 person-years (95% CI = 1.4, 5.1) but the authors did not give separate results for those who took PEP and those who did not. They reported that 11.8 cases of HIV would have been expected (compared to 11 observed) during the period of study follow up in this high risk group with an expected incidence of HIV of 3.1 per 100person-years compared to 2.9 per 100 person-years observed. The authors conclude that although PEP was safe and did not appear to be associated with increases in reported high-risk behaviour there was limited public health impact of this intervention. As with PEP failure post-occupational exposures, there are reported failures of PEP after non-occupational exposure. In the non-occupational setting, it is difficult to exclude on-going risk exposure which may lead to subsequent infection that is not PEP failure. In an observational cohort of HIV uninfected individuals in San Francisco reporting sexual (95%) or injection drug use, HIV exposure in the 72 hours preceding a 28-day regimen of antiretroviral therapy in a nonrandomised trial, HIV seroconversion was detected in seven subjects (1%; 95% CI: 0.4%, 2%) (320). Three subjects reported no further risk after PEP initiation, but initiated PEP >45 hours after exposure, and four had additional ongoing exposure to HIV after PEP initiation. All seven had completed the 28 days of PEP but three reported significant missed doses. This study suggests that PEP may not be completely effective in preventing HIV infection following non-occupational exposure, but that it remained unclear if seroconversion resulted from failure of PEP or ongoing exposure. Further studies report on the observational cohorts of individuals with non-occupational exposure to HIV and the occurrence of PEP failures. These studies report that PEP is acceptable and reasonably tolerated in the non-occupational setting, but that difficulties remain including establishing the HIV serostatus of the source, ensuring compliance with PEP, that there was a longer time lag until the onset of prophylaxis than with occupational exposures, and that the potential for repeated or unreported exposures may limit efficacy in this setting (321–324).

5.2 Treatment guidelines on post exposure prophylaxis

PEP is now widely used as a strategy to reduce the risk of HIV transmission, following exposure to HIV in both occupational and non-occupational settings (20;29;325). However, limited data on the efficacy of PEP means that recommendations are usually based on direct evidence and expert opinion, rather than being based on hard evidence seen from randomised controlled trials. As mentioned above, trials to assess the efficacy of PEP would be unethical (due to already available evidence in the use of antiretrovirals to reduce the risk of transmission in pMTCT and animal studies) and impractical (required sample sizes are huge due to the small risk of transmission) (326).

The IAS-USA panel does not publish recommendations for the use of PEP so here guidelines compiled by EACS, WHO and two by DHHS are considered (35;43;44;327). The WHO guidelines on the PEP were written together with the International Labour Organisation (ILO) following a joint consultation in 2005. WHO expects and encourages clinics and countries to adapt these guidelines to complement their individual situations. Guidelines on PEP provide recommendations on eligibility of PEP, in what manner PEP should be used, choice of antiretroviral drugs and other important issues such as counselling and follow-up (Table 4). However no two guidelines are identical in their recommendations.

It is generally agreed that PEP should be offered if the source patient is known to be HIV positive or, if their HIV status is unknown but there is a high risk of acquiring HIV infection. If possible, the source patient should be tested for HIV; however initiation of PEP should not await the result. If the source is later found to be HIV-negative, PEP should be discontinued. All guidelines strongly recommend that PEP be initiated as soon as possible after the exposure, if it is considered that the exposure has a strong potential to transmit HIV. Both the DHHS guidelines and WHO guidelines recommend that PEP should be taken within 72 hours. The two guidelines both base this 72 hour time limit on the animal and modelling studies reviewed above. EACS guidelines on the other hand recommend that PEP should be taken within 48 hours. All guidelines recommend the duration of PEP to be 28 days. Although the optimal duration is unknown due to the paucity of data on the use of PEP, animal studies have shown that 28 day courses are more effective than alternative shorter courses. The full PEP regimen should be taken unless there are reasons for stopping, such as the source patient testing HIV negative.

PEP regimens can be dual or triple therapy. Triple therapy is usually only recommended in resource-rich settings if drug resistance is suspected or known, or for situations where there is an increased risk of HIV transmission. Dual therapy regimens are preferred given the benefits of fewer side effects, better drug adherence and being a cheaper option. However, there are no definitive data which show that dual therapy PEP regimens are more efficacious than triple therapy PEP regimens. As a result, guidelines recommend for PEP regimens to be considered on a case-by-case basis, according to the circumstances, including the source's treatment history and resistance test (if this was possible). In particular, efavirenz should never be used in pregnant women or women of childbearing age. Nevirapine is also generally avoided due to its toxicities. Individuals should be made aware of the potential side effects of antiretrovirals that they may experience and of the signs and symptoms of primary HIV infection.

Laboratory monitoring is an important aspect of the PEP course. Although required or desirable tests differ between guidelines, most recommend HIV antibody testing for both the exposed and source patient, complete blood counts, and pregnancy tests in the case of sexual exposure in women of childbearing age. Follow-up HIV testing is also recommended, although the timing of this varies slightly between guidelines. Other recommended procedures and monitoring practices are as follows. EACS guidelines suggest a re-evaluation of PEP indication by an HIV expert within 48 to 72 hours of exposure. A full sexual health screen should also follow exposures of a sexual nature. Both the DHHS and WHO guidelines recommend psychological counselling.

PEP is not always routinely available and even when it is, the uptake may be lower than ideal for several reasons. People exposed to HIV may be unaware of it, or unaware that PEP is available and could potentially reduce the risk of infection. In addition, the short time scale in which PEP should be administered after exposure (as soon as possible but definitely within 48–72 hours) is not feasible in some situations

Consequences of PEP use include side effects, especially if triple therapy regimens are used instead of dual. Side effects are not uncommon when using PEP, so it is important to consider carefully whether an individual should be given it, especially when it is not absolutely clear if the source was HIV-positive. Further, cost-utility analyses have shown that providing PEP to all non-occupational exposures is not cost-effective (328). There are behavioural implications too, with some researchers suggesting that an increase in availability of PEP may lead to increase in risk taking (329). An observational study has seen that within one HIV-negative MSM community, the men who were actually seeking PEP, were those who were at particularly high risk of subsequently acquiring HIV (330).

The appropriate use of PEP is not well-defined. Many European countries have issued their own guidelines (160–162;165;166;331). The important message, which most recommendations are in agreement of, is that PEP is not always effective and PEP policies need to emphasise the importance of risk prevention in the first place in all settings where there is a risk of HIV transmission.

Other national and international guidelines not considered here also recommend the use of PEP in both occupational and non-occupational exposures (332–335). Many suggest that it only be used in circumstances where the risk of HIV transmission is high. Differences in PEP regimens remain due to a lack of certainty about the efficacy of antiretrovirals used in this context, as well as availability and disparities in opinion. There has been an effort to harmonise the use of PEP in Europe after it was found that a major difference between country guidelines was related to choice of regimen (336). A European survey revealed that most national guidelines for PEP were aimed at occupational exposures (337;) which subsequently led to a further pan-European project to propose recommendations for the use of non-occupational PEP (333).

Table 4. Recommendations for post-exposure prophylaxis in both occupation and non-occupational settings, by guidelines

Guidelines	Recommended eligibility criteria for PEP	PEP regimen	Recommended laboratory testing
EACS (2011)	• Within 48 hours of exposure (ideally within 4 hours) • Source patient is HIV+ or has unknown HIV serostatus but presence of HIV risk factors • Exposure with: blood (subcutaneous or intramuscular penetration, percutaneous injury with sharp instrument or needle, or contact > 15 minutes of mucous membrane or non-intact skin), genital secretions (anal sex, vaginal sex or receptive oral sex with ejaculation) or intravenous drug usage (exchange of syringe, needle, preparation material or any other material)	**Recommended:** • TDF + FTC + LPV/r[1] **Alternative:** • ZDV + 3TC + LPV/r[1]	**Exposed person:** • HIV serology • HBV + HCV testing • Pregnancy test (for women) • Transaminases, HCV-PCR and HCV serology (if source is/suspected HCV+) • Syphilis serology (sexual exposure only) **Source person:** • Rapid HIV test (if serostatus unknown) • Rapid HCV test • Resistance testing (if HIV+, on ART and have detectable viral load)
DHHS (2005) Non-occupational exposure[2]	• Within 72 hours of exposure • Source patient is known to be HIV+ or suspected HIV+ • Exposure of: vagina, rectum, eye, mouth or other mucous membrane, intact/nonintact skin, or percutaneous contact • Exposure with: blood, semen, vaginal secretions, rectal secretions, breast milk, urine, nasal secretions, saliva, sweat, tears of any other body fluids	**Recommended:** • EFV + 3TC + (ZDV or TDF) • LPV/r + 3TC + ZDV **Alternative:** • EFV + 3TC + (ABC or DDI or D4T) • ATZ + 3TC + (ZDV or D4T or ABC or DDI) or (TDF + RTV [100mg/day]) • FOS + 3TC + (ZDV or D4T or ABC or TDF or DDI) • FOS/r [low dose] + 3TC + (ZDV or D4T or ABC or TDF or DDI) • IND/r [low dose][3] + 3TC + (ZDV or D4T or ABC or TDF or DDI) • LPV/r + 3TC + (D4T or ABC or TDF or DDI) • NEL/r + 3TC + (ZDV or D4T or ABC or TDF or DDI) • SAQ/r (hgc or sgc)[4] + 3TC + (ZDV or D4T or ABC or TDF or DDI) • ABC + 3TC + ZDV (only when NNRTI or PI-based regimen cannot be used) FTC can be used instead of 3TC	**Exposed person:** • HIV antibody testing • Complete blood count with differential • Serum liver enzymes • Blood urea nitrogen/creatinine • HBV + HCV testing • STI screen • Pregnancy test (for women) **Source person:** • HIV antibody test (or rapid HIV test) • HBV + HCV testing • STI screen • HIV viral load and CD4 measurement • HIV resistance testing

Guidelines	Recommended eligibility criteria for PEP	PEP regimen	Recommended laboratory testing
DHHS (2005) Occupational exposure	• Within 24-36 hours of exposure (preferably within hours) • Source patient is HIV+ or has unknown HIV status but has HIV risk factors or if unknown source but in settings in which exposure to HIV+ persons is likely • Exposure of: percutaneous injury, contact of mucous membrane or non-intact skin • Exposure with: blood, tissue, other body fluids that are potentially infectious (blood and visibly bloody body fluids, semen and vaginal secretions), other potentially infectious fluids (cerebrospinal, synovial, pleural, peritoneal, pericardial and amniotic) • Or any direct contact to concentrated virus in a research laboratory or production facility requires clinical evaluation.	**Recommended:** • ZDV + (3TC or FTC) • D4T + (3TC or FTC) • TDF + (3TC or FTC) • Third agent: LPV/r Alternative third agents: ATZ, FOS, IDV/r, SQV/r and NFV Triple therapy regimens are warranted only when there is an increased risk of HIV transmission (i.e severe or large volume of exposure)	**Exposed person:** • HIV antibody testing • Drug toxicity testing • Complete blood count • Renal and hepatic function tests **Source person:** • Rapid HIV test (if serostatus unknown)
WHO (2011)	• Within 72 hours of exposure (preferably within few hours) • Exposed individual is not known to be HIV-positive • Source is HIV-positive or has unknown serostatus. • (Occupational exposure) Exposure with: blood, body, tissues, visibly blood-stained fluid, concentrated virus, cerebrospinal/synovial/pleural/peritoneal/pericardial/amniotic fluid. Exposure penetrated the skin with spontaneous bleeding/deep puncture/splash of significant amount of fluid to mucous membrane/prolonged contact of an at risk substance with non-intact skin and if the skin was penetrated, exposure was from a recently used hollow bore needle/other sharp object visibly contaminated with blood. • (Sexual exposure): Defined risk of exposure: receptive vaginal or anal intercourse without a condom or with a condom that broke or slipped and contact between the perpetrator's blood or ejaculate and mucous membrane or non-intact skin during the assault.	**Recommended:** • ZDV + 3TC • ZDV + 3TC + LPV/r **Alternative:** • (TDF or D4T) + 3TC • (ZDV or TDF or D4T) + 3TC + (ATZ/r or SAQ/r or FOS/r) FTC can be used instead of 3TC In general countries are advised to use the same antiretroviral drugs for PEP as what is being used as their NRTI backbone in first line therapy. Children to be given appropriate formulations and doses for their weight.	**Exposed person:** • HIV tests • HBV + HCV testing • HBV PEP and vaccination • Pregnancy test or emergency contraception (for women of childbearing age) • Medication to manage side effects • Haemoglobin (for ZDV-containing PEP regimens) **Source person:** • Rapid HIV test (if feasible)

[1] *LPV/r tablets 400/100 mg bid*

[2] *Also includes considerations for vulnerable populations (i.e. pregnant women and women of childbearing potential, children, sexual assault survivors, inmates and IDUs)*

[3] *Use of ritonavir with indivinavir might increase risk for renal adverse events*

[4] *hgc: hard-gel saquinavir capsule, sgc: soft-gel saquinavir capsule.*

5.3 Current practices of PEP in Europe – evidence from observational and surveillance studies

As mentioned above in brief, historically the uptake of PEP has been quite low. However, recent studies have shown that the awareness, uptake and quality of PEP have considerably improved. In one Swiss hospital, the number of PEP requests over ten years increased by 850% (338). In addition, one successful protocol is in operation in Amsterdam, where PEP is available at any time of the day at any hospital and individuals who are prescribed PEP are subsequently referred for follow-up treatment and care (339). Another study in Amsterdam which analysed the use of PEP in MSM between 2000 and 2007, documented that the vast majority (91%) of men completed the full 28-day course of PEP (321). With increased access to PEP, cost-effectiveness has become an important issue and debates have been on-going (340;;341;). Other recent study topics include use of CCR5 antagonists as part of a PEP regimen (342), as well as strategies to evaluate the tolerability of combination therapy regimens (343;344)

6. Other considerations

6.1 Pre-exposure prophylaxis (PrEP)

This review concentrates on ART being given to people with HIV to prevent transmission (or in the case of PEP to prevent HIV becoming established). Pre-exposure prophylaxis (PrEP), i.e. the use of oral antiretrovirals (containing tenofovir and usually also emtricitabine) amongst HIV negative individuals at high risk of HIV acquisition, is an additional ART-based potential HIV prevention strategy so merits some mention. Although a formal literature search for PrEP has not been performed, nonetheless the major studies investigating the issue (345-349), all of which are RCTs, are summarised in Table 5. The study which has had perhaps the greatest impact so far is iPrEX (345), in which 2 499 MSM and transgendered women in Brazil, Ecuador, Peru, South Africa, Thailand and the United States were assigned to either tenofovir and emtricitabine or placebo. There was a 44% reduction in HIV incidence in those receiving PrEP compared to placebo, and a 73% reduction in those with high levels of adherence. This study has led to a change in guidance on pre-exposure prophylaxis (PrEP) for high risk MSM in the United States (350). Promising results were also seen in the PARTNERS PrEP study (347;351), which enrolled 4 758 hetero-sexual serodiscordant couples in Uganda and Kenya, with HIV negative participants allocated to receive either tenofovir and emtricitabine, tenofovir alone, or placebo. In July 2011, interim results were released that showed a reduction in HIV incidence in both of the active treatment arms: 73% reduction among those on two drugs, and 62% reduction in those on one drug. Participants receiving placebo were reassigned to either tenofovir and emtricitabine or tenofovir alone, and the final results of this study are expected in 2013. In the Botswana TDF2 study (348), which allocated 1 200 men and women to receive either tenofovir and emtricitabine or placebo, a reduction in HIV incidence of 63% was observed in those on the active treatment, rising to 78% in those known to have a supply of drugs.

Despite some encouraging results, a number of questions remain unanswered in this area. Firstly, the efficacy of these strategies amongst women is not yet established. The Partners PrEP study suggests that PrEP is protective for both men and women engaging in heterosexual vaginal sex (351). However, the Fem-PrEP study (346), comparing tenofovir and emtricitabine with placebo in nearly 2 000 women in Kenya, South Africa and Tanzania, was stopped for futility in April 2011, although another large RCT of women, the VOICE trial, is still ongoing. The VOICE trial has recruited over 5 000 women in Uganda, South Africa and Zimbabwe (349). Participants were randomised to one of five treatments: oral tenofovir, oral tenofovir and emtricitabine, oral placebo, tenofovir gel, or placebo gel. In September 2011, the oral tenofovir arm was stopped for futility, but results for the remaining arms are expected by early 2013.

A further issue that requires further investigation is the cost-effectiveness of PrEP in the long term, which is likely to depend on high levels of adherence (352). Furthermore, the potential side effects for individuals receiving antiretrovirals who are not HIV positive and are not in need of ART for their own health, and the potential risk of development of resistant HIV if individuals do seroconvert, must also be considered. PrEP availability has implications for timely PEP access and use, because if PrEP use is introduced then even if there is poor adherence as prophylaxis this could effectively lead to more rapid PEP access, if people have drugs already available to them.

Table 5 Major studies of oral pre-exposure prophylaxis

Study Name	Population	Intervention	Efficacy (reduction in incidence)
iPrEX (345)	2 499 18–67 year-old MSM or transgendered women in Brazil, Ecuador, Peru, South Africa, Thailand and USA	Oral once-daily dose of FTC/TDF or placebo	44% (15–63; p=0.005) 73% (41–88; p<0.0001) when pill use >90%
Fem-PrEP (346)	1 950 sexually active 18–35 year old women in Kenya, South Africa and Tanzania	Oral once-daily dose FTC/TDF or placebo	Stopped for futility (Apr 2011)
PARTNERS PrEP (347;351)	4 758 HIV serodiscordant couples in Uganda and Kenya	Oral once-daily dose FTC/TDF, TDF or placebo	TDF: 62% (34–78; p=0.0003) FTC/TDF: 73% (49-85; p<0.0001)
Botswana TDF2 (348)	1 200 sexually active 18–39, healthy men and women in Botswana	Once oral-daily dose FTC/TDF or placebo	63% (21-84; p=0.0133) 78% (41-94; p=0.0053) among participants known to have a supply of study drugs
VOICE (MTN003) (349)	5 029 women in Uganda, South Africa and Zimbabwe	5 arms (daily dose): (1) TDF pill. (2) TDF/FTC pill, (3) placebo pill; (4) TDF gel; (5) placebo gel	Stopped for futility (oral TDF arm; Sep 2011)

6.2 Combination with non-antiretroviral interventions

6.2.1 Sexual transmission – use of condoms, circumcision and assisted reproduction

There is some evidence that personal perception of the risk of onwards transmission in people with HIV may impact on the consistency of condom use. A meta-analytic review considering prevalence of unprotected sex found that in people with HIV, there was no difference between those on and off ART, or between those with undetectable and detectable viral loads (144). However, the same review found that people with or without HIV were more likely to have unprotected sex if they believed that the risk of onwards transmission of HIV was lower in HIV positive persons who were on ART or who had an undetectable viral load.

