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Surveillance of human immunodeficiency virus suggests that younger men who have sex with men are at higher risk of infection, European Union, 2003 to 2012

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In 2012, newly reported human immunodeficiency virus diagnoses in the European Union /European Economic Area remained stable at around 30,000 cases. Since 2003, cases in men who have sex with men (MSM) aged 20 to 29 years-old doubled, while the proportion of late presenters in this group remained stable. Persistent declines occurred among older MSM age groups, particularly that between 30 and 39 years-old. Interventions targeting younger MSM are needed to prevent a resurgence of the epidemic in Europe.

Since 2008, the European Centre for Disease Prevention and Control (ECDC), together with the World Health Organization (WHO) Regional Office for Europe, has been coordinating an enhanced human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) surveillance for European Union (EU) Member States and European Economic Area (EEA) countries. The 2012 data collection and analysis offered the opportunity to re-examine the distribution and trends of HIV infection by risk and age group.

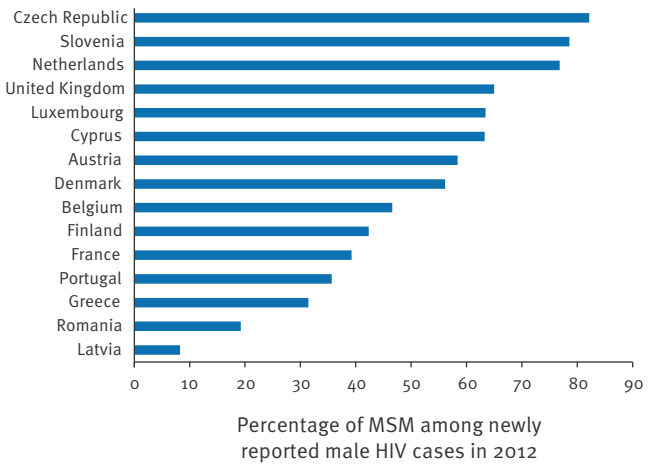
Human immunodeficiency virus infections in the European Union/European Economic Area

In 2012, a total of 29,381 new HIV diagnoses were reported by 30 EU/EEA countries, resulting in a rate of 5.8 per 100,000 population [1]. When adjusted for reporting delay [2], this figure rises to 30,900 cases and a rate of 6.2 per 100,000 population [1]. Notification rates in men and women were 9.1 and 2.7 per 100,000, respectively, for a male-to-female ratio of 3.2. Among all new HIV diagnoses (29,381), young people aged 15 to 24 years accounted for 11% (3,114) of all the new HIV diagnoses reported. The largest proportion of new diagnoses, however, was observed among 30 to 39 year-olds (33%, 9,782).

Between 2006 and 2012, the overall rate of reported diagnoses in EU/EEA countries decreased by 3% when adjusting for reporting delay (from 6.4 to 6.2 per 100,000 population). During this time, 14 countries reported decreasing rates whereas increases were reported in 16 countries. The highest proportion of new HIV diagnoses in 2012 continued to be reported among men who have sex with men (MSM) (40%, 11,877 cases), followed by heterosexual transmission (34%, 9,944 cases). The latter includes 12% (3,474 cases) of heterosexually-acquired cases originating from sub-Saharan African countries with generalised epidemics. People who inject drugs (PWID) accounted for 6% (1,785 cases) of all HIV cases.

Figure 1

Proportion of men who have sex with men among newly reported male human immunodeficiency virus cases in 2012 in 15 European Union Member States, 2012 (n=11,774)

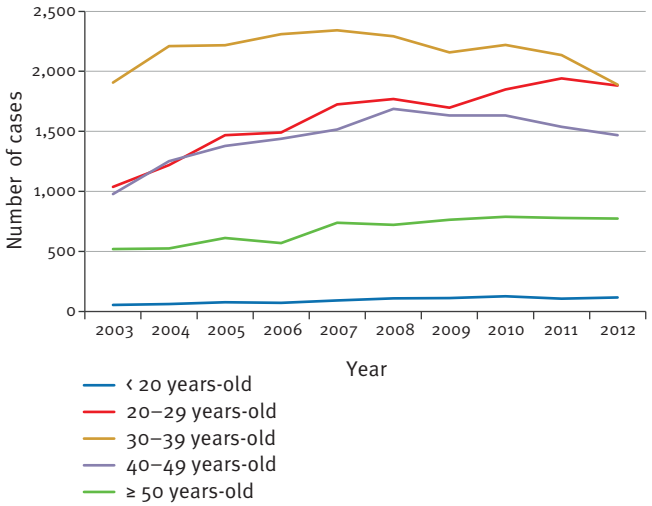


HIV: human immunodeficiency virus; MSM: men who have sex with men.

The 15 countries in the Figure include those which reported the mode of transmission for more than 50% of their cases and consistently reported CD4 counts for the period from 2003 to 2012.

Figure 2

Distribution of newly reported HIV cases through men who have sex with men transmission by year and age group among 15 European Union Member States, 2003–2012 (n=59,992)



HIV: human immunodeficiency virus.

The data in the Figure originate from 15 European Union Member States, which reported the mode of transmission for more than 50% of their HIV cases and consistently reported CD4 counts for the period from 2003 to 2012.

These 15 countries include Austria, Belgium, Cyprus, Denmark, the Czech Republic, Finland, France, Greece, Latvia, Luxembourg, the Netherlands, Portugal, Romania, Slovenia and the United Kingdom.

Data on CD4 cell count at the time of HIV diagnosis for more than 50% of cases were provided by 19 countries (overall completeness in 2012: 56%). Among these countries 16,150 cases were reported, of which 7,924 (49%) were categorised as 'late presenters' (CD4 cell count less than 350/mm^3), including 4,759 (30%) of cases with advanced HIV infection (CD4 <200/mm^3). The highest proportion of late presenters was observed among heterosexually-acquired cases (59%, 3,817 of 6,472), especially among those originating from sub-Saharan countries (62%, 1,454 of 2,361), the lowest among cases due to mother-to-child (23%, 18 of 80) and MSM (38%, 2,857 of 7,458) transmission.

New human immunodeficiency virus diagnoses and late presentation in men who have sex with men in the European Union

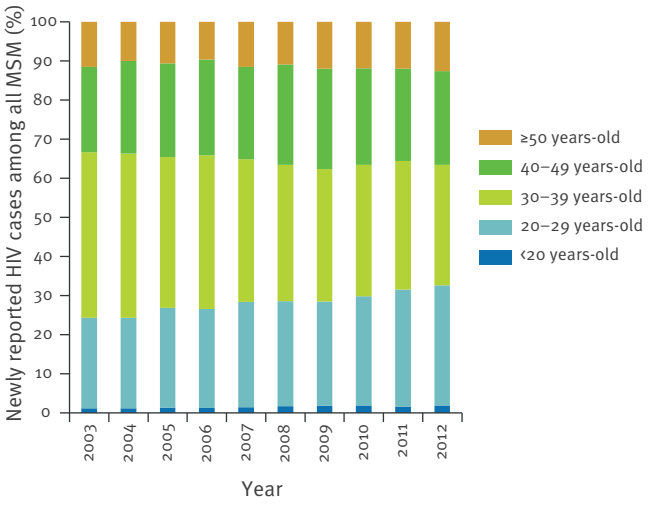
The analysis included data from 15 countries reporting between 2003 and 2012 which had recorded the mode of transmission for more of 50% of their cases and consistently reported CD4 counts. Among these countries, the proportion of MSM transmission reported among men in 2012 were highest in the Czech Republic 82% (152 of 185 cases), Slovenia 79% (33 of 42 cases) and the Netherlands 77% (636 of 828 cases) (Figure 1).

In the 15 countries included in the analysis, the number of reported HIV diagnoses among MSM increased by 36%, from a total 4,501 cases in 2003 to 6,130 cases in 2012; the number of cases has remained stable since the peak of 6,585 cases in 2008. Trends by age group varied (Figures 2 and 3): among males aged 20 to 29 years, the number of cases during this period almost doubled from 1,037 to 1,881 cases (81% increase). However, among very young MSM under 20 years-old, a much smaller group, an even larger increase was observed from 54 to 116 cases. An increase in cases among MSM younger than 29 years-old was also observed at individual country level in the majority of the 15 countries, reflecting the overall increase.

CD4 cell counts were available for 38,463 HIV diagnoses reported among MSM between 2003 and 2012, increasing from 2,149 cases in 2003 to 4,588 in 2012. In 2012, of 4,588 cases acquired through MSM contact, 37% (1,691 cases) were categorised as late presenters and 18% (845 cases) presented with advanced HIV infection. These figures show improvement since 2003, when of 2,149 cases, the proportion of late presenters and cases with advanced infection at the time of HIV diagnosis were 45% (974 cases) and 25% (537 cases), respectively. The largest drop in the proportion of late presenters was among 30 to 39 year-olds (19% in 2003, 406 cases of 2,149, down to 11%, in 2012, 493 of 4,588) (Table). In all other age groups, the proportion of late

Figure 3

Proportion of HIV newly reported cases among MSM by age group among 15 European Union Member States, 2003–2012 (n=59,992)



HIV: human immunodeficiency virus; MSM: men who have sex with men.

