Antiretroviral therapy for prevention of HIV transmission: implications for Europe

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The aim of this review is to summarise the evidence on the population-level effect of antiretroviral therapy (ART) in preventing HIV infections, and to discuss potential implications in the European context of recommending starting ART when the CD4 count is above 350 cells/mm³. The ability of ART to reduce the risk of HIV transmission has been reported in observational studies and in a randomised controlled trial (HPTN 052), in which ART initiation reduced HIV transmission by 96% within serodiscordant couples. As yet, there is no direct evidence for such an effect among men having sex with men or people who inject drugs. HPTN 052 led international organisations to develop recommendations with a higher CD4 threshold for ART initiation. However, there remains a lack of strong evidence of clinical benefit for HIV-positive individuals starting ART with CD4 count above 350 cells/mm³. The main goal of ART provision should be to increase ART coverage for all those in need, based on the current guidelines, and the offer of ART to those who wish to reduce infectivity; increased HIV testing is therefore a key requirement. Other proven prevention means such as condom use and harm reduction for people who inject drugs remain critical.

Introduction

Human immunodeficiency virus (HIV) infection continues to be a key public health issue in Europe. In 2012, despite concerted efforts to prevent new HIV infections occurring, there were over 131,000 cases of HIV diagnosed and reported in the World Health Organisation (WHO) European Region [1]. Rates of HIV infection vary considerably across geographical areas but in most European countries, the epidemic is concentrated among certain risk groups. The epidemic in western and central Europe is largely driven by sexual transmission among men who have sex with men (MSM) and heterosexually acquired infections. In western Europe however, a large proportion of infections due to heterosexual transmission occur in individuals originating from countries with a generalised HIV epidemic [1]. In eastern Europe, which has had the highest rates of new HIV diagnoses over the past decade, most infections are attributable to heterosexual sex or sharing injecting equipment [1]. However, there is thought to be some under-ascertainment of infections in MSM within this region due to the ongoing presence of stigma and discrimination.

The idea that antiretroviral therapy (ART) could be used not only to reduce morbidity and mortality among HIV-positive people, but also to prevent onward sexual transmission of HIV, by reducing the infectiousness of HIV-positive people, is not new. The ability of ART to suppress HIV RNA is well documented [2-4] and many observational studies have found a strong association between plasma HIV-RNA viral load and the risk of onward transmission [5-8].

In January 2008, researchers in Switzerland formulated what is often referred to as the 'Swiss Statement' [9], stating that 'the risk of sexual transmission of HIV is negligibly low if three conditions are met: (i) the HIV-positive person 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 diseases] STDs are present in either of the partners'. This ignited a vigorous debate on whether there was strong enough evidence to support this statement. The statement recommends that healthcare providers discuss the preventive effects of ART with their patients.

Then, in 2011, a randomised controlled trial (RCT) provided compelling evidence that initiating ART can prevent sexual transmission of HIV among HIV-serodiscordant heterosexual couples [10]. This result led international organisations, such as PEPFAR (the United States President's Emergency Plan for AIDS Relief) and WHO to formulate recommendations for treatment of the HIV-positive person with antiretrovirals in serodiscordant couples, regardless of the CD4

count of the HIV-positive person. United States guidelines now recommend ART for all HIV-infected individuals, not only those in serodiscordant couples [11;12]. The aim of this paper is to review the population-level effects of ART use in preventing new infections and to discuss the potential implications of recommendations in this regard in Europe.

Methods

A formal literature review on the effects of ART in preventing new HIV infections was performed in September 2011 and updated in November 2013. The focus of the review was the population-level effect, but individual-level effects were considered where relevant. The first search was conducted as part of a technical report commissioned by the European Centre for Disease Prevention and Control, aimed at evaluating HIV treatment as prevention (including ART as prevention in HIV-positive people, prevention of mother-to-child transmission and post-exposure prophylaxis) in the context of Europe [13].

All databases available on Web of Knowledge: Web of Science, MEDLINE, BIOSIS Citation Index, BIOSIS Previews and Journal Citation Report were searched on 5 September 2011 and on 19 November 2013. We searched for all papers written in English (excluding case reports, biographies, editorials, books, corrections, reports, reviews, patents, meetings, news, bibliographies, letters), in several relevant 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) in the period 2006 to 2013 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 search was restricted to studies published after 1 January 2006 because this is the period in which most studies concerned with the impact of ART for prevention have been published. Important papers published before 2006 (e.g. [7]) were selected by hand searching papers already known to the authors and by checking the references of all selected papers and were also included in the review. A possible limitation is that the search was restricted to papers written in English. Nevertheless, journals with the highest impact factor are generally published in English and therefore the likelihood that important studies were omitted from our review is minimal.

Papers found through computerised database searching of Web of Knowledge were combined with those identified by hand searching to identify papers eligible for full-text appraisal. Two authors (JO and VC) independently screened the records identified in September 2011 and VC screened those identified after September 2011. The papers included were assessed based on the full text and information on the type of study, setting, follow-up period, sample size, population and outcome measures collected. All studies that evaluated the impact of ART on preventing new HIV infections compared with absence or delayed treatment in HIV-positive populations were included in the review, regardless of study design. There were no specific requirements regarding the outcome measure used; any measure of HIV incidence or prevalence was considered acceptable.

Results

A total of 5,805 papers were identified in the computerised database search and 34 through hand searching. After removing duplicates and excluding references considered not relevant by two independent persons, 205 publications were fully reviewed and 62 were included in the formal literature review. The results of the search are shown in the Figure and the papers identified by these literature searches are summarised in the Table.

Evidence that antiretroviral therapy prevents HIV infection through heterosexual sex

The association between HIV-RNA viral load and heterosexual transmission of HIV-1 has been reported by many observational studies of HIV-serodiscordant heterosexual couples [5;7;14-16]. The first large epidemiological study to explore the relationship between HIV-RNA viral load and transmission was the Rakai Study [7], conducted in Uganda, which observed a significant dose–response relationship between amount of HIV-RNA plasma and HIV transmission, with no transmission occurring among discordant couples if the HIV-infected partner had levels of plasma HIV-RNA below 1,500 copies/ml. This was regarded as very convincing evidence, but it was in a setting without access to ART. Subsequently, several observational studies of HIV-serodiscordant heterosexual couples, both cross-sectional and longitudinal, found an association between use of ART and HIV prevalence and incidence. In particular, they found that transmission was rare in patients on ART, especially in those with low HIV-RNA concentrations [17-19]. Several meta-analyses have been conducted to estimate the risk of HIV transmission, according to ART status [20-24]. A meta-analysis [20] on observational cohort studies of heterosexual HIV-serodiscordant couples observed no transmission among couples where the HIV-positive partner was treated with ART and had HIV-1 RNA levels below 400 copies/ml (rate of 0 per 100 person-years; 95% confidence interval (CI): 0–1.27). Loutfy et al. [24] considered the level of detectability specific to each study (which varied from 50 to 500 copies/ml) and estimated the risk of HIV transmission in people fully suppressed on ART to be 0 (95% CI: 0–0.05) per 100 person-years when viral load was confirmed at the time of transmission and 0.14 (95% CI: 0.04–0.31) per 100 person-years when the viral load was not confirmed. In a meta-analysis [21] of observational studies of serodiscordant couples, restricted to data with adequate follow-up and in which triple ART was used, it was estimated that ART reduces the risk of HIV transmission by 64% (risk

Table A

Summary of literature search on antiretroviral therapy for prevention of HIV transmission

First author, year of publication and journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Randomised controlled trials				
Cohen,2011,New England Journal of Medicine [10]	To compare the effect of early vs delayed ART on HIV transmission (early = ART at diagnosis; delayed = ART after two consecutive CD4 counts ≤250 cells/mm^3)	RCT	1,763 HIV serodiscordant couples from nine countries: Botswana, Kenya, Malawi, South Africa, Zimbabwe, Brazil, India, Thailand and United States 2005–2010	A total of 39 HIV transmission events were observed, of which 28 were virologically linked (incidence rate: 1.2 per 100 person-years; 95% CI: 0.9–1.7). Of 28 linked transmissions, 1 was in the early-therapy group. A hazard ratio in the early-therapy group of 0.11 (95% CI: 0.04–0.32; p<0.001). HIV- positive people starting ART at study entry had clinical benefit compared with people starting ART when CD4 falls below 250 cells/mm^3. Results support the use of ART as a part of a public health strategy to reduce the spread of HIV infection.
Ecological studies				
Das, 2010, PLoS One [66]	To assess relationships between mean and total community viral load and annual numbers of newly diagnosed HIV cases	Ecological/ cohort study	All reported HIV-positive individuals in San Francisco, United States (n=12,512) 2004–2008	Decreases in annual measures of mean and total community viral load were observed and were significantly associated with temporal decreases in the number of new HIV diagnoses.
Dukers, 2002, AIDS [67]	To investigate whether dramatic increases in sexually transmitted diseases and sexual risk behaviour among homosexual men in Amsterdam, the Netherlands, indicate a resurgence of the HIV epidemic	Ecological study/ cohort study	3,090 male participants from Amsterdam, who participated in 1991–2001 HIV prevalence surveys, who self-identified as homosexual (approximately 15% of all participants) and who consented to blood HIV testing (96.3% of all homosexual participants) were included.	The incidence of HIV increased during the study period, as did rates of syphilis and gonorrhoea. The authors also reported an increase in risk behaviour among homosexual men, highlighting the need for for preventive action, especially for those who have recently been infected.
Fang, 2004, Journal of Infectious Diseases [68]	To estimate the HIV transmission probability ratio in the Taiwanese population, before and after the implementation of the free-ART policy	Ecological/ cohort study	4,390 HIV-positive individuals included in Taiwan's HIV surveillance data 1984–2002	The authors noted that there was a 53% decrease in the HIV transmission rate during the period of free access to ART compared with the previous time period, and this contributed to the control of the HIV epidemic in Taiwan. Therefore, they concluded that the widespread use of ART can be an effective measure to control HIV epidemics in countries with a low prevalence. To differentiate the effect of ART from that of behavioural changes, the incidence of syphilis in the general population and among HIV-positive patients was also analysed, 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, 2007, AIDS [69]	To investigate whether combining clinical data with the serological testing algorithm for recent HIV seroconversion (STARHS) reliably identifies otherwise unrecognised recent infections and to observe their trends	Ecological study/ cohort study	Individuals who presented to the HIV treatment centre at Brighton and Sussex University Hospitals, United Kingdom, between January 1996 and December 2005	The authors reported that 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, the authors observed an increasing proportion of individuals newly diagnosed with HIV as being recently infected with HIV, suggesting an increase in transmission over recent years. This trend was particularly marked amongst MSM. This finding demonstrates that ongoing HIV transmission was occurring, despite the awareness of effective HIV prevention strategies and the potential for ART to reduce HIV transmission. This could be an indirect consequence of the beneficial effects of ART on HIV-related morbidity and mortality.