A model has been used to estimate HIV incidence rates in serodiscordant couples, where the HIV positive partner is on ART and has an undetectable viral load (65). Compared to a scenario where condoms are used for 80% of sex acts, with efficacy of 95% per act, incidence of infection was estimated to be four times higher if condoms were not used at all. Using the same model, it was estimated that even if such serodiscordant couples did not use condoms at all, they had a lower infection risk than serodiscordant couples where the HIV positive partner was untreated, even if condoms were used for 100% of acts (353). These results suggest that the use of ART as prevention may be more effective at reducing the risk of transmission than condoms alone, but a greater reduction in incidence can be attained with a combination of effective ART and consistent use of condoms. However, as a belief in a reduced risk of infection through ART use could result in decreased levels of condom use, this may be difficult to achieve. The two strategies for prevention of transmission, condoms or ART, have not been directly compared in an RCT. A caveat to note related to this is that 96% of couples where the HIV positive person was on ART reported consistent condom use in the HPTN 052 trial, so the absolute risk of transmission on the early ART arm (1 in 893) does not represent the risk through condom-less sex when the HIV positive person is on ART; it represents the risk in the context of 96% consistent condom use plus ART. The risk of transmission through condom-less vaginal and anal sex for a person who has suppressed plasma viral load remains uncertain. Furthermore, another advantage of using condoms to prevent HIV transmission is that they also prevent other STIs. As well as the clinical benefit of preventing an STI, this also confers benefit with respect to HIV transmission, as presence of certain STIs may increase risk of HIV acquisition.

Male circumcision has been found to reduce the risk of HIV infection in men, and is now in use as a prevention intervention across sub-Saharan Africa (14;15;354;355). The individual impact of male circumcision on the infection risk in women is uncertain, although, at the population level, a likely consequence of reduced HIV prevalence in circumcised men in the long term is that women will be less at risk of exposure to HIV. Currently, there is no strong evidence that male circumcision has an effect on HIV incidence in MSM (356). The possible impact of male circumcision combined with the use of ART as prevention is unknown, and the settings in which male circumcision is targeted as an intervention makes the availability of such data unlikely.

If an HIV positive man and HIV negative woman wish to conceive, then assisted reproduction with sperm washing is an established and effective technique that avoids HIV transmission (357). However, there has been some debate in recent years on whether unprotected sex restricted to fertile days is an acceptable alternative to assisted reproduction where the partner with HIV is on ART and has an undetectable viral load (358).

6.2.2 Mother-to-child transmission – caesarean sections and formula feeding

A European trial during the period 1993 to 1998 randomised 436 pregnant women with HIV to either elective caesarean section or vaginal delivery, and found that elective caesarean section reduced the risk of MTCT by 80% (303). Current European guidelines on the treatment of pregnant women with HIV recommend delivery by elective caesarean section, to be performed prior to the onset of labour and rupture of membranes, in women with high viral load (Section 4.3). However, in women successfully treated with ART who have a low viral load, it remains uncertain whether delivery by elective caesarean confers any additional reduction in the risk of MTCT than planned vaginal delivery. An observational study assessing the impact of interventions to reduce MTCT in the United Kingdom and Ireland during the period 2000 to 2006 found that, for women on ART regimens recommended in the national guidelines, the transmission rate was 0.7% both in those who had an elective caesarean and in those who had a planned vaginal delivery (249). As the risk of MTCT is very low in women on currently recommended ART regimens, any study to determine whether the risk could be further reduced by the choice of delivery method would likely require a large sample size (24).

6.2.3 Transmission in people who inject drugs – needle exchanges

There is evidence that opioid substitution therapy reduces transmission of HIV in people who inject drugs (359), and reductions in HIV transmission have also been achieved through needle exchange programs (138). Combining opioid substitution treatment with needle exchange programs has been shown to be particularly effective (360). HIV-infected injecting drug users who are receiving opioid substitution treatment have been found to have increased levels of adherence to ART (361;362). As studies in people who inject drugs focus on infection rates in those who are not infected with HIV, onwards transmission rates in HIV positive people infected through injecting drugs are unknown. It is plausible that onwards transmission risk in this population would be reduced if on ART and virally suppressed, but as yet there is no evidence for this.

6.3 Implications of earlier treatment for the HIV positive individual

Earlier treatment may put the HIV positive individual at risk of experiencing side effects, and of developing resistance (363). As treatment at this time is primarily for the prevention of transmission, the severity of side effects that are tolerated may be lower than in a patient being treated for their own health. Sub-optimal adherence, possibly related to side effects experienced by the patient, may lead to the development of resistance and of virologic failure. This would result in an increased risk of HIV transmission, potentially of a resistant strain. The resistance may also result in the loss of future drug options for the patient. As reviewed above, ongoing trials (START) will help to tell whether ART initiation in people with CD4 counts > 500 cells/mm^3 is of net benefit to the individual's health. For treatment as prevention to be viable in the future, there is a continuing need for antiretrovirals with improved toxicity profiles, and for adherence support.

6.4 Earlier treatment – the need for earlier diagnosis

It is clear that the use of treatment as prevention of onwards transmission depends on early diagnosis of people with HIV so that they are in the position to start ART, predominantly for their own health. Data from ECDC suggest that the proportion of late presenters (CD4 count <350 cells/mm^3 at presentation) is high at 51%. Therefore, extra efforts are needed to ensure higher diagnosis rates. One example of a success story is the introduction of opt-out testing in several European countries for all pregnant women. In this setting, uptake has been high at over 90%, and has led to a larger proportion of HIV-positive women being diagnosed at CD4 counts >350 cells/mm^3. The HIV in Europe initiative aims to share knowledge and improve the knowledge base around the important issues of earlier testing and care (http://www.hiveurope.eu/). Furthermore, ECDC have launched guidance on HIV testing in 2010 to support Member States in increasing the uptake and effectiveness of HIV testing in Europe.[2]

[2] Available at: http://ecdc.europa.eu/en/publications/Publications/Forms/ECDC_DispForm.aspx?ID=588

7. Key messages and future research needs

Antiretroviral treatment has well documented benefits in reducing transmission of HIV and has had a major population level impact on HIV acquisition in children from HIV positive mothers. Wider ART use is likely to have benefits in reducing ART transmission through other routes, but this policy cannot be employed for ART initiation in all people with diagnosed HIV without understanding whether there is a benefit for personal health. However, there is a strong rationale for a new policy whereby all people with high CD4 count - such that they are not currently considered to require ART for their own health - have this potential benefit of ART explained to them, along with the substantial caveats, and ART offered for this indication if the individual so wishes.

In the contexts of heterosexual (vaginal) transmission and transmission from mother to child, there is good evidence that for an HIV-positive person, being on ART with an undetectable plasma viral load results in markedly reduced chances of virus transmission. While this strongly suggests that there may well be similar reductions in infectivity through other routes, direct evidence for an effect of ART in reducing infectivity in the context of anal sex and sharing injection equipment is lacking. Given important biologic differences in transmission mechanisms for these transmission routes, the existing evidence based on vaginal and mother-to-child transmission cannot be extrapolated confidently. While immediate policy may need to be developed based on this assumption, it is important that research in these areas is prioritised.

For prevention of mother-to child-transmission, the principle of using ART for the mother is established policy throughout the world, even if the exact means of using ART remains the subject of active research and discussion. Here, the main task for the European context is to ensure the widespread implementation of existing best practice.

In contrast, with regard to use of ART to prevent sexual transmission between adults or through sharing injecting equipment, policy implications of recent and on-going research still remain to be considered. There are several considerations to bear in mind when establishing appropriate policy as a result of current knowledge.

Firstly, ART is designed to treat the HIV positive person, and if we wish to derive benefit from its properties of reducing infectivity, we need to first consider the person who is to be treated. While for a mother it has been well accepted that avoiding infection to her child essentially over-rides possible negative consequences of ART on her own health, this cannot be taken for granted in the context of avoiding transmission to sexual partners and needle-sharers. The on-going START trial will help to establish whether any risks of very early ART initiation (i.e. starting when the CD4 count is above 500 cells/mm^3) will be outweighed by the benefits to the individual, in terms of reduction in risk of serious clinical disease (151). If this is found to be the case then it makes sense clinically as well as from a public health perspective to recommend early ART initiation in all HIV diagnosed. If, on the other hand there is found to be net harm of this strategy, then a policy of earlier ART initiation in order to reduce transmission risk may be inappropriate in most circumstances. A result whereby risks and benefits appear to balance will leave the decision to initiate ART to be based on considerations of whether the individual wishes to use ART in order to reduce transmission risk. Thus, to a large extent, policy in this area will be driven by the results of the START trial, together with clinical considerations and individual choice.

An important distinction is between use of earlier ART for HIV-positive individuals to prevent transmission to a specific sexual partner, and a widespread change in ART initiation policy for all HIV diagnosed as part of a prevention strategy. In the former case, for heterosexual couples there is good evidence from the HPTN 052 trial and observational studies that use of ART reduces the transmission risk markedly. Some HIV-positive individuals with a CD4 count above the ART initiation threshold may have a strong desire to start ART in order to reduce the chance of transmission to their partner. Individuals may therefore wish to take ART despite the fact that the risk or benefits to their personal health are not currently established. There are strong arguments for introduction of a policy whereby all HIV diagnosed with a CD4 count not currently considered to require ART for their own health are informed of this potential benefit of starting ART, although it must also be explained that ART may not necessarily benefit their health, and could even be harmful. In such circumstances the individual will need to also consider, amongst other things, what would happen if the relationship with the current partner ends, as interruption of ART has a harmful effect and is not recommended (364). Further, if ART initiation were to result in a reduction or cessation of condom use, it is not clear whether the transmission risk would be reduced or increased as a result, as the two strategies for prevention have not been directly compared in an RCT. The absolute risk of transmission In the HPTN 052 trial on the early ART arm (1 in 893) does not represent the risk through condom-less sex when the HIV positive person is on ART; rather it represents the risk in the context of 96% consistent condom use plus ART. The risk of transmission through condom-less vaginal and anal sex for a person who has suppressed plasma viral load remains uncertain and represents another knowledge gap. The PARTNER study, which is taking place in Europe amongst serodiscordant couples, is addressing this question (365).

The greatest uncertainty falls when considering a widespread policy of ART initiation for all HIV diagnosed, irrespective of CD4 count, explicitly as part of a prevention strategy. This is an area in which there are no trials, although community randomised trials in which some communities are allocated to higher testing and immediate ART initiation and others to standard of care, with HIV incidence as outcome, are in development in sub-Saharan Africa. It does not seem likely that such trials will be feasible in Europe. Ecologic analyses and modelling studies have been extensively employed to try to understand what the impact of such a policy would be. The ecologic studies are limited by the fact that new infections are not observed and so diagnosis is used as a proxy for infection. To be of real use, these types of ecologic analyses are best done within the framework of an underlying transmission model that allows consideration of the undiagnosed population. The ecological studies that have been published have tended to suggest appreciable benefits of population adult ART for prevention.

Modelling studies have varied in their conclusions, although most have suggested potential appreciable beneficial effects on HIV incidence of a policy of earlier ART initiation. Given their importance for policy, there is a need for some co-ordination in modelling efforts so discrepancies between models can be better understood. There have been moves towards this in a modelling consortium established by the Bill and Melinda Gates Foundation. A common theme with modelling work has been the fact that sexual risk behaviour change (change in condom use and numbers of partners) has a strong influence on HIV incidence and that any tendency for this to increase could outweigh benefits of ART for prevention. Models have differed substantially in the level of detail incorporated. Very few have thus far captured all the various processes that we have a reasonable understanding of due to extensive data sets. (e.g. sexual risk behaviour, testing, primary infection, viral load, CD4 count, use of ART, adherence, resistance, drug failure, drug interruption, loss to follow-up, occurrence of AIDS, non-AIDS death, etc). This is not surprising as this requires a complex and highly parameterised model which has the disadvantage over simpler models in that it is difficult to analyse and interpret. However, such models are being developed and may play a useful role in providing more quantitative predictions of the effect on HIV incidence of greater testing and earlier ART initiation in a given setting. Such models also have the advantage of carrying a level of detail which makes them suitable to be used as a basis for detailed economic analyses. There is an important connection here with the above discussion on the individual benefits of early ART. If the START trial indicates that there is a beneficial effect of early ART on clinical events, the absolute risk of such events is likely to mean that early ART initiation may nevertheless not be cost-effective if only considered in terms of the treated person. It may well be that demonstration of population benefits in terms of reduced incidence of HIV are required in order for earlier ART initiation to be paid for.

It is inherently very difficult to study whether use of ART within hours of infection (post-exposure prophylaxis - PEP) makes a substantial difference in preventing acquisition of HIV. The good rationale and some low level evidence from animal and observational studies suggest that it may well do so. It is unlikely that further definitive research studies addressing this question will be forthcoming, so policy in this area will continue to be made based on limited evidence. Post-exposure pfophylaxis use varies across countries and between groups and it is unclear to what extent it is used by those who are truly at increased risk. In some settings (e.g. in some clinics in London) it is widely accessed by some MSM. In men who regularly access PEP, the possibility of prescribing pre-exposure prophylaxis (PrEP) clearly arises as a possibility. Potential for use of PrEP in HIV uninfected people to prevent acquisition of HIV has been the subject of several trials in heterosexual couples and one in MSM but was the focus for this review. There is diversity of opinion with respect to the policy on recommending (and paying for) PrEP and, if so, with what indication. New studies are planned in Europe of the effectiveness of PrEP (e.g. the PROUD study in the UK and an ANRS trial in France and Canada).

The future research needs in the area of use of ART for prevention of transmission should focus on obtaining the evidence on the efficacy of ART in reducing onward sexual transmission through anal sex and sharing injecting equipment. Secondly, there is a need to understand the impact of the early ART strategy on condom use. There remains the potential of attenuated or even negative net effects of new prevention interventions due to their introduction leading to decreased condom use (although data thus far do not suggest this as has been the issue with male circumcision). In addition, if ART is to be explicitly used for prevention of sexual transmission, a full understanding needs be developed on the transmission rate in successfully virally suppressed conditions where condoms are not being used (366). Next, it is important that reliable data become available on the risks and benefits for HIV diagnosed with CD4 counts higher than 350 /mm^3 of initiating ART. The on-going START trial, which involves many clinical sites in Europe and its world-wide network, should provide substantive evidence on this issue. Perhaps the best evidence for the adoption of a policy of use of early ART for all HIV diagnosed would come from community (cluster) randomised trials where there is randomisation of communities as to whether the policy is introduced or not, with HIV incidence as outcome. As mentioned above, trials with such a design are planned for sub-Saharan Africa. It is unclear if such studies would ever be feasible in Europe. A further need is for development of increasingly detailed and well-calibrated models which reflect the many complexities relating to HIV acquisition risk, progression of infection and the effect of ART, including effects of adherence and resistance. Such models will be used to inform us of the potential effectiveness and cost-effectiveness of a policy of ART in all people diagnosed with HIV.

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Appendix 1 Search terms

A1.1 Use of HIV treatment as prevention

A complete review of the literature using Web of Knowledge and all available databases has been conducted using the following search criteria:

Topic = (HIV* and antiretroviral* and (prevent* or transmit*)

NOT Topic=('child*' or 'mother*' or 'vertical' or 'prophylaxis' or 'pregnan*' or 'herpes' or 'breast*' or 'tuberculosis') .

AND Timespan = 2006–2011.

AND Languages=(ENGLISH)

[excluding] Document type = (CASE REPORT OR BIOGRAPHY OR EDITORIAL OR BOOK OR CORRECTION OR REPORT OR REVIEW OR PATENT OR MEETING OR NEWS OR BIBLIOGRAPHY OR LETTER)

AND subject areas =(infectious diseases, virology, social issues, behavioural sciences, social sciences other topic, mathematics, life sciences, biomedicine other topics, biomedical social sciences, mathematical computational biology)

Date of search: 5th September 2011

Results: 2 105

Included for full text review: 146

Extra references identified in the grey literature: 20

Total papers included in formal literature review: 32

A1.2 Mother-to-child transmission

A complete review of the literature using Web of Knowledge and all available databases has been conducted using the following search criteria:

Topic=((prevent* OR transmission) AND ("mother to child" OR "mother-to-child" OR vertical OR paediatric)) AND Topic=(HIV* AND antiretroviral*)

[excluding] Document Type=(NEWS OR BIOGRAPHY OR EDITORIAL OR CORRECTION OR REVIEW OR CASE REPORT OR BOOK) AND Languages=(ENGLISH)

Timespan=All Years.

Search language=Auto Lemmatization=On

Date of search: 24th August 2011

Identified by Web of Knowledge: 1 894, reduced to 1 808 after removal of duplicates

Included for full text review: 216

Studies identified through grey literature: 9

Total papers included in formal literature review: 113

A1.3 Post Exposure Prophylaxis (PEP)

A complete review of the literature using Web of Knowledge and all available databases has been conducted using the following search criteria:

Topic=("HIV" or "HIV Infections"* "transmission" and "post exposure prophylaxis")

Timespan=All Years.