The data in the Figure originate from 15 European Union Member States, which reported the mode of transmission for more than 50% of their HIV cases and consistently reported CD4 counts for the period from 2003 to 2012.

These 15 countries include Austria, Belgium, Cyprus, Denmark, the Czech Republic, Finland, France, Greece, Latvia, Luxembourg, the Netherlands, Portugal, Romania, Slovenia and the United Kingdom.

Table

Percentage of cases reported to have a CD4 cell count <350/mm³ among all MSM HIV cases with known CD4 counts, by age group, among 15 European Union Member States, 2003–2012 (n=59,992)

Age group in years	Percentage of cases among MSM HIV cases with a CD4 cell count <350/mm³, by year									
	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
<20	0.47	0.35	0.34	0.20	0.39	0.30	0.25	0.52	0.46	0.39
20–29	7.72	7.21	8.30	8.64	8.64	8.46	7.59	8.01	8.15	8.65
30–39	18.89	15.90	16.80	14.77	13.69	14.04	12.33	11.82	12.05	10.75
40–49	10.75	11.67	10.64	11.92	11.98	11.91	11.93	11.45	10.25	10.09
>50	7.49	6.93	5.68	5.99	7.34	6.48	6.59	6.54	5.93	6.97
All	45.32	42.07	41.77	41.52	42.05	41.20	38.69	38.35	36.83	36.86

HIV: human immunodeficiency virus; MSM: men who have sex with men.

The data in the Table originate from 15 European Union Member States, which reported the mode of transmission for more than 50% of their HIV cases and consistently reported CD4 counts for the period from 2003 to 2012.

These 15 countries include Austria, Belgium, Cyprus, Denmark, the Czech Republic, Finland, France, Greece, Latvia, Luxembourg, the Netherlands, Portugal, Romania, Slovenia and the United Kingdom.

presenters among all newly diagnosed HIV cases remained fairly stable.

Discussion and conclusion

The EU/EEA 2012 surveillance data indicate that new HIV infections remain concentrated in key populations at higher risk of HIV infection, such as MSM, heterosexual people originating from high-endemic countries and, to a lesser extent, people who inject drugs. European surveillance data are heavily dependent on national testing strategies, good case-detection and comprehensive reporting of all cases on a national and European level. Reporting the mode of transmission is key to allow the correct interpretation of data and to improve targeted prevention. Unfortunately, stigma and limited access to low-threshold healthcare facilities still hamper the disclosure of sexual preference in many countries [3] and this is likely to result in underreporting of MSM transmission [4].

The relatively high proportion of late diagnoses in many countries is a worrying indication of delays in accessing HIV testing. Although we found a stable prevalence of late diagnosis among young MSM (20 to 29 years-old), the concomitant increase in absolute numbers of new HIV infections in this age group is worrying as well. A study from an Australian state whereby testing for HIV among MSM was performed, revealed that MSM under the age of 35 years were more likely than older MSM to have never previously been tested for HIV. In 20 cities in the United States (US) awareness of HIV-positive status in 2008 and in 2011 among MSM increased significantly by age [5,6]. A modelling study among MSM based on the Swiss HIV Cohort Study estimated that by the end of 2010, 13.5% of infected MSM were undiagnosed, however they were estimated to account for almost 82% of new infections due to continuing risky sexual behaviour [7], hence the conclusion by the authors that HIV testing needs to be scaled up.

The increases in new HIV infections among young MSM aged 20 to 29 years reported here are similar to findings during the period between 1994 and 2011 in the US and Australia [5,8-10]. In Norway, although an increase in new HIV cases was found to have occurred from 2003 to 2011, no difference in median age (36 years) among these newly diagnosed HIV cases was observed among MSM between 1995 and 2011 [11]. In Australia, Canada, Germany, the Netherlands, the United Kingdom and the US, the weighted median age was even found to have increased from 34 to 36 years between 1996 and 2005 [12]. Studies showing increasing trends in co-infections with other sexually transmitted infections (STIs) [11-14] suggest high levels of sexual risk behaviour among MSM that augments the likelihood of acquiring HIV and hence might be one of the reasons for the increase in young MSM reported here [11-15].

In Australia, increases in new HIV infections, particularly in young MSM, were found to be strongly correlated with increasing trends, since 1998, of MSM younger than 30 years not taking combination antiretroviral therapy (cART) [8]. In Scotland, younger MSM (<25 years-old) increasingly engaged in higher levels of sexual risk behaviour (2 or more partners with unprotected anal intercourse in the previous 12 months) between 2000 and 2002 [16] and which could be a driving factor for the increasing trends.

In the data presented here we saw a decrease in late presenters in 30 to 39 year-old MSM, which supports the hypothesis that testing increased in this age group over the last decade, probably due to increased

awareness among older MSM [6] or changing testing strategies over time. Despite this, access to and uptake of testing still needs to improve as 37% of all new infections in MSM in 2012 presented at a stage where treatment is already needed.

There are several limitations in this analysis and the results presented. First, data submitted over the years are incomplete, particularly for CD4 cell count, and our interpretation might be biased as cases for which no information on CD4-cell count was given might differ from those reported. To overcome this issue, we strictly limited our analysis to those countries which consistently reported the mode of transmission for more than 50% of cases as well as the CD4 cell count in all years analysed. Second, our results are influenced by countries with large numbers of new HIV infections and a concomitant complete reporting of the mode of transmission. Third, surveillance data is prone to delays in reporting and underreporting. In our MSM analysis, we did not take the reporting delay into account and data for 2012 might still underestimate the true picture. This analysis also does not take into account changes in HIV testing strategies and reporting patterns.

In the last decade, the largest increase in new infections has been seen among young MSM. Throughout Europe, HIV counselling and testing services need to be continuously promoted, made more accessible and targeted at key populations at higher risk to ensure earlier diagnosis and initiation of HIV treatment and linkage to care [17]. This will result in improved treatment outcomes and clinical benefits, as well as contribute to preventing or further reducing HIV transmission.

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Conflict of interest

None declared.

Authors' contributions

JJ developed the concept of the manuscript, collected and analysed the data, wrote the first draft of the manuscript and responded to reviewer comments. KH contributed to the concept of the manuscript, interpreted the results critically, contributed to writing the manuscript and revised the article to ensure important intellectual content. GS contributed to the concept of the manuscript and analysis, contributed to writing the manuscript and revision of the article. MvL, GL and AA developed the surveillance instrument, critically reviewed the article and provided important feedback on the article. All authors read and approved the final manuscript.

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Human immunodeficiency virus among people who inject drugs: Is risk increasing in Europe?

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In most European Union (EU)/European Economic Area (EEA) countries, between 2010 and 2012, reports of new human immunodeficiency virus (HIV) diagnoses among people who inject drugs have been stable or declining. HIV outbreaks in Greece and Romania, first reported in 2011, continue and economic conditions hinder provision of effective response coverage. When measured against some established thresholds, prevention coverage remains inadequate in at least one-third of EU/EEA countries. Urgent consideration to scale up prevention efforts is merited.

Introduction

In response to sharp increases in human immunodeficiency virus (HIV) notifications reported among people who inject drugs (PWID) in Greece and Romania, a risk assessment of HIV transmission among PWID was carried out in the European Union/European Economic Area (EU/EEA), Croatia and Turkey, in 2011. The report, covering 31 countries, confirmed outbreaks among PWID in Greece and Romania and noted a potential for outbreaks elsewhere [1,2]. This update, based on a survey conducted in mid-2013, summarises developments in HIV transmission and injecting risks among PWID since 2010 and identifies areas where scale-up of evidence-based preventive measures is needed to avoid further outbreaks.

Data collection for indicators and analysis

This study analysed multiple sources of disease and prevention service data for the period 2010 to 2012 collected from 31 countries, including 27 EU Member States, Croatia, two EEA countries (Iceland and Norway) as well as Turkey. The data were provided through the regular monitoring systems of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and the European Centre for Disease Prevention and Control (ECDC). These data were augmented with a rapid enquiry of their respective expert networks in May-June 2013. The enquiry used an excel table pre-filled with data previously reported for 2010 and 2011 for purposes of validation or correction. The table also served as a survey tool to report 2012 data. The data of interest focused on three groups of indicators, as well as on questions regarding HIV prevention funding, such as if this funding was adequate, if it had changed between 2010 and 2012 and if changes were expected in the coming two years.

The three groups of indicators analysed for the period between 2010 and 2012 comprised the following: (i) HIV trend: data on HIV case reports with injecting drug use as mode of transmission for the period from 2010 to 2012 notified to ECDC through the European Surveillance System (TESSy) were analysed alongside data on HIV prevalence among PWID, (ii) transmission risk: data on prevalence of injecting drug use trends, changes in injecting risk behaviour, and trends in hepatitis C virus (HCV) prevalence, and (iii) data on prevention service coverage routinely reported to the EMCDDA [3,4], including opioid substitution treatment (OST) and needle and syringe programmes (NSP) coverage.

For each country, the first two indicators were characterised either as 'no alert', 'concern' or 'alert'. As the classification of levels of NSP and OST coverage is based on established thresholds, the third indicator could only be qualified as 'alert' or 'no alert'.