AIDS: acquired immunodeficiency syndrome; ART: antiretroviral therapy; CLAI: condomless anal intercourse; CI: confidence interval; HIV: human immunodeficiency virus; IRR: incidence rate ratio; IQR: interquartile range; PWID: people who inject drugs; MMC: medical male circumcision; MSM: men who have sex with men; RCT: randomised controlled trial; STI: sexually transmitted infections.

Table B

Summary of literature search on antiretroviral therapy for prevention of HIV transmission

First author, year of publication and journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Grulich, 2008, Sexual Health [70]	To describe trends in HIV notifications and in other measures of HIV incidence in homosexual men in developed countries	Literature review of ecological studies (search conducted in 2007)	Surveillance data from Europe, Canada, United States, Australia and New Zealand. Data from 1996	The study concluded that there was a near-universal increase in notification of HIV diagnoses in homosexual men in the developed world. They reported that determining the degree and extent of the increases in incidence in homosexual men is very important for being able to develop appropriate public health responses in the evolving HIV epidemic.
Montaner, 2010, Lancet [71]	To estimate the association of new HIV-positive tests with viral load, year and number of individuals on ART	Ecological/ cohort study	British Columbia, Canada 1996–2009	The number of individuals actively receiving ART 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 ART and number of new HIV diagnoses per year was –0.89 (p<0.0001).
Mathematical models				
Abbas, 2006, Journal of Acquired Immune Deficiency Syndromes [74]	To estimate the potential impact of ART on the heterosexual spread of HIV 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 15–49 years of age	The authors suggested that implementing ART at 5% HIV prevalence to 100% of AIDS cases would decrease the number of new HIV infections and cumulative deaths from AIDS after 10 years by 11.2% (IQR: 1.8–21.4) and 33.4% (IQR: 26–42.8), respectively. A later implementation of ART at endemic equilibrium (40% prevalence) was predicted to be less effective, decreasing new HIV infections and cumulative deaths from AIDS by 10.5% (IQR: 2.6–19.3) and 27.6% (IQR: 20.8–36.8), respectively. The authors concluded that ART is predicted to have individual and public health benefits that increase with time and with the proportion of infected persons treated.
Alsallaq, 2013 PLoS One, [85]	To assess the impact on HIV incidence of an intervention combining high coverage of HIV testing and counselling, risk reduction following HIV diagnosis, male circumcision for HIV-uninfected men, and ART for HIV-infected persons To identify the factors that influence this impact, and whether there is a synergy between the components	Mathematical model	The model was calibrated to data from KwaZulu-Natal, South Africa	The authors found that, compared with current levels of HIV testing, circumcision, and ART, the intervention with ART initiation at CD4 count <350 cells/mm^3 could reduce HIV incidence by 47% (from 2.3 new infections per 100 person-years to 1.2 per 100 person-years) and by almost 60% (to 1 per 100 person-years) within 4 and 25 years respectively. Drivers of the short-term impact were uptake of testing and reductions in risk behaviour following testing, while drivers of the long-term effects were the periodic HIV testing and retention in ART programmes. If the intervention included ART initiation upon diagnosis, HIV incidence could be reduced by 63% and 76% respectively within 4 and 15 years. The authors found a synergy between the intervention components and highlighted that it takes 10–15 years to see the full impact.
Andrews, 2012 Journal of Infectious Diseases, [73]	To evaluate the importance of structural assumptions regarding linkage to care and population mobility	Mathematical model	The model was parameterised using demographic, clinical, migration, emigration and linkage data from a township in Cape Town, South Africa	The authors used a previously published model and refined modelling linkage to care and population mobility. They found that elimination of HIV transmission (defined as an incidence of <0.1%) would not occur within 30 years, even with optimistic assumptions about the linkage rate. In addition they reported that models were more sensitive to structural assumptions about linkage to care than to parameter values, and that including population mobility further attenuated the reduction in HIV incidence due to ART as prevention.

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Table C

Summary of literature search on antiretroviral therapy for prevention of HIV transmission

First author, year of publication and journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Anglaret, 2013 Antiviral Therapy, [86]	To understand the circumstances under which starting ART upon entry to care, rather than at CD4 count ‹350 cells/mm^3 could lead to more risks than benefits for patients with high CD4 counts	Mathematical model	Model parameters were chosen to mimic the HIV epidemic among sub Saharan-African adults with CD4 counts ›500 cells/mm^3	15-year mortality was 56.7% if the eligibility criteria to initiate ART is CD4‹350 cells/mm^3 and 51.8% if people initiate ART upon entry to care. 15-year mortality was consistently lower with immediate ART unless the rate of fatal ART toxicity was ›1.0/100 person-years or the rate of withdrawal from care was ›1.2-fold higher or the rate of ART failure due to poor adherence was ›4.3-fold higher if the eligibility criterion to initiate ART was CD4 count ‹350 cells/mm^3 compared with upon entry to care. In multivariate sensitivity analysis, the authors reported higher mortality when ART was initiated upon entry to care compared with CD4 count ‹350 cells/mm^3 when moderate rates of fatal ART toxicity (0.25/100 person-years) were combined with increased rates of withdrawal from care (›1.1-fold higher) and increased rates of treatment failure (›2.1-fold higher).
Baernighausen, 2012, Proceedings of the National Academy of Sciences of the United States of America [87]	To evaluate whether it is possible to achieve the same impact, obtainable by initiating ART upon entry into care, and possibly at a lower cost, by increasing coverage of MMC and ART at CD4 count ‹350/mm^3	Mathematical model	The model was calibrated to data from South Africa	The impact of high ART coverage together with high MMC coverage on HIV incidence is approximately the same as obtained by initiating ART upon entry to care, for USD 5 billion less over 2009–2020. The cost per infection averted is respectively USD 1,096 for MMC, USD 6,790 for ART and USD 8,375 for treatment as prevention (defined here as frequent testing of the entire population and initiation of ART upon entry to care). The cost per death averted is USD 5,198 for MMC, USD 5,604 for ART and USD 7,739 for treatment as prevention. The authors concluded that the most cost-effective HIV prevention strategy is to expand MMC coverage and then scale up ART, but the most cost-effective HIV-mortality reduction strategy is to scale up MMC and ART together.
Baggaley, 2006, PLoS Medicine [75]	To explore through the use of modelling, the epidemiological impacts of alternative strategies of initiating ART	Mathematical model	The model parameter set was chosen to mimic an epidemic in a resource-poor setting.	The authors reported that ART cannot be seen as a direct prevention measure for HIV transmission, regardless of the degree of coverage and therefore that counselling of patients to promote safe sexual practices is crucial and must aim to be durable over time. Scaling up treatment of pre-AIDS patients resulted in higher number of infections being averted per person-year of treatment, but the absolute number of infections averted remained small.
Bendavid, 2010, Archives of Internal Medicine [76]	To assess the epidemiological health effect of four different treatment strategies including test and treat, linkage to care and reducing loss to follow-up	Mathematical model	The model parameter set was chosen to mimic the South African HIV population where HIV transmission is predominantly heterosexual	The authors estimated that the number of new infections in the adult South African population that would occur over the next 10 years is 4.5 (95% CI: 3.8–5.1) million in the status quo strategy, and 1.2 (95% CI: 0.9–1.6) million in a comprehensive strategy; a 73.2% reduction. They found that even relatively modest improvements in linkage to care and prevention of loss to follow-up could lead to substantial reductions in mortality and number of new HIV infections. A 10% higher linkage and 6% reduction in loss to follow-up was associated with a 36% reduction in HIV infections compared with universal testing and treatment alone.