Search language=Auto Lemmatization=On

Date of search: 15th October 2011

Identified by Web of Knowledge: 512

Selected for full text review: 52

Identified by grey literature: 4

Included in literature review: 8

Appendix 2. Summary tables of literature search

A2.1 Treatment as prevention

Author, Year of Publication and Journal	Aim	Study Design	Study Population	Results/Conclusions
Cohen (82), 2011, New England Journal of Medicine	Compare effect of early vs delayed ART on transmission Early = ART at diagnosis Delayed = ART after 2 consecutive CD4 counts ≤250	RCT – HPTN 052 2005–2010	1 763 Serodiscordant couples 9 countries: Botswana, Kenya, Malawi, South Africa, Zimbabwe, Brazil, India, Thailand, and US	A total of 39 HIV-1 transmission events were observed, of which 28 were virologically linked (incidence rate, 1.2 per 100 person-years;95% CI, 0.9 to 1.7) Of 28 linked transmissions, 1 was in the early therapy group A hazard ratio in the early-therapy group of 0.11 (95% CI, 0.04 to 0.32; P<0.001) Early ART had clinical benefit for both HIV-1–infected persons and their uninfected sexual partners Results support the use of ART as a part of a public health strategy to reduce the spread of HIV-1 infection
Das (76), 2010, PLoS One	To assess relationships between mean and total CVL and the primary outcome: annual numbers of newly diagnosed HIV cases	Ecological/cohort study 2004–2008	All reported HIV-positive individuals in San Francisco (12 512)	Decreases in annual measures of mean and total CVL in San Francisco were significantly associated with temporal decreases in the number of new HIV diagnoses
Dukers (79), 2002, AIDS	To investigate whether dramatic increases in sexually transmitted diseases and sexual risk behaviour among homosexual men in Amsterdam indicate a resurgence of the HIV epidemic	Ecological study/cohort study	Data were used only from male participants in the 1991–2001 HIV prevalence surveys, who identified themselves as being homosexual (approximately 15% of all participants) and who consented to blood testing for the presence of HIV (96.3% of all homosexual participants). In total, 3 090 homosexual men were included in the study	The incidence of HIV is increasing among homosexual attendees of an Amsterdam STD clinic. Together with the rising rates of syphilis, gonorrhoea, and related risk behaviour among homosexual men, this finding calls for preventative action, especially for those who have recently been infected

Author, Year of Publication and Journal	Aim	Study Design	Study Population	Results/Conclusions
Fang (77), 2004, Journal of infectious diseases	To estimate the HIV transmission probability ratio in the Taiwanese population, before and after the implementation of the free-HAART policy.	Ecological/cohort study	4 390 HIV positive individuals included in Taiwan's HIV surveillance data	Providing free HAART to all HIV-infected citizens was associated with a 53% decrease in the HIV transmission rate and contributed to the control of the HIV epidemic in Taiwan The widespread use of HAART can be an effective measure to control HIV epidemics in countries with a low prevalence To differentiate the effect of HAART from that of behavioural changes, the incidence of syphilis in the general population and among HIV-positive patients was also analyzed, for comparison There was no statistically significant change in the incidence of syphilis, in the general population or among HIV-positive patients, during the same period
Fisher (81), 2007, AIDS	To investigate whether combining clinical data with the serological testing algorithm for recent HIV seroconversion (STARHS) reliably identifies otherwise unrecognized recent infections and observe their trends	Ecological study/cohort study	The data for this study came from individuals who presented to the HIV treatment centre at Brighton and Sussex University Hospitals over a 10-year period between January 1996 and December 2005	Adjunctive use of STARHS with clinical data identified a high and increasing proportion of new HIV diagnoses as recent infections, confirming significant ongoing transmission Over the study period we observed an increasing proportion of individuals newly diagnosed with HIV to have been recently infected, supporting the assertion that transmission has increased over recent years. This trend is particularly marked amongst MSM. This demonstrates that ongoing HIV transmission is occurring alongside changing sexual behaviour, despite the awareness of effective HIV prevention strategies and the potential for HAART to reduce the transmission of HIV, and may be an indirect result of the beneficial effects of HAART on HIV-related morbidity and mortality
Grulich (80), 2008, Sexual health	To describe trends in HIV notifications and in other measures of HIV incidence in homosexual men in developed countries	Literature review of ecological studies	Surveillance data from Europe, Canada, USA, Australia and New Zealand were included in this study	In conclusion, there is a near-universal increase in notification of HIV diagnoses in homosexual men in the developed world. Determining the degree and extent of the increases in incidence in homosexual men is an issue of crucial importance in developing appropriate public health responses in the evolving HIV epidemic

Author, Year of Publication and Journal	Aim	Study Design	Study Population	Results/Conclusions
Montaner (78), 2010, Lancet	To estimate the association between the outcome (new HIV positive tests per 100 population) and the covariates (viral load, year and number of individuals on HAART)	Ecological/cohort study 1996–2009	All people on HAART or accessing viral load testing in the province of British Columbia, Canada	The number of individuals actively receiving HAART in British Columbia increased from 837 to 5 413 (547%; p=0.002), and the number new HIV diagnoses fell from 702 to 338 cases per year (–52%; p=0.001) The overall correlation between number of individuals on HAART and number of new HIV diagnoses per year was -0.89 (p<0.0001)
Abbas (83), 2006, JAIDS	To estimate the potential impact of antiretroviral therapy on the heterosexual spread of HIV-1 infection and AIDS mortality in resource-limited settings	Mathematical model	The model parameter set was chosen to mimic an epidemic in a sub-Saharan African nation reaching an endemic prevalence of 40% in the sexually active population 15 to 49 years of age	Implementing antiretroviral therapy at 5% HIV-1 prevalence and administering it to 100% of AIDS cases are predicted to decrease new HIV-1 infections and cumulative deaths from AIDS after 10 years by 11.2% (inter-quartile range [IQR]: 1.8%–21.4%) and 33.4% (IQR: 26%–42.8%), respectively Later implementation of therapy at endemic equilibrium (40% prevalence) is predicted to be less effective, decreasing new HIV-1 infections and cumulative deaths from AIDS by 10.5% (IQR: 2.6%–19.3%) and 27.6% (IQR: 20.8%–36.8%), respectively Antiretroviral therapy is predicted to have individual and public health benefits that increase with time and the proportion of infected persons treated
Baggaley (84), 2006, PLoS Medicine	To explore through the use of modelling, the epidemiological impacts of alternative strategies of initiating ART	Mathematical model	Parameter values were selected after a review of literature	Our analysis found that ART cannot be seen as a direct transmission prevention measure, regardless of the degree of coverage. Counselling of patients to promote safe sexual practices is essential and must aim to effect long-term change Scaling up treatment of pre-AIDS patients resulted in more infections being averted per person-year of treatment, but the absolute number of infections averted remained small

Author, Year of Publication and Journal	Aim	Study Design	Study Population	Results/Conclusions
Bendavid (85), 2010, Arch Intern Med	To assess epidemiologic health effect of 4 different treatment strategies including test and treat, linkage to care and reducing loss to follow-up	Mathematical model	Parameter values were based on the South African HIV population where HIV transmission is predominantly heterosexual	We estimate the number of new infections in the adult South African population over the next 10 years to be 4.5 (3.8–5.1) million in the status quo strategy, and 1.2 (0.9–1.6) million in a comprehensive strategy, a 73.2% reduction Even relatively modest improvements in linkage to care and prevention of LTFU provide substantial mortality and prevention benefits A 10% higher linkage and 6% reduction in LTFU are associated with 36% fewer HIV infections compared with universal testing and treatment alone
Bezemer (70), 2008, AIDS	To evaluate the separate impact of risk behaviour, HIV testing behaviour and HAART on the HIV epidemic in Dutch MSM	Mathematical model	Dutch MSM	Our model, however, suggests that the only way to reverse epidemic spread, and get R well below one, is to reduce the risk behaviour rate from current levels Our analysis made it possible to compare the relative changes over time in risk behaviour rate between infectious and negative MSM, the 'hidden' information that cannot be measured by survey data, and our results indicate that whatever measures individuals are taking to 'serosort' are not proving effective at the population level and have not offset epidemic spread The most effective intervention is to bring risk behaviour back to pre-HAART levels

Author, Year of Publication and Journal	Aim	Study Design	Study Population	Results/Conclusions
Blower (86), 2000, Science	To predict the effectiveness of ART with respect to mortality and preventing new infections in the San Francisco gay community	Mathematical model	MSM in San Francisco	Increasing the usage of ART in San Francisco would decrease the AIDS death rate and could substantially reduce the incidence rate Recent increases in risky behaviour have been found The most important key factor that decreased the effectiveness of ART (both in terms of the number of deaths averted and the number of infections prevented) was the degree of increase in risk behaviour Even under pessimistic assumptions, a high usage of ART decreased the incidence rate however, an increase in risky behaviour of only 10% was enough to counterbalance the benefits of ART
Charlebois (87), 2011, Clinical Infectious Diseases	To determine the impact of offering ART to all patients in care on incident HIV infection in the MSM population of San Francisco	Mathematical model	Inputs were based on data from the local health department and electronic patient databases of the San Francisco General Hospital outpatient HIV treatment clinics that contain information on 95% of individuals known to be HIV infected in San Francisco	Modelling of expanding antiretroviral treatment to all HIV infected adults already in care in San Francisco predicts reductions in new HIV infection at 5 years of 59% among MSM Addition of annual HIV testing for men who have sex with men to universal treatment decreases new infections by 76%

Author, Year of Publication and Journal	Aim	Study Design	Study Population	Results/Conclusions
El-Sadr (95), 2011, AIDS	To predict the epidemic impact of treating HIV-discordant couples to prevent transmission	Mathematical model	The model was parameterised using data from Ghana, Lesotho, Malawi and Rwanda	Country-specific differences in the reduction in HIV incidence due to treatment of discordant couples to prevent transmission depends on two factors: HIV prevalence and the percentage of couples that are discordant. The higher the HIV prevalence and/or the greater the percentage of couples in discordant partnerships the more incidence will be reduced; therefore, the greatest reduction (among the four countries we have analyzed) is anticipated to occur in Lesotho Our modelling shows that treatment of discordant couples is unlikely to be the sole answer for controlling HIV epidemics. However, we have shown that if high treatment coverage levels are reached for discordant couples, this intervention could significantly reduce incidence and prevent a substantial number of infections in certain countries
Granich (88), 2009, Lancet	To explore the effect of various HIV testing and treatment strategies on the long-term dynamics of the epidemic using a deterministic transmission model	Mathematical model	Study used available data from South Africa as the test case for a generalised HIV epidemic Hypothetical test case assumed, as in South Africa, that almost all transmission was heterosexual rather than homosexual	The model suggests that only universal voluntary HIV testing and immediate initiation of ART could reduce transmission to the point at which elimination might be feasible by 2020 for a generalised epidemic, such as that in South Africa

Author, Year of Publication and Journal	Aim	Study Design	Study Population	Results/Conclusions
Heymer (89), 2011, Sexual Health	To investigate the impact of increasing testing rates and using treatment as a form of prevention To distinguish between gay men who are socially engaged with the gay community and those who are not	Mathematical model	MSM in South Australia	Our model-based findings suggest that increasing testing rates alone will have minimal impact on reducing the expected number of infections compared to current conditions. However, in combination with increases in treatment coverage, this strategy could lead to a 59-68% reduction in the number of HIV infections over the next 5 years The proportion of potential infections averted would increase to almost 70% if all undiagnosed individuals are tested twice per year Targeting men who are socially engaged with the gay community would result in the majority of potential reductions in incidence, with only minor improvements possible by reaching all other MSM Investing in strategies that will achieve higher coverage and earlier initiation of treatment to reduce infectiousness of HIV-infected individuals could be an effective strategy for reducing incidence in a population of MSM
Law (96), 2001, AIDS	To assess competing effects of combination ART and increases in unsafe sex on HIV incidence in MSM	Mathematical model	Model parameters were based on a population of MSM in Australia	The models presented in this paper suggest that reduced HIV transmissions through apparently large decreases in infectiousness as a result of combination ART could be counterbalanced by much more modest increases in the levels of unsafe sex Decreases in infectiousness of 10-fold would be counterbalanced by an increase of 70% in unsafe sex

Author, Year of Publication and Journal	Aim	Study Design	Study Population	Results/Conclusions
Long (90), 2006, AIDS	To understand the effectiveness of HAART in slowing the HIV epidemic in Russia To evaluate treatment strategies that target non-IDUs and IDUs as well as untargeted strategies that provide HAART without regard to injection drug use status	Mathematical model	Parameter values were based on a population of IDUs and non-IDUs from St. Petersburg, Russia	If treatment were targeted to IDUs, over 40,000 infections would be prevented (75% among non-IDUs) Our analysis indicated that expanded use of antiretroviral therapy, if appropriately implemented, could dramatically reduce HIV incidence among the general population in Russia and would result in enormous population-wide health benefits The importance of treatment for IDUs is highlighted by our finding that targeting HAART exclusively to IDUs prevented more HIV infections among non-IDUs than did targeting HAART exclusively to non-IDUs Our analysis also showed that the strategy of focusing treatment resources almost exclusively on non-IDUs, which is the current strategy in Russia, provided the least health benefit, was the least economically efficient, and will likely fail to slow the spread of HIV among IDUs or the general population Our findings emphasize the critical need to include plans to treat both IDUs and non-IDUs as antiretroviral treatment is expanded in Russia
Long (91), 2010, Ann Intern Med	To evaluate the effects on the US HIV epidemic of expanded ART, HIV screening, or interventions to reduce risk behaviour	Mathematical model	High-risk (injection drug users and men who have sex with men) and low-risk persons aged 15 to 64 years in the United States We assessed relevant demographic data for each risk group, including population sizes, HIV prevalence, entry and maturation rates, and mortality rates The model was populated using 2007 data	Expanding HIV screening and treatment simultaneously offers the greatest health benefit and is cost-effective. However, even substantial expansion of HIV screening and treatment programs is not sufficient to markedly reduce the U.S. HIV epidemic without substantial reductions in risk behaviour To substantially decrease the size of the U.S. HIV epidemic, a multimodal approach of testing, treatment, and behaviour change would be needed

Author, Year of Publication and Journal	Aim	Study Design	Study Population	Results/Conclusions
Lou (92), 2009, BMC Public Health	To examine the effect of HAART on controlling the HIV spread in the MSM population	Mathematical model	MSM in China	Our simulations suggest that both antiretroviral therapy and a potential vaccine are powerful interventions, even if disinhibition is considered Several early mathematical modelling studies raised the concern that any possible benefit of HAART on the spread of HIV could be readily offset by even modest increases in HIV risk behaviour . However, our model shows that antiretroviral therapy for MSM in China will have both individual and public-health benefits even if risk behaviour increases
McCormick (93), 2007, Clinical Infectious Diseases	To estimate the effects of ART on the secondary transmission of HIV among men who have sex with men	Mathematical model	2 cohorts of men who have sex with men: (1) a cohort of individuals who were not receiving ART and (2) a cohort of individuals treated with US guideline–concordant ART	We estimated that the use of ART resulted in a reduction in the number of secondary HIV transmissions from 1.9 to 1.4 transmissions per person during the initial 10 years after infection, assuming no increase in risk behaviour and no changes in available therapy However, this increase is not inevitable and may be attenuated by the identification of new and effective ART regimens and other effective treatment options, as well as by decreased sexual activity resulting either from the aging of the ART cohort or from specific risk-reduction interventions The total number of transmissions for the treated cohort began to exceed the total number of transmissions for the untreated cohort 33 years after infection; over the entire course of infection, treatment with ART led to a 23% increase in secondary infections. All estimates of the impact of ART on secondary transmission were sensitive to changes in risk behaviours In conclusion, the relationship between ART and lifetime infectiousness is complex, with an initial benefit over the short term but an eventual increase in total infections transmitted over the lifetime of an HIV-infected cohort suggesting that ART alone will not eradicate the HIV epidemic Thus, it will be important to implement complementary programs that target reduction in secondary transmission, in addition to ART, to further decrease HIV transmission

Author, Year of Publication and Journal	Aim	Study Design	Study Population	Results/Conclusions
Walensky (94), 2010, Clinical Infectious Diseases	To assess the impact of a Test and Treat strategy on individual patient and population-wide outcomes	Mathematical model	Parameters values were designed to be representative of the population with HIV infection in Washington DC	Evaluated combinations of HIV screening and ART initiation Compared with current practice Test and Treat decreases the proportion of time with transmissible viral load over a 5 year time horizon from 64.3% to 54.2% Comparable results achieved in sensitivity analysis Suggestions that Test and Treat may eradicate HIV epidemic may be unrealistic Success of Test and Treat hinges on several components: making HIV test offers, completing tests, linkage to care, maximising effectiveness of ART
Wilson (65), 2008, Lancet	To estimate the cumulative risk of HIV transmission from HIV-discordant couple, where the index partner is effectively treated over a prolonged period.	Mathematical model of heterosexual and homosexual discordant couples		The risk of HIV transmission in heterosexual couples in the presence of effective treatment is low but non-zero and the transmission risk in male homosexual partnerships is high over repeated exposures. There is potential for substantial increase in HIV incidence
Jin (19), 2010, AIDS	Estimate per-contact probability of HIV transmission in homosexual men due to various forms of unprotected anal intercourse (UAI) in the era of ART.	Health In Men (HIM) study, observational longitudinal cohort study. June 2001 to June 2007	1 427 community-based HIV-negative homosexual men. Sydney, Australia.	Estimated per-contact probability of HIV transmission: 1.43% (95% CI: 0.48–2.85) for receptive UAI if ejaculation occurred inside the rectum 0.65% (95% CI 0.15–1.53) for receptive UAI if withdrawal prior to ejaculation 0.11% (95% CI 0.02–0.24) for insertive UAI in circumcised men 0.62% (95% CI 0.07–1.68) for insertive in uncircumcised men.
Reynolds (62), 2011, AIDS	Evaluate the impact of ART on HIV-1 transmission rates among HIV-1 sero-discordant couples	Observational cohort study. 2004 and 2009 Rakai study, Uganda	250 HIV sero-discordant couples.	42 HIV-1 transmissions over 459.4 pys prior to ART initiation (incidence 9.2 per 100 pys, [95%CI 6.59–12.36]). In 32 couples in which the HIV-1 index partners started ART, no HIV-1 transmissions occurred during 53.6 pys.
Del Romero (61), 2010, BMJ	Estimate the risk and probability of heterosexual transmission of HIV-1 from people living with HIV on ART.	Cross-sectional and longitudinal analysis on a cohort study. 1989 and 2008 Madrid, Spain.	476 stable (reporting this sexual relationship as the only risk exposure) HIV sero-discordant couples.	9.2% HIV prevalence in non-index partners at enrolment, where the index partner was not on ART (n=44), 0% in couples where the index partner was on ART (n=149). They concluded that transmission of HIV from successfully treated people cannot be excluded.