HIV trend in the countries was classified under 'alert' if there was a significant ($p < 0.05$) increase in HIV case reports or prevalence between 2010 and 2012. Classification as 'concern' was assigned if there was a significant increasing trend in HIV prevalence at subnational level (e.g. in a city or a region) during the same period or a consistent but non-significant rise in HIV cases at national level. 'No concern' indicated that there was no evidence of increasing HIV cases or prevalence in a country.

Risk for increased HIV transmission was characterised as an 'alert' if any of the following conditions were reported through national drug focal points or reporting systems: increased or high (>50%) HCV prevalence

among PWID; increased prevalence of injecting drug use; or changes in drug use patterns such as increased stimulant injection. A 'concern' was defined as a subnational increase. There was 'no alert' when no evidence of increases occurred with regard to HCV prevalence, prevalence of injecting drug use, and stimulant injection among PWID.

Prevention service coverage was classified as 'alert' if the proportion of problem opioid users receiving OST (OST coverage) was less than 30% and/or if the annual average number of syringes distributed by NSPs per PWID (NSP coverage) was less than 100/PWID/year.

All data reported were validated by national HIV surveillance and national drug focal points to ensure that the most recent available data were included.

Results

Characteristics of each of the indicators considered in this study, by country, are shown in the Table.

Human immunodeficiency virus case reports and prevalence among people who inject drugs

Except for Liechtenstein, which did not take part in the risk assessment, data on HIV diagnoses with injecting drug use as the mode of transmission from 2010 to 2012 were provided by all EU/EEA countries, as well as by Croatia and Turkey. Information on HIV prevalence among PWID during the period from 2010 to 2012 was given by 26 countries, eight of which (Belgium, Bulgaria, Estonia, Germany, Lithuania, Netherlands, Sweden and the United Kingdom) only had subnational data. No data on HIV prevalence among PWID were available from Croatia, Denmark, Finland, Iceland and Ireland.

Twenty-five countries reported stable or declining population rates of HIV diagnoses in PWID over the past three years, continuing the trend observed throughout much of the EU/EEA from the mid-2000s [5]. In 2012, rates of new HIV diagnoses associated with injecting drug use were below 1.0 per 100,000 population for 26 countries, between 1.0 and below 4.0 for Romania and Lithuania and above 4.0 for Greece, Latvia and Estonia (Figure).

Greece and Romania report ongoing outbreaks [6-9] leading to an almost 20-fold increase in new diagnoses among PWID between 2010 and 2012. Taken together, these two countries reported more than one third of the HIV diagnoses associated with injecting drug use in the 31 countries in 2012, compared to only 2.2% in 2010. These outbreaks are concentrated in the capital cities, with reported HIV prevalence among PWID in Athens of 20% [10] and Bucharest of 53% [9].

In Austria, Bulgaria, Estonia and Latvia, the extent to which the recent evolution in HIV trends represents a significant risk is unclear. In Estonia and Latvia, after major HIV outbreaks between the late 1990s and the early 2000s leading to high prevalence [11,12], new HIV case reports declined until 2008 in Estonia and until 2009 in Latvia [5], but incidence remains high in 2012 (>4/100,000 population) (Figure). Between 2010 and 2012, HIV diagnoses have slightly risen in both countries, while HIV prevalence studies among PWID in Latvia (national level: 20.2%) and Estonia (Kothla-Jarve: 61.8%) showed high levels of HIV. In Austria, the number of HIV diagnoses rose slightly over the period between 2010 and 2012 and HIV prevalence among PWID at low-threshold facilities in Vienna increased fivefold from 0.8% in 2010 to 4.9% in 2012. In Bulgaria, HIV diagnoses fluctuated at national level, but a doubling of prevalence of HIV among young PWID in Sofia from 3.1% in 2010 to 6.1% in 2011 was noted (Table).

Human immunodeficiency virus transmission risk

Trends in HCV prevalence among PWID are an indicator of injecting risk and high HCV prevalence can be a proxy for HIV transmission risk [13]. In 2012, increases in HCV or very high prevalence of HCV among PWID (50–80%) were reported in nine countries: Belgium (Flemish community), Bulgaria (Sofia), Cyprus, Estonia (Narva), Greece, Italy (several regions), Latvia, Romania (Bucharest), and Turkey.

Increased injecting of stimulants was reported in four countries. In Romania and Hungary, this reflected the appearance of new stimulant drugs on the market, such as cathinones, leading to more frequent injecting among traditional opiate users [14]. Austria and Greece previously reported increases in methamphetamine injecting [1]. However in Athens, Greece, opiates continue to be the main drug of use.

Prevention coverage and funding

Data on prevention coverage were available for 25 countries (OST: 20; NSP: 13) (Table). Most countries have implemented relatively high levels of prevention services, but 10 countries report low prevention coverage, either for OST (6 countries with coverage ranging from 4 to 20%) or for NSP (7 countries report distributing less than 100 needles and syringes/PWID/year, including Turkey where NSP is not available).

In Greece, scale-up of prevention coverage from low activity started in 2011 [15]; this has been impeded by financial constraints since late 2012 [16]. In Romania, coverage has reduced substantially since 2010, when a Global Fund grant ended, with the rate of 47 syringes per PWID reported (Bucharest, 2012) far below estimated need [6] and OST remains limited. Since July 2013 the main harm reduction provider (Romanian Anti-AIDS Association, ARAS) had to halve services [17] due to limited resources. In Bulgaria, a Global Fund grant will end in 2014.

Discussion

The previous assessment, carried out in 2011 identified worrying spread of HIV among PWID in Greece

Table

Assessment of human immunodeficiency virus trends among people who inject drugs, in EU/EEA, Croatia and Turkey, 2010–2012 (n=31 countries[a])

	Countries[a]																														
	AT	BE	BG	HR	CY	CZ	DK	EE	FI	FR	DE	EL	HU	IS	IE	IT	LV	LT	LU	MT	NL	NO	PL	PT	RO	SK	SI	ES	SE	TR	UK
HIV trend HIV case reports[b] and prevalence[c]																															
Transmission risk prevalence of injecting drug use, changes in injecting risk behaviour																															
OST coverage Percent of estimated problem opiate user population receiving OST: cut-off 30%																															
NSP coverage Number of syringes given out per PWID per year: cut-off 100 syringes																															

	NO ALERT – no evidence for increase in HIV case reports or HIV/HCV prevalence and/or transmission risk and/or low intervention coverage.
	CONCERN – subnational increase in HIV/HCV prevalence and/or transmission risk or consistent but non-significant rise at national level.
	ALERT – evidence for significant increase in HIV case reports or HIV/HCV prevalence and/or increase in transmission risk and/or low intervention coverage.
	Information unknown/not reported to EMCDDA/ECDC.

ECDC: European Centre for Disease Prevention and Control; EMCDDA: European Monitoring Centre for Drugs and Drug Addiction; HCV: hepatitis C virus; HIV: human immunodeficiency virus; NSP: needle and syringe programmes (NSP); PWID: people who inject drugs; OST: opioid substitution treatment.

[a] Liechtenstein did not take part in the study. Countries included in the Table are Austria (AT), Belgium (BE), Bulgaria (BG), Croatia (HR), Cyprus (CY), Czech Republic (CY), Denmark (DK), Estonia (EE), Finland (FI), France (FR), Germany (DE), Greece (EL), Hungary (HU), Iceland (IS), Ireland (IE), Italy (IT), Latvia (LV), Lithuania (LT), Luxembourg (LU), Malta (MT), Netherlands (NL), Norway (NO), Poland (PL), Portugal (PT), Romania (RO), Slovakia (SK), Slovenia (SL), Spain (ES), Serbia (SE), Turkey (TR), United Kingdom (UK).