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Table D

Summary of literature search on antiretroviral therapy for prevention of HIV transmission

First author, year of publication and journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Bezemer, 2008, AIDS [104]	To evaluate the separate impact of risk behaviour, HIV testing behaviour and ART on the HIV epidemic in Dutch MSM	Mathematical model	The model parameter set was chosen to mimic the epidemic among MSM in the Netherlands	The authors reported that their model, suggests that the only way to reverse the epidemic spread was through reduction in risk behaviour from current levels. Using the model, they compared the relative changes over time in risk behaviour rate in infectious and HIV-negative MSM (something that cannot be measured by survey data). They found that whatever measures people take to 'serosort', this was not proving effective at the population level and was not working in offsetting the epidemic spread. They concluded that the most effective intervention is to reduce risk behaviour to the level in the pre-ART era.
Blower, 2000, Science [102]	To predict the effectiveness of ART with respect to mortality and preventing new infections in the gay community of San Francisco, United States	Mathematical model	The model parameter set was chosen to mimic the epidemic among MSM in San Francisco	Increasing ART usage in San Francisco would decrease the AIDS death rate and could substantially reduce the HIV incidence rate. Even under pessimistic assumptions, a high usage of ART decreased the incidence rate although an increase in risky behaviour of only 10% was enough to counterbalance the benefits of ART.
Brown, 2013, HIV Medicine [105]	To evaluate whether high retention in HIV care and treatment coverage is sufficient to reduce HIV incidence	Mathematical model (multiparameter evidence synthesis (MPES) method)	The model used data from the national United Kingdom cohort of MSM with diagnosed HIV infection and estimates of the number of undiagnosed men for 2006–2010	The authors found that if all MSM diagnosed with HIV with CD4 counts ‹500 cells/mm^3 in 2010 had been on ART, this would have reduced the overall proportion of infectious men from 35% to 29% and further to 21% if, in addition, the proportion of undiagnosed MSM was halved.
Charlebois, 2011, Clinical Infectious Diseases [100]	To determine the impact of offering ART to all patients attending clinics for HIV care on incident HIV infection in the MSM population of San Francisco, United States	Mathematical model	The model was parameterised using data from local health department and electronic patient databases of San Francisco General Hospital outpatient HIV treatment clinics. These contain information on 95% of individuals known to be HIV-positive in San Francisco	The model predicted that expansion of ART to all HIV infected adults already in care in San Francisco would reduce new HIV infection at 5 years by 59% among MSM. Addition of annual HIV testing for MSM to universal treatment would decrease new infections by 76%.
Cremin, 2013, AIDS [72]	To evaluate the potential impact and cost-effectiveness of ART-based HIV prevention strategies (pre-exposure prophylaxis for HIV-negative persons and ART initiation at higher CD4 count for HIV-positive persons)	Mathematical model	The model reflects a hyperendemic setting with relatively low levels of condom use	Provision of ART to more HIV-positive individuals at a higher CD4 cell count, rather than providing pre-exposure prophylaxis to HIV-negative individuals, leads to a higher number of infections being averted and more quality-adjusted life-years. Nevertheless ART alone is unable to reduce HIV incidence to very low levels.

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Table E

Summary of literature search on antiretroviral therapy for prevention of HIV transmission

First author, year of publication and journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Eaton, 2012, PloS Medicine [88]	To compare the results from several mathematical models simulating the same ART intervention programmes to understand the extent to which models agree about the epidemiological impact of expanded ART	12 independent mathematical models	Models were calibrated to South Africa	For a scenario in which 80% of HIV-infected people start ART on average 1 year after the CD4 count falls below 350 cells/mm^3 and 85% remain on treatment after 3 years, the models found that HIV incidence would be 35–54% lower 8 years after the introduction of ART, compared with a counterfactual scenario where ART is not available. The models found heterogeneity in long-term projections (38 years) of HIV incidence, as well as on the impact of more optimistic interventions, such as immediate ART initiation. The number of person-years of ART per infection averted over 8 years varied from 5.8 to 18.7. Considering the actual roll-out of ART in South Africa, seven models estimated that current HIV incidence was 17% to 32% lower than it would have been if ART were not available.
El-Sadr, 2011, AIDS [77]	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	The model suggested that reduction in HIV incidence due to treatment of discordant couples will be greatest in populations with higher HIV prevalence and/or a greater percentage of couples in discordant partnerships. The authors conclude that, although treatment of discordant couples is unlikely to be the sole answer for controlling HIV epidemics, it could significantly reduce HIV incidence and prevent a substantial number of infections in certain countries if high coverage levels are reached.
Granich, 2009, Lancet [78]	To explore the effect of various HIV testing and treatment strategies on the long-term dynamics of the epidemic	Deterministic mathematical model	The model parameter set was chosen to mimic the epidemic in South Africa as the test case for a generalised HIV epidemic, assuming an almost exclusively heterosexual epidemic	The model suggests that universal voluntary HIV testing and immediate initiation of ART in the context of other prevention interventions could reduce transmission to the point at which elimination might be feasible by 2020 in a generalised epidemic, such as that in South Africa.
Granich, 2012, PLoS One [89]	To investigate the cost-effectiveness of expanded ART access in South Africa	Mathematical model and economic analysis	The model parameter set was chosen to mimic the adult South African HIV epidemic from 2011 to 2050, assuming 90% annual HIV testing coverage. Four ART eligibility scenarios were considered, offering ART at: (i) CD4 count<200 cells/mm^3 (current practice); (ii) CD4<350 cells/mm^3; (iii) CD4<500 cells/mm^3; (iv) any CD4 count	Over 40 years, 7.6 million new HIV infections and 10.4 million deaths were predicted under current standards (scenario (i)). For the other scenarios. these figures were (ii) 6.2 and 8.9 (iii) 4.7 and 7.4 (iv) 3.3 and 6.5, respectively. All scenarios were cost-saving compared with scenario (i), with breakeven by (ii) 2013 and (iv) 2023. Sensitivity analyses suggested that poor retention in care and predominant acute phase transmission could reduce savings by 7%. Expanding access to care could potentially reduce the number of new infections and result in cost savings.
Heymer, 2011, Sexual Health [96]	To investigate the impact on HIV incidence of increasing testing rates and using treatment as a form of prevention	Mathematical model	The model parameter set was chosen to mimic the epidemic among MSM in south Australia	The model suggested that increasing testing rates will have minimal impact on reducing the expected number of infections compared with current conditions unless combined with increases in treatment coverage. The authors concluded that this combined strategy could lead to a 59–68% reduction in the number of HIV infections over the next 5 years. This could increase to almost 70% if all undiagnosed individuals are tested twice a year. The authors conclude that investment 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.

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Table F

Summary of literature search on antiretroviral therapy for prevention of HIV transmission

First author, year of publication and journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Johnson, 2012, Journal of the Royal Society Interface [79]	To assess the extent to which prevention and treatment programmes have reduced HIV incidence	Two dynamic mathematical models (STI-HIV Interaction Model and ASSA2003 AIDS and Demographic Model)	The models mimic the adult South African HIV epidemic from 2000 to 2008, using household survey and antenatal HIV prevalence data and death data to estimate HIV incidence	STI-HIV: Real-life incidence of HIV estimated to be 2.11 (95%CI: 1.97–2.26) in 2000–2005 and 1.86 (95%CI: 1.73–2.00) in 2005–2008. Incidence was reduced by 37% (95%CI: 34–41%) compared with if no condoms had been used, and by 8.1% (95%CI: 6.0–9.4%) in the absence of ART, ASSA2003: Real-life incidence of HIV was estimated to be 1.90 (95%CI: 1.77–2.03) in 2000–2005 and 1.62 (95%CI: 1.45–1.79) in 2005–2008. Incidence was reduced by 23% (95%CI: 14–34%) compared with if no condoms had been used, and by 1.4% (95%CI: 0.7–2.6%) in the absence of ART. Increased condom use therefore appears to be the most significant factor explaining the recent decline in HIV incidence in South Africa.
Kretzschmar, 2013, Proceedings of the National Academy of Sciences of the United States of America [107]	To determine whether a treatment as prevention strategy can lead to HIV elimination, and whether achieving this goal is likely to be cost-effective	Deterministic mathematical model	A number of hypothetical HIV epidemics were considered, defined according to their basic reproduction number (R_0)	When infectivity is set at its baseline values, annual treatment uptake of more 70% is needed for elimination, which corresponds, to approximately 85% coverage. The authors found that elimination is only feasible in populations with very low Ro (approximately 2 or lower) and high annual treatment uptake.
Law, 2001, AIDS [97]	To assess the 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. A 10-fold decrease in infectiousness would be counterbalanced by a 70% increase in unsafe sex.
Li, 2012, AIDS [92]	To compare the epidemiological impact and cost-effectiveness of four different approaches to voluntary counselling and testing, expanded ART and harm reduction programmes	Deterministic compartmental mathematical model	The model mimics the adult HIV epidemic in China between 2010 and 2040. Four interventions were compared to the current situation	Compared with the base case (30% start ART by one year since CD4 count falls below 350 cells/mm^3 and additional 5% for each following year), in 30 years' time, the percentage of HIV infections prevented and the cost-effectiveness thresholds, in USD, were: (i) 8.2% (95% CI: 3.2–16.1) and 56,440 USD (95% CI: 32,440–92,410) if expanded voluntary counselling and testing; (ii) 10.0% (95% CI: 5.2–14.0) and 4,840 (95% CI: 3,960–5,980) if increased uptake of ART among those with CD4 count ‹350 cells/mm^3; (iii) 20.7% (95% CI: 3.2–33.6) and 5,090 USD (95% CI: 1,120–15,380) if harm reduction strategies introduced; and (iv) 36.8% (95% CI: 22.3–44.1) and 1,6490 USD (95% CI: 8,410–20,960) if all three strategies introduced. VCT, expanded ART and harm reduction programmes are all necessary to reduce HIV incidence in China.
Long, 2006, AIDS [108]	To understand the impact of ART on the HIV epidemic in Russia	Mathematical model	Parameter values were based on a population of PWID and non-PWID from Saint Petersburg, Russia	If treatment were targeted at PWID, over 40,000 infections would be prevented (75% among non-PWID). The model suggested that appropriate implementation of expanded ART targeted at PWID could dramatically reduce HIV incidence among the general population in Russia and would result in enormous population-wide health benefits. The authors conclude by emphasising the critical need to include plans to treat both PWID and non-PWID as ART is expanded in Russia

AIDS: acquired immunodeficiency syndrome; ART: antiretroviral therapy; CLAI: condomless anal intercourse; CI: confidence interval; HIV: human immunodeficiency virus; IRR: incidence rate ratio; IQR: interquartile range; PWID: people who inject drugs; MMC: medical male circumcision; MSM: men who have sex with men; RCT: randomised controlled trial; STI: sexually transmitted infections.