Author, Year of Publication and Journal	Aim	Study Design	Study Population	Results/Conclusions
Donnell (55), 2010, Lancet	Assess the effect of ART use by patients infected with HIV-1 on risk of transmission to their uninfected partner	Observational analysis of RCT data (Partners in HSV/HIV transmission study). 14 sites in 7 African countries in East and Southern Africa.	3 381 HIV sero-discordant couples; the index HIV+ person infected with HIV and herpes simplex virus type 2 with a CD4>=250.	Primary outcome was genetically linked HIV-1 transmission with the study partnership. 1/103 of genetically linked HIV-1 transmissions was from an infected participant who had started ART, corresponding to transmission rates of 0·37 (95% CI 0·09–2·04) per 100 pys in those who had initiated ART and 2·24 (1·84–2·72) per 100 pys in those who had not—a 92% reduction (adjusted IRR 0·08, 95% CI 0·00–0·57, p=0·004)
Lu (63), 2010, JAIDS	Estimate the HIV transmission risk and assess the behavioural, clinical, and quality-of-life risk factors for HIV transmission	Observational cohort study. January 2006 and December 2008 Henan, China	1927 HIV sero-discordant heterosexual couples (former plasma donor).	84 HIV-1 transmissions occurred over 4918 pys, incidence 1.71/100 pys. Most respondents (80.4%) had spouses who were on ART. No statistical difference in the sero-conversion rates between those couples who had a spouse on ART (4.8%) and those couples whose HIV-positive spouse was not on ART (3.2%) (P = 0.12).
Baggaley (64), 2010, International Journal of Epidemiology	Assess the per-act and per-partner HIV transmission risk from anal intercourse exposure for heterosexuals and MSM and its implications for HIV prevention.	Systematic review and meta-analysis	4 publications reporting per act and 12 reporting per partner studies.	The predicted HIV transmission probabilities per-act for vaginal intercourse (VI) or unprotected insertive anal intercourse (UIAI) and unprotected receptive anal intercourse (URAI) with successful ART are 0.013 and 0.061%, respectively, i.e. 96% lower than without therapy. Using another function of infectivity by HIV-RNA plasma viral load , the predicted per-act VI/UIAI and URAI estimates with successful ART are 0.0002 and 0.0011%, respectively, i.e. 99.9% lower than without therapy.
Attia (53), 2009, AIDS	Synthesize the evidence on the risk of HIV transmission through unprotected sexual intercourse according to HIV-RNA in plasma (BPVL)and treatment with ART	Systematic review and meta-analysis of observational cohort studies of HIV sero-discordant couples	11 cohorts reporting on 5 021 sero-discordant couples and 461 HIV-transmission events.	The rate of transmission overall from ART-treated patients was 0.46 (95% CI 0.19–1.09) per 100 pys, based on 5 events. The transmission rate from a seropositive partner with BPVL below 400 copies/ml on ART, based on 2 studies, was 0 with an upper 97.5% confidence limit of 1.27 per 100 pys, and 0.16 (95% CI 0.02–1.13) per 100 pys if not on ART, based on 5 studies and 1 event.
Melo (60), 2008, Sexually Transmitted Diseases,	Estimate sexual transmission rates and assess the behavioural and clinical factors for HIV transmission	Observational cohort study. 2000-2006 Porto Alegre, Southern Brazil.	93 HIV-sero-discordant couples with no prior antiretroviral use	Among couples where the index person started ART (n=41) no sero-conversions occur, while in the remaining 54 6 sero-conversions were observed (Incidence 11.5%, 95% CI: 4.81-22.45)

Author, Year of Publication and Journal	Aim	Study Design	Study Population	Results/Conclusions
Castilla (54), 2005, JAIDS	Estimate HIV prevalence among steady HIV sero-discordant couples, according to ART.	Cross-sectional analysis. 1991-2003 Madrid, Spain	393 steady HIV sero-discordant couples.	HIV prevalence among partners of index cases who had not received ART was 8.6%, whereas no partner was infected in couples in which the index case had been treated with ART (P = 0.0123). HIV prevalence among nonindex partners declined from 10.3% during the pre-ART period (1991–1995) to 1.9% during the late ART period (1999–2003; P = 0.0061).

CVL=community viral load. HAART=highly active antiretroviral therapy. ART=antiretroviral therapy. IQR=inter-quartile range. MSM=men who have sex with men. IDU=intravenous drug user.

A2.2 Relationship between HIV RNA in plasma and in the genital tract in adults on antiretroviral treatment

Author, Year of Publication and Journal	Aim	Study design	Study Population	Results/Conclusions
Ananworanich (97), 2011, Int J STD AIDS	Assess the relationship between plasma HIV-RNA and genital shedding of HIV in patients on intermittent ART and assess predictors of detectable genital HIV RNA	Observational analysis on a substudy of STACCATO RCT	430 Patients with chronic HIV infection, HIV RNA <50 copies/ml and CD4>350 cells/µl randomized to continuous therapy or CD4-guided arms. Bangkok, Thailand	Genital secretion of HIV RNA became detectable once ART was interrupted in those with previously undetectable genital HIV RNA while on ART This suggests increased HIV infectiousness following treatment interruption. After adjusting for ART status and gender, the only independent predictors of detectable HIV RNA in genital secretions were older age and increasing concentrations of plasma HIV RNA
Kelley (100), 2011, JID	Assess the impact of rectal sexually transmitted infections (STIs) on rectal HIV-1 shedding	Observational prospective cohort study March 2004 and June 2006	80 MSM (59 on ART) 3 US cities: Denver (CO); Minneapolis (MN) and St. Louis (MO)	39% of men had detectable HIV-RNA in rectal swabs. Rectal HIV detection was associated with plasma virus loads above 3.15 log10 copies/mL (95% CL: 2.73, 3.55) and paired rectal viral loads and plasma viral loads were correlated. Rectal STIs were not associated with rectal viral load, neither in those with low HIV-RNA in plasma.
Dulioust (108), 2010, AIDS	Estimate the prevalence of detectable HIV-RNA in semen among men in MAP	Observational retrospective cohort study 2002-2009	455 HIV infected men on continuous ART since at least 6 months, with VL<50 copies/ml from couples requesting MAP. France	17 (3.7%) of 455 men had at least once an HIV-RNA positive seminal sample, ranging from 25 to 3000 copies/ml
Halfon (109), 2010, Plos One	Assess the residual risk of HIV presence in semen in patients under ART	Observational cohort study October 2001 to March 2009	332 HIV-1 infected men who provided 394 paired blood and semen samples, enrolled in medical assisted procreation (MAP) France	10 (3%) seminal plasma samples had detectable HIV-1 RNA despite undetectable plasma HIV-RNA for at least 6 months under ART.
Sheth (111), 2009, AIDS	Estimate prevalence of detectable HIV-RNA in semen among men starting ART	Observational prospective cohort study	25 HIV infected men starting ART. Toronto, Canada	Despite undetectable HIV RNA in plasma, isolated semen HIV shedding was detected at more than one visit in 48% of participants

Author, Year of Publication and Journal	Aim	Study design	Study Population	Results/Conclusions
Marcelin (110), 2008, AIDS	Estimate the prevalence of detectable HIV-RNA in semen among men in MAP with undetectable plasma HIV-RNA	Observational cohort study January 2002 - January 2008	145 HIV+ men in MAP. France	5% harboured detectable HIV RNA in semen, despite not having another STI and undetectable blood plasma HIV-RNA
Chan (98), 2008, Current HIV Research	Assess the correlation between BPVL and seminal plasma (SPVL).	Observational Cross-sectional study. August 2003 - December 2006	119 MSM living with HIV-1. Sydney, Australia.	At baseline all treated patients (n=81) had HIV-RNA in plasma <50 copies/ml and HIV-RNA in semen <250 copies/ml and a positive correlation between seminal HIV-RNA and HIV-RNA in plasma was observed.
Neely (116), 2007, JAIDS	Identify factors associated with cervical HIV-1 RNA shedding	WIHS April 2000 and March 2003	290 Women with low or undetectable quantities of HIV-1 RNA in plasma (<500 copies/mL) USA	44 (15%) had detectable HIV-1 RNA in cervical specimens. In a multivariate model, shedding was independently associated with NNRTI (vs. PI) use and illicit drug use. Genital shedding was common, and associated with NNRTI-based ART regimen (vs. PI-based ART)
Kovacs (102), 2001 Lancet	Investigate the relationship between HIV-1 shedding in female genital secretions and other factors	Cross-sectional study within the WIHS Jan 1997 – Jul 1998.	311 HIV positive women. USA	HIV-1 RNA was detected in 57% (152/268) of genital secretions and in only 6% (17/271) of blood samples. Genital tract HIV-1 shedding was found in 80% (130/163) of women with detectable plasma RNA and 33% (27/83) of women with less than 500 copies/mL plasma RNA
Vernazza (106), 2000, AIDS		Observational prospective study	114 male patients on ART and HIV-RNA in plasma below 400 copies/ml Switzerland and USA	HIV-RNA in semen was detected in only 1.8% compared with a detection frequency of 67% in untreated controls.
Kovacs (101), 1999, JAIDS	Assess HIV-1 RNA in plasma and genital tract secretions in women infected with HIV-1	Cross sectional study within WIHS, prospective longitudinal cohort study October 1994 - November 1995	56 women within three CD4 categories (22 <200 cells/mm^3; 23 200–499 cells/mm^3; 11 ≥500 cells/mm^3) who provided both HIV-RNA in blood and in cervical samples. USA	HIV-RNA was detected in 59% of cervical samples and was associated with higher level of plasma HIV-RNA. Mean HIV-1 RNA levels in cervical samples increased with decreasing CD4 counts (p = 0.002,) and with increasing plasma HIV-1 RNA (p<0.001). Treatment did not seem to affect RNA detection in cervical samples after adjusting for plasma RNA and CD4.

Note: Studies included in this table are not part of formal literature review for treatment as prevention. This study summarises the evidence for an association between HIV RNA levels in the plasma with HIV RNA levels in the genital tracts

MAP=medically assisted procreation. WIHS=Women's Interagency HIV Study

A2.3 Prevention of mother to child transmission

Author, Year of publication and Journal	Aim	Study design	Study Design			Results
			Major characteristics of mothers	pMTCT strategies evaluated	Number included[#]	HIV Transmission rate
Agmon-Levin, 2009, International Journal of STD and AIDS (184)	Investigate the MTCT rate in Israel	Observational, Jan00-Oct05 Israel	Median Age 30yr. 86% Ethiopian. 5% breastfed. 63% diagnosed during pregnancy/labour. Mean CD4 406. 54% undetectable VL.	76% received ARVs (of this 86% HAART, 9% ZDV+3TC and 5% ZDV). 88% neonates got ZDV for 6 weeks, 16% received neonatal sdNVP.	300	Overall: 3.6% Received Neonatal ZDV: 45% infected vs. 91% uninfected ZDV in labour: 27% vs. 82% ARV in pregnancy: 10% vs. 79%
Andiman, 1999 NEJM (268)	Investigate the relationship between mode of delivery and MTCT rates	Meta analysis of 15 cohort studies, up to end of 1996 Worldwide	10% caesarean delivery, advanced disease in 1101.	(1) ART in all three periods* (2) ART in 1 or 2 periods (3) No ART (4) Unknown *Prenatal, intrapartum, neonatal ART predominantly following 076 guidelines	(1) 1451 (2) 871 (3) 5944 (4) 227	(1) 6.6% (AOR 0.31) (2) 15.6% (AOR 0.70) (3) 18.2% (AOR 1.00 ref) (4) 18.1%
Azcoaga-Lorenzo 2011, AIDS Care (264)	Estimate the coverage of a pMTCT regimen and estimate the risk of MTCT	Prospective observational, 2006-2008 Kenya	99% vaginal delivery. 69% breastfeeding. 36.5% 18-25y.	Protocol: HAART or short-course ZDV (from 36w) + maternal sdNVP+ ZDV/3TC. Neonatal sdNVP+ ZDV 7d (1) Complete protocol (2) Partial protocol (3) No intervention	Overall: 309 (1) 80 (2) 205 (3) 24	Overall: 15.86% (1) 3.8% (2) 15.1% (3) 62.5%
Bajunirwe, 2004 African Health Sciences (367)	Investigate the efficacy of short course ZDV with sdNVP in a clinical setting	Observational study, June-October 2000 Uganda	Mean age 26 yrs, 14% rural, 26% WHO Stage ¾, 66% breasfed	(1) Short course ZDV from 36w to 1w post-partum or sdNVP+ neonatal sdNVP or neonatal 1-2 weeks of oral ZDV (2) No treatment	(1) 109 (48 ZDV, 61 sdNVP) (2) 90	(1) 16.5% (16.7% ZDV and 16.4% sdNVP) (2) 47.8%
Bedri (SWEN), 2008 Lancet (275) and Omer 2011 AIDS (276)	Three RCTs of efficacy of neonatal NVP to reduce MTCT during the breastfeeding phase	Three RCTs, combined for primary analysis Ethiopia, India and Uganda,	Mean age ~25yrs, ~16% caesarean, CD4 count~400, 98% breastfed	All uninfected at birth (1) sdNVP+neonatal sdNVP (2) sdNVP+ neonatal sdNVP + neonatal NVP days 8-42	(1) 986 (2) 901	(1) 6 weeks: 5.27%; 6 months: 8.98%; 12m 10.4% (2) 6 weeks: 2.95%; 6 months 6.91%; 12m 8.9%

Author, Year of publication and Journal	Aim	Study design	Study Design			Results
Bera, 2010, South African Journal Obs Gynae (230)	Estimate MTCT rate and investigate factors associated with this	Observational study, 2006-2008 South Africa	Women initiating life-long ART included. Median CD4 128, median ART 8 weeks. Median age 29. Median 12 weeks on ART during pregnancy. 90% undetectable VL at delivery	2NRTIs+EFV (733), 2NRTIs+NVP (97), 2 NRTIs+LPV/r (8) 81.4% neonatal sdNVP +/- short course ZDV	838	Overall: 2.4% <10w ART: 4.2% >10w ART: 1.2% VL>1000: 7.8% VL<1000: 1.5% Neonate sdNVP: 2.9% Neonate sdNVP +ZDV: 2.3% ART>10w+VL<1000: 0.3%
Birkhead, 2010, J Public Health Management Practice (228)	Assess the outcome of pMTCT efforts over two decades	Surveillance data, 1998-2008 USA	Survillance data of New York State, 62% black, 26% hispanic, >½ mother 25-34 years, 43% C-section 15% unknown. 69% diagnosed with HIV prior to pregnancy, 2% known breastfed	75% pre-natal ART, 12% unknown 78% intrapartum ART, 1% unknown 89% newborn ART 68% all 3 interventions 6% none 14% unknown	8972	OR (No vs. Yes) Pre-Natal ARV: 8.44 Intrapartum ARV: 6.00 Newborn: 7.73 3 interventions: 1.00 (ref) Some 3.55 None 14.33
Black, 2008, JAIDS (251)	Describe the safety and efficacy of initiating HAART in an integrated antiretroviral antenatal clinic	Retrospective observational analysis, August 2004-February 2007 South Africa	Mean age 29.2yrs; 77% diagnosed during pregnancy, 2% previously received sdNVP. Mean baseline CD4 154. 8% with TB. 99% formula feed. Mean gestationage at HAART initiation 27 weeks.	(1) d4T+3TC+EFV (2) d4T+3TC+NVP (3) ZDV+ddI+LPV/r (4) Other NRTIs+ NNRTI (5) Other NRTIs+PI 99.9% neonatal sdNVP	(1) 47 (2) 509 (3) 1 (4) 29 (5) 34	Overall: 5% If received >7 weeks of HAART: 0.3%
Boer, 2007, B J Obs Gynae (229)	Explore pregnancy outcomes in HIV+ and HIV- women and MTCT rates according to mode of delivery under use of HAART	Observational Dec1997-Jul2003 Netherlands	51% 26–34 years, 76% black. 62% vaginal delivery, 22% elective Caesarean, 15% emergency Caesarean. 19% got HAART in 1st trimester	(1) CBV+NFV (93) (2) CBV+NVP (50),	(1) 93 (2) 50	(1) 0% (2) 0%
Bruno, 2001, ICAAC (181)	Evaluate efficacy and infant outcome in children born to HIV+ mothers treated with HAART during pregnancy	Observational May99-dec00	Combination therapy was indicated in mothers with viral charge more than 10,000 copies	(1) None (2) short course ZDV (3) short course ZDV+3TC (4) ZDV+3TC+(NVP or PI)	(1) 76 (2) 126 (3) 48 (4) 77	(1) 19.2% (2) 4.8% (3) 2.1% (4) 2.6%

