Population-based HIV-1 incidence in France, 2003–08: a modelling analysis

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Summary

Background Routine national incidence testing with enzyme immunoassay for recent HIV-1 infections (EIA-RI) has been done in France since January, 2003. From the reported number of HIV infections diagnosed as recent, and accounting for testing patterns and under-reporting, we aimed to estimate the incidence of HIV infection in France in 2003–08.

Methods We analysed reports from the French National Institute for Public Health Surveillance for patients who were newly diagnosed with HIV between January, 2003, and December, 2008. Missing data were imputed with multiple imputation. Patients were classified with non-recent or recent infection on the basis of an EIA-RI test, which was calibrated with serial measurements from HIV seroconverters from the French ANRS-PRIMO cohort. We used an adapted stratified extrapolation approach to calculate the number of new HIV infections in men who have sex with men (MSM), injecting drug users (IDUs), and heterosexual men and women by nationality. Population sizes were obtained from the national census and national behavioural studies.

Findings After accounting for under-reporting, there were 6480 (95% CI 6190–6780) new diagnoses of HIV infection in France in 2008. We estimate that there were 6940 (6200–7690) new HIV infections in 2008, suggesting an HIV incidence of 17 per 100 000 person-years. In 2008, there were 3550 (3040–4050) new infections in heterosexuals (incidence of 9 per 100 000 person-years), 3320 (2830–3810) in MSM (incidence of 1006 per 100 000 person-years), and 70 (0–190) in IDUs (incidence of 86 per 100 000 person-years). Overall HIV incidence decreased between 2003 and 2008 ($p<0·0001$), but remained comparatively high and stable in MSM.

Interpretation In France, HIV transmission disproportionately affects certain risk groups and seems to be out of control in the MSM population. Incidence should be tracked to monitor transmission dynamics in the various population risk groups and to help to target and assess prevention strategies.

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Introduction

The HIV-1 epidemic in France and other European countries has chiefly been monitored by analysis of data for new diagnoses of HIV infection, which are reported by regional or national case surveillance.[1] However, because of the long and variable time from infection to diagnosis, case surveillance of new HIV diagnoses does not show present patterns of virus transmission. In the past 15 years, laboratory-based methods have been developed to estimate incidence of HIV with a cross-sectional approach.[2,3] This method proved applicable with case-based surveillance data.[4] To monitor the dynamic of HIV infection in France, routine incidence testing with an enzyme immunoassay for recent HIV infections (EIA-RI) has been implemented as part of the national HIV case surveillance since its introduction in 2003. We aimed to estimate HIV incidence in France by use of this serological assay for recent infection.

Methods

Procedures

For calibration of the EIA-RI assay, we defined an assay threshold that discriminated recent HIV infection from longstanding infection, and estimated the distribution of time spent in a recently infected state—called the recent-infection-testing algorithm (RITA) duration[5]—from a reference population sample. The EIA-RI test had initially been developed to detect recent HIV infection through an algorithm that combined standardised measures of antibody binding to the immunodominant epitope of gp41 and the V3 region of gp120.[6] In this first design of the EIA-RI assay, recent infection was defined as being infected for less than 180 days and the biomarkers threshold was estimated for the specific purpose of classification according to time since infection.

To estimate incidence of HIV infection, we further defined the properties of the EIA-RI assay as follows. The time for which the EIA-RI assay biomarker remains less than a given threshold from the beginning of the infection (RITA duration) was estimated from a large number of seroconverter samples. Therefore, the recent-infection status is a transient biological state rather than a dichotomised time since infection. Furthermore, because the original development of the test showed that the most discriminatory antigen was immunodominant epitope

alone or in combination with V3,[6] we calibrated the assay with immunodominant epitope alone to improve model parsimony. The reference population sample was 952 serial measurements from 298 seroconverters from the French National Agency for Research on AIDS and Viral Hepatitis (ANRS) PRIMO cohort[7] between 1996 and 2006. The proportion (43%) of samples from patients infected with viruses of non-B subtypes was much the same as that in new diagnoses. Date of infection was estimated as previously described.[6] Sequential serum samples from these patients were obtained during the first 2 years after diagnosis of HIV primary infection and while patients were untreated (from one to seven samples per patient). These samples were tested as dried serum spot by EIA-RI.