Table G

Summary of literature search on antiretroviral therapy for prevention of HIV transmission

First author, year of publication and journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Long, 2010, Annals of Internal Medicine [90]	To evaluate the effects of expanded ART, HIV screening and interventions to reduce risk behaviour on the HIV epidemic in the United States	Mathematical model	The model parameter set was chosen to mimic the epidemic in the United States in 2007	The authors concluded that simultaneous expansion of HIV screening and treatment offers the greatest health benefit and is cost-effective. However, even substantial expansion is not sufficient to markedly reduce the HIV epidemic without substantial reductions in risk behaviour.
Lou, 2009, BMC Public Health [93]	To examine the effect of ART on controlling the HIV spread in the MSM population	Mathematical model	The model parameter set was chosen to mimic the epidemic among MSM in China	The model suggested that both ART and a potential vaccine could be powerful interventions to reduce the HIV epidemic, even after accounting for potential increases in risky behaviour.
McCormick, 2007, Clinical Infectious Diseases [103]	To estimate the effects of ART on secondary transmission of HIV among MSM	Mathematical model	Two hypothetical cohorts of MSM in the United States were created: (i) men not receiving ART and (ii) men treated according to current International Antiviral Society-USA guidelines	The authors estimated that ART use reduced the number of secondary HIV transmissions from 1.9 to 1.4 transmissions per person during the initial 10 years after infection, but increased the number after 33 years of infection assuming no increase in risk behaviour and no changes in available therapy. This increase could be offset by identification of new ART regimens and decreases in sexual activity. The authors conclude that it will be important to implement complementary programmes that target reduction in secondary transmission, in addition to ART, to further decrease HIV transmission.
Murnane, 2012, PLoS One [80]	To investigate the utility of viral load-guided ART initiation to prevent HIV transmission	Mathematical model	The model uses data from an RCT of 3,381 HIV serodiscordant couples without ART from 7 countries in southern and east Africa	Treating all with persons with a CD4 count ‹500 cells/mm^3 would avert 1,569 (47.6%) new infections. Treating all with persons with a viral load ≥500,000 copies/ml would avert 1,336 (40.5%) new infections. Treating all persons with a viral load ≥100,000 copies/ml would avert 2,401 (72.8%) new infections. Universal treatment would avert 3,165 (96.0%) new infections. Inclusion of viral load in ART initiation guidelines could permit targeting ART resources to HIV-1-infected persons who have a higher risk of transmission.
Palombi, 2012, Clinical Infectious Diseases [81]	To model the effect of initiating ART at CD4 count ›350 cells/mm^3 on HIV transmission, with the intent of extending ART to the entire HIV-positive population within a short period of time	Mathematical model	The model mimics the HIV epidemic in sub-Saharan Africa using cohort data from the Drug Resource Enhancement Against AIDS and Malnutrition (DREAM) Program (in Malawi and Mozambique). January 2002–July 2009	A 5-fold reduction in infectivity (from 1.6% to 0.3%) occurred within 3 years when triple ART was used. The annual incidence of HIV infection decreased from 7% to 2% in 2 years, and the prevalence was halved, from 12% to 6%, in 11 years. The authors concluded that treatment of all infected individuals could result in substantial reductions in incident HIV infections and argue that a targeted implementation strategy with wide population coverage would be feasible in sub-Saharan Africa.
Phillips, 2013, PLoS One [106]	To increase the understanding of changes in sexual risk behaviour, rates of HIV testing, and ART-induced virological suppression on HIV incidence over the past 15 years	Mathematical model	Model parameters were chosen to mimic the HIV epidemic among MSM in the United Kingdom between 1980 and 2010	The model suggested that, despite high ART coverage, HIV incidence has risen in United Kingdom MSM in the presence of only modest increases in levels of condomless sex. The authors concluded that ART has had an impact on reducing HIV incidence and that higher rates of HIV testing combined with initiation of ART at diagnosis could lead to substantial reductions in HIV incidence if combined with the promotion of increased condom use.

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Table H

Summary of literature search on antiretroviral therapy for prevention of HIV transmission

First author, year of publication and journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Ramadanovic, 2013, PLoS One [95]	To examine the role that either increasing or decreasing risk behaviours may play in influencing the population-level impact of treatment as prevention	Mathematical model	Model parameters were chosen using data from the HIV epidemic in Vancouver, Canada	The authors concluded that their study findings suggest that treatment as prevention has a substantial potential for controlling the HIV epidemic but that substantial gains in reducing HIV incidence and prevalence can only be achieved at or near critical coverage levels for ART or other interventions. They suggest that determining critical ART coverage levels may help in the development of more effective treatment as prevention programmes.
Sood, 2013, Clinical Infectious Diseases [101]	To simulate effects of increased testing and early ART initiation on epidemiological outcomes, for MSM in Los Angeles County, United States	Mathematical model	MSM in Los Angeles County 2000–2009	The model projected a 34% reduction in new HIV infections, a 19% reduction in HIV-related deaths, and a 39% reduction in new AIDS cases by 2023. However, these results were counterbalanced by a near doubling of the prevalence of multidrug resistance (9.06% compared with 4.79%) in 2023. The authors concluded that despite the fact that test and treat generates substantial benefits in the reduction of HIV incidence, this approach will not eliminate the epidemic for MSM in Los Angeles County. They argue that the benefits of test and treat are counterbalanced by large increases in multidrug resistance.
Sorensen, 2012, PLoS One [99]	To assess the effect of improvements in the following five components of a test-and-treat strategy on new HIV infections over a 20 year period: annual HIV testing rate, notification of test results, linkage to care, initiation of ART and viral load suppression	Mathematical model	The model mimics the HIV epidemic among MSM in New York, United States	Compared with the base case (current level of the five components of test and treat), when all interventions were simultaneously implemented at intermediate levels of improvement (including beginning ART at a CD4 count of 500 cells/mm^3), there was a 39.3% reduction in new HIV infections over 20 years. The authors concluded that improvements in the five components of a test-and-treat strategy could result in substantial reductions in HIV incidence among urban MSM.
Wagner, 2013, Mathematical Biosciences and Engineering, [82]	To model the potential impact of a universal test-and-treat strategy, based on annual HIV testing for all South African adults and providing immediate ART for all HIV-positive adults regardless of CD4 count	Mathematical model	The model mimics the adult HIV epidemic in South Africa	The authors found that modelling an increased length of survival time on ART in order to reflect a more realistic situation than previous studies had a significant impact on the probability of HIV elimination using a test-and-treat strategy. The authors concluded that an increased length of survival time on ART reduces the probability of eliminating HIV and decreases the cost-effectiveness of using universal test-and-treat strategies.
Walensky, 2010, Clinical Infectious Diseases [91]	To assess the impact of a test-and-treat strategy on individual patient and population-wide outcomes	Mathematical model	The model parameter set was chosen to mimic the epidemic in Washington, DC, United States	Compared with current practice, test-and-treat decreases the proportion of time with transmissible viral load over a 5-year time period from 64.3% to 54.2%. Comparable results were achieved in a sensitivity analysis. Suggestions that test-and-treatmay eradicate HIV epidemic may be unrealistic. The success of test-and-treat hinges on several components, including making HIV test offers, completing tests, linkage to care, and maximising effectiveness of ART.
Walensky, 2013, New England Journal of Medicine [83]	To compare cost-effectiveness of early initiation of ART (CD4 count between 350 and 550 cells/mm^3) compared with delayed ART (<250 cells/mm^3), for five-year and lifetime outcomes of cumulative HIV transmissions	Mathematical model	Model of HIV-positive partners in heterosexual serodiscordant couples in South Africa and India (using data from HPTN 052 study)	Early ART remained very cost-effective over a lifetime under most modelled assumptions in the two countries. The authors concluded that early ART for serodiscordant couples in resource-limited settings could have individual, public health, and economic benefits.