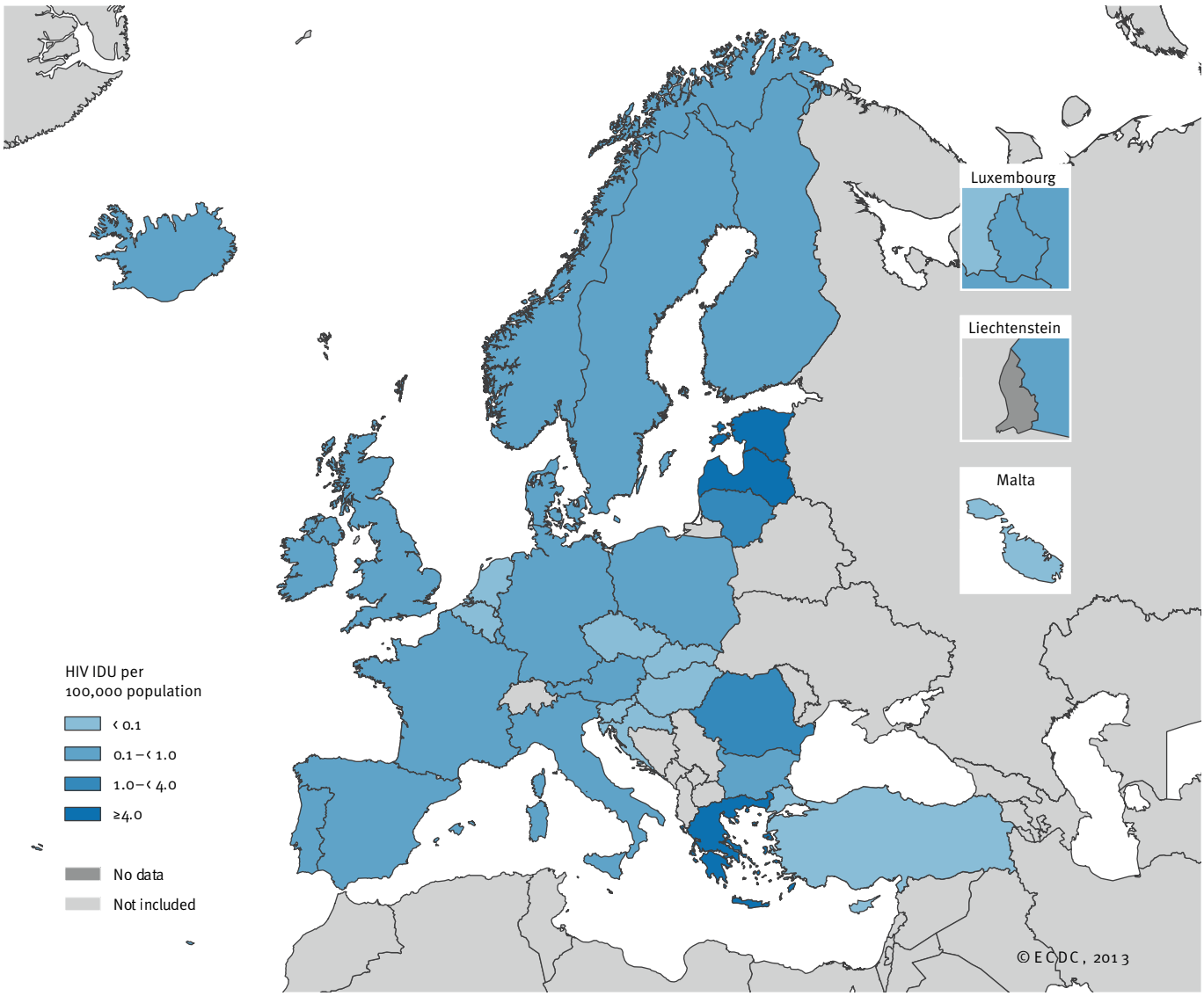
[b] Except for Liechtenstein, data on HIV diagnoses with injecting drug use as the mode of transmission from 2010 to 2012 were provided by all EU/EEA countries, as well as Croatia and Turkey.

[c] No data on HIV prevalence among PWID were available from Croatia, Denmark, Finland, Iceland and Ireland. Only subnational data were available from Belgium, Bulgaria, Estonia, Germany, Lithuania, Netherlands, Sweden and the United Kingdom.

For further detail and information about data sources see Supplementary Table available from: http://www.emcdda.europa.eu/publications/joint-publications/hiv-in-injecting-drug-users/update-2013/supplementary-table

Figure

Rates of newly diagnosed human immunodeficiency virus (HIV) infections with injecting drug use as mode of transmission in EU/EEA, Croatia and Turkey, 2012 (n=32 countries)



EEA: European Economic Area; EU: European Union; HIV IDU: HIV infections with injecting drug use as mode of transmission.

and Romania [1,2]. This updated assessment confirms these continuing and serious outbreaks and also provides the most recent data on trends in HIV among PWID in the EU/EEA region as a whole. It is based on a considerable amount of hitherto unpublished data on drug-related indicators, which were gathered through a rapid inquiry in May-June 2013.

Apart from Greece and Romania, HIV among PWID appears to be stable or declining in much of the EU/EEA. However, in at least eight other countries, data suggests that substantial populations of PWID have limited access to OST and NSP services and may therefore be vulnerable with regard to outbreaks in the future.

Vigilance is required where indicators of potential risk for increased HIV transmission, such as increases in HCV infection, high HCV prevalence, and increased stimulant injecting are reported. Increased injection of stimulants poses challenges for prevention services, requiring increased NSP provision to cover more frequent injecting and more emphasis on active outreach. Recent reports of increased injecting of cathinones leading to an HIV outbreak among PWID in Israel underline this [18]. Increased reported stimulant use also implies that greater attention be paid to

sexual transmission among PWID. In London a possible increase in stimulant injection among men who have sex with men (MSM) and subsequent increase in HIV transmission has been reported [19].

There are limitations to this assessment. Data on HIV notifications for 2012 are liable to revision due to adjustment for reporting delays. For several countries, prevention coverage could not be estimated due to missing data or lack of a denominator. For example, coverage of OST could not be calculated for Belgium, Bulgaria, Denmark, Estonia, Finland, Iceland, Portugal, Romania, Slovenia, Sweden, and Turkey due to a lack of estimates of the prevalence of opiate use.

Effective control of HIV transmission among PWID requires a comprehensive public health policy including adequate provision of both NSP and effective treatment of drug dependence together with health promotion, accessible HIV testing, targeted service delivery, and antiretroviral treatment (ART) for HIV positive persons [20]. To avoid high long-term healthcare costs and preventable future morbidity and mortality, reaching and maintaining an adequate level of prevention is needed in all EU/EEA countries but most urgently in those identified as vulnerable to increases in HIV among PWID. In some cases, economic conditions and funding shortages threaten adequate responses.

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Conflict of interest

None declared.

Authors' contributions

Dagmar Hedrich, Otilia Sfetcu, Eleni Kalamara, Anastasia Pharris, Lucas Wiessing and André Noor designed the protocol for the rapid survey. Eleni Kalamara analysed the trends in drug-related datasets and Otilia Sfetcu the trends in HIV case reports. Dagmar Hedrich was the lead author. All authors reviewed and commented on the manuscript throughout its production.

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Increase of new HIV diagnoses among men who have sex with men in Poland, 2000 to 2011

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Re-emergence of the human immunodeficiency virus (HIV) epidemic among men who have sex with men (MSM) has been observed in countries of western Europe, North America and Australia since the mid-1990s. We aimed to describe the trends in notification rate of HIV infection among MSM in Poland in order to provide evidence for further public health action. We performed a descriptive analysis of 2000–11 surveillance data, accounting for missing information on transmission category through multiple imputations. There were 9,286 new HIV diagnoses in Poland in 2000–11, ranging from 546 to 1,095 per year. A total of 6,896 cases were male, 1,943 female. For 5,615 (60.5%) new diagnoses, the transmission category was not reported; among the rest, MSM constituted 24.1% (n=885/3,671). The rate of new HIV diagnoses among MSM per million men increased from 2.5 in 2000 to 33.8 in 2011; in the Mazowieckie region, which includes Warsaw, it rose from 2.2 to 88.8, when adjusting for missing data on transmission category. Our results suggest the need for enhanced, comprehensive prevention among MSM, especially in regions where the increasing rate of new HIV diagnoses suggests ongoing transmission.

Introduction

The global HIV epidemic is considered to have peaked during the second half of the 1990s [1]. However, several regions are experiencing increases of new infections, notably eastern Europe and central Asia, but also western Europe and North America. In particular, re-emergence of the HIV epidemic among men who have sex with men (MSM) has been observed in western Europe, North America and Australia since the mid-1990s [2]. In the European Union, the number of new HIV diagnoses among MSM increased by 33% between 2004 and 2011 [3]. In 2011, 39% of newly detected HIV infections were attributed to sex between men, 23% to heterosexual contacts and 5.4% to injecting drug use [3].

In contrast, the HIV epidemic in Poland remained stable until approximately 2005, at relatively low levels (<20 newly diagnosed HIV infections per million population), with injecting drug use as the major mode of transmission [4,5]. People who inject drugs accounted for over 75% of HIV cases with known transmission category [4,5]. New HIV diagnoses among people infected through sexual intercourse were uncommon. However, the testing rate among the general population was among the lowest in Europe (at 8.3 per 1,000 population in 2011) [3] and the high proportion of late-presenting cases among sexually infected individuals (20–32%) indicated possible underestimation in the surveillance data of the sexual spread of the virus [4-6]. Until 2005, a slight increase in detection rate was attributed to epidemic maturation [7]. However, a significant increase in new HIV diagnoses across age cohorts occurred after 2005, suggesting emergence of the epidemic [7]. Changes in distribution of the main transmission categories among the people with new diagnoses were also reported, with increasing importance of MSM and heterosexual women and men who do not inject drugs [5,6,8]. However, conclusions were hampered by the high proportion of diagnoses with missing transmission category (over 60%) in routine surveillance data [3,5,6].

HIV prevention services for MSM in Poland remain limited. Monitoring of prevention efforts revealed that in 2007–10, only a few local outreach or community programmes, including education and condom distribution, were targeted at MSM [9]. Additional education was provided through a network of HIV voluntary counselling and testing centres located throughout the country, reaching an estimated 1,500–4,500 MSM clients annually [9]. Internet campaigns were also used. Novel methods such as pre-exposure prophylaxis, which has proved effective and safe [10], are unlikely to be implemented in Poland in near future.

The aim of our study was to analyse the trends in new HIV diagnoses among MSM in Poland, adjusting for missing transmission category in routine surveillance data.