The calibration process also involved an estimation of the proportion of patients with long-term HIV infection who would test as recent infection. This proportion was designated the false-recent rate. The estimate was based on 250 chronically infected patients, who were tested more than 2 years after HIV diagnosis, but were clinically without AIDS, and 143 patients tested at the clinical AIDS stage (ANRS SEROCO and HEMOCO cohorts[8]).

Since Jan 1, 2003, newly diagnosed HIV infections in France have been mandatorily reported to the National Institute for Public Health Surveillance. The notification form included demographic data (sex, age, and nationality), clinical stage, transmission category, and history of previous HIV testing.[9] Remnant serum from the diagnosis sample was sent as a dried serum spot to the National HIV Reference Centre (Tours, France), where the EIA-RI test was done. We analysed reports from patients newly diagnosed with HIV between January, 2003, and December, 2008. Patients diagnosed with clinical AIDS were classified as having a non-recent infection.

We accounted for completeness of reporting to the surveillance system and provided yearly incidence estimates for six subgroups of the population: men who have sex with men (MSM), injecting drug users (IDUs), heterosexual French-national men and women, and heterosexual non-French-national men and women. Men and women whose reported route of transmission was not sex or drug use accounted for less than 1% of diagnoses and were grouped in the heterosexual category. To calculate incidence, we obtained subpopulation sizes from the national census and a French national random probability survey of sexual behaviours (CSF).[10] The proportion of men aged 18–69 years in the CSF who reported having had sex with men within the previous 12 months was applied to the overall male population as of 2008. We obtained the number of IDUs from the French Monitoring Centre for Drugs and Drug Addictions.[11] We worked out the number of exclusively heterosexual adults aged 18–69 years from the proportion of adults reporting opposite-sex relationships in the CSF and applied this value to the overall population, from which numbers of IDUs and MSM were discounted. Sizes of overall and non-national population in France were obtained from the National Institute of Statistics and Economic Studies.[12]

Statistical analysis

For calibration of the EIA-RI assay, both linear and non-linear random-effects mixed models were tested to characterise the growth of immunodominant epitope response (measured as a standardised optical density value) against time since infection. For the linear model, the natural logarithm of both optical density values and time were chosen. Non-linear models used a Gompertz link function and untransformed values. The optical density threshold was chosen to minimise the false-recent rate.

Missing data for diagnoses of HIV infection were estimated by use of multiple imputation by chained equations (ICE) with Stata 9.2.[13] Because the history of previous HIV testing had to be completed before imputation of the delay between a last negative test (if any) and the positive test was possible, imputation consisted of a two-stage process. First, history of previous HIV testing was jointly imputed with nationality, transmission group, clinical stage, and EIA-RI result, and five datasets were generated. Second, the time delays between tests were estimated conditionally on a previous HIV test, and three datasets were imputed from those obtained at the first stage. We generated 15 datasets and calculated estimates and standard errors by use of Rubin's rules.

We did a non-parametric estimation of the distribution of reporting delays to adjust the number of diagnoses reported.[14] The resulting estimated number was compared with the number of confirmed diagnoses obtained by a national postal survey of testing activity in all public and private laboratories in France, to estimate the completeness of reporting to the surveillance system (Le Strat Y, unpublished data).