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Table 1

Summary of literature search on antiretroviral therapy for prevention of HIV transmission

First author, year of publication and journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Wilson, 2008, Lancet [36]	To estimate the cumulative risk of HIV transmission from HIV-discordant couples, where the index partner is effectively treated over a prolonged period	Mathematical model	Mathematical model of heterosexual and homosexual discordant couples applying HIV transmission risk calculated using data from the Rakai study to estimate HIV transmission risk and Australian data for sexual risk behaviour	The risk of HIV transmission in heterosexual couples in the presence of effective treatment is low but not zero and the transmission risk in male homosexual partnerships is high over repeated exposures. There is potential for substantial increase in HIV incidence.
Wirtz, 2013, International Journal of STD & AIDS [98]	To project the impact of providing combinations of HIV prevention interventions and ART access and uptake	Mathematical model	The model mimics the HIV epidemic among MSM in Peru, Ukraine, Kenya and Thailand 2012–2016	The authors found that across epidemics, 14–25% of infections among MSM may be averted between 2012 and 2016 if MSM interventions are implemented and MSM have equal access to expanded ART for adults.
Yusuf, 2012, Journal of Biological Dynamics [84]	To model the effect of change in sexual habits and increased ART coverage to find the optimal combination of the two measures that will minimise cost while reducing HIV incidence	Mathematical model	Model parameters were chosen to mimic the HIV epidemic in South Africa 2006	The authors concluded that implementation of a proposed strategy whereby individuals remain faithful to their sexual partners, reduce the number of sexual partners to the minimum possible and avoid extra-marital affairs for the rest of their lives and initiation of ART in people in the pre-AIDS stage would reduce the number of new cases leading towards eradication by 10 years.
Zhang, 2012, Sexual Health [94]	To estimate the effect of expanded HIV testing and ART use on HIV incidence.	Mathematical model	The model mimics the HIV epidemic in China between 2011-2015	The authors found that a 10-fold increase in the rate of ART coverage could reduce the number of new infections by one quarter by 2015. The authors concluded that increasing HIV testing and treatment coverage are important public health strategies.
Observational Studies				
Anglemyer, 2013, Journal of the American Medical Association, [21]	To evaluate the association of ART with risk of HIV transmission in serodiscordant couples	Meta-analysis	9 observational studies (49,083 couples) and 1 RCT (1,763 couples) of HIV transmission risk in serodiscordant couples according to whether the HIV-positive partner was on ART. Observational studies: Italy, Brazil, Spain, China, Zambia, Rwanda, Uganda, Botswana, Kenya, South Africa, and Tanzania. RCT: Botswana, Brazil, India, Malawi, Kenya, South Africa, Thailand, United States and Zimbabwe Published 1994–2012	ART was associated with a lower risk of transmission partners in 8 observational studies (rate ratio ranged from 0.08 to 0.91), while in one study no association was found. The estimated summary rate ratio of 0.58 (95%CI: 0.35–0.96) was obtained for the 9 observational studies. In sensitivity analyses, excluding the studies without adequate person-time data or in which only one antiretroviral drug was used, the summary rate ratio was 0.36 (95% CI: 0.17–0.75).
Apondi, 2011, AIDS [119]	To investigate HIV heterosexual transmission risk among HIV-positive adults on ART	Prospective cohort study	928 HIV serodiscordant couples in Uganda with the HIV-positive partner receiving ART; 81% had more than 3 years' follow-up	Estimated HIV transmission risk decreased by 91% from 47.3 per 1,000 person-years at study entry to 4.2 per 1,000 person-years after 36 months. Despite increased sexual activity among HIV-positive individuals over 3 years on ART, risky sex and estimated risk of HIV transmission remained lower than baseline levels.

AIDS: acquired immunodeficiency syndrome; ART: antiretroviral therapy; CLAI: condomless anal intercourse; CI: confidence interval; HIV: human immunodeficiency virus; IRR: incidence rate ratio; IQR: interquartile range; PWID: people who inject drugs; MMC: medical male circumcision; MSM: men who have sex with men; RCT: randomised controlled trial; STI: sexually transmitted infections.

Table J

Summary of literature search on antiretroviral therapy for prevention of HIV transmission

First author, year of publication and journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Attia, 2009, AIDS [20]	To synthesise the evidence on the risk of HIV transmission through condomless sexual intercourse according to HIV-RNA levels in plasma and treatment with ART	Systematic review and meta-analysis of observational cohort studies of HIV serodiscordant couples	11 cohorts reporting on 5,021 serodiscordant 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 person-years, based on 5 events. The transmission rate from a seropositive partner with viral load <400 copies/ml on ART, based on 2 studies, was 0 (95% CI: 0.0–1.27) and 0.16 (95% CI: 0.02–1.13) per 100 person-years if not on ART, based on 5 studies and 1 event.
Baggaley, 2010, International Journal of Epidemiology [33]	To 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 publications reporting per-partner studies	The predicted HIV transmission probabilities per-act for vaginal intercourse (VI) or condomless insertive anal intercourse (CLIAI) and condomless receptive anal intercourse (CLRAI) 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.
Baggaley, 2013, Epidemiology [23]	To systematically review the effect of ART on HIV transmission and to conduct a meta-analysis of HIV-1 infectiousness per heterosexual partnership	Systematic review and meta-analysis of observational prospective studies	9 studies where it was possible to compare between ART and non-ART users within studies (ART-stratified studies) and 41 studies that did not stratify by ART use	The authors estimate that incidence rates were 0.2 per 100 person-years (95%CI: 0.07–0.7) and 3.6 per 100 person-years (95% CI: 2.0–6.5) for couples where the HIV-positive partner was on ART and not on ART, respectively (p<0.001). This represents a 91% (95% CI: 79–96%) reduction in per-partner HIV-1 incidence rate with ART use. [The results are reported only for the 9 studies where the comparison was between ART and non-ART users.]
Birungi, 2012 Journal of the International AIDS Society [29]	To evaluate the association between the HIV-positive partner being on ART and the risk of the HIV-negative partner of becoming infected with HIV	Observational cohort study	586 serodiscordant heterosexual couples aged ≥18 years, where the HIV-positive partner was a client of The AIDS Support Organization in Jinja, rural Uganda. The HIV-positive partner was on ART if eligible (CD4 count ≤250 cells/mm^3 or World Health Organization Stage III or IV disease) or not on ART, if not yet eligible	There were 9 new HIV infections in serodiscordant couple where the HIV-positive partner was on ART and 8 new infections in couples where the HIV positive partner was not on ART, for an overall incidence rate ratio of 1.16 (p=0.564). Therefore the authors did not find an association between the HIV-positive partner being on ART and the risk of the partner becoming infected with HIV.
Castilla, 2005, J Acquir Immune Defic Syndr [18]	To estimate the impact of ART use on HIV prevalence among steady HIV serodiscordant couples	Cross-sectional analysis	393 steady HIV serodiscordant couples seen in care between 1991 and 2003 in Madrid, Spain	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 non-index partners decreased from 10.3% during the pre-ART period (1991–1995) to 1.9% during the late ART period (1999–2003; p=0.0061).
Del Romero, 2010, British Medical Journal [6]	To estimate the risk and probability of heterosexual transmission of HIV from people living with HIV on ART	Cross-sectional and longitudinal analysis of a cohort study	476 stable (reporting this sexual relationship as the only risk exposure) HIV serodiscordant heterosexual couples followed in 1989 and in 2008 in Madrid, Spain	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). The authors concluded that transmission of HIV from successfully treated people cannot be excluded.

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Table K

Summary of literature search on antiretroviral therapy for prevention of HIV transmission

First author, year of publication and journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Donnell, 2010, Lancet [19]	To assess the effect of ART use by HIV-positive people on risk of transmission to their uninfected partner	Observational analysis of RCT data (Partners in HSV/HIV transmission study)	Study of 3,381 HIV serodiscordant couples from 14 sites in 7 countries in East and Southern Africa followed between November 2004 and October 2008; the index HIV-positive person was both HIV and herpes simplex virus positive with a CD4 count ≥250 cells/mm^3	1/103 genetically linked HIV transmissions were from an infected participant who had started ART, corresponding to transmission rates of 0·37 (95% CI: 0·09–2·04) per 100 person-years in those who had initiated ART and 2·24 (95% CI: 1·84–2·72) per 100 person-years in those who had not – a 92% reduction (adjusted IRR: 0·08; 95% CI: 0·00–0·57; p=0·004).
Jia, 2013, Lancet [27]	To investigate the rate of HIV transmission between heterosexual HIV serodiscordant couples, according to ART status of the HIV-positive partner	Retrospective observational cohort study	38,862 HIV serodiscordant heterosexual couples (101,295 person-years of follow-up) participating in national HIV epidemiology and treatment databases between 1 January 2003 and 31 December 2011 in China	Rates per 100 person-years of HIV infection were 2.6 (95% CI: 2.4–2.8) among couples where the HIV-positive partner was ART-naive, and 1.3 (95% CI: 1.2–1.3) among couples where the HIV-positive partner was receiving ART. Adjusted hazard ratio was 0.74 (95% CI: 0.65–0.84) for ART-naive vs treated. This reduction was seen across almost all demographic subgroups except for intravenous drug users. Therefore treatment as a prevention strategy is a feasible public health strategy.
Jin, 2010, AIDS [37]	To estimate per-contact probability of HIV transmission in homosexual men due to various forms of CLAI in the era of ART	Health In Men (HIM) study, observational longitudinal cohort study	1,427 community-based HIV-negative homosexual men in Sydney, Australia followed from June 2001 to June 2007	Estimated per-contact probability of HIV transmission: 1.43% (95% CI: 0.48–2.85) for receptive CLAI if ejaculation occurred inside the rectum; 0.65% (95% CI: 0.15–1.53) for receptive CLAI if withdrawal prior to ejaculation; 0.11% (95% CI: 0.02–0.24) for insertive CLAI in circumcised men; 0.62% (95% CI: 0.07–1.68) for insertive CLAI in uncircumcised men.
Loutfy, 2013, PLoS One [24]	To estimate the risk of heterosexual HIV transmission between serodiscordant couples when the HIV-positive partner has a fully suppressed viral load on ART	Systematic review and meta analysis	Systematic review of 1 RCT and 5 cohort studies estimating HIV transmission rate when an HIV-positive partner has a fully suppressed viral load on ART, published up to November 2012	The estimated HIV incidence was 0 (95% CI: 0–0.05) per 100 person-years when the suppressed viral load was confirmed at the time of transmission and 0.14 (0.04–0.31) per 100 person-years regardless of whether the viral load was confirmed as suppressed or not. This corresponds to a pooled odds ratio for on ART vs not on ART of 0.05 (95% CI: 0.01–0.17). The authors suggest there is minimal risk of sexual HIV transmission for heterosexual serodiscordant couples when the HIV-positive partner had full viral suppression on ART, with caveats regarding sexual intercourse type, STIs and condom use.
Melo, 2008, Sexually Transmitted Diseases [17]	To estimate sexual HIV transmission rates and assess the behavioural and clinical factors for HIV transmission	Observational cohort study	93 HIV-serodiscordant couples from Porto Alegre, southern Brazil, followed between 2000 and 2006 with no prior ART use	Among couples where the index person started ART (n=41) no seroconversions occurred, while in the remaining couples, 52 sero-conversions were observed (incidence: 11.5%; 95% CI: 4.81–22.45).
Reynolds, 2011, AIDS [25]	To evaluate the impact of ART on HIV transmission rates among HIV serodiscordant couples	Observational cohort study (Rakai)	250 HIV serodiscordant heterosexual couples in Rakai, Uganda, followed between 2004 and 2009	42 HIV transmissions were seen in 459.4 person-years before ART initiation (incidence: 9.2 per 100 person-years; 95% CI: 6.59–12.36). In 32 couples in which the HIV index partners started ART, no HIV transmissions occurred during 53.6 person-years.