Methods

Data sources

We used data from routine HIV/acquired immunodeficiency syndrome (AIDS) surveillance in Poland, which is a comprehensive case-based national system using European Union case definitions [3]. New HIV diagnoses are reported by laboratories and clinicians to regional public health departments. Regional departments collate the clinical and laboratory reports, collect additional information and forward the forms to the National Institute of Public Health - National Institute of Hygiene. The notifications may be name-based, but the patient has the right to refuse to reveal personal information on the report form. The system relies on paper forms and an electronic registry using a name-based identifier is maintained only at the central level. Clinical and epidemiological information (transmission category) is usually not available in the reporting laboratories. As the laboratories report more cases than clinicians do, there is a high proportion of patients with missing data (clinical characteristics and transmission category). The first AIDS-indicative disease is also reportable, by the diagnosing clinician, and reports of HIV infection and AIDS related to the same person are linked at the regional and/or central level. Therefore, reported HIV cases who develop AIDS are more likely to have complete information regarding transmission category.

In order to minimise the effects of reporting delay, we used data on cases diagnosed up to the end of 2011, but reported by July 2012. The reporting delay was estimated once using all reported cases, and a second time excluding those cases that were notified only as a result of reporting completeness control activities.

We also used the results of an annual survey sent by mail to laboratories that offer HIV screening tests (as opposed to the laboratories performing confirmatory HIV tests, who report new diagnoses), for which data were available for 2003–11. In 2003–11, the number of participating laboratories ranged from 140 to 266, reflecting changes in the market of diagnostic services for HIV. The survey is voluntary and the response rate varied from 59% to 85% in 2003–11. Aggregated data on the number of diagnostic HIV tests performed in each laboratory were collected, excluding tests of blood donors. The reporting form allows disaggregation by transmission category and sex, but only several laboratories are able to provide this information. Only laboratories reporting 10 or more tests among MSM in a given year were included in the analysis in order to exclude data from laboratories not routinely collecting information on transmission category, acknowledging that we will also exclude those who test only a few MSM per year.

Adjustment for missing information on transmission category

Transmission category may be missing in the surveillance data because it is not known to clinicians or, even if known, may not be reported to the public health system by clinicians. In data reported by clinicians (e.g. AIDS case reports), transmission category is not specified for approximately 12% of cases, which suggests that lack of these data may be mostly due to inadequate completeness of reporting. The fact of reporting by a clinician is unlikely differential to transmission category. However, clinicians may be more likely to report cases diagnosed with AIDS, thus bias could result from a more common occurrence of AIDS in one of the categories. As the proportion of missing values for transmission category increased over time and as we expect regional differences related to local collaboration of public health services with clinicians, we assumed that the information is missing at random in any given the year of diagnosis, region and time of diagnosis (late presenter or other). We used a multiple imputation procedure imputing concurrently age (years), sex and transmission category (MSM vs other, conditional on sex) with five imputed datasets [11]. Iterative chained equations were used to account for non-normal distribution of the imputed variables [12]. In this method, the variables with missing values are iteratively imputed on the basis of regression equations estimated on an imputed dataset from the previous step, including as explanatory variables other variables that are being imputed as well as other available covariates.

We used logistic regression for sex and transmission category (MSM vs other) and linear regression for age. Additional explanatory variables included year of diagnosis, region and late presentation (yes vs no). Due to lack of data on CD4 count at diagnosis, we could not use the late presenter consensus definition as outlined in [13]. In our study, a late presenter was defined as person who developed AIDS within a year of HIV diagnosis. Estimates were then produced for each imputed dataset and combined using the Rubin's combination rule [11,12]. The analysis was conducted in STATA 10.1 using 'ice' and 'mim' commands [12].

Results

There were 9,286 new HIV cases diagnosed in Poland from 2000 to 2011, of whom 6,896 (78.0%) were male and 1,943 (22.0%) female (information on sex was missing for 447 cases). The transmission category was not reported for 5,615 (60.5%) cases. Among the rest (n=3,671), transmission categories included MSM (n=885, 24.1%), people who inject drugs (n=1,881, 51.2%), heterosexual men and women (n=861, 23.5%), children of HIV-positive mothers (n=141, 3.8%).

The evolution of characteristics of new HIV diagnoses among men in the study period is shown in Table 1. We note a remarkable shift in the transmission category distribution. Among cases with known transmission

Table 1

Characteristics of men with newly detected HIV infections, Poland, 2000–2011 (n=6,896)

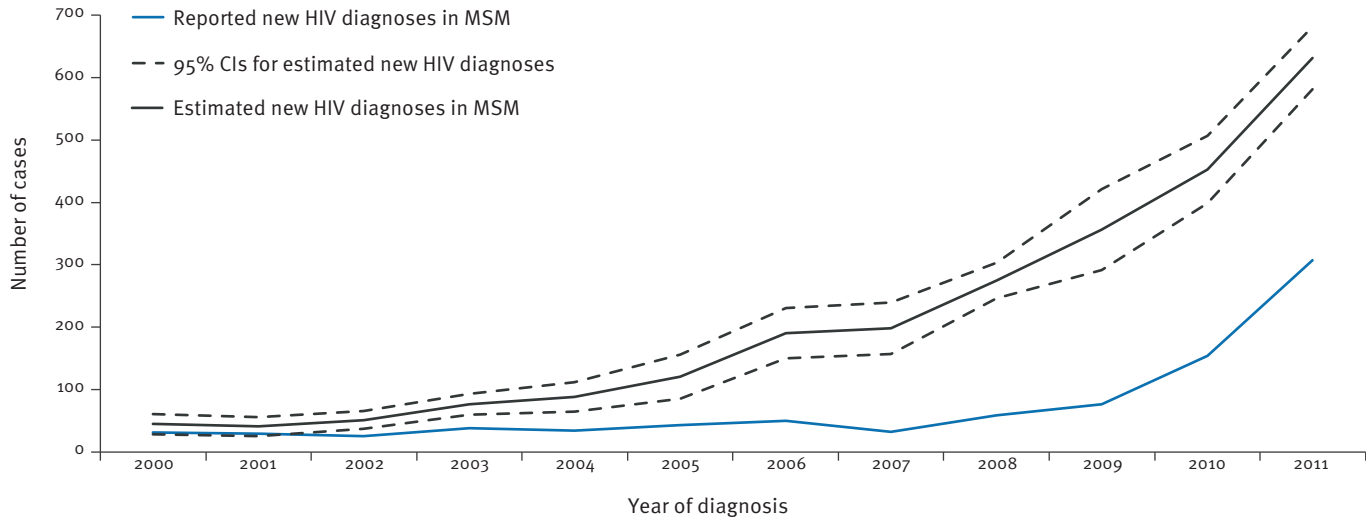
Characteristic	Year of diagnosis					p value[b]
	Total (2000–2011)	2000–2002	2003–2005	2006–2008	2009–2011	
	Number (%)[a]	Number (%)[a]	Number (%)[a]	Number (%)[a]	Number (%)[a]	
Age group (years)						
<25	1,241 (18.7)	356 (28.9)	284 (20.0)	282 (16.6)	319 (13.9)	<0.0001
25–34	2,978 (44.8)	497 (40.4)	619 (43.5)	779 (45.9)	1,083 (47.3)	–
35–44	1,561 (23.5)	271 (22.0)	324 (22.8)	403 (23.7)	563 (24.6)	–
≥45	863 (13.0)	107 (8.7)	196 (13.8)	235 (13.8)	325 (14.2)	–
ND	253	53	54	90	56	–
Transmission category						
Men (non-injectors) who have sex with men	885 (31.5)	88 (11.4)	117 (16.8)	142 (28.2	538 (64.4)	<0.0001
Men who inject drugs	1372 (48.8)	603 (77.9)	447 (64.2)	205 (40.7)	117 (14)	–
Men (non-injectors) who have sex with women only	487 (17.3)	75 (9.7)	116 (16.7)	131 (26)	165 (19.8)	–
Children of HIV-positive mothers	65 (2.3)	8 (1)	16 (2.3)	26 (5.2)	15 (1.8)	–
ND	4,087	510	781	1,285	1,511	–
Late presenter[c]						
No	6,189 (89.8)	1,162 (90.5)	1,302 (88.2)	1,588 (88.8)	2,137 (91.1)	0.010
Yes	707 (10.3)	122 (9.5)	175 (11.9)	201 (11.2)	209 (8.9)	–
Residence						
Urban	3,778 (89.3)	815 (93.9)	1,022 (92.1)	798 (86.3)	1,143 (86.1)	<0.0001
Rural	452 (10.7)	53 (6.1)	88 (7.9)	127 (13.7)	184 (13.9)	–
ND	2,666	416	367	864	1,019	–
Region of residence						
Dolnośląskie	1,009 (17.9)	230 (22.0)	276 (22.9)	231 (17.4)	272 (13.3)	<0.0001
Kujawsko-pomorskie	253 (4.5)	51 (4.9)	47 (3.9)	69 (5.2)	86 (4.2)	–
Lubelskie	143 (2.5)	39 (3.7)	27 (2.2)	22 (1.7)	55 (2.7)	–
Lubuskie	164 (2.9	30 (2.9)	23 (1.9)	46 (3.5)	65 (3.2)	–
Łódzkie	416 (7.4)	97 (9.3)	95 (7.9)	101 (7.6)	123 (6.0)	–
Małopolskie	291 (5.2)	31 (3.0)	53 (4.4)	90 (6.8)	117 (5.7)	–
Mazowieckie	105 (18.7)	89 (8.5)	172 (14.3)	272 (20.5)	517 (25.3)	–
Opolskie	125 (2.2)	23 (2.2)	26 (2.2)	30 (2.3)	46 (2.3)	–
Podkarpackie	110 (2.0)	26 (2.5)	24 (2.0)	28 (2.1)	32 (1.6)	–
Podlaskie	112 (2.0)	30 (2.9)	21 (1.7)	16 (1.2)	45 (2.2)	–
Pomorskie	363 (6.5)	74 (7.1)	103 (8.6)	78 (5.9)	108 (5.3)	–
Śląskie	624 (11.1)	127 (12.2)	142 (11.8)	100 (7.5)	255 (12.5)	–
Świętokrzyskie	62 (1.1)	6 (0.6)	14 (1.2)	19 (1.4)	23 (1.1)	–
Warmińsko-mazurskie	291 (5.2)	90 (8.6)	70 (5.8)	69 (5.2)	62 (3.0)	–
Wielkopolskie	345 (6.1)	35 (3.4)	52 (4.3)	96 (7.2)	162 (7.9)	–
Zachodniopomorskie	266 (4.7)	67 (6.4)	60 (5.0)	60 (4.5)	79 (3.9)	–
ND	1,272	239	272	462	299	–
Reporting delay in months[d]						
Mean (SD)	ND	ND	1.99 (3.9)	1.7 (3.1)	2.4 (3.8)	0.0001
Median (IQR)	ND	ND	1 (1–2)	1 (1–2)	1 (1–2)	–