Author, Year of publication and Journal	Aim	Study design	Study Design			Results
Bucceri, 2002, Human Reproduction (231)	Investigate the side effects, vertical transmission rates and neonatal outcomes associated with different ART regimens	Observational case series, Jan 98-Sept 2000 Italy	Median 21 weeks of ART, At delivery median CD4 466, 45% undetectable VL. No breastfeeding. 97% Caesarean section.	All receiving ART 77% dual, 23% HAART. 46% on ART at conception.	100	Overall: 1%
Burgard, 2010, CID (209)	Evaluate interventions used and neonatal outcomes of HIV-2 positive pregnant women	Observational data, 1986-2007 France	2.6% with HIV-2. All sub-Saharan origin 11%<200 CD4 at delivery, <1% breastfed. ~ 50% vaginal delivery	1994-6: ZDV monotherapy 97-99: dual NRTI or HAART 00-04: PI-based HAART according to CD4 05-07: PI-based HAART 24% ZDV monotherapy 22% dual NRTI 54% HAART (44% PI-based). 81% post natal prophylaxis	8660	HIV-1: No ART: 16.3% ART 2.2% NRTI mono 4.5% NRTI dual 1.3% HAART 1.3% HIV-2: No ART: 0.7% ART 0.5% NRTI mono 0% NRTI dual 0% HAART 2.9%
Chama, 2007 J Obs Gynae (258)	Examine the value of HAART in the prevention of MTCT	Observational, 2002-4 Nigeria	51% breastfed.	(1) sdNVP (not eligible for ART) (2) NVP+d4T+3TC (eligible for ART) 100% neonatal sdNVP	(1) 9 (2) 22	(1) 33% (2) 9.1%
Chama, 2010, J Obs Gynae(252)	Assess the outcome of MTCT using HAART	Observational, 2007-8 Nigeria	72% aged 25–34yrs, 79% CD4<200. 62% received ART>24 weeks. 84% vaginal delivery	3TC+NVP+ZDV 61% (all CD4<200) 3TC+ZDV+IDV/r 21% All CD4>200	446	Total: 1.1% VL<1000: 0%
Chasela (BAN), 2010, NEJM (278)	Evaluate the efficacy of maternal triple prophylaxis or infant prophylaxis during breastfeeding to prevent postnatal MTCT	RCT 2008 Malawi	All breastfeed for 24-28 weeks, then rapid weaning Median age 26. 93% vaginal delivery. All CD4>250	All maternal sdNVP then 7d ZDV+3TC Neonatal: zZDV+3TC 7d After birth: During breastfeeding: (1) Mothers CBV+NVP/NFV/LPV/r (2) neonatal NVP (3) Nothing	(1) 849 (2) 852 (3) 668	HIV infection Day 42: (1) 0.9% (0.4%–1.9%) (2) 0.1% (0.0%–0.9%) (3) 2.0% (1.2%–3.6%) Day 203: (1) 2.9% (1.9–4.4) (2) 1.7% (1.0–2.9) (3) 5.7% (4.1–8.0)

Author, Year of publication and Journal	Aim	Study design	Study Design			Results
Chi (HIV NET 024), 2005, AIDS (205)	Determine whether timing of maternal or infant was associated with MTCT between delivery and 6 months post-partum	Observational analysis of RCT data Sub-Saharan Africa	Mean age 26 years, 349 CD4 count, 4.2 log VL, 6% Caesarean	sdNVP and neonatal sdNVP	1491. Only babies negative at birth included	8.1% transmission in 0-6w Time from maternal dose until delivery < 2 h: 6.3% 2–24h: 8.1% 24–48h: 9.2% > 48h: 10.5% Time from delivery until infant dose < 4 h:8.2% 4–24: 8.2% 24–72: 7.7% > 72 h: 8.1%
Chi, Lancet 2007 and JAIDS 2008 (210;211)	Investigate whether single dose TDF+FTC reduces maternal viral resistance to sdNVP strategy	RCT (secondary endpoint and post-hoc analysis), March05-Feb07 Zambia	92% breastfed. Only those not requiring ART for their own health (CD4>200?) included. Average age 26. CD4 ~460. 28% VL undetectable at delivery	sdNVP +short course (32 w to delivery) ZDV neonatal sdNVP+7d ZDV Then: (1) FTC+TDF once during labour (2) Nothing	(1) 180 (2) 175	(1) 5.6% (2) 8.0% (p=0.635)
Chigwedere, 2008, AIDS Res Hum Retro (194)	Estimate the efficacy of ARVs in reducing MTCT in Africa	Meta-analysis 1997-2007 Africa	10 studies	ARVs vs. placebo	139-1979 per study	ARV: 10.6% (8.6, 13.1) Placebo: 21.0% (15.5, 27.7)
Chung, 2005, AIDS (271)	Compare the effect of HIVNET012 and Thai-CDC regimens on breast-milk viral shedding	RCT (secondary endpoint), March-Oct 2003 Kenya	All planned to breastfeed. Median age 25y. CD4 ~475. 100% vaginal birth	(1) sdNVP + neonatal sdNVP (2) short course ZDV (34 w+)	56	(1) 6.8% (2) 30.3% (p=0.02)
Chung, 2008, Antivir Ther (271)	Investigate the effects of HAART on breast-milk viral shedding	RCT (secondary endpoint), Nov 03-Mar 05 Kenya	All CD4 200-500. Median 25 years. All breastfeed.	(1) 34w–6m post delivery: ZDV+NVP+3TC (2) 34 w-delivery: ZDV+ sdNVP+neonatal sdNVP	(1) 26 (2) 25	(1) 7.7% (2) 4.0%
Connor (ACTG 076), 1994, NEJM (23)	Investigate the effect of ZDV therapy on pMTCT rates	RCT, Apr 1991-Dec 1993 USA and France	Median age 25. Median 550 CD4. 61% vaginal, 23% Caesarean, 18% are white ethnicity. Median 11 weeks of ZDV in arm (1)	(1) ZDV (study entry), ZDV during delivery +neonatal ZDV (6w) (2) Placebo	409	18m: (1) 8.3% (3.9%, 12.8%) (2) 25.5% (18.4%, 32.5)%
Cooper (WITS), 2002, JAIDS (168)	Evaluate the impact of different ART regimens on pMTCT rates at the population level	Observational Jan 1990-Jun 2000 USA	82% minority race. Median 28 years. 26% Caesarean. Median CD4% 28%. 21% VL<400. No breastfeeding	(1) no ART (2) ZDV mono (3) multi-ART (4) HAART	(1)396 (2)710 (3)186 (4)250	(1) 20.0% (16.1%–23.9%); (2) 10.4% (8.2%–12.6%) (3) 3.8% (1.1%–6.5%) (4) 1.2% (0%–2.5%)

Author, Year of publication and Journal	Aim	Study design	Study Design			Results
Coovadia HPTN046, 2011, , CROI Abstract (281)	Evaluate the incremental benefit of extending prophylaxis to 6 months post-delivery	RCT South Africa, Tanzania, Uganda, Zimbabwe	All babies uninfected at 6w All babies breastfed exclusively to 6m. CD4 at 6w post-partum (1) 560 (2) 528	(1) Neonatal ZDV to 6m (2) Neonatal ZDV to 6w All: 29% mother ART for own health	(1) 759 (2) 763	6m: (1) 1.1 (.3–1.8) (2) 2.4 (1.3–3.6) 12m: (1) 2.0 (1.0–3.1) (2) 3.0 (1.8–4.3)
Cotton 2009, South African Journal of HIV Medicine (220)	Evaluate efficacy of antenatal, intrapartum and postnatal antiretroviral components of a public service pMTCT programme	Prospective Observational, South Africa	Free formula feed for 6 months	ZDV (28/34 w to delivery), sdNVP mother, neonatal sdNVP+ ZDV 7 d	656	5.9% (4.4%–8.0%) Antenatal ART vs none: OR=0.40 (0.19–0.90) Intrapartum and postpartum ART no association
Dabis, (DITRAME ANRS049a) 1999, Lancet (182)	Assess the acceptability, tolerance and acceptability of short course ZDV	RCT, Sep 95-Feb 98, Cote d'Ivoire and Burkina Faso	All Breastfeeding. Median 25 years. 2.5% Caesarean. Median 550 CD4.	(1) ZDV until 7d post delivery (2) Placebo	(1) 192 (2) 197	Day 180: (1) 18.0% (12.4–23.5) (2) 27.5 (21.1, 33.9)
Dabis (DITRAME plus), 2005 AIDS (221)	Evaluate the efficacy of two pMTCT drug interventions	Observational, 2001-2003, Cote d'Ivoire	21.8% eligible for HAART (1) median 21 days treatment (2) median 29 days treatment (3) 50 days Median age ~26 yr Median CD4 ~400 ~5% Caesarean ~2/3 Breastfed	(1)1995-2000: ZDV (~36w to delivery) (2)2001–2002: ZDV (36w to delivery)+ sdNVP. Neonatal sdNVP+7d ZDV (3)2002–2003: ZDV+3TC (36w to delivery)+sdNVP. Neonatal sdNVP+7d ZDV	(1) 351 (2) 420 (2) 373	(1) 12.5% (AOR 1.00) (2) 6.5% (3.9%–9.1%) (AOR 0.28; 0.14, 0.55) (3) 4.7% (2.4%–7.0%) (AOR 0.24; 0.12, 0.88)
Dal Fabbro, 2005, Brazilian J Infec Dis (269)	Describe use of pMTCT and efficacy rates	Prospective, Observational, May96-Oct01, Brazil	57% Caesareans. 51% diagnosed during pregnancy. Average 24 years. 32%<80 cps/ml at delivery. 1% breastfed.	(1) All 3 components (2) Two components (3) One component	(1) 58 (2) 15 (3) 3	(1) 0% (2) 0% (3) 67%
De Menezes Succi, 2007, Cadernos de Saude Publica (259)	Assess MTCT rates in Brazil and the factors associated with transmission	Observational, 2000-1, Brazil	6% (182/2 849) breastfed. 2/3<30 years. ~40% vaginal delivery	(1) None (2) Monotherapy (3) Dual therapy (4) ≥3 ARVs	(1) 699 (2) 983 (3) 431 (4) 811	(1) 23% (2) 5.4% (3) 2.3% (4) 1.1%
De Vincenzi (Kesho Bora) 2011, Lancet Infect Dis (226)	Assess the efficacy and safety of triple antiretroviral vs. ZDV and sdNVP prophylaxis in HIV+ pregnant women	RCT, Kenya, Burkina Faso, and SA	All with CD4 200-500. 88% vaginal delivery. 77% breastfed (1) 64%<300 cps/ml. (2) 30%<300 cps/ml.	(1) ZDV+3TC+LPV/r (34w gestation until cease breastfeeding) (2) ZDV (34w until delivery)+ sdNVP+7d ZDV/3TC All neonatal sdNVP + ZDV for 7 d	(1) 412 (2) 412	6 weeks: (1) 3.3%(1.9–5.6) (2) 5.0 (3.3–7.7) 12 months: (1) 5.4 (3.6–8.1) (2) 9.5 (7.0–12.9)

Author, Year of publication and Journal	Aim	Study design	Study Design			Results
Dorenbaum (PACTG316), 2002, JAMA (272)	Evaluate the addition of 2-dose NVP to standard ART on MTCT transmission rates	RCT, May 97-June2000 , US Europe Brazil Bahamas	23% ZDV mono; 28%, ZDV+3TC dual; 8% other no PI; 41%, ART with PI Median age 28. 58% black. Median 434 CD4. 46% vaginal delivery. 34% elective caesarean. 52% VL<400.	(1) Standard ART with sdNVP+neonatal sdNVP (2) Standard ART with placebo	(1) 631 (2) 617	(1) 1.4% (2) 1.6%
Duran, 2006, Medicina Buonas Aires (178)	Describe the impact of strategies to reduce vertical transmission and evaluate ART-related toxicity	Observational, Argentina	Median 27 years. 69% diagnosed prior to pregnancy. Median CD4 375. No information on breastfeeding	(1) Complete 076 (2) Incomplete 076 (3) no ART (4) Combined therapy	(1)94 (2)24 (3)52 (4)123	(1) 4.3% (2) 20.8% (3) 36.5% (4) 0%
Edwards, 2001, HIV Med (253)	Describe experience of NVP use with respect to immunological, virological, tolerability and pregnancy outcome	Case series, Jan 97-Sep 99 UK	85% Black African. 13% prior AIDS. 89% VL<400 copies/ml	NVP with (ZDV+ddI, ZDV+3TC or d4T+ddI)	46	0 infections
Ekouevi, 2008, AIDS (260)	Describe pregnancy outcomes in women receiving HAART	Observational, Mar2001-Jul2003 Cote d'Ivoire	Median CD4 (1) 177 (2) 182. Median duration of ART (1) 4.9 weeks (2) 11.7 weeks. 2/3 aged<30 years. Breast feeding (1) 48% (2) 65%	(1) short course ZDV or ZDV+3TC +sdNVP (2) HAART (available 2003+ if eligible)	(1) 175 (2) 151	12 months: (1) 16.1% (11.2–22.9) (2) 2.3% (0.7–6.9)
Ferguson, 2011, Ped Infect Dis J (232)	Evaluate the efficacy and safety of 4-week vs. 6-week neonatal prophylaxis	Observational, 1999-2008 Ireland	Median age 28. 56% vaginal delivery. 3% monotherapy, 5.6% dual therapy, 87% triple therapy, 4.3% none	All offered HAART at 20-28 weeks. Intrapartum ZDV given. Occasionally ZDV mono+caesarean. Neonatal: 1999 to 2002: ZDV or ZDV+3TC 2002 onwards: ZDV monotherapy or triple therapy with NVP (if mothers high risk). All get 4w ZDV+3TC	957	Overall: 1.06 (1.04–1.08)
Fiscus, 2002, Ped Infect Dis J (212)	Evaluate changes in use of ART and mode of delivery amongst HIV+ pregnant women	Observational, 1998-1999, USA	57% vaginal delivery	(1) Maternal monotherapy (2) Maternal dual/HAART (3) None	(1)477 (2)199 (3)170	(1) 4.2% (2.6%–6.4%) (2) 1.5% (0.3%–4.3%) (3) 26.5% (20%–33.8%)

Author, Year of publication and Journal	Aim	Study design	Study Design			Results
Fitzgerald, 2010, SAMJ (254)	Examine uptake of ART among pregnant women referred to an ART centre and associated MTCT rates and risk factors for transmission	Observational, Sep 02-Mar 08, South Africa	Median 28 years. Median 134 CD4. Median VL 28282.	(1) ZDV/3TC/NVP (2) [ZDV 36w to delivery or ZDV/3TC 32w to delivery] with sdNVP and neonatal ZDV 7d (3)None	(1)265 (2)74 (3)29 241	Overall: 4% On ART: 5.1% OR 0.8 (0.64, 1.0) of transmission per week longer ART
Galli, 2005, JAIDS (183)	Relationship between infant's gender and rate of MTCT	Observational, 1985-2001, Italy	1985-1995 (pre076): 3.1% breast fed. 17% elective Caesarean. 92% no ART, 9% mono 1996-2001 (post 076): 1.1% breast fed. 74% elective Caesarean. 17.2% no ART, 38.2% mono. 44.6% combination therapy	(1) No ART (2) Monotherapy (3) Combination ART	4151	Overall: 11.8% 1985-1995: No ART: 17.1% Mono: 11.9% 1996–2001: No ART: 16.5% Mono: 3.7% Comb: 1.1%
Galli, 2009, CID (222)	Evaluate the effects of discontinuing ART during pregnancy on rates of MTCT	Observational, Italy,	9% interrupt ART 92% Caesarean. 5% CD4<200. No breastfeeding. 48%<500 cps/ml	Maternal ART: (1a)Mono (2a)Dual (3a)Triple Neonatal ART (1b) No (2b) Yes	(1a)99 (2a)187 (3a)651 (1b)22 (2b)915	Overall: 1.3% (0.7–2.3) Interrupt in Trimester 1: AOR: 4.9 (1.9–13.2) Interrupt in Trimester2: AOR: 18.2 (4.5–72.7) (1a)5.1% (2a)0.5% (3a)0.9% (1b)4.5% (2b)1.2%
Garcia-Tejedor, 2009, Acta Obs Gynae Scan (213)	Analyse influence of HAART on risk factors for MTCT	Observational study, 1984-2006, Spain	Pre-1997: 27% mono/dual, rest none 1997+: 91% on any ART (77% of which HAART, 23% mono/dual). No breastfeeding. Median 27 yr	(1)None (2)Mono or dual (3)Triple therapy	(1)214 (2)116 (3)159	Overall 10.2% (1) 18.2% (2) 8.6% (3) 0.6%
Geddes, 2011, SAMJ (214)	Describe the operational effectiveness of pMTCT programmes	Retrospective Observational, Mar 04-Feb 07 South Africa	35% vaginal delivery. No info on breast feeding. All neonates received ART 84% received sdNVP+1w ZDV	Maternal: (1) None (2) sdNVP (3) dual (4) triple (5) unknown	(1) 7 (2) 101 (3) 85 (4) 373 (5) 5	Overall: 2.8% (1.7%-4.6%) (1) 0% (2) 6.9% (3) 1.2% (4) 2.1% (5) 0%

Author, Year of publication and Journal	Aim	Study design	Study Design			Results
Giaquinto (ECS), 2005, CID, (255)	Examine risk factors for MTCT in the HAART era and describe infants who were vertically infected, despite exposure to pMTCT interventions	Observational, 1997-2004, Europewide	Median age 31. 57% white, 37% black, 10% cd4<200. 44% undetectable VL. 23% vaginal, 61% elec. Caesarean	72% any ART 39% already receiving HAART when became pregnant	1602	Overall: 2.87% (2.11%-3.81%) Untreated: 11.5% Receiving HAART: 1.20%
Giaquinto (ECS), 2006, AIDS (256)	Carry out an epidemiological analysis of the emerging epidemic in an Eastern European country and compare to pMTCT approaches in Western Europe	Observational, 1985-2004 Western Europe [WE] and Ukraine [Uk]	WE: 72% white, 57% diagnosed before pregnancy, Uk: 98% white, 20% diagnosed before pregnancy	WE 1985–1994: 96% none, 4% mono 1995–1999: 24% none, 47% mono, 11% dual, 18% HAART 2000–2004 10% none 8% mono 10% dual 72% HAART Uk 2000–2004: 18% none 23% maternal sdNVP+neonatal sdNVP. 8% mono without sdNVP 4% mono with sdNVP 2% HAART	WE: 4537 Uk: 1251	WE: 85–94 None: 15.4% Mono: 12.3% 95-99 None: 12.8% Mono: 6.1% Dual: 0.83% HAART: 2.69% 00-04 None: 4.65% Mono: 4.0% Dual: 0.8% HAART: 1.0% 00-04 None: 19.8% sdNVP(Mother+infant): 6.8% Mono without sdNVP: 7.8% Mono with sdNVP: 4.2% HAART: 0%
Gray 2005, JAIDS (274)	Evaluate efficacy of neonatal sdNVP vs. ZDV for infants whose mothers had no prior ART	RCT, Oct 00-Sep 02 South Africa	Mothers first tested for HIV post-delivery. Median CD4 467. Median VL 21800. 82% formula feeding. Median age 25yr. 92% vaginal delivery.	No ante or intrapartum ART (1) neonatal sdNVP at birth (2) neonatal ZDV for 6 weeks	(1) 351 (2) 367	Birth: (1) 7.0% (2) 5.8% 12 weeks: (1) 14.3% (2) 18.1%