To construct our incidence model, we used a stratified extrapolation approach to estimate the yearly incidence of HIV infections in various transmission groups in France. Our model was based on the method developed by Karon and colleagues.[15] HIV diagnoses were stratified into subpopulation groups, and diagnoses observed as recent infection were assumed by the model to be a random sample of the population of HIV infections occurring within 1 year (incident cases). The model assumed that (after imputation) a result for recent infection testing was available for every HIV diagnosis, and calculated the corresponding sampling probability as the probability of being tested within 1 year after infection ($p1$) multiplied by the probability of being detected as recent infection when diagnosed within a year after infection (pw). $p1$ was estimated separately for individuals who reported a negative test before diagnosis (termed repeat testers) and for those diagnosed at their first test (new testers). These conditional probabilities were primarily established by testing history ($p1$ for repeat testers), proportion of HIV infections diagnosed at AIDS

stage (*p1* for new testers), and mean RITA duration (for *pw*). We used a distribution of the AIDS incubation periods according to the European AIDS case definition, corresponding to a median incubation time between infection and AIDS of 10 years.[16] The number of incident cases within a subpopulation was then derived from the size of the sample divided by its sampling probability. For *N* diagnoses, we calculated the true number of HIV diagnoses in recent infection (*Nr*) as follows:

$$Nr = \frac{Or - N(1 - \textit{false-recent rate})}{\textit{false-recent rate}}$$

With *Or*, the number of cases observed as recent.

Variances and 95% CIs were calculated by use of the delta method and included the variability due to multiple imputation and variance associated with the estimation of completeness of case reporting. Temporal trends were assessed by means of variance-weighted least-square regressions.[17] We did a sensitivity analysis by simultaneously simulating different values of the false recency rate from 0% to 5% and proportions of repeat testers in new diagnoses from 20% to 80%. We assessed the robustness of incidence model results by comparison of the range of estimates within these extreme scenarios and 95% CIs. Apart from multiple imputation, analyses were done with SAS software version 9.1.

Role of the funding source

This study was supported by the French National Institute for Public Health Surveillance (InVS) and French National Agency for Research on AIDS and Viral Hepatitis (ANRS). The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. SLV had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

For calibration of EIA-RI, the chosen optical density threshold led to a mean RITA duration of 179·7 days (95% CI 167·2–192·2) and a false recent rate of 0·8% (0–3·1%) in patients without AIDS and 5·6% (2·7–10·8%) in patients with AIDS. The range of possible RITA durations was 25–731 days, with 95% of durations lasting less than 358 days, and 99% less than 480 days.

26 760 new diagnoses of HIV infection were reported between Jan 1, 2003, and Dec 31, 2008. With under-reporting (estimated average of 37%), we estimated that 42 330 (95% CI 40 030–44 840) people were newly diagnosed with HIV in this time. Data were missing for 29·2% of diagnoses for category of transmission group, 23·5% for EIA-RI testing results, and 19·2% for the history of a previous negative test. Table 1 shows the number and characteristics of new diagnoses by year, after multiple imputation and accounting for under-reporting. Overall number of diagnoses decreased by an average of 3·7% per year from 2003 to 2008 (p<0·0001). 25% of new HIV diagnoses were classified as recent by the EIA-RI assay; this proportion did not vary during 2003–08 (table 1). MSM were the most commonly (40%) diagnosed during recent infection, compared with French-national heterosexual women (28%) and men (22%), heterosexual non-French-national women (16%) and men (12%), and IDUs (15%). The proportion of people who previously tested HIV negative before diagnosis increased from 2003 to 2008 (p<0·0001; table 1). Although the baseline proportion varied between different transmission groups, the same increasing trend was observed in all groups (data not shown). In 2003–08, 28% of new diagnoses were in heterosexual men, 37% in heterosexual women, 32% in MSM, and 3% in IDUs. Female non-French-nationals, mainly from sub-Saharan Africa, accounted for 25% of all HIV diagnoses. Between 2003 and 2008, the percentage of female non-French-nationals with new diagnosis of HIV decreased, whereas percentage of newly diagnosed MSM increased (figure 1).