HIV: human immunodeficiency virus; IQR: interquartile range; mothers; ND: no data available; SD: standard deviation.

[a] Percentages were not calculated for variables for which data were not available.
[b] p value for change of the characteristic distribution across the study period.
[c] In our study, a late presenter was defined as person who developed AIDS within a year of HIV diagnosis.
[d] Excluding cases reported as a result of control activities.

Figure 1

New HIV diagnoses among men who have sex with men, Poland, 2000–2011[a]

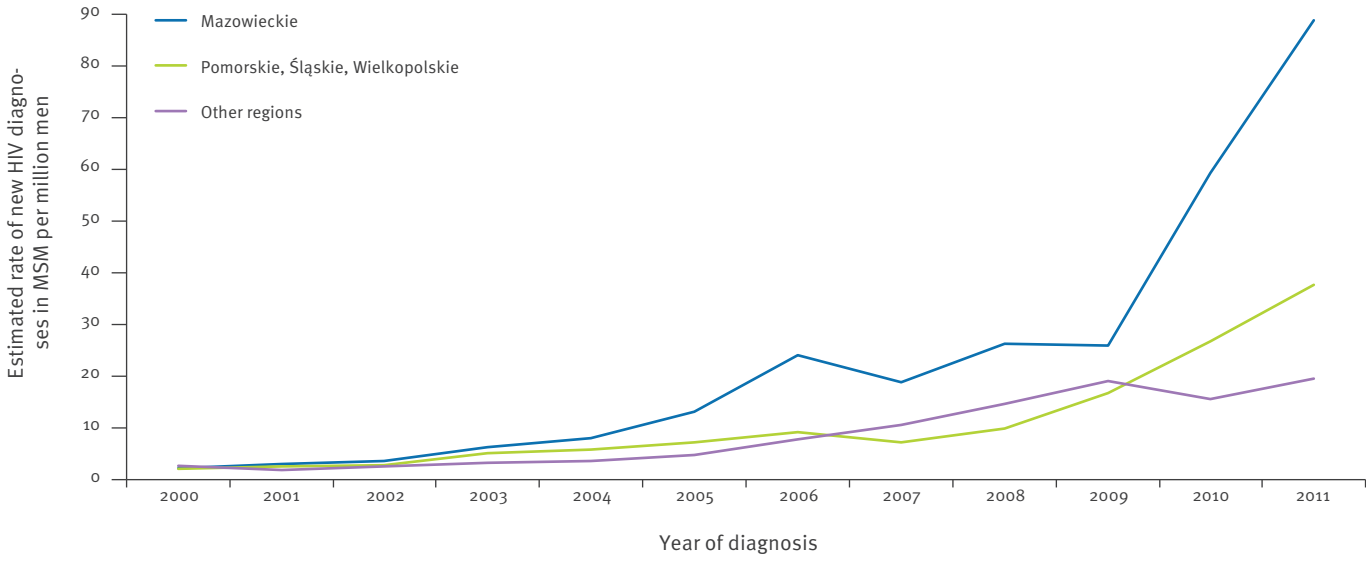


CI: confidence interval; HIV: human immunodeficiency virus; MSM: men who have sex with men.

[a] Reported number and the number estimated using multiple imputations of transmission category.

Figure 2

Estimated rate of new HIV diagnoses in men who have sex with men[a] per million men by region[b], Poland, 2000–2011



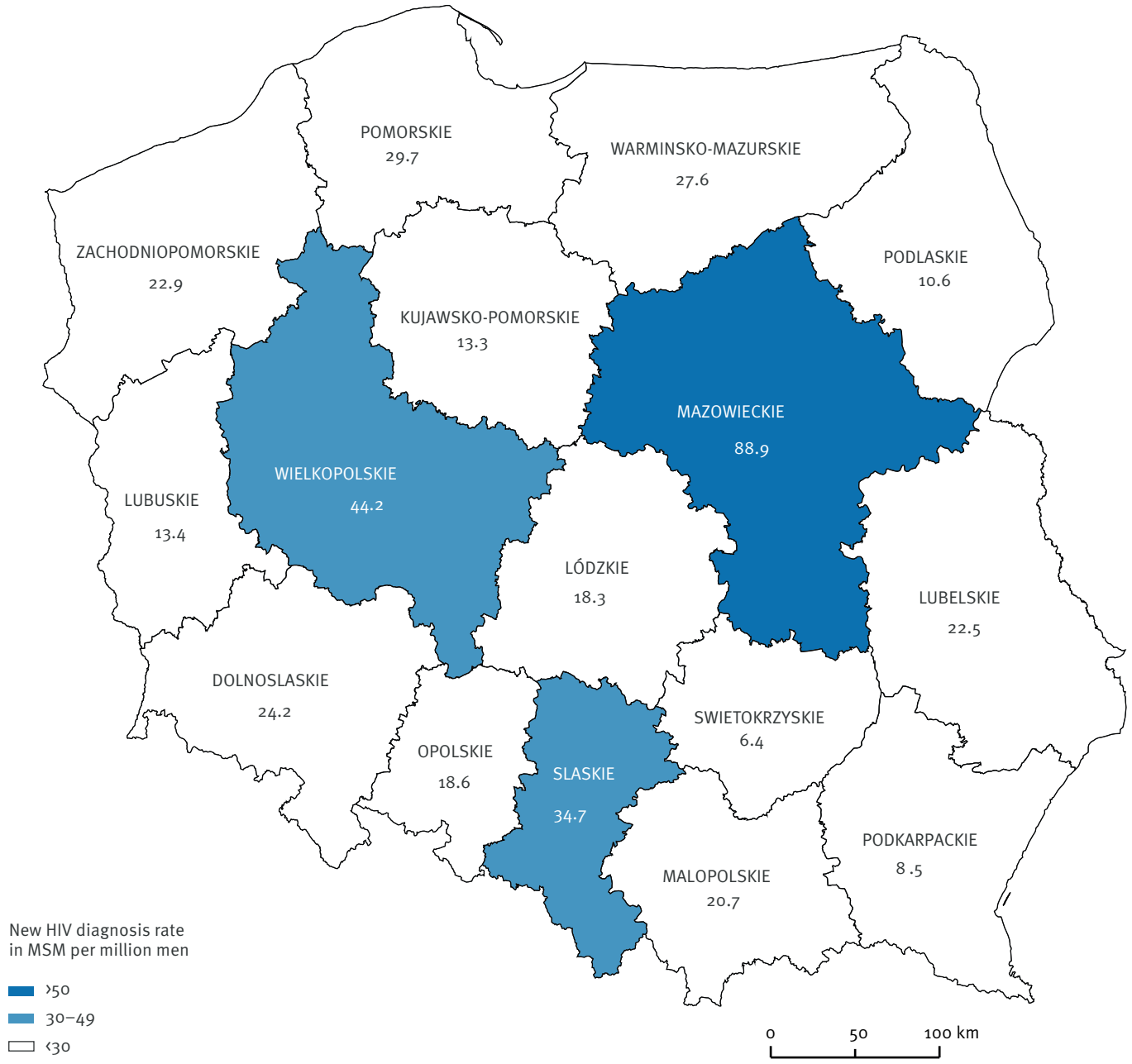
HIV: human immunodeficiency virus; MSM: men who have sex with men.

[a] Estimated rate based on multiple imputations of transmission category.

[b] Regions were grouped according to the rate of detection in MSM in 2011: 88.9/million men in Mazowieckie (region including the capital, Warsaw); 31.4–45.5/million men (Pomorskie, Śląskie, Wielkopolskie); 7.4–25.3/million men (other regions).