Author, Year of publication and Journal	Aim	Study design	Study Design			Results
Gray, 2006, AIDS (215)	Report the preliminary efficacy of 4 different NRTI regimens for the prevention of MTCT	RCT, May 99-May 00, South Africa	All Formula feed. Median VL 4.3 logs, Median CD4 431. 100% black. Median age 35yr. 15% elective caesarean.	Study entry (~34w) to delivery: (1) d4T (2) ddI (3) d4T+ddI (4) ZDV Neonatal: same regimen as mother for 6w	(1) 91 (2) 94 (3) 88 (4) 89	Birth: (1) 3.3% (2) 2.1% (3) 2.3% (4) 4.5% 24 weeks: (1) 12.1% (6.2%–20.6%) (2) 10.6% (5.2%–18.7%) (3) 4.6% (1.3%–11.2%) (4) 5.6% (1.9%–12.6%)
Grosch-Worner 2000, AIDS (185)	Investigate ZDV with elective caesarean to reduce MTCT	Cohort, 1985-1999 Germany	With ART: 91% Caesarean, Median age 28y. 100% formula fed. Median CD4 442. Median VL 2000. Without ART: 64% Caesarean, Median age 28y. 97% formula fed. Median CD4 454. Median VL 4150.	(1) No ART (2) ZDV from 32-34w+ZDV during delivery+ 10d neonatal ZDV+caesarean (3) other	(1) 93 (2) 48 (3) 25	Total: 12.6% (1) 14.0% (2) 0% (3) 0%
Hillis 2010, JAIDS (202)	Evaluate influence of type and timing of prophylaxis on MTCT rates	Surveillance data, 2004-2007 Russia	76% 21-30 years. 5% elective caesarean section. 82% no VL data. 46% CD4>350 and 46% no CD4. 86% vaginal delivery	(1) Full course dual/triple ARV (antenatal, intrapartum, neonatal) (2) Full course ZDV (antenatal, intrapartum, neonatal) (3) mother+ neonatal sdNVP (4) Incomplete	(1) 149 (2) 607 (3) 173 (4) 230	(1) 2.7% (2) 4.1% (3) 9.3% (4) 12.2%
Ioannidis, 2001, JID (284)	Evaluate MTCT rates and risk factors for this	Collaboration of RCTs/cohorts, up to mid 1999 Europe and USA.	All mother<1000 cps/ml at delivery, Mean age 27 yrs. Mean CD4 609 (transmitted), 441 (no transmission). 35% caesarean.	(1) All with VL<1000 cps/ml (2) Those on ART (3) Those not on ART	(1) 1202 (2) 834 (3) 368	(1) 3.7% (2) 1.0 (3) 9.8% aOR: Maternal ART: 0.10 Caesarean: 0.30 CD4 per 100: 0.86
Italian Register, 2003, Arch Ped Adolesc Med (180)	Evaluate time trends in prophylactic interventions and determinants of transmission both before and after the introduction of ART	Observational, Jun 85-Dec99, Italy	(1) 17% elective caesarean. 95% formula feed (2) 64% elective caesarean. 98% formula feed.	(1)1985-1995 (1a) None: 92%. (1b) Incomplete PACTG076 regimen: 8%. (1c) Complete PACTG regimen 0.1% (2) 1996-1999 (2a) None: 20%. (2b) Incomplete PACTG076 regimen: 27%. (2c) Complete PACTG regimen 27%. (2d) Combined ART 26%	(1)2658 (2)1112	(1)15.5% (1a) 17.2%. (1b) 13.1%. (1c) 6.7% (2) 5.8% (2a) 20.6% (2b) 4.9% (2c) 2.9% (2d) 1.6%

Author, Year of publication and Journal	Aim	Study design	Study Design			Results
Jackson (HIVNET012), 2003, Lancet (200)	Report safety and efficacy of short course NVP for prevention of MTCT	RCT, Nov 97 – Apr 99 Uganda	Median age 25y. median CD4 ~450. VL 26000 cps/ml. 99% Breastfeed. 13% caesarean	(1) intrapartum ZDV+neonatal ZDV for 7d (2) sdNVP+neonatal sdNVP	(1) 313 (2) 313	Birth: (1) 10.3 (6.9–13.8) (2) 8.1 (5.1–11.2) 14–16 weeks: (1) 22.1 (17.3–26.8) (2) 13.5 (9.7–17.4) 18 months: (1) 25.8 (20.7–30.8) (2) 15.7 (11.5–19.8)
Jamieson (RETRO-CI), 2003, JAIDS (176)	Examine the risk factors for HIV transmission by 1 and 24 months for breastfeeding women	RCT, April 96 – Feb 98 Cote d'Ivoire	99% breastfeeding. 23% CD4<350. 47% VL<10000 at delivery. 42%<25 years.	(1) Placebo (2) ZDV 36w onwards + intrapartum ZDV. No neonatal or post-delivery ART	(1) 124 (2) 126	1 month (KM estimate) (1) 21.9% (2) 11.9% 24 months (1) 29.2% (2) 22.1%
Joao, 2003, AIDS (261)	Evaluate the MTCT rate and factors associated with this in a cohort in Brazil	Observational 1996-2001 Brazil	Limited information	39% ZDV only 28% ZDV+3TC 7% dual therapy (other) 26% triple therapy	297	3.57% (1.82–5.91)
Kakehasi, 2008, Memorias de Instituto Oswaldo Cruz (186)	Assess the determinants of and the temporal trends in vertical transmission rates	Observational, 1998-2005 Brazil	Baby positive: 38% elective Caesarean Median CD4 330 92% VL>1000 34% breastfeed Baby negative: 63% elective Caesarean Median CD4 465 47% VL>1000 4% breastfeed	Baby positive vs negative: None 71% vs 13% ZDV monotherapy 15% vs. 22% Dual 8% vs. 9% HAART 9% vs. 7%	900	6.2%
Kilewo (Mitra), 2008, JAIDS (206)	Investigate the possibility of reducing MTCT through breastfeeding by prophylaxis ART of the infant	Cohort study, Aug 2001- Aug 2003 Tanzania	All breastfeed with short weaning period. Median age 26y. Median 411 CD4. 19% caesarean.	Antepartum: from 36w ZDV+3TC until labour, sdNVP in labour, 1w ZDV+3TC post partum. Neonatal ZDV+3TC for 1week, then 3TC onwards	398	6 weeks: 3.8 (2.0–5.6) 6 months: 4.9 (2.7–7.1)
Kilewo (Mitra plus), 2009, JAIDS (263)	Aim to reduce breast-milk transmission of HIV by treating pregnant women with ART	Cohort study, , Tanzania	All breastfeed with short weaning period. Median age 26y. Median 415 CD4. 18% caesarean. VL 14621.	HAART from 34w or earlier if CD4<200. sdNVP during labour. ZDV+3TC+NVP/NFV during breastfeeding. Neonatal ZDV+3TC for 1w.	441	6w: 4.1% (2.2–6.0) 6m: 5.0% (2.9–7.1) 12m: 5.8% (3.6–8.0) 18m: 6.0% (3.7–8.3)

Author, Year of publication and Journal	Aim	Study design	Study Design			Results
Kouanda, 2010, AIDS Care (262)	Assess the efficacy over 18 months of maternal HAART vs. perinatal short course ART to prevent MTCT	Observational, 2003-2006 Burkina Faso,	~65% aged 25-34. HAART: 51% CD4<200, 41% 200-500, 23%>500. 76% breastfeed Short course ART: 10% CD4<200, 62% 200-500, 29%>500. 89% breastfeed	(1) HAART (ZDV/3TC/NVP for 44%, d4T/3TC/NVP for 50%, 2NRTI+PI, 6%) (2) short-course ART (NVP 93%, ZDV 7%) 83% received neonatal sdNVP, 13% 7d ZDV. 4% no neonatal ART	(1)195 (2)259	Overall: (1) 0.0% (2) 4.6% 2–6 months: (1) 0.0% (2) 6.2% of those tested (n=162)
Kowalska, 2003, Medycyna wieku rozwojowego (233)	Assess the effect of ART on pregnancy outcomes	Observational, Poland	Vaginal deliveries 67.9% women on non-PI HAART and 76.5% of non-treated women. Elective caesarean monotherapy 28.1% of women under monotherapy and non-treated 17.6%	ART 81 (79.4%); ZDV monotherapy 35 (34.4%). PI-based HAART 18 (17.6%) patients. Non-PI based HAART 28 (27.4%)	102	(1) Any ART 8.8% (2) No ART 25% (3) HAART 0%
Kumwenda (PEPI) 2008, NEJM (279) and Taha 2011, JAIDS (280)	Evaluate effectiveness of different strategies to prevent MTCT during breast-feeding phase	RCT, Apr 2004-Aug 2007 Malawi	Mean age 26y. Median CD4~400. 95% vaginal delivery. All breastfeed for 6 months. Only babies HIV- at birth were included	All mothers offered sdNVP during labour Neonatal: (1) sdNVP +1w ZDV (2) sdNVP +1w ZDV + NVP until 14w (3) sdNVP +1w ZDV+ NVP/ZDV until 14w	(1)1003 (2)1016 (3)997	9m (excluding those infected at birth): (1) 11.12 (2) 5.01% (3) 6.02% 24m (excluding those infected at birth): (1) 15.57 (2) 10.76% (3) 11.17%
Lallemant (Perinatal HIV Prevention Trial (Thailand), 2000, NEJM (195)	Determine the optimal duration of ZDV administration to prevent MTCT	RCT Jun 97-Dec 99 Thailand	Median age 25y. Median CD4 360. 83% vaginal delivery. No breastfeeding	(1) ZDV 28w gestation, intrapartum ZDV, neonatal ZDV to 6w (2) ZDV 35w gestation, intrapartum ZDV, neonatal ZDV to 3d (arm stopped early) (3) ZDV 28w gestation, intrapartum ZDV, neonatal ZDV to 3d (4) ZDV 35w gestation, intrapartum ZDV, neonatal ZDV to 6w	(1) 401 (2) 229 (3) 340 (4) 338	At Apr 98: (1) 4.1 (1.4–6.7) (2) 10.5 (6.4–14.4) Final analysis (1) 6.5 (4.1–8.9) (3) 4.7 (2.4–7.0) (4) 8.6 (5.6–11.6)
Lallemant (Perinatal HIV Prevention Trial PHPT-2 (Thailand)), 2004, NEJM (218)	Evaluate whether addition of sdNVP to ZDV regimens would further reduce MTCT transmission rates	RCT, Jan 2001-Feb 2003 Thailand	All formula fed. Median age 26y. Median VL 4.1 log. Median CD4 370. 20% caesarean.	During pregnancy: ZDV during 3rd trimester (median 29w) Plus (1) sdNVP during delivery + neonatal sdNVP+7d ZDV (2) sdNVP during delivery + neonatal placebo+7d ZDV (3) placebo during delivery + neonatal Placebo+7d ZDV	(1) 724 (2) 721 (3) 360	First interim analysis (before (3) was stopped) (1) 1.1 (0.3–2.2) (2) 2.1 (0.6–3.7) (3) 6.3 (3.8–8.9) Final analysis: (1) 1.9 (0.9–3.0) (2) 2.8 (1.5–4.1)

Author, Year of publication and Journal	Aim	Study design	Study Design			Results
Limpongsanurak, 2001, J Med Assoc Thai (196)	Assess efficacy of intrapartum ZDV in reduction of maternal VL and its potential role in reducing MTCT amongst women with no prior ART	Prospective observational Thailand	Median VL 29,401 in labour and 32,555 delivery	ZDV during delivery	26	19.2% (4–34).
Limpongsanurak, 2001, J Med Assoc Thai (197)	Evaluate the effectiveness of short course ZDV to reduce MTCT	RCT. Thailand,	No breastfeeding.	(1) short course of ZDV from 38w + ZDV in delivery (2) placebo	182	6m: (1) 14.9% (11.1–18.7) (2) 16.3% (12.3–20.9)
Lolekha, 2001, ICCAC (208)	Describe the efficacy and safety of ZDV with 3TC	Feb 99- Nov 00, pilot study Thailand,	No breastfeeding Mean VL and CD4 4.26 log10 and 314. At delivery, the mean VL reduction at delivery 1.48 log10L,79% vaginal and 21% caesarean	Short course ZDV+3TC from 34w until delivery, ZDV+3TC during labour. Neonatal ZDV for 4w.	109	4.7% (0.6–8.8%).
Lopez-Cortes, 2007, TDM (234)	Evaluate the efficacy of SQV/r plus 2 NRTIs using a therapeutic drug monitoring approach	Prospective observational, Spain	Median age 31y. Median CD4 441. Median VL at entry 3710. 88% VL<50 at delivery. 52% vaginal delivery	SQV+2 NRTIs on average at 20w, ZDV during labour. Neonatal ZDV 6w.	49	0%
Lyall, 1998, BMJ (179)	Examine change in uptake of interventions to reduce MTCT	Retrospective observational, 1994-1997 UK	No breastfeed. 53% Caesarean. CD4 at delivery 305. VL 3.6log at delivery.	69% some ART. 46% 076 complete regimen 12% 076 incomplete regimen 9% ZDV+3TC 2% ZDV+3TC+IDV	57	Overall: 12% (3–22) Any ART: 8% No ART: 22%
Magder, 2005, JAIDS (235)	Identify predictors of in utero and intrapartum HIV transmission	Prospective observational, 1990-2000 USA	No breastfeeding. 79% vaginal delivery. Age 29% 25-29y. 46% CD4%>30%	(1) Overall (2) none in pregnancy (3) monotherapy in pregnancy (4) combination in pregnancy (5) HAART in pregnancy	(1) 1709 (2) 520 (3) 691 (4) 169 (5) 299	(1) Overall: 9.7% In utero: 3.3% After birth: 6.7% (2) In utero:5.2%; After birth: 12.8% (3) In utero:2.9%; After birth: 6.4% (4) In utero:3.0%; After birth: 0.6% (5) In utero:0.3%; After birth: 0.7%

Author, Year of publication and Journal	Aim	Study design	Study Design			Results
Makokha, 2002, East African Med J (187)	Investigate the effects of short course ZDV on maternal immune responses and risk of infant infection	Prospective Kenya	All breastfed	Short course ZDV from 36w pregnancy, ZDV during labour, maternal ZDV 4w post-delivery	59	20%
Mandelbrot, 2001, JAMA (216)	Assess safety of perinatal ZDV+3TC therapy, its effects on viral load, acquisition of drug resistance and MTCT rates	Prospective observational Feb97-Sep98 + retrospective controls May 94-Feb 97 France	(1) Age median 30y. median CD4 426. 22% elective caesarean. 0.5% breastfeed. VL at enrolment 3.6 log (2) Age median 29y. median CD4 436. 16% elective caesarean. 0.3% breastfeed. VL at enrolment 3.6 log	(1) Standard 076 complete regimen+3TC 32w pregnancy, neonatal 3TC 6w (2)Standard 076 complete regimen	(1)445 (2)899	(1) 1.6% (0.7%–3.3%) (2) 6.8% (5.1%–8.7%),
Marazzi (DREAM), 2007, Eur J Ped (236)	Evaluate the implementation of ART to prevent MTCT in a public health setting	May 02-Dec 05, observational Mozambique	Formula feed. Median age 24y. Median CD4 489. 90% VL<1000 at delivery.	HAART during pregnancy (median 27w) to 6m post-partum.	1259	1 month: 3.8% (3.1–4.5) 6 months: 5.3% Neonatal ZDV at 1 month: Yes 3.8%, No 3.1%
Marazzi (DREAM), 2010, AIDS (237)	Evaluate the effect of extended triple ART on infant outcomes	Retrospective cohort, Jul 05-Dec 09, Malawi and Mozambique	46% CD4<350. Majority breastfeed. No info on mode of delivery.	HAART 14w if required for own health and 25w if for PMTCT until 6m if breastfeeding	3148	1 month: 0.8% 6 months (not infected at 1): 0.9% 12m (not infected at 6): 0.3% HIV-infections. 12 months (total): 2.0%, HAART before delivery: 0.9% HAART at delivery or post-delivery: 5.1%
Martinelli, 2008, HIV Clin Trials (238)	Analyse changes over 2 decades in HIV positive women followed at a specialised regional centre	1985-2006, Prospective observational Italy	Mean age 31y. CD4 at delivery (1)32% vaginal delivery. 37% CD4>500. (2)6% vaginal delivery. 38% CD4>500.	(1) Pre-HAART 1985-1996 27% ZDV monotherapy during pregnancy (2)HAART 1997-2006 During pregnancy: 10% no ART 19% ZDV monotherapy 20% dual therapy 51% HAART During delivery: 98% ZDV Neonatal: 100% ZDV	(1)44 (2)157	(1) 36% (22%–51%) (2) 0.6% (0%–3.5%)