We estimated that nearly 7000 people were newly infected with HIV in France in 2008, of whom 48% were MSM (table 2). Of new infections attributed to heterosexual transmission, about half were in women. Only 1% of new HIV infections occurred in IDUs. Non-French-nationals living in France accounted for around 23% of all new infections and 45% of the infections by heterosexual transmission. Overall HIV incidence decreased significantly from 8930 new infections in 2003 to 6940 in 2008 (p=0·002). This decrease was recorded for all heterosexual groups, whereas HIV incidence was

	Year of diagnosis						Overall
	2003	2004	2005	2006	2007	2008	
EIA-RI result							
Recent	24·1%	23·7%	25·2%	24·8%	26·4%	27·0%	25·2%
Non-recent (non-AIDS)	56·3%	58·7%	58·2%	59·8%	58·6%	59·8%	58·7%
Non-recent at AIDS stage*	19·7%	17·6%	16·6%	15·4%	14·9%	13·2%	16·1%
Ever tested negative for HIV infection	32·4%	37·4%	43·8%	48·7%	53·1%	58·9%	46·2%
HIV diagnoses	7370 (6880–7920)	7580 (7120–8090)	7480 (7090–7900)	6990 (6620–7400)	6440 (6140–6750)	6480 (6190–6780)	42 330 (40 030–44 840)

Data are (%) or number (95% CI). Missing data were redistributed by multiple imputation. *Diagnoses at AIDS stage were classified as non-recent irrespective of routine incidence testing (EIA-RI) result.

Table 1: **New HIV-1 diagnoses in France, 2003–08**

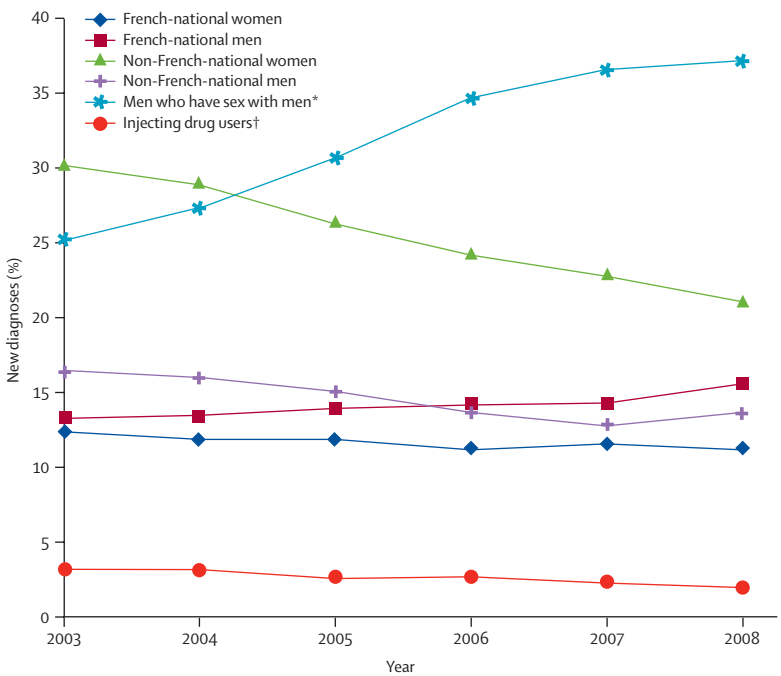

Figure 1: **New HIV-1 diagnoses in France, 2003–08**
*All nationalities. †All nationalities, both sexes.

	New HIV-1 infections (95% CI)	Estimated population size	Incidence per 100 000 person-years (95% CI)
Heterosexual	3550 (3040–4050)	40 836 530	9 (7–10)
French women	810 (620–1000)	18 363 590	4 (3–5)
French men	1140 (830–1440)	18 848 440	6 (4–8)
Foreign women	940 (700–1180)	1 739 760	54 (40–68)
Foreign men	660 (460–870)	1 884 740	35 (24–46)
Men who have sex with men*	3320 (2830–3810)	329 950	1006 (857–1155)
Injecting drug users†	70 (0–190)	81 000	86 (0–192)
Overall	6940 (6200–7690)	41 247 480	17 (15–19)

Population (aged 18–69 years) size estimates at Jan 1, 2008 from Bajos and colleagues,[10] Costes and colleagues,[11] and National Institute of Statistics and Economic Studies.[12] *All nationalities. †All nationalities, both sexes.