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Table L

Summary of literature search on antiretroviral therapy for prevention of HIV transmission

First author, year of publication and journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Sullivan, 2009, IAS abstract [26]	To estimate the incidence density of HIV transmission by ART status of the HIV-infected partner in the serodiscordant couples	Observational cohort study	2,993 HIV-discordant couples in Rwanda and Zambia followed for 5,609 person-years in 2002–2008	There were 4 new HIV infections in the couples where the HIV-positive partner was on ART, and 171 in the couples where the partner was not on ART. The estimated HIV incidence density was 0.7% in couples where the HIV-positive partner was on ART, and 3.4% when off ART (rate ratio: 0.21; 95% CI: 0.08–0.59).
Tanser, 2013, Science [30]	To assess whether substantial reductions in HIV incidence can be obtained in practice, outside of RCTs and in the context of sub-Saharan Africa	Observational prospective cohort study	Cohort of individuals who were HIV-negative at baseline (total follow-up 16,667 person-years) in rural KwaZulu-Natal, South Africa followed between 2004 and 2011	The authors found that the risk of HIV acquisition for a certain individual decreased significantly with increasing ART coverage in the surrounding local community.
Wang, 2010, J of Acquir Immune Defic Syndr [28]	To estimate the HIV transmission risk and assess the behavioural, clinical, and quality-of-life risk factors for HIV transmission	Observational cohort study	1,927 HIV serodiscordant heterosexual couples followed between January 2006 and December 2008 in Henan, China. HIV-positive individual was former plasma donor	84 HIV transmissions occurred over 4918 person-years, an incidence of 1.71/100 person-years. Most respondents (80.4%) had spouses who were on ART. There was no statistical difference in the seroconversion 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).

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ratio: 0.36; 95% CI: 0.17–0.75). Baggaley et al. [23] systematically reviewed the data on observational cohort study of serodiscordant couples. Using the studies where it was possible to quantify the impact of ART on the risk of HIV transmission, they estimated that ART reduces per-partner HIV-1 incidence rate by 91% (95% CI: 79–96%).

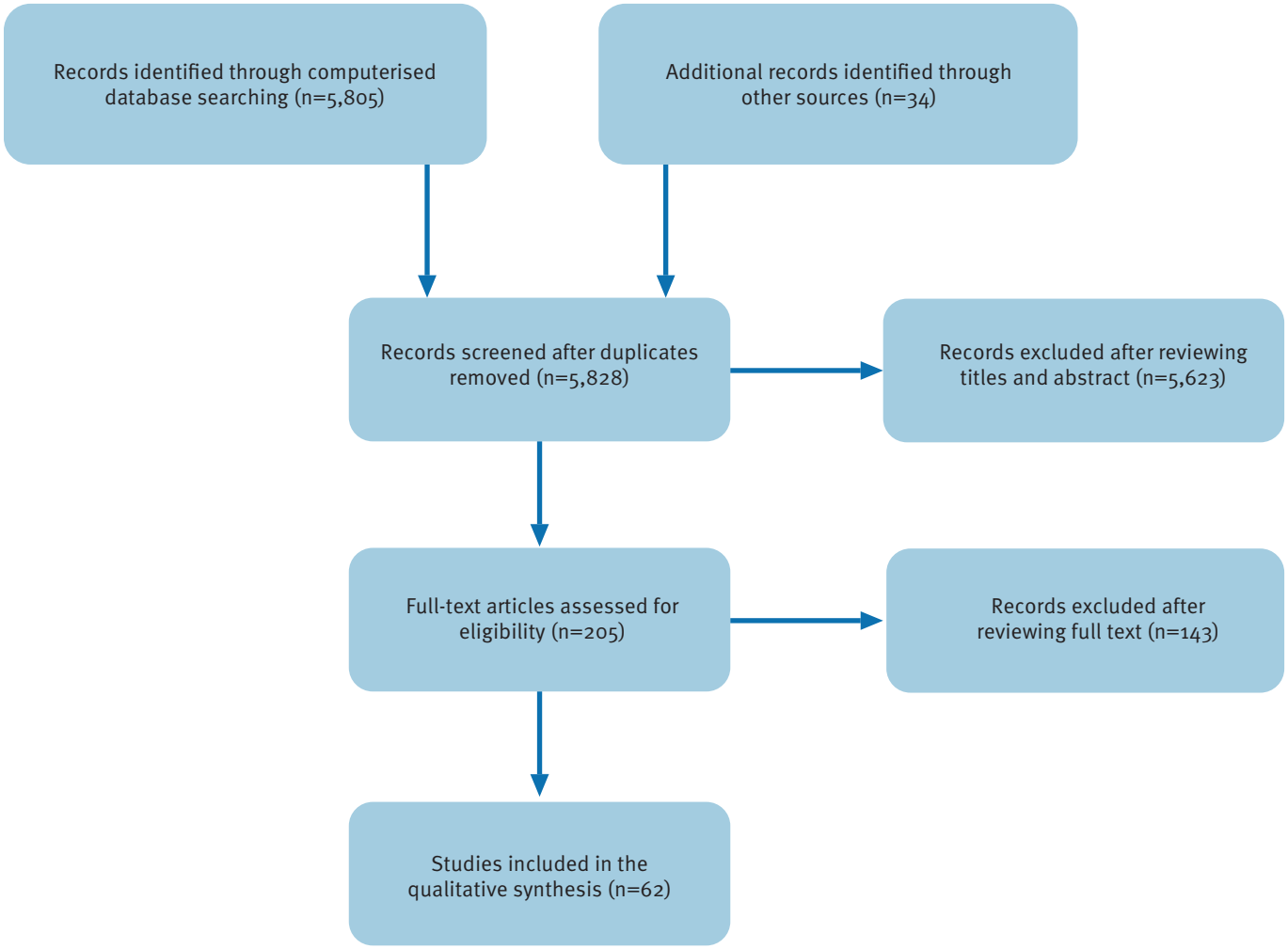
In 2010, a very large observational study [19] observed 103 genetically linked HIV-1 transmissions of which only one occurred from an infected participant who had started ART, corresponding to a transmission rate of 0.37 (95% CI: 0.09–2.04) per 100 person-years, compared with 2.24 (95% CI: 1.84–2.72) per 100 person-years in those who had not initiated ART. This finding was supported by other longitudinal studies [6;25-27], but not all [28;29]. These last two contrasting results came respectively from China and Uganda. One possible explanation for not finding an effect of treatment in reducing the risk of HIV transmission could be the low rates of viral suppression in those on ART. Additionally, in a large observational prospective study of serodiscordant couples, an association was found between ART and risk of HIV transmission, although this was not the case among people who inject drugs [27].

Evidence that ART is reducing HIV incidence in real life, outside of randomised controlled trials, came from a very large cohort of HIV-uninfected individuals living in Kwala Zulu Natal, South Africa [30]. They observed that people living in areas with high coverage of ART had a lower risk of HIV transmission than people living in areas with low coverage (e.g. the risk of HIV acquisition for a person living in a community with an ART coverage of 30–40% of all HIV-infected individuals was 38% less than for someone living in a community where ART coverage was less than 10% of all HIV-infected individuals).

The strongest evidence to date on the ability of ART to reduce heterosexual HIV transmission comes from the HPTN 052 RCT [10]. This study compared the effect of early versus delayed ART on transmission of HIV. A total of 1,763 heterosexual serodiscordant couples in which the HIV-positive person was ART naive and had a CD4 count between 350 and 550 cells/mm^3 were recruited from nine countries: couples were randomised to either immediate ART or delayed initiation (ART was started after two consecutive CD4 counts of ≤250 cells/mm^3). The primary endpoint was genetically linked HIV infection in HIV-negative partners. Three months after baseline, 89% of participants in the early therapy group had achieved viral suppression (HIV-RNA <400 copies/ml) compared with 9% of the delayed therapy group. A total of 28 virologically linked transmissions were observed; only one occurred in the early

Figure

Flowchart of literature search on antiretroviral therapy for prevention of HIV transmission



therapy arm. This represents a 96% relative reduction in linked HIV transmissions as a result of initiating ART early compared with deferral (hazard ratio: 0.04; 95% CI: 0.01–0.27; p<0.001). These findings are believed to be a result of sustained suppression of HIV-RNA load in genital secretions [10] and provide support for the use of ART in the prevention of HIV among heterosexual men and women.