Author, Year of publication and Journal	Aim	Study design	Study Design			Results
Martinson, 2007, JAIDS (294)	Compare the effectiveness of sdNVP in preventing peripartum MTCT in successive pregnancies	Observational (1)Jun 03-Apr 05 (2)Mar 01-Jul 03 (1) South Africa (2) Cote d'Ivoire	(1) Median age 26y. Median CD4 400. 79% vaginal delivery. 100% formula feed 1st pregnancy, 91% 2nd pregnancy. (2) Median age 28y. Median CD4 462. 98% vaginal delivery. 22% formula feed 1st pregnancy, 8% 2nd pregnancy.	(1) HIVNET012 regimen (2) ZDV or ZDV/3TC during pregnancy. sdNVP during labour. Neonatal sdNVP+ZDV 7d.	(1) 90.1st (1) pregnancy. 108 2nd pregnancy. (2) 38 1st pregnancy. 37 2nd pregnancy.	in the first pregnancy exposed to sdNVP were (1) 11.1% (5.5%–19.5%), 1st pregnancy. 11.1% (5.9%-18.6%) 2nd pregnancy (2) 13.2% (4.4%–28.1%) 1st pregnancy. 5.4% (0.6%–18.2%) 2nd pregnancy
Martinson, 2009, AIDS (295)	Assess the impact of prior exposure to sdNVP on MTCT and genotypic resistance in HIV positive women	Observational, Jun03-Apr05 South Africa	(1) Median age 28y. Median CD4 400. 16% caesarean. 10% breastfed. (2) Median age 29y. Median CD4 375. 16% caesarean. 8% breastfed.	All receive HIVNET012 regimen (1) Previous sdNVP experienced. (2) Previous sdNVP naïve.	(1)108 (2)193	(1)11.1% (5.9–18.6) (2) 4.2% (8–8.0)
Matida, 2011, JAIDS (239)	Estimate vertical transmission rates in Sao Paolo, Brazil and identify potentially associated factors	Cross-sectional, 2006 Brazil	Mean age 29y. 73% caesarean. 98% formula fed.	(1) Overall (2) Mother HAART vs no HAART (3) mother any prophylaxis vs no (4) mother ART at delivery vs none (5) neonatal prophylaxis vs no	(1) 982 (2) 259 vs 530 (3) 750 vs 46 (4) 705 vs 68 (5) 743 vs 13	(1) 2.7% (1.86-3.94) (2) 3.1 vs 3.6 (3) 2.7 vs 15.2 (4) 2.4 vs 11.8 (5) 2.2 vs 23.1
McConnell, 2007, JAIDS (296)	Evaluate efficacy of repeat sdNVP to prevent MTCT	(1) Retrospective cohort 1997-1999 (2) Prospective cohort Jul 04-May 06 Uganda	(1a) median 4m breastfeeding. (1b) median 4m breastfeeding (2a) median age 27y. median CD4 459. Median VL at delivery 14100. 93% vaginal delivery. 78% breastfeeding. (2b) median age 25y. median CD4 470. Median VL at delivery 20200. 85% vaginal delivery. 74% breastfeeding.	(1a) HIVNET012 regimen no prior sdNVP (1b) HIVNET012 regimen with prior sdNVP exposure (2a) HIVNET012 regimen no prior sdNVP (2b) HIVNET012 regimen with prior sdNVP exposure	(1a) 42 (1b) 62 (2a) 64 (2b) 39	(1a) 16.7% (1b) 11.3% (2a) 6w 18.7% 12m18.7% (2b) 6w 17.9% 12m 20.5%
McGowan, 1999, Obs Gynae (240)	Describe the safety, efficacy and perinatal transmission rates of HIV with combination therapy in pregnancy	Retrospective observational, Sep 96-Sep 98, USA	Median age 29y. Median CD4 285. 65% ART-experienced. 43% VL undetectable at delivery. 68% vaginal delivery. All formula fed.	All receive cART for median of 26w. 50% dual NRTIs 43% PI+2NRTIs 7% NNRTI+2NRTIs	30	0
Melvin, 1997, JAIDS (188)	Determine the effect of pregnancy and ZDV on viral load in HIV-positive women	Jun 91-Aug 95, Prospective observational, USA	(1) Median CD4 442. (2) Median CD4 534	(1) 23/44 initiated ZDV monotherapy at median 23w. (2) 17 untreated (although 5 received ZDV during delivery)	44	(1) 4% (0.9–18.9%) (2) 12.5% (4–38%)

Author, Year of publication and Journal	Aim	Study design	Study Design			Results
Mirkuzie, 2010, BMS Health Serv Res (223)	Examine trends in in pMTCT service utilisation and assessed MTCT rate in relation to policy changes in national pMTCT programmes	Retrospective observational, Feb 04-Aug 09, Ethiopa	Surveillance data. Recommendation of exclusive breastfeeding from 2006 onwards	Pre-2008: sdNVP during pregnancy, neonatal sdNVP Post-2008: ZDV from 28w +3TC/sdNVP during labour + ZDV postpartum 7d Neonatal ZDV/sdNVP + 7d or 28d ZDV 42.4% (41.4-43.5) mothers received ART 31.0% (30.0-31.0) neonatal ART	896	2006: 14.3% (7.92–24.0) 2007: 15.0% (9.8–22.1) 2009 (those on multidrug ZDV regimen) 8.2% (5.55–11.97)
Moodley, (PHPT-1), 2003, J Infect Dis, (217)	Determine efficacy and safety of 2 inexpensive and easily deliverable ARV regimens for the prevention of MTCT during labour and delivery	RCT May 99- Feb00 South Africa	Women randomized during labour Median age 25y Median CD4 at delivery around 400 71% vaginal delivery VL<400 at delivery 13% 47% ever breastfed	(1) maternal sdNVP + neonatal sdNVP (2) intrapartum ZDV/3TC + ZDV/3TC 1w post delivery + neonatal ZDV 1w	(1) 506 (2) 497	Intrauterine: (1) 7.0 (5.0–9.0) (2) 5.9 (4.1–7.7) Intrapartum to 8w: (1) 5.7 (3.7–7.8) (2) 3.6 (2.0–5.3) All to 8w: (1) 12.3 (9.7–15.0) (2) 9.3 (7.0–11.6)
Morris, 2005, JAIDS (241)	Better understand effects of PI use during pregnancy on prematurity, maternal and infant adverse events and infant outcomes	Observational, retrospective Dec 97-Dec 01 USA	Median age 27y. Median CD4 at 2st visit 372. At delivery 410. 20% first visit-56% delivery VL<400.34% vaginal delivery, 56% elective caesarean.	92% NFV+NRTIs 93% ZDV+3TC backbone	231	0.9 (0.1–3.1)
Namukwaya, 2011, JAIDS (242)	Describe the ARV drugs given in Malawi in pMTCT program and its impact on early infant transmission rates	Retrospective review, Jan 07-May 09, Uganda	(1) Age 60% 20–29y. CD4<350 45%. 94% breastfeeding (2) Age 66% 20–29y. CD4<350 45%. 98% breastfeeding (3) Age 63% 20–29y. CD4<350 86%. 89% breastfeeding (4) Age 69% 20–29y. CD4<350 18%. 92% breastfeeding (5) Age 70% 20–29y. CD4<350 16%. 96% breastfeeding	(1) maternal sdNVP +ZDV/3TC 7d postpartum (2)ZDV from 28w plus sdNVP in labour (CD4>350) (3) ZDV/3TC from 33w +maternal sdNVP in labour (CD4>350) (4) HAART (ZDV/3TC/NVP) (CD4<250) (5) None All neonates (except (5)): sdNVP+7d ZDV	(1)367 (2)694 (3)23 (4)788 (5) 22	(1)11.2% (2)4.6% (3)4.9% (4)1.7% (5)36.4%

Author, Year of publication and Journal	Aim	Study design	Study Design			Results
Naver, 2006, JAIDS (243)	Describe the HIV epidemic among childbearing women and their children in Sweden	1982-2003, Observational, Sweden	Breastfeeding prohibited nationally (1) Age 25–29y 40%. 83% vaginal delivery. (1) Age 25–29y 35%. 52% vaginal delivery. (1) Age 25–29y 23%. 2% vaginal delivery.	(1)1982-1993 None: 98% ZDV only: 2% (2)1994-1998 None: 11% ZDV only: 53% Dual therapy: 17% 3 or more drugs: 17% Unknown: 1% (3)1999-2003 None: 4% ZDV only: 16% Dual therapy: 15% 3 or more drugs: 61% Unknown 5%	(1) 87 (2) 92 (3) 178	(1) 24.7 (16.4–34.1) (2) 5,7 (2.3–12.1) (3) 0.6 (0.1–3.1)
Nielsen-Saines NICHD HPTN 040/PACTG 1043, 2011 CROI Abstract (273)	Evaluate the safety and efficacy of adding 1 or 2 ARVs to a standard ZDV prophylaxis in formula fed infants in mothers not receiving ART prior to labour	RCT Apr 04- Jul 2010 Brazil, South Africa, Argentina, USA	Median age 26y Median CD4 463 Median VL 4.2 log 64% Vaginal delivery Women undiagnosed during labour/after delivery All babies formula fed (except 9.3% breastfed before HIV diagnosis obtained)	(1) neonatal ZDV 6w (2) neonatal ZDV 6w + 3 doses NVP (3) ZDV 6w + 3TC/NFV 2w No maternal ART except 41% ZDV in labour	1684	In utero: (1) 6.8 (5.0–9.3) (2) 5.1 (3..5–7.3) (3) 5.2 (3.6–7.4) Intrapartum: (1) 4.9% (3.3%–7.2%) (2) 2.2 (1.2%–4.0%) (3) 2.5 (1.4%–4.3%) 6m: (1) 11.0 (8.7–14.0) (2) 7.1 (5.2–9.6) (3) 7.4 (7.3–10.0)
Panburana, 2004, Amer J Obs Gynae (207)	Evaluate the effect of elective caesareans plus ZDV+3TC regimens on mothers and their infants	1999-2000 single-arm interventional study, Thailand	100% Caesarean section. 335 at study entry. 420 at delivery. VL 3.65log at study entry, 1.12 log at delivery. 0% breastfeeding. Mean age 26.4y.	3TC/ZDV from 34w, ZDV during delivery, neonatal ZDV 4w	46	4.3 (0.5–15.7)
Parisaei, 2007, Int J STD AIDS (257)	Compare deliveries in women with HIV to the general antenatal hospital population	Observational, retrospective, 1994-2004, UK	80% Caesarean section. Mean age 29y. CD4>350 at study entry47%, at delivery 62%. VL<50 19% at study entry to 55% at delivery	Pregnancy: ZDV mono 11% 77% triple therapy 1% ZDV+3TC 2 1% quadruple drugs 63% intrapartum ZDV.	113	1.8%

Author, Year of publication and Journal	Aim	Study design	Study Design			Results
Patchen, 2001, AIDS Reader (189)	Determine MTCT rates when ZDV was given to mothers during labour, to their infants postnatally or both	Jan1992-Jul1998, Observational study, USA	?	No ART during pregnancy. (1) Any ZDV during delivery or neontatally (2) ZDV during delivery (3) ZDV during delivery+ neonatal ZDV (4) neonatal ZDV alone	(1) 59 (2) 9 (3) 37 (4) 13	(1) 11.9 (4.9–22.9) (2) 11.1 (0.3–48.2) (3) 13.5 (4.5–36,0) (4) 7.7 (0.2–36.0)
Patel, 2009, JAIDS (244)	Evaluate the efficacy of triple ART on pMTCT rates	Dec02-Oct07. Prospective observational, India	Median age 26y. No breastfeeding. CD4>200 in 79%. Median CD4 at delivery 462. 58% Caesarean section.	No Art given intrapartum Neonatal ZDV 6w 61% ZDV/3TC/NVP 36% ZDV/3TC/NFV 2% ZDV/3TC/LPV/r 1% d4T/3TC/EFV	89	5.55%
Peltier, 2009, AIDS (245)	Assess the 9-month HIV-free survival of children with two strategies to prevent MTCT	Prospective interventional study, Man05-Jan07, Rwanda	Median age 29y. median CD4 461. 16% caesarean section	From 28w during pregnancy: CD4<350 received: d4T/3TC/NVP CD4>350 ZDV/3TC/EFV Neonatal sdNVP+ZDV 7d (1) Formula feed (2) Breastfeed+7 m HAART during breastfeeding	(1) 305 (2) 227	(1) 6w: 1% (0.3–3.0%).6m: 1% (0.3–3.0%). (2) 6w: 1.3% (0.4–4.1%) 6m: 1.8% (0.7–4.8%),
Saba (PETRA), 2002, Lancet (267)	Assess the efficacy of short-course regimens with ZDV+3TC in a predominantly breastfeeding population	RCT, Tanzania, South Africa, Uganda	Median age 26. Median CD4 about 440. 74% breastfed. 33% caesarean.	(1) ZDV/3TC at 36w, ZDV/3TC intrapartum, ZDV/3TC 7d post partum, neonatal ZDV/3TV 7d (2) no ART in pregnancy ZDV/3TC intrapartum, ZDV/3TC 7d post partum, neonatal ZDV/3TV 7d (3) No ART in pregnancy or post partum ZDV/3TC intrapartum (4) Placebo (no ART)	(1) 268 (2) 251 (3) 255 (4) 253	6w: (1) 5.7 (2) 8.9 (3) 14.2 (4) 15.3 18m: (1) 14.9 (9·4–22·8), (2) 18·1% (12·1–26·2) (3) 20·0% (12·9–30·1) (4) 22·2% (15·9–30·2)
Samelson (PACTG 367), 2000, Amer J Obs Gynae (246)	Evaluate MTCT rates according to ART and VL during pregnancy	Retrospective data extraction, 1998-2000, USA	Elective Caesarean increased from 12% to 29%. 16% VL below detection. Median CD4 392, median VL 4000.	(1) No ART (2) ZDV or NVP monotherapy (3) combination NRTI (4) NNRTI-containing regimen (5) PI-containing regimen	2087.	Overall 3.6% From 4.3 (1998) to 1.6% (2000) (1) 20% (2) 5.3% (3) 1.8% (4) 2,4% (5) 1.6%

Author, Year of publication and Journal	Aim	Study design	Study Design			Results
Shaffer, 1999 Lancet (193)	Investigate the safety and efficacy of short course oral ZDV administered during late pregnancy and labour	RCT May 96 – Dec97 Thailand	(1) Median age 24y. Median CD4 427. Median VL 29952. 84% vaginal delivery. No breastfeeding (2) Median age 24y. Median CD4 411. Median VL 33933. 88% vaginal delivery. No breastfeeding.	(1) 36w ZDV and during delivery. (2) Placebo	(1) 194 (2) 198	6m: (1) 9.4% (2) 18.9% In utero: (1) 4.8 (2.4–8.6) (2) 6.7 (3.8–10.9) Intrapartum: (1) 5.2 (2.6–9.3) (2) 13.5 (9.0–19.1)
Shapiro (Mma Bana), 2010, NEJM (277)	Evaluate the most effective HAART regimen to prevent MTCT and transmission during breast-feeding	(1) RCT plus (2) observational study, Jul 06-May08, Botswana	(1) All CD4>200. All breastfed. Median age ~26y. median VL at entry ~30,000. VL<400 at delivery 1a 96% 1b 93% (2) CD4<200. Median age 29y. median VL at entry 9100. VL<400 at delivery 92%.	All: Neonatal sdNVP+4w ZDV (1a) ABA/3TC/ZDV from 26-34w gestation until weaning/6m post partum (1b) LPV/r/ZDV/3TC from 26-34w gestation until weaning/6m post partum (2) NVP/3TC/ZDV from 18-34w gestation	(1a) 283 (1b) 270 (2) 156	6m: (1a) 2.1% (1b) 0.4% (2) 0.6%
Shapiro, 2006, AIDS (224)	Determine whether maternal NVP dose could be eliminated from MTCT regimens in the setting of short course ZDV	RCT, Jun 02-Oct 03, Botswana	Baseline CD4 |360. VL 4.3 log. 50% breastfed.	All: ZDV from 34w gestation or HAART if CD4<200. Intrapartum ZDV Neonatal sdNVP +1m ZDV. (1) sdNVP to mother in labour (2) placebo to mother in labour	(1)327 (2)329	1m: (1) 4.3% (2) 3.7%
Sirinavin, 2000, Int J infect Dis (190)	Describe the effects of various ZDV regimens on vertical transmission of HIV	Observational, Nov 91-Feb 99, Thailand	Advised not to breastfeed. (1) Median age 26y. 100% vaginal delivery. (2) Median age 25y. 85% vaginal delivery. (3) Median age 28y. 79% vaginal delivery. (4) Median age 26y. 69% vaginal delivery.	(1) No ZDV (1991-1996) (2) ZDV at 34-36w gestation until labour (95-98) (3) ZDV at 34-36w gestation until labour + neonatal ZDV for 4-6w (97-98) (4) ZDV at 34-36w gestation until labour + neonatal ZDV for 4-6w+intrapartum ZDV (98-99)	(1) 48 (2) 47 (3) 28 (4) 13	18m: (1) 22.9% (12.0–37.3 (2) 21.3% (10.7–35.7) (3) 0% (0.0%–12.3%) (4) 0.0% (0.0%–24.7%)
Taha (Postnatal NVP+ZDV trial), 2004, JAMA (203)	Determine risk of MTCT when wither standard NVP or NVP with ZDV is administered to infants born to women tested at delivery	RCT, April 00-Mar 03, Malawi	Mean age 25y. Mean VL 4.4 log. 94% vaginal delivery. All breastfed.	All: Maternal sdNVP during delivery. Neonatal: (1) sdNVP (2) sdNVP+ZDV 7d	(1) 389 (2) 408	Birth: (1) 8.1% (2) 10.1% 6-8w (1) 14.1% (10.7–17.4) (2) 16.3% (12.7–19.8)