Table 2: **Estimated new HIV-1 infections and incidence for France in 2008, by transmission group**

high and stable among MSM and low and stable among IDUs (figure 2). Incidence was 200 times higher in MSM than in the French-national heterosexual population, 18 times higher in IDUs, and nine times higher in non-French nationals. Incidences for people from sub-Saharan Africa were 29 times higher in men and 69 times higher in women than they were for respective French-national heterosexuals (data not shown).

Discussion

Overall incidence of HIV infection in France decreased between 2003 and 2008. Our results support previous findings of a disproportionately high number of transmissions among MSM and a very low number of transmissions among IDUs. Because the test for recent infection has been routinely applied since the start of case surveillance in 2003, we were able to calculate trends in incidence of HIV transmission in the most relevant groups of population in France.

With 48% of all new infections and a persistently high incidence of 1% per year, the HIV epidemic seems to be out of control in the MSM population. In France and several other industrialised countries, the number of new diagnoses of HIV in MSM has increased in recent years.[18–20] In one review,[21] incidence of HIV transmission in MSM was stable and high during 1995–2005 in selected samples in several industrialised countries. Incidence measurements were obtained from selected samples of MSM in urban communities, but not for entire countries. This sampling strategy might explain why the reported mean incidence of 2–3% per year was high compared with our estimates of 1% per year in France as a whole. Our estimated incidence for the general population in France in 2008 (17 per 100 000 person-years) is comparable to those reported for the USA in 2006 (23 per 100 000 person-years).[4] In both countries, around half of yearly new infections were in MSM. Several factors explain the high rate of HIV transmission between MSM in France. Behavioural studies suggest an increase in unprotected anal sex and number of sexual partners in MSM with and without HIV infection.[22] An increase in transmission of primary and secondary syphilis and rectal lymphogranuloma venereum has been reported between MSM.[23] These risk factors, combined with a high HIV prevalence in the MSM population, are probably interacting to maintain the high incidence, despite the probable effect of antiretroviral treatment for reduction of transmission at the population scale.[24,25] Renewed safer-sex initiatives or new alternative prevention strategies targeting MSM are urgently needed.

Conversely, the number of new infections related to drug injection remained very low during 2003–08 (1–2% of new infections every year). This situation is probably attributable to, at least in part, a successful harm-reduction policy that was established in France in the mid 1990s to reduce unsafe injecting practices by promotion of access to clean needle and syringes and opioid-substitution treatments.[26] The low number of new infections in IDUs might also be attributed to a secular change in the pattern of drug use and the large number of deaths in drug users during the late 1980s and early 1990s.

Incidence of HIV infections in heterosexuals has decreased since 2003. However, without precise data for sexual partners, characterisation of heterosexuals at high risk of HIV infection in France is difficult from a surveillance system perspective. The decline we report in incidence in heterosexuals might be attributed to the effect of potent antiretroviral treatment within a population in which, unlike for MSM, HIV prevalence is low.[24] The proportion of patients receiving highly active antiretroviral therapy increased in France from 75% in