Evidence that antiretroviral therapy prevents sexual HIV infection among men who have sex with men

No direct empirical evidence regarding the relationship between ART use and the risk of HIV transmission among MSM is currently available [31].

The risk of HIV transmission is usually measured per partnership or per sexual act. The first measurement can be applied to MSM who enter into or are in a serodiscordant steady partnership in which condoms are not used or are only used infrequently; the second measurement, per sexual-act probability of HIV transmission, is more applicable to non-steady partnerships.

There is evidence that the per sexual act probability of HIV transmission risk through anal intercourse is generally more than 10-fold higher than through vaginal intercourse [32]. In particular, it has been estimated that the risk per partnership of condomless receptive anal intercourse was 40.4% (95% CI: 6.0–74.9) and of condomless insertive anal intercourse was 21.7% (95% CI: 0.2–43.3) [33]. Most of these estimates were derived from observations made when ART was either not used or was not very effective in reducing viral load.

The potential reduction in HIV infectivity due to the effect of ART has been estimated, using two published mathematical functions of infectivity, based on studies of HIV-serodiscordant heterosexual couples [34-36]. The predicted HIV transmission probabilities per act with successful ART estimated by the two different functions for condomless vaginal intercourse or condomless insertive anal intercourse were 0.013% and

0.0002%. For condomless receptive anal intercourse, estimates from the same two functions were 0.061% and 0.0011%, reflecting transmission rates that were 96% and 99.9% lower respectively than without therapy.

There is a paucity of data on the relationship between transmission and viral load in homosexual men [32;37;38], especially at low viral loads [20;39]. Few papers have estimated the risk of transmission through anal sex among MSM in longitudinal observational studies [37;40;41]. The best evidence comes from a cohort of initially HIV-negative MSM in Sydney, Australia, [37] where people were followed over time and information on the potential source of infection was collected but without genetically linking the infections. This study observed that the per act probability of HIV transmission due to condomless insertive anal intercourse was similar to estimates reported from developed countries in the pre-ART era [33], despite the fact that most men diagnosed with HIV infection in Sydney were on ART with undetectable HIV-RNA viral loads. Potential explanations as to why risk of transmission did not decrease despite the increased number of people on effective treatment are that there was an increase in the prevalence of other sexually transmitted infections (STIs) (which are known to increase the risk of HIV transmission [42;43]) in Sydney in the post-ART compared with the pre-ART era [37], as was the case in many other MSM populations [44;45], and higher levels of condomless sex [45;46]. Two other theoretical possibilities are competing exposures through other routes of transmission not reported, such as intravenous drug use, and that the study participants' partners may not be representative of the wider Australian homosexual population [38].

Generalisability of HPTN 052 results and implications for policy

Although HPTN 052 [10] provides the most definitive evidence currently available to support the use of ART to prevent sexual transmission of HIV, it is not without its limitations. Trial participants were in stable HIV-serodiscordant heterosexual relationships and may not be a representative sample of the heterosexual population. However, there is no doubt about the biological effect of ART in reducing HIV infectiousness, particularly in the case of heterosexual transmission.

This strong evidence in the context of heterosexual (vaginal) transmission suggests that there may well be similar reductions in HIV infectivity through other routes. However, given important biological differences in transmission mechanisms for these transmission routes, it is not possible to confidently extrapolate existing evidence based on vaginal transmission. In particular, due to the higher per sexual act probability of HIV transmission through anal intercourse compared with vaginal intercourse, it may be that the transmission threshold through anal intercourse may be lower and therefore that the risk of HIV transmission in people virologically suppressed as a result of ART may not be negligible [31;32]. It is therefore important that research in these areas is prioritised to support policy decisions regarding the use of ART as prevention.

A further consideration of the trial is that both members of the couple received condoms free of charge, intensive HIV prevention counselling and STI management [10]. It is not possible to quantify how much of an impact these factors had on the findings of the trial, although it is unlikely to result in a serious bias between the arms.

Reported condom use in the HPTN 052 study was extremely high: 96% of those in the early-therapy group and 95% of those in the deferred-therapy group reported 100% condom use during the study. These very high reported condom use rates are unlikely to reflect real-life conditions and may be due to social-desirability bias. In the Swiss cohort, an increase in reported condomless sex has been observed in steady partnerships after the release of the Swiss Statement [47]. This could reflect a real increase in sex without condom use, but it could be a consequence of an increase in reporting sex without condom use due to less concern about social desirability.

For clear ethical reasons, HPTN 052 trial compared the effect of condoms alone among those not receiving ART and the effect of condoms and ART for the HIV-positive person on the probability of HIV transmission. Therefore the absolute risk of transmission on the early-therapy arm (1 in 893) does not represent the risk arising from condomless sex when the HIV-positive person is on ART; rather, the risk in the context of self-reported condom use plus ART. The absolute risk of transmission through condomless 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 among serodiscordant couples, is addressing this question [48].

If the use of ART to reduce sexual transmission of HIV were to result in a reduction or cessation of condom use, it is not clear whether the transmission risk among individuals using ART as prevention without condoms would be higher or lower than that observed when condoms are consistently used in the context of no ART. Further research in this area is needed but studies suggest that condomless sex does not increase in people starting ART [49;50].

The same consideration should be given to STI management, as the impact of less frequent monitoring on the risk of transmission (in HPTN 052, individuals attended clinics monthly for the first three months and quarterly thereafter) and less ready access to treatment of STIs in the real world compared with an RCT setting is unclear.

In addition, HPTN 052 considered the risk of HIV transmission in individuals who already had a CD4 count of less than 550 cells/mm^3. The impact of ART on the risk of transmission among HIV-positive individuals with CD4 counts above this level has not been studied. There are currently no RCTs planned to answer this question, and it is unlikely that there will be, given that most people are diagnosed when the CD4 count is below this threshold.

In the light of the evidence described above, WHO released *Guidelines on couples HIV testing and counselling and treatment and prevention for serodiscordant couples* [51], which recommend that voluntary HIV testing and counselling with support for mutual disclosure should be offered to couples in antenatal care settings and to individuals with known HIV status and their HIV-negative partners. In addition, they recommend that in serodiscordant couples where the HIV-positive partner has a CD4 count >350 cells/mm^3, the person should be offered to initiate ART if they wish, to reduce HIV transmission to the uninfected partner.

Implications for HIV-positive individuals

The decision on when to start ART in a treatment-naive person has always been quite controversial. After a phase in the late 1990s, when in some settings ART was started in almost all people diagnosed with HIV in the hope of being able to eradicate HIV, the decision on when to start ART has been driven by the clinical prognosis of the HIV-positive individual. But given that HPTN 052 has shown that initiating treatment reduces the risk of sexual transmission, some guidelines now recommend that the effects of ART in reducing infectiousness are discussed with all patients and that ART can be started for this reason if the patient wishes [52], despite a lack of full understanding of the potential impact on the individual's health. It has not been established in a randomised trial whether initiating ART when the CD4 count is above 350 cells/mm^3 is associated with a clinical benefit for the HIV-positive person compared with deferral to when the CD4 count reaches this level. It is important that this is made clear to people in whom ART is being initiated with a view to reducing infectiousness.

Guidelines differ in the recommendations for initiating ART when the CD4 count is above 350 cells/mm^3. Both United States guidelines (International Antiviral Society-USA and Department of Health and Human Services guidelines) recommend starting ART in all HIV-infected individuals [11;12]. WHO now recommends initiating ART when CD4 counts fall below 500 cells/mm^3 [53]. The European AIDS Clinical Society (EACS) guidelines state that use of ART is always recommended if the CD4 count is less than 350 cells/mm^3 and should be considered and actively discussed if the CD4 count is above 350 cells/mm^3 for asymptomatic patients and people wishing to reduce transmission of HIV [54]. As mentioned above, some guidelines suggest a more nuanced approach in which the benefits of early ART for prevention as well as lack of evidence at the individual level is explained to patients, who themselves then make the decision to start ART [52]. As reflected by the variation in recommendations across different guidelines, there is no definitive agreement among the scientific community, and experts differ in the amount of evidence that they consider necessary and on the level of current evidence [55].