Author, Year of publication and Journal	Aim	Study design	Study Design			Results
Taha (NVAZ), 2003, Lancet (204)	Determine whether post-exposure neonatal prophylaxis with NVP or NVP plus ZDV is more effective in reducing MTCT rates	RCT, Apr 00-Jan 02, Malawi	All women late presenters (within 2h of giving birth). Mean age 25y. Mean VL 4.5 log.99.4% vaginal delivery. 99.7% breastfed.	(1) Neonatal sdNVP (2) Neonatal sdNVP+ ZDV 7d	(1)557 (2)562	6-8w: (1) 20.9% (2) 15.3% 6/8w (excluding HIV+ at birth): (1) 12.1% (2) 7.7%
Tariq (ECS), 2011, JAIDS (247)	Compare ZDV-sparing with ZDV-containing HAART in relation to maternal VL at delivery, MTCT rates and congenital abnormality	Observational, Jan 00-Jun 09, Europewide	(1) 18.4% detectable VL (2) 28.6% detectable VL	(1) ZDV-sparing HAART (2) ZDV-containing HAART	(1) 1199 (2) 6374	(1) 0.8% (2) 0.9%
Thior, 2006, JAMA (219) (Mashi)	Compare efficacy and safety of 2 infant feeding strategies for the prevention of post-natal MTCT	2x2 factorial RCT, Mar 2001-Oct 2003, Botswana		All: ZDV from 34w gestation and during labour. (1a) sdNVP (both maternal and neonatal) (2a) placebo (1b) 6m breastfeeding + 6m neonatal ZDV (2b) formula+1m neonatal ZDV		7m: (1a) 4.9% (1b) 9.3% (2a) 9.0% (2b) 5.6%
Thomas (KiBs), 2011, PLOS Med (265)	Investigate whether maternal triple ART designed to maximally suppress VL in late pregnancy and first 6 months of lactation is safe, well tolerated and effective	Intervention study, Jul 03-Feb 09, Kenya	All breastfed. Median age 23y. Median CD4 398. Median Baseline VL 33975. 76% vaginal delivery. 33% VL<50 at delivery.	(1) ZDV/3TC/NVP or (2) ZDV/3TC/NFV for 34-26w gestation until 6 months post-delivery. Neonatal sdNVP. Median 5.6w ART.	(1)288 (2)203	Birth: 2.5% 6w: 4.2% 6m: 5.0% 12m: 5.7% 24m: 7.0%
Thorne, 2001, AIDS (177)	Describe changes over a 15-year period in characteristics and management of HIV-positive pregnant women in Europe	Cohort study, 1985-2000 Europewide	Average age 27 years, IDU declined from 82% to 33% over study period, 52% mothers diagnosed in pregnancy, median CD4 440. 2% breastfed. Elective caesareans rose from 10% in 1992 to 71% in 99/00	(1) Incomplete 076 regimen: (2) Complete 076 regimen: (3) Combination therapy: (4) None	(1) 612 (2) 494 (3) 118 (4) ?	Overall: Declined from 15.5% (94) to 2.6% (98-00) (1) 5.7% AOR=0.41 (0.25–0.67) (2) 4.0% AOR=0.34 (0.18–0.63) (3) 1.7% AOR=0.15 (0.002, 1.13) (4) reference

Author, Year of publication and Journal	Aim	Study design	Study Design			Results
Thorne, 2009, BMC Infect Dis (248)	Evaluate uptake and effectiveness of interventions to prevent MTCT within operational settings	Prospective observational, 2000-Jan 08, Ukraine	45%<25 years. 1% breastfed. 38% elective caesarean. No CD4/VL available	Antenatal/intrapartum ART (1) None (2) sdNVP (3) ZDV (4) ZDV+sdNVP (5) HAART	(1) 120 (2) 395 (3) 286 (4) 813 (5) 76	Overall: 11.4 (9.9–13.0) (1) 26.7% (19.0–35.5), (2) 15.7% (12.3–19.7) (3) 7.0% (4.3–10.6) (4) 9.2% (7.3–11.4) (5) 3.9% (0.8–11.1)
Townsend, 2008, AIDS (249)	Explore impact of different strategies to prevent MTCT at a population level	2000-2006, Prospective observational, UK and Ireland	56% undetectable at delivery. Median age 30y. 57% elective caesarean. 0.6% breastfeeding. 35% CD4>500.	(1) None (2) Monotherapy (3) Dual therapy (4) HAART	(1) 143 (2) 638 (3) 126 (4) 4120	(1) 9.1% (aOR 10.2; 5.33-19.53) (2) 0.5% (aOR 0.48; 0.15-1.56) (3) 0.8% (aOR: 0.82; 0.11-5.98) (4) 1.0% (1.00; reference)
Van Dyke, 1999, JID (191)	Study clinical and biological factors that contribute to MTCT	Apr 93- Mar 95, Prospective observational, USA	Median entry CD4 461. 163 vaginal delivery.	81% ARV during pregnancy. 67% intrapartum ART. 67% neonatal ZDV.	209	9.1 (5.2-13.0)
Von Linstow, 2010, HIV Med (250)	Describe trends in the management of pregnancies in HIV-infected women and their outcomes	Jun 1994-Jun 2008, national Retrospective cohort, Denmark	Mean age 31y. 2% breastfeeding. CD4 at delivery median 444. 81% undetectable VL at delivery. 84% caesarean.	51.5% on ART prior to pregnancy. 8% never received ART during pregnancy. 91% intrapartum ZDV.	258	2.4% overall. No infections occurred amongst those receiving ART
Wade, 2004, JAIDS (270)	Describes factors associated with perinatal transmission from 1997-2000	Observational, 1997-2000, USA	42% 20-29y. 764% vaginal birth. CD4 and VL and feeding unavailable	(1) No ART (2) PN, IB, NB (3) IP, NB (4) NB only (5) other (6) unknown	(1) 1036 (2) 568 (3) 824 (4) 708 (5) 141 (6) 192	(1) 19,4% (aOR 1.0) (2) 3.3% (0.1; 0.1–0.2) (3) 9.4% (0.4; 0.2–0.7) (4) 11.9% (0.5; 0.3–0.8)) (5) 4.7% (0.2; 0.1–0.4) (6) 12.5% (-)
Warszawski, 2008, AIDS(285)	Identify factors associated with MTCT from mothers receiving antenatal ART	Observational 1997-2004 France	CD4 at delivery: <200 10.2%, >350 67.7%. 46% elective caesarean, 33.5% vaginal delivery. No breastfeeding	All received ART Maternal: (1a) HAART 47.8% (2a) Dual 33.2% (3a) mono 19.1% Intrapartum (1b) Yes 95.6% (2b) No 4.4% Neonatal: (1c) dual/HAART 23% (2c) Monotherapy 76.3% (3c) none/late 0.7%	5271	(1a) 1.2% (2a) 1.3% (3a) 1.5% (1b) 1.2% (2b) 3.1% (1c) 1.8% (2c) 1.2% (3c) -

Author, Year of publication and Journal	Aim	Study design	Study Design			Results
Wiktor (CDC Short course ZDV trial), 1999, Lancet, (192)	Assess safety and efficacy of short-course perinatal ZDV	RCT, Apr 96-Feb 98 Cote d'Ivoire	All breastfed. Median age 26y. 54% CD4>500. 1% caesarean.	(1) ZDV from 36w, intrapartum ZDV (2) Placebo	(1) 115 (2) 115	4w: (1) 21.7% (2) 12.2% 3m: (1) 26.1% (2) 16.5%
Bhoopat(198), 2005, JAIDS	Determine the optimal duration of ZDV prophylaxis for subtype E and confirm its effectiveness at the histological level	RCT, Thailand	No breastfeeding. Median CD4 ~370. Median VL at baseline ~3.8 log.	(1)ZDV from 35-38w gestation, intrapartum ZDV (2) ZDV from 27-31w gestation, intrapartum ZDV	(1) 27 (2) 23	(1) 14.8% (2) 0%
Kiarie(201), AIDS 2003	Evaluate compliance to ART regimens to prevent MTCT	RCT, Kenya, Nov 99-Jan 01	Median age 25y. >90% vaginal delivery. 66% breastfed. No CD4 or VL available.	(1) ZDV from 36w + intrapartum ZDV (2) maternal+neonatal sdNVP	(1) 55 (2) 55	6w: Overall: 15% (8%, 22%) (1) 9% (2) 22% (p=0.07)
Thistle(199), Central African J Med, 2004	Assess practicality and effectiveness of ultra-short ZDV regimen to prevent MTCT	RCT, Zimbabwe, unknown dates	Women presenting for care before 36 weeks	(1) ZDV from 36w gestation, intrapartum ZDV (2) intrapartum ZDV, neonatal ZDV for 3d	(1) 90 (2) 89	6w (1) 18.9 (10.8–27.0) (2) 15.7 (8.1–23.4) (equivalence demonstrated)
Thistle(225), 2007, CID	Compare MTCT rates seen with NVP vs. NVP plus ZDV regimens	RCT, Zimbabwe, Dec 02-Aug 04	Mean age 26y. 91% spontaneous delivery. 91% breast fed. 0% mixed feeding. No CD4 or VL available	(1) intrapartum ZDV+sdNVP. Neonatal sdNVP+ZDV for 3d. (2) intrapartum ZDV. Neonatal ZDV for 3d.	(1) 312 (2) 297	Birth (1) 5.1% (2) 5.1% 6w (1) 14.4% (2) 16.5% Difference: 1.8 (-4.9, +8.4)

[#]Evaluable for HIV MTCT rate (not necessarily total study sample size).

ZDV=zidovudine. 3TC=lamivudine, sdNVP=single dose nevirapine. NVP=nevirapine. NFV=nelfinavir. ABA=abacavir. LPV/r=lopinavir/ritonavir. NNRTI=non nucleoside reverse transcriptase inhibitor. PI=protease inhibitor. NRTI=nucleoside reverse transcriptase inhibitor. D4T=stavudine. EFV=efavirenz. IDV=indinavir. SQV=saquinavir. ddI=didanosine. CBV=combivir (combined ZDV+3TC). ART=antiretroviral therapy.

HAART=highly active antiretroviral therapy.

VL=viral load. RCT=randomised controlled trial. OR=odds ratio. aOR=adjusted odds ratio. Ref=reference category

All CD4 counts given in cells/mm^3. All viral loads given in copies/ml.

PN=prenatal. IP=intrapartum. NB=newborn.

y=years; m=months; w=weeks; d=days

Where numbers are given in parentheses these are 95% confidence interval estimates unless otherwise stated

A2.4 Post exposure prophylaxis

Author, Journal and Year	Title	Type of study, Population and Setting	Aim	Main Results/Conclusions
Animal models				
Böttiger et al AIDS. 1997 (315)	Prevention of simian immunodeficiency virus, SIVsm, or HIV-2 infection in cynomolgus monkeys by pre- and post exposure administration of BEA-005	Animal model assessing efficacy of pre and post exposure therapy to prevent transmission of simian immunodeficiency virus (SIV) in macaque monkeys	To study the effect of 2,3'-dideoxy-3'-hydroxymethyl cytidine (BEA-005) on acute SIV and HIV-2 in macaques	RESULTS: Treatment with BEA-005 for 3 days blocked infection with SIV in 4 out of 4 monkeys if given 1,3 or 8 hours after exposure. Infection was prevented in 1 out of 2 monkeys when initiated at 24h after virus inoculation. Treatment initiated 3 or 6 days after virus inoculation did not prevent infection CONCLUSIONS: Administration of PEP conferred no benefit if given later than 72 hours post exposure. Greatest benefit was seen if given within first 8 hours.
Martin et al. JID, 1993 (324)	Effects of initiation of 3'-azido,3'-deoxythymidine (zidovudine) treatment at different times after infection of rhesus monkeys with simian immunodeficiency virus.	Animal model assessing efficacy of post exposure therapy with AZT to prevent transmission of simian immunodeficiency virus (SIV) administered intravenously to macaque monkeys	To study the effects of initiating treatment with zidovudine for 28 days at different times after inoculation of SIV in rhesus monkeys compared to controls	RESULTS: Treatments initiated 1–72 h AI prevented the establishment of persistent SIV antigenemia; greater effects were observed with earlier initiation of treatment. CONCLUSIONS: Early initiation of AZT treatment post exposure to SIV in macaques may be important for limiting initial viral replication and dissemination in cases of known exposure
Tsai et al J Virol. 1998 [23]	Effectiveness of postinoculation (R)-9-(2-phosphonylmethoxypropyl) adenine treatment for prevention of persistent simian immunodeficiency virus SIV infection depends critically on timing of initiation and duration of treatment	Animal model assessing if timing affects efficacy of pre post exposure therapy to prevent infection with simian immunodeficiency virus (SIV) in macaque monkeys	To assess if timing of post exposure delivery of a nucleoside analogue (PMPA) is relevant to prevent establishment of SIV infection after IV injection in macaques	RESULTS: All macaques (n=4) treated with PMPA (Tenofovir) for 28 days initiated <24 hours post exposure uninfected with SIV at the end of treatment. Initiation of treatment at 48 or 72 h post exposure reduced effectiveness in preventing establishment of persistent infection. In addition only half of the macaques treated for 10 days, and none of those treated for 3 days, were completely protected when treatment was initiated at 24 h CONCLUSIONS: Both time of initiation of PEP and duration of treatment are crucial factors for prevention of acute SIV infection in the macaque model.

Author, Journal and Year	Title	Type of study, Population and Setting	Aim	Main Results/Conclusions
Otten RA et al. J Virol. 2000 [25]	Efficacy of postexposure prophylaxis after intravaginal exposure of pig-tailed macaques to a human-derived retrovirus in HIV-2	Animal model in macaque monkeys given PEP after intravaginal exposure to HIV-2	To assess the potential efficacy of post exposure therapy to prevent infection with HIV-2 in macaque monkeys after intravaginal exposure	RESULTS: PEP was given for 28 days with tenofovir initiated 12 to 72 h following HIV-2 exposure. Infection was not detected in the 12 and 36 hour initiation groups. Breakthrough infection was detected in the 72 hour initiation group at week 16 post exposure. CONCLUSIONS: PEP is effective if given at 12 and 36 hours post intra vaginal exposure to HIV-2, but not if given at 72 hours
Occupational				
Cardo DM, et al. N Engl J Med 1997 [17]	A case-control study of HIV seroconversion in health care workers after percutaneous exposure.	Case control study in France, Italy, UK and USA. Cases (n=33): HCW with documented occupational percutaneous exposure to HIV infected blood who HIV seroconverted. Controls (n=665): HCW exposed percutaneously to HIV who did not seroconvert	To assess risk factors for transmission of HIV to a health care worker after percutaneous exposure to HIV infected blood.	RESULTS: 9/33 (27%) cases and 247/679 (36%) controls took zidovudine (AZT). 67% of controls and 89% of cases had first dose AZT <4 hours after exposure and 66% controls and 44% cases took AZT for at least 28 days. On multivariate analyses, cases had significantly lower odds of taking AZT than controls (OR 0.19, 95% CI 0.06,0.53), a reduction of 81%. Other significant risk factors for HIV transmission were deep injury (OR 15, 95 CI 6.0, 41), visible blood on the device (OR 6.2; 95% CI 2.2, 21), needle placed in patients artery or vein (OR 4.3; 95% CI 1.7,12), and source advanced HIV disease (OR 5.6; 95CI 2.0, 16). CONCLUSIONS: Postexposure prophylaxis with AZT appears to be protective against HIV transmission
Non Occupational				
Schechter et al for the Praca Onze Study Team. JAIDS 2004 [28]	Behavioural impact, acceptability, and HIV incidence among homosexual men with access to post exposure chemoprophylaxis for HIV.	Observational cohort study in 200 high-risk HIV negative MSM in Rio de Janeiro, Brazil, given a 4-day supply of zidovudine and lamivudine, and instructed to begin PEP immediately after an eligible exposure.	To assess the incidence of HIV infection in persons with easy access to Post sexual exposure prophylaxis (PEP) to prevent HIV	RESULTS: PEP was initiated 109 times by 68 participants (34%). There were 11 HIV seroconversions, 10 among non-PEP users and 1 in the group that took PEP. The overall seroincidence was 2.9 per 100 person-years (95% CI = 1.4, 5.1). CONCLUSION: PEP was safe and did not appear to be associated with increases in reported high-risk behavior in our cohort. Ready access to PEP did not appear to substantially affect HIV transmission, suggesting a limited public health impact of this intervention.

Author, Journal and Year	Title	Type of study, Population and Setting	Aim	Main Results/Conclusions
Roland et al. Clin Infect Dis. 2005 [29]	Seroconversion following non-occupational post-exposure prophylaxis against HIV.	Observational cohort of HIV uninfected individuals in San Francisco reporting sexual (95%) or injection drug use HIV exposure in 72 h preceding a 28-day regimen of antiretroviral therapy and counselling in a nonrandomized trial	To describe episodes of HIV seroconversion in 12 weeks after PEP initiation in individuals with non occupational exposure to HIV	RESULTS: 702/877 subjects (95% male) given 28 days PEP and assessed 12 weeks after HIV exposure. Seroconversion was detected in 7 subjects (1%; 95% CIL: 0.4%, 2%). 3 reported no further risk after PEP initiation, but initiated PEP >45 hours after exposure, and 4 had additional ongoing exposure to HIV after PEP initiation. All 7 completed the 28 days of PEP but 3 reported significant missed doses. CONCLUSIONS: Findings suggest PEP is not completely effective in preventing HIV infection following non-occupational exposure in an observational cohort. Potential difficulties in determining if seroconversion resulted from failure of PEP or ongoing exposure.
Sonder et al. Sex Trans Dis, 2010 [30]	Comparison of two HIV PEP regimens among men who have sex with men in Amsterdam: adverse effects do not influence compliance.	Observational cohort	To compare 2 regimens for HIV PEP as to safety, adherence, outcome, and follow-up in MSM in Amsterdam.	RESULTS: Of 261 MSM who took PEP, 237 (91%) completed 28 days. 5 HIV seroconverted despite good adherence to PEP. None of their viruses were resistant to the PEP regimen used. CONCLUSIONS: No difference in adherence was found between the 2 regimens used. The 5 seroconversions were not likely caused by PEP failure, but rather by ongoing HIV exposures.