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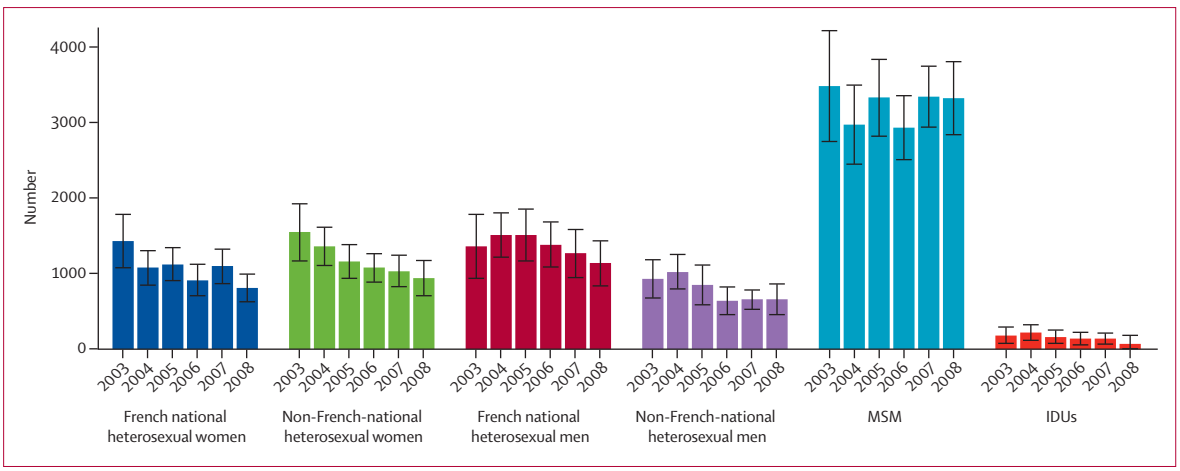

Figure 2: **Estimated number of new HIV-1 infections by transmission group in France, 2003–08**
MSM=men who have sex with men. IDUs=injecting drug users.

2001 to 85% in 2008, and the proportion of treated patients with viral load less than 500 copies per mL increased from 70% in 2002 to 92% in 2008.[27] Furthermore, investigators reported[18] an increase in the mean age at HIV diagnosis for heterosexuals between 2003 and 2008, which is consistent with the decreasing trend in heterosexual transmission we noted.

For heterosexuals, non-French nationals were most affected, especially women from sub-Saharan Africa. As in other European countries, the epidemic in Africa is having an important role in transmission rates in France.[1,28] The number of new infections has, however, decreased between 2003 and 2008 in immigrant populations (figure 2). This decrease is unlikely to be explained by a change in migration pattern, because immigration was stable between 2003 and 2007.[18] Specific prevention efforts targeting migrants started since 2002 might have been effective.[29]

Our model and the available data have several limitations. The incidence estimation model is mainly based on three parameters: the number of HIV diagnoses classified as recent infection, the mean RITA duration, and the probability of diagnosis within 1 year after infection. The first two parameters were dependent on the assay calibration process. In a previous study,[30] we noted that factors such as viral subtype or geographical origins of patients affected the EIA-RI test results. Therefore, we ensured that the reference sample used for assay calibration was sufficiently diverse for virus subtypes, geographical origin, and time since infection. Because we were able to identify, through surveillance data, individuals diagnosed at AIDS stage and correct the estimated number of new infections to account for false recent infection, we addressed the main concerns about misclassification attributed to all tests for recent infection.[3]

For the third parameter—probability of diagnosis within 1 year after infection—the model required the assumption of independence between infection and testing time.[15] In certain circumstances, this assumption does not hold. In particular, testing could be motivated by seroconversion illness or recent exposure, resulting in overestimation of the number of recent infections and thus incidence.[31] The effect of this potential bias needs to be addressed through analysis of questionnaire data on motivation for seeking tests (particularly a question about recent exposure). This item has been added to the questionnaire used in the national HIV case-reporting system.

Calculation of incidence necessitates, as a denominator, a precise estimation of the size of the different at-risk subpopulations. Potentially socially stigmatised behaviours such as sex between men or drug use are prone to under-reporting in questionnaire surveys. Therefore, use of national behavioural data to extrapolate these behaviours to the overall population might have led to an underestimate of the size of the at-risk populations, and thus an overestimate of incidences.

Furthermore, we could not distinguish from available data whether diagnoses were attributable to infection acquired in France or abroad. Our estimates of incidence for people not of French origin are for the population that can potentially be diagnosed in France, once infected. Reliability of our estimates is dependent on the stability of migration in HIV-infected individuals, which cannot be measured in France.