The HPTN 052 trial compared clinical outcomes as co-primary outcome. There was a significantly reduced risk of clinical disease in the intervention group, mainly driven by a reduction in extrapulmonary tuberculosis, although the study power was low for serious clinically manifest disease endpoints. In a subset of participants in the Strategies for Management of Antiretroviral Therapy (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 upon entry into the study compared with those who deferred it (CD4 count <250 cells/mm^3), but the size of this subsample was small [56]. Both these trials were based on a comparison involving deferral until the CD4 count falls below 250 cells/mm^3, which is now no longer the standard of care. Therefore the potential long-term risks, such as adverse events and acquisition of drug resistance, of initiating ART at CD4 levels above 350 cells/mm^3 remain uncertain. The Strategic Timing of Antiretroviral Treatment (START) trial aims to answer this research question, in particular to determine whether very early ART (initiation when CD4 count >500 cells/mm^3) is superior to deferred ART (CD4 count <350 cells/mm^3, or when a person has been diagnosed with AIDS or other symptoms of HIV infection) in delaying the occurrence of a composite outcome consisting of AIDS, non-AIDS, or death from any cause. This trial will help to establish whether any risks of very early ART initiation will be outweighed by the benefits to the individual, in terms of reduction in risk of serious clinical disease [57]. The TEMPRANO trial is evaluating the impact on mortality and severe HIV-related disease of initiating treatment upon recruitment in the study (with a CD4 count between the threshold for ART eligibility according to the most recent WHO guidelines and 800/mm^3) and/or six-month isoniazid prophylaxis for tuberculosis, compared with the standard of care (ART initiation as recommended by WHO) in Abidjan, Cote d'Ivoire [58]. If the benefits of initiating ART at a higher CD4 count outweigh the disadvantages, then it makes sense clinically as well as from a public health perspective to recommend early ART initiation in all people diagnosed with HIV infection. If, on the other hand, there is found to be net harm as a result of this strategy, then a policy of earlier ART initiation in order to reduce transmission risk may be inappropriate in most circumstances. But if the risks and benefits appear to balance, the decision to initiate ART would take into consideration an individual's preference, and in particular 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 and the

TEMPRANO trial (and any similar trials that might take place), together with clinical considerations and individual choice [59]. Unfortunately the TEMPRANO trial is not scheduled to be completed before the end of 2014 [58] and the START trial before 2015 [57;59].

Although it might be considered difficult to imagine that starting ART earlier would result in a higher risk of mortality or morbidity, based on current knowledge, there is no evidence to guarantee that this is not the case. In addition to this main consideration when deciding whether to start treatment earlier, an HIV-positive person should take into consideration other factors. Firstly, the person should know that once treatment is started it should be continued for life, because interrupting ART increases AIDS-related and non-AIDS-related morbidity and risk of death [60]. Secondly, high levels of adherence to ART should be maintained over time. This factor is crucial to achieve and maintain virological suppression and therefore to delay disease progression, minimise the risk of resistance development and of onward HIV transmission. Thirdly, the person should bear in mind that although antiretroviral drugs available now are much better tolerated, they can still have side effects. Tolerability may be an issue if a person is aware that these drugs could potentially not yet have any benefit for their own health, and that the long-term effects of some drugs are still unknown. Some wonder whether it is ethically acceptable to offer the possibility of starting treatment earlier in absence of this evidence. Most would probably agree that it is ethical if the patient has received all the information necessary to make an informed decision.

European population-level impact

There is consensus that people who require ART for their own health should always be prioritised and the need for condom use, possibly with the exception of a narrow set of circumstances along the lines outlined in the Swiss statement, should continue to be reinforced. A key question is how many people not yet eligible to receive ART based on current treatment guidelines (using CD4 <350 cells/mm^3 as threshold, which is the level at which ART initiation is unequivocally recommended for clinical benefit in European EACS guidelines [54]) might be offered earlier ART for the benefit of reducing transmission? This requires modelling that takes account of testing and diagnosis rates and is informed by a recent European cohort study that reported that the median times from seroconversion to CD4 counts of <500, <350 and <200 cells/mm^3 were 1.2, 4.2 and 7.9 years respectively [61].

Further data from a pan-European cohort collaboration showed that late presentation, defined as an HIV diagnosis with CD4 count <350 cells/mm^3 or an AIDS diagnosis within six months of HIV diagnosis, has decreased over time across Europe: 57.3% in 2000 to 51.7% in 2010–11 [62]. These data show that half of all diagnoses are in people who are in immediate need of ART [61;62].

The current debate, especially in countries with generalised epidemics, is whether ART should be initiated for all persons diagnosed with HIV infection (irrespective of CD4 count) as a preventive public health policy. Most of the discussion revolves around the implementation of such a programme, the affordability and sustainability of this strategy in the long term and which type of monitoring is cost-effective. This is an area in which there are no trials, although community randomised trials – in which some communities are allocated to higher levels of testing and immediate ART initiation and others to standard care, with HIV incidence as outcome – are currently ongoing in sub-Saharan Africa (PopART Study [63], Treatment As Prevention (Tasp) trial in Kwala Zulu Natal, South Africa [64] , An HIV Prevention Program for Mochudi in Botswana [65]). It seems unlikely that such trials will be feasible in Europe, given the lower HIV incidence. Ecological analyses [66-71] and modelling studies have been extensively employed to try to understand what the impact of such a policy would be in a generalised HIV epidemic and in the context of a concentrated epidemic, such as in MSM in developing countries. The ecological studies are limited by the fact that the true HIV incidence is unknown, and so diagnosis is used as a proxy for infection, and by the other usual limitations of observational analyses, particularly the high risk of confounding. To be of most use, these types of ecological analyses are perhaps best done within the framework of an underlying transmission model that allows consideration of the undiagnosed population. The ecological studies that have been published [66-71] have tended to suggest appreciable benefits of ART for prevention in adults.

Modelling studies have explored the widespread use of ART but mainly in sub-Saharan settings [72-89], in the United States [90;91], in China [92-94], Canada [95] and for some specific groups, such as MSM in Australia [36;96;97], in Peru, Ukraine, Kenya and Thailand [98] and in different cities in the United States [99-103]; only a few of them model the HIV epidemic in European countries (MSM in Amsterdam, the Netherlands [104] and in the UK [105-107] and people who inject drugs in Russia [108]). They varied in their conclusions, although most have suggested potential appreciable beneficial effects on HIV incidence of introducing ART initiation at a higher CD4 count as a policy at a population level. We are likely to need to rely on modelling studies to help to tell us what the population-level impact of a policy of earlier ART initiation would be on HIV incidence. However, such studies are as good and as valid as the assumptions made. A common theme with modelling work has been the fact that change of sexual risk behaviour (change in condom use and numbers of partners) has a strong influence on HIV incidence and that any tendency for such behaviour to increase could outweigh benefits of ART for prevention [104;106]. Another key issue is the need to improve rates of diagnosis: levels of HIV testing are

very low in most European countries and approaches to increase these are vital to maximise the number of people in need of ART who are on treatment.

Another key issue that has been highlighted by modelling work is the fact that epidemics, particularly those in MSM, can be driven to a disproportionate degree by people who are at the acute infection stage. Rates of transmission from people in primary infection have been found to be particularly high [109]. There are three reasons for this [110-112]. Firstly, viral load levels are at their highest during this period. Secondly, particular amino acids in the HIV envelope protein that confer a selective advantage during transmission or early infection are more likely to be present in a person recently infected (as once within the new host there is probably evolution of the virus, which results in loss of this property) [113;114]. Thirdly, there is variability over time in the number of new partners that people have. A person will tend to become infected during a period of higher new-partner acquisition, and hence once infected will tend to have more partners during this period than in other periods in their life [112]. This effect is likely to be most apparent in MSM populations, in which sexual partner numbers tend to be larger than among heterosexual populations, although condom use tends to be higher as well [106]. There is some direct evidence that a high proportion of new infections come from persons recently infected people [106;115-118]. Efforts should be made to better understand the role of primary HIV infection in HIV epidemics among MSM, in order to be able to assess the potential role of increased access to ART for people with CD4 counts above 350 cells/mm^3, but it has been suggested that ART can still have substantial prevention benefits, even in epidemics driven by outbreaks of primary HIV infection [106].

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 datasets (e.g. sexual risk behaviour, testing behaviour, 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 have a useful role in providing more quantitative predictions of the effect of increasing the level of testing and earlier ART initiation in a given setting on HIV incidence. Such models also have the advantage of carrying a level of detail that 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 and the TEMPRANO trial indicate that there is a beneficial effect of early ART on clinical events, the absolute risk of such events is such 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 infection are required in order for earlier ART initiation to become cost-effective and hence be paid for.

Conclusions

Wider ART use is likely to produce benefits in reducing HIV transmission through all transmission routes, but more evidence is needed, both on the clinical benefit for the HIV-positive individual in starting treatment earlier, as well as on the efficacy of treatment as prevention among MSM and people who inject drugs. This information would be particularly important if such a policy were to have a substantial impact, especially in western and central Europe. When available, results from the PARTNER study will provide the most relevant information within the European setting on rates of heterosexual transmission. Most people in western Europe should be able to achieve and maintain virological suppression, provided they have good access to ART and good adherence is maintained. There is a strong rationale for a policy whereby all people with high CD4 counts – such that they are not currently considered to require ART for their own health – have this potential benefit of reduced transmission risk as a result of ART explained to them, along with the substantial caveats, and ART offered for this indication if the individual so wishes.

Appreciable population benefits of such a policy would probably not accrue unless there is a change in HIV-testing culture, such that testing becomes frequent and routine. This would apply to all risk groups within Europe, but particularly among the most vulnerable and neglected, such as MSM and people who inject drugs.

In summary, ART use has had a limiting effect on HIV epidemics in Europe. ART coverage for all those in need for health benefit, and the offer of ART to those who wish to take it to reduce infectivity, should be the main goal of ART provision and increased HIV testing is a key requirement to achieve that. Other proven prevention means such as condom use and harm reduction for people who inject drugs remain critical. The impact on public health, cost-effectiveness, affordability, implementation and sustainability of such a public health policy needs to be studied further and enhanced surveillance mechanisms need to be put in place to monitor its effectiveness.

Authors' contributions

All authors had substantial input into the drafting of the manuscript. In addition MVDL and AP formulated the research question, VC and JO conducted the systematic review and FN reviewed the guidelines. VC, JO, FN, RL, AR, FL, CS, ANP wrote the first draft of the manuscript and all contributed to the editing of the final version.

Conflict of interest

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