Figure 3

Estimated rate of new HIV diagnoses in men who have sex with men[a] per million men by region, Poland, 2011

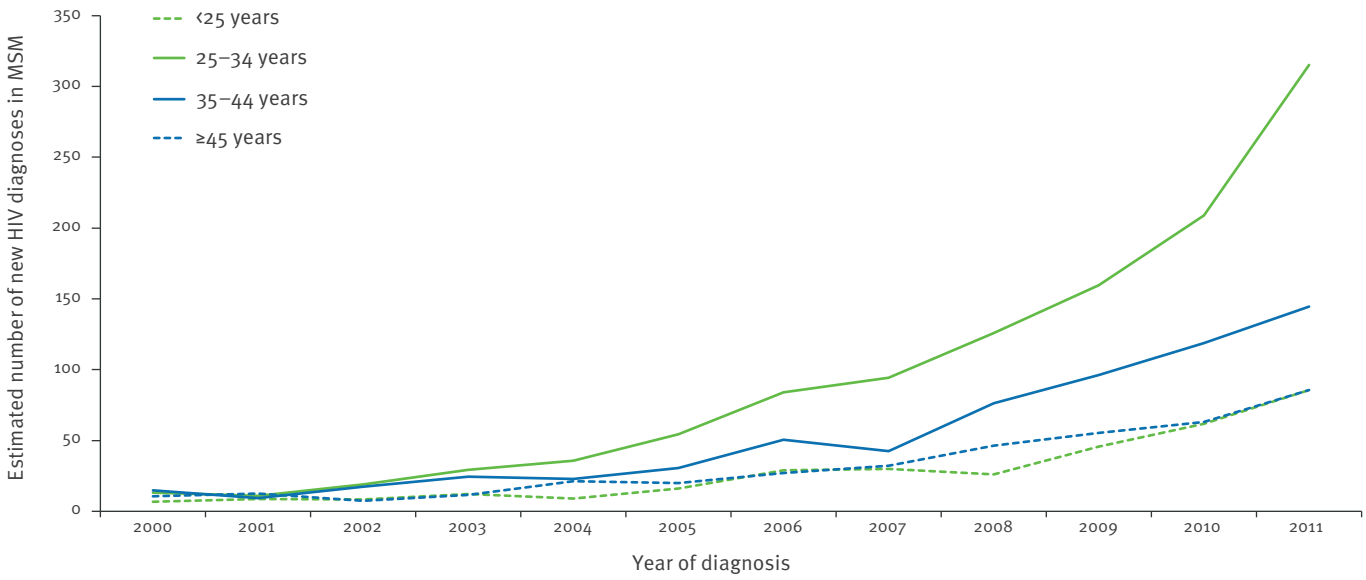


HIV: human immunodeficiency virus; MSM: men who have sex with men.

[a] Estimated rate based on multiple imputations of transmission category.

Figure 4

Estimated number of new HIV diagnoses in men who have sex with men[a] by age group, Poland, 2000–2011



HIV: human immunodeficiency virus; MSM: men who have sex with men.

[a] Estimated number based on multiple imputations of transmission category

category, the dominating category – men who inject drugs (77.9% (603/774) in 2000–02) was gradually replaced by MSM (non-injectors) and men (non-injectors) who have sex with women only (64.4% (538/835) and 19.8% (165/835) respectively in 2009–11).

Of the 5,396 cases with information on reporting delay, 4,966 (92.0%) were reported within 12 months of diagnosis and 87.7% (n=4,733) within six months of diagnosis. Excluding 351 cases reported as a result of control activities in one laboratory in 2010, the proportions reported within 12 months and 6 months were 98.4% and 93.8% respectively and the median delay was one month (interquartile range: 1–2) (Table 1).

Between 2000 and 2011, the annual number of reported new HIV diagnoses among MSM increased almost 10-fold; when imputing data on missing transmission category, the increase was 14-fold (from 2.5 per million in 2000 to 33.8 per million in 2011). Moreover, whereas the imputed data showed the increase already in 2005–06, it was only evident in 2009-10 in the raw reported data (Figure 1).

Trends by administrative region demonstrate especially high rates of new HIV diagnoses in Mazowieckie (the region including the capital city of Warsaw) (Figure 2). In this region, adjusting for missing data on transmission category, the rate of new HIV diagnosis in MSM increased from 2.2 per million men in 2000 to 88.9 per million men in 2011. The rates of new HIV diagnosis in MSM in 2011 ranged from 6.4 to 88.9 per million men across regions (Figure 3).

The most rapid increase in the number of new HIV diagnoses among MSM occurred in those aged 25–34 and 35–44 years (Figure 4). The estimated annual number of (reported) HIV diagnoses among MSM aged 25–34 years increased over 20 times, from 13 in 2000 to 315 in 2011.

Data on HIV prevalence among MSM presenting for diagnostic testing at selected laboratories across Poland that participated in an annual survey from 2003 to 2011 shows that the positivity rate per 100 tests increased significantly after 2005, and stabilised at a higher level in 2009–11 (Table 2).

Discussion

Our study suggests a 14-fold increase in the number of new diagnoses among MSM in Poland from 2000 to 2011, when imputing data on missing transmission category. This increase occurred concomitantly in all age groups, but was more pronounced among younger MSM (aged 25–44 years).

There were no systematic changes in the surveillance system or testing policy during the study period. However, testing for HIV, especially self- initiated testing was repeatedly encouraged. Additionally, the number of voluntary testing and counselling sites offering free-of-charge, anonymous testing increased [14]: such

Table 2

Prevalence of HIV among men who have sex with men presenting for diagnostic testing at selected laboratories[a], Poland, 2003–2011

Data collected	Year of diagnosis				p value
	Total (2003–2011)	2003–2005	2006–2008	2009–2011	
Number of participating laboratories[b]	26	19	11	10	–
Number of regions in which the participating laboratories were located[c]	14	14	10	8	–
Number of reported tests among men who have sex with men	4,216	1,385	1,239	1,592	–
Number of positives[d]	401	75	200	126	–
Positivity rate per 100 tests	9.5	5.4	16.1	7.9	<0.0001 (Poisson regression – categorical) 0.061 (Poisson regression – linear trend)

HIV: human immunodeficiency virus; IQR: interquartile range; MSM: men who have sex with men.

[a] Laboratories participating in an annual survey; only laboratories reporting 10 or more tests among MSM in a given year were included in the analysis.

[b] Only six laboratories were included in all three time periods.

[c] Of the 16 regions in Poland, Lubelskie and Śląskie were not covered as no laboratories from these regions were able to provide a breakdown by exposure category.

[d] Positive in screening test (data on whether the test result was confirmed were not collected).

sites were mentioned as the last test setting by 45% of MSM in Poland in 2010 [15].

Previous studies (in 2004 and 2005) estimated that in MSM, a large proportion of HIV infections – larger than that among people who inject drugs – might have been undiagnosed [16,17]. Improving access to testing over the study period could have led to a rise in the testing rates among MSM and, in consequence, contributed to the observed increase in notification rate. However, we also noted an increase in HIV prevalence among MSM coming for testing (from 5.4% in 2003–05 to 16.1% in 2006–08 and 7.9% in 2009–11). Although this increase alone would not fully explain the notification trend, it indicates that an upsurge of new HIV infections may also play a role. To further support the hypothesis of increasing HIV incidence among MSM, other studies found a high proportion (>30%) of recent infections confirmed by recent infection testing algorithm (RITA) testing among new diagnoses among MSM [18,19]. On the other hand, the proportions of respondents in behavioural surveys who reported having ever been tested were comparable in 2004 and 2010, 57% and 62% respectively, although it must be borne in mind that the study designs were different [15,16]. Either increased frequency of testing among those who were tested or a possible increase in disclosure of MSM status when testing for HIV may be additional factors that affect the surveillance trend. The observed trend is likely to be influenced by a number of factors, but the available information supports the hypothesis of emergence of the HIV epidemic among MSM in Poland.

Re-emergence of the HIV epidemic in MSM was noted in several western countries and attributed to increasing frequency of high-risk behaviours among MSM [2,20-22]. Inconsistent condom use and a high number of partners was also confirmed in Poland in a community-based survey among clients of HIV voluntary counselling and testing sites in 2004–07 [14,16] as well as (more recently) by an Internet survey among MSM (EMIS) [15]. The proportion of MSM who reported 10 or more partners in the past 12 months in these studies was estimated at 20%. In the community-based survey, past-12 months consistent condom use with non-stable or casual partners was approximately a third; in the Internet survey, the level rose to a half of the respondents. This level of risky behaviour is similar to that seen in western European countries [23], some of which noted an increasing HIV incidence in the recent past [2]. In contrast, the proportion of non-testers is higher in Poland than it is in western European countries. An important proportion of undiagnosed infections reaching an advanced phase could have contributed to increased spread of the virus. It has been suggested that in longer-lasting epidemics, individuals in the advanced stages of disease who are not diagnosed (and not treated) could contribute greatly to re-emergence of the epidemic [24]. Once the new infections start to appear, the epidemic could

pick up with transmission at the acute infection stage. A recent molecular study showed clustering of strains from recently infected MSM, suggesting transmission events often occur from a recently infected MSM as a source [25]. Transmission from long-standing undiagnosed infections followed by intensified transmission from recently infected individuals was proposed to explain the increasing spread of HIV among MSM in Germany in the early 2000s [26].