Our results provide a new perspective on the HIV epidemic in France, which could not be garnered from data for HIV-diagnosis reporting alone.[18,19] Despite an overall decline in HIV incidence, the high rates estimated for MSM and sub-Saharan Africans living in France warrant renewed prevention strategies. Incidence should be tracked to monitor transmission dynamics in the various population risk groups and to help target and assess prevention strategies.

Contributors

SLV had the idea for the study, analysed the data, and drafted the report. SLV, VB, and YLS designed the statistical analysis. FB, SB, DT did the biological analyses and helped to write the report. CS, JP, FC, and LM contributed to data collection, provided input to the study design, and revised the report. LM and J-CD supervised the experiments and reviewed the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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Reduction of HIV incidence in men who have sex with men

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Despite great advances in the collective understanding of the HIV epidemic, men who have sex with men (MSM) continue to be disproportionately affected. In the USA, the Centers for Disease Control and Prevention estimated that more than 55 000 new infections occur every year and more than half of these infections are in MSM.[1] Similarly, in Canada, MSM are proportionally most affected.[2,3] Alarmingly, in western Europe the number of new HIV diagnoses in MSM nearly doubled from 2538 in 1999 to 5016 in 2006,[4] and, after infections from immigrants from other countries are accounted for, MSM had the highest number of new infections of any transmission group in western Europe in 2006.[5] Elsewhere, significant increases in new HIV infections in MSM have been reported in Asian countries, such as China where the prevalence of HIV infection in MSM in some major cities seems to be rapidly increasing.[6] HIV prevalence for MSM is high throughout Latin America, Russia, and some countries in sub-Saharan Africa.[7] Data for other regions are often difficult to find, but the number of new infections in MSM is very high in most regions of the world.

In *The Lancet Infectious Diseases* today, Le Vu and colleagues[8] provide further evidence that the number of new infections in MSM is unacceptably high. Although the overall rate of new HIV infections decreased in France from 8930 in 2003 to 6940 in 2008, the number of new infections in MSM was stable. In 2008, 3320 (48%) of new infections in France were attributed to MSM. Incidence of HIV infections was low and stable in 2008 in IDUs, accounting for 1% of new infections.

The pattern of the HIV epidemic reported in France is very similar to that in British Columbia, Canada.[9] After introduction of highly active antiretroviral therapy (HAART) in 1996, the number of new positive HIV tests in the province fell by about 50%.[9] Much of the early reduction in new HIV cases was in MSM. However, the number of new HIV positive tests in MSM has remained largely unchanged in recent years, especially since 2003, with about 150–180 new infections reported every year.[10] By contrast, a reduction in the number of new HIV infections was observed in British Columbia in IDUs after use of HAART increased from 2004.[10]

How can the number of new HIV infections in MSM living in France and elsewhere be reduced? A combined prevention approach, as proposed by Michel Sidibé (the Executive Director of UNAIDS), is needed.[11] This approach should include targeted structural interventions directed at specific populations, behavioural interventions directed at individuals, and new biomedical interventions, including expanded coverage of antiretroviral therapy to all HIV infected individuals who meet eligibility criteria for treatment.[12]

Despite a large body of evidence for the secondary preventive value of antiretroviral therapy, the HIV/AIDS community has failed to fully capitalise on the synergy between treatment and prevention. The aim should not be improved treatment or improved prevention, but rather optimisation of both, because treatment is prevention. Recent therapeutic guidelines[13] fully recognise that late initiation of antiretroviral therapy is associated with worse outcomes both at the individual and societal scales. From a public health perspective, expansion of the number of individuals with HIV infection who are eligible for therapy is a unique opportunity to curb the growth of the epidemic. This expansion should decrease HIV/AIDS-related morbidity and mortality in those infected and help to reduce community viral load (and consequently the risk of new infections).[14,15] The status quo cannot remain.

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