Our results show that the highest diagnosis rate and the fastest, over 40-fold, increase during the past decade occurred in one region, Mazowieckie, which includes the capital, Warsaw. The increase could be related to the higher proportion of MSM in the capital and more extensive sexual networks. Although we have no data on this for Mazowieckie, a higher concentration of MSM was noted in London, for example, as compared with other part of the United Kingdom [27].

Our study has several limitations. Firstly, we based on surveillance data, which are prone to various biases related to case ascertainment and collection of sensitive information. We cannot exclude misclassification of transmission category by reporting clinicians. Secondly, we relied on the small fraction of cases for whom we obtained reliable clinical reports: the rest was assumed to be missing at random. However, taking into consideration stigmatisation of same-sex relationships in Poland, MSM are rather less likely to reveal their exposures than heterosexual persons or people who inject drugs, so we are more likely to underestimate than to overestimate the HIV rates among MSM. Thirdly, we did not fully account for reporting delay. However, we noted that less than 10% of cases were notified with a delay of over six months, so only a small correction is expected after this time.

Our findings call for enhanced, comprehensive prevention among MSM, including revision of testing strategies, treatment of other sexually transmitted infections and possibly implementation of recently proven techniques such as pre-exposure prophylaxis, along with expanding individual- and community-level behavioural interventions for the prevention of HIV and other sexually transmitted infections and continued access to antiretroviral therapy for those already infected [28-31]. These efforts should be a priority especially in regions with the highest transmission; however, more data are needed on possible regional differences and specific behaviours driving the epidemic in Poland as well as more generally in countries with marked regional differences.

It is of note that the increase in number of new HIV diagnoses among MSM was evident several years earlier when using the imputed dataset compared with the raw surveillance data. This underscores the need to assure data quality and improve the analysis of routine data by correcting for missing data on important descriptors such as transmission category.

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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.

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 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

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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	648 stable (reporting this sexual relationship as the only risk exposure) HIV serodiscordant heterosexual couples (476 of the index partners were not on treatment, 149 on ART and 23 mono/dual therapy) recruited between 1989 and 2008 in Madrid, Spain	In serodiscordant couples with available follow-up, 0 infections in couples where the index partner was on ART (n=144) over 417 couples-years of follow-up (7,400 condomless coital acts), corresponding to a risk of transmission per coital act of zero (95% CI: 0–0.0005 per condom-less intercourse). In contrast, 5 infections were observed in couples where the index partner was not on ART (n=341) over 863 couples-years of follow-up (11,000 condomless coital acts), corresponding to a risk of transmission of 4 per 1,000 condomless intercourses (95% CI: 0.0001–0.0010). The authors concluded that transmission of HIV from successfully treated people cannot be excluded.

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 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.

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 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).

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.

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%).

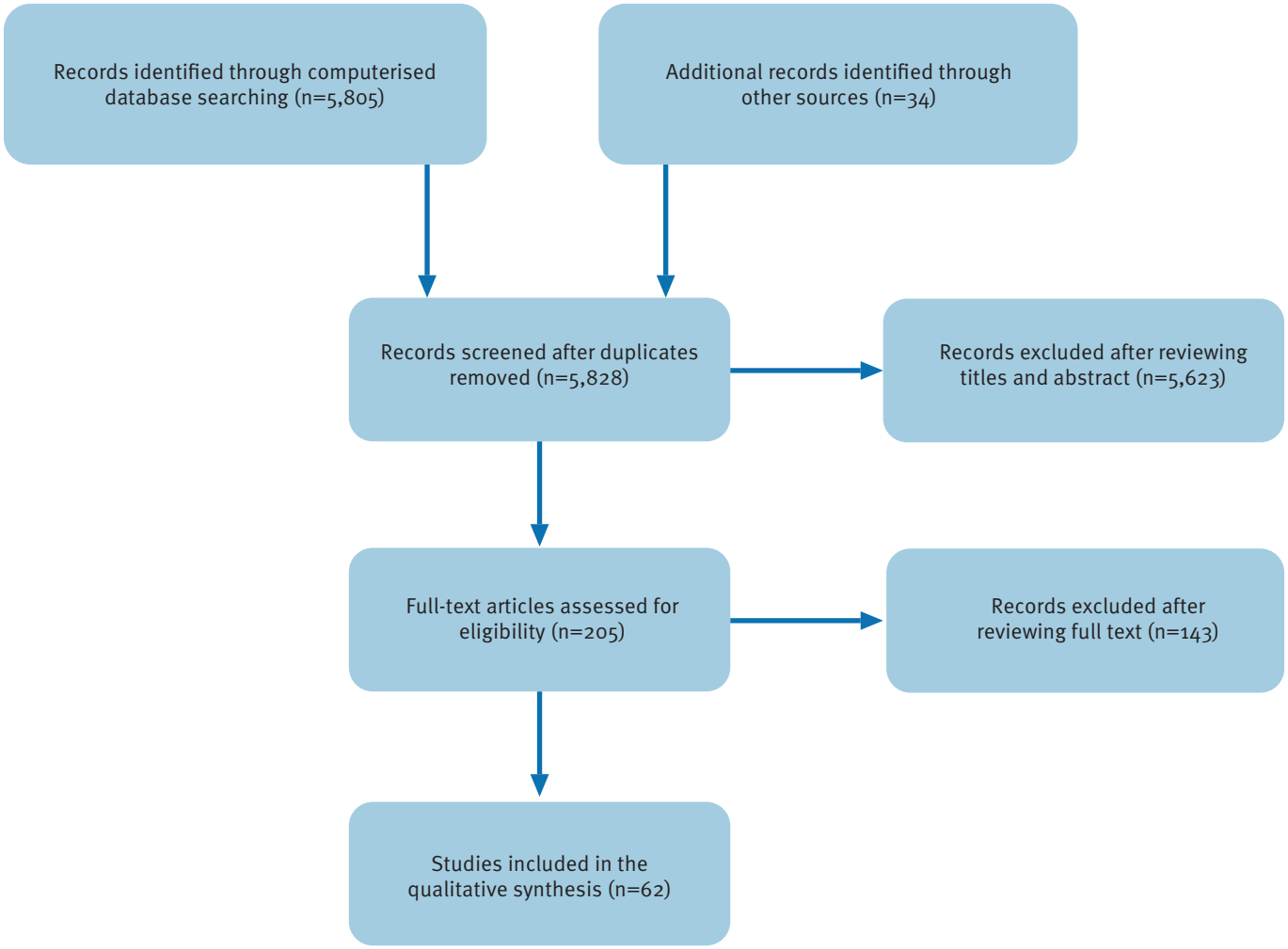
In 2010, a very large observational study [19] observed 103 genetically linked HIV-1 transmissions of which only one occurred from an infected participant who had started ART, corresponding to a transmission rate of 0.37 (95% CI: 0.09–2.04) per 100 person-years, compared with 2.24 (95% CI: 1.84–2.72) 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' correction

The following corrections were made at the request of the authors on 17 March 2014: in Table J, last row, describing the article of Del Romero (2010, British Medical Journal), the information in 'Study population and study period' and 'Results/conclusions' was revised.

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

This work has been funded by European Centre for Disease Prevention and Control, Publication Reference OJ/04/04/2011-PROC/2011/021. The authors prepared a technical report entitled Evaluating HIV treatment as prevention in the European context in addition to this manuscript.

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Special Eurobarometer reveals television as main source of information for developments in science and technology

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According to the Special Eurobarometer 401, 'Responsible Research and Innovation (RRI), Science and Technology' published in November 2013, a large number of Europeans (40%) do not feel 'very well informed' about science and technology and an additional 18% feel that they are 'not at all informed'. This means that a majority of Europeans (58%) do not feel informed about such developments [1]. However, this does not mean that people are uninterested in science and technology as 53% replied that they are either 'fairly interested' or 'very interested'.

When polled about their main sources of information, two thirds of the respondents (65%) stated television as the main source of information, followed by newspapers (33%) and websites (32%). Scandinavians and people living in the Baltic region are more likely than central and eastern Europeans to turn to the Internet for information.

A large majority (66%) of the respondents stated that those best qualified to explain the impact of scientific and technological developments on society are scientists working at universities or in government laboratories. In comparison with an earlier study in 2010, respondents are less likely to mention medical doctors and government representatives as those best qualified. For medical doctors, the number dropped from 26% in 2010 to 19% in 2013 whereas for government representatives the corresponding numbers were 11% and 6% [2].

This special Eurobarometer is based on a survey carried out in the 27 Member States of the European Union (EU) and in Croatia between 26 April and 14 May 2013. Some 27,563 respondents from different social and demographic groups were interviewed face-to-face at home in their mother tongue

The Eurobarometer is an instrument used by the European Commission to map public opinion in the EU. The standard Eurobarometer is based on about 1,000 face-to-face interviews per Member State. These are conducted between two and five times per year and reports are published twice a year. Special Eurobarometer reports such as the above are based on in-depth thematical studies [3].

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