Testing the hypothesis that treatment can eliminate HIV: a nationwide, population-based study of the Danish HIV epidemic in men who have sex with men

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Summary

Background Worldwide, approximately 35 million individuals are infected with HIV; about 25 million of these live in sub-Saharan Africa. WHO proposes using treatment as prevention (TasP) to eliminate HIV. Treatment suppresses viral load, decreasing the probability an individual transmits HIV. The elimination threshold is one new HIV infection per 1000 individuals. Here, we test the hypothesis that TasP can substantially reduce epidemics and eliminate HIV. We estimate the impact of TasP, between 1996 and 2013, on the Danish HIV epidemic in men who have sex with men (MSM), an epidemic UNAIDS has identified as a priority for elimination.

Methods We use a CD4-staged Bayesian back-calculation approach to estimate incidence, and the hidden epidemic (the number of HIV-infected undiagnosed MSM). To develop the back-calculation model, we use data from an ongoing nationwide population-based study: the Danish HIV Cohort Study.

Findings Incidence, and the hidden epidemic, decreased substantially after treatment was introduced in 1996. By 2013, incidence was close to the elimination threshold: 1·4 (median, 95% Bayesian credible interval [BCI] 0·4–2·1) new HIV infections per 1000 MSM and there were only 617 (264–858) undiagnosed MSM. Decreasing incidence and increasing treatment coverage were highly correlated; a treatment threshold effect was apparent.

Interpretation Our study is the first to show that TasP can substantially reduce a country’s HIV epidemic, and bring it close to elimination. However, we have shown the effectiveness of TasP under optimal conditions: very high treatment coverage, and exceptionally high (98%) viral suppression rate. Unless these extremely challenging conditions can be met in sub-Saharan Africa, the WHO’s global elimination strategy is unlikely to succeed.

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Research in context

Evidence before this study
Worldwide, approximately 35 million individuals have HIV. About 25 million of these live in resource-constrained countries in sub-Saharan Africa. WHO and UNAIDS propose using treatment as prevention (TasP) to eliminate HIV worldwide, and have set the elimination threshold at one new HIV infection per 1000 individuals. Their plan is based on the results of the HPTN 052 trial, which showed that providing treatment to the HIV-infected partner in a discordant couple (a couple where one partner is infected, and the other is not) was 96% effective in preventing infection. This finding showed that TasP was effective at the individual level. More recently, findings showed that treatment reduced an individual’s risk of HIV infection in a rural community in South Africa and in sex workers in Kenya.

However, no published studies have shown that TasP can substantially reduce a country’s HIV epidemic, and would be an effective elimination tool. The magnitude of the epidemic-level effect of TasP will depend on how many people are treated and their level of adherence to treatment. For TasP to be effective in reducing HIV epidemics, treatment would need to substantially reduce the incidence.

We searched PubMed with the terms “HIV” AND “treatment as prevention” AND (“undiagnosed” OR “incidence”) to identify studies that are looking, or have looked, for an effect of TasP on reducing incidence; studies published, in any language, between Jan 1, 2010, and Feb 29, 2016. We identified 87 studies. Currently, four clinical trials are evaluating the effectiveness of TasP on reducing incidence; however, their results will not be available for several years.

Added value of this study
Our study is the first to show that TasP can substantially reduce a country’s HIV epidemic. Our results show this effect in Denmark’s HIV epidemic in men who have sex with men, an epidemic that UNAIDS has identified as a priority for elimination. In our study, we found that TasP had reduced the incidence rate close to the WHO elimination threshold, showing that TasP has the potential to be an effective elimination tool. Notably, our results show that the TasP can be effective in a resource-rich country where treatment programmes are exceptional; Denmark has high treatment coverage and a 98% viral suppression rate (due to high adherence). Importantly, we have shown that a threshold effect exists; our results imply that TasP will not be effective in reducing incidence unless treatment coverage is high.

Implications of all the available evidence
Our results have important implications for global health policies, and for the control of the HIV pandemic. In both resource-rich and resource-constrained countries, TasP will be effective in protecting some individuals. TasP will reduce HIV epidemics in countries where the treatment programmes are exceptional, as in Denmark. For TasP to be effective at the epidemic level in sub-Saharan Africa, treatment programmes will need to be more successful than many of the current programmes in resource-rich countries. If this does not occur, the WHO’s global elimination strategy is unlikely to succeed.

Figure 1: Temporal trends in diagnosis and treatment rates in MSM in Denmark
MSM=mens who have sex with men. (A) HIV diagnosis rates for all MSM diagnosed with HIV infection in Denmark between 1991 and 2013. (B) Uptake of treatment and increase in viral suppression rates after the introduction of combination therapies in 1996 (Danish HIV Cohort Study data).
mandatory in 1990; after 1995, the DHCS included all diagnosed individuals. In the past 25 years, the HIV diagnosis rate in MSM has varied substantially (figure 1A), as reflected in both the national surveillance data and the DHCS data. After the introduction of effective HIV treatments in Denmark in 1996, treatment coverage rapidly increased (figure 1B). The Danish treatment eligibility guidelines have changed over time. From 1996 to 2008, HIV-infected individuals were treated only after their CD4 cell count fell lower than 300 cells per μL. The treatment eligibility threshold was raised to 350 cells per μL in 2008. Beginning in 2011, all HIV-infected individuals (irrespective of CD4 cell count) became eligible for immediate treatment. As coverage increased, so did the viral suppression rate (ie, the percentage of patients who have a viral load of less than 200 copies per mL; figure 1B). The current viral suppression rate in Denmark is 98% because of very high adherence. These high adherence rates have resulted in negligible levels of transmitted drug resistance.

Methods

We used a CD4-staged Bayesian back-calculation approach and data from a nationwide, population-based study (which began as an open cohort study) to estimate the annual incidence rate in MSM in Denmark, and the size of the hidden epidemic. An HIV-infected individual’s CD4 cell count is a marker of time since infection: the lower the count, the longer (on average) the individual has been infected. Following the method of Sweeting and colleagues, the back-calculation model includes four CD4-stratified stages: stage one (≥ 500 cells per μL), stage two (350–500 cells per μL), stage three (200–350 cells per μL), and stage four (<200 cells per μL). This classification is used to fit the
model to the DHCS CD4-stratified diagnosis data. No approval from an ethics committee was necessary because we did an analysis of a dataset that was stripped of identifiers.

We used data from the DHCS; this includes data for all MSM, diagnosed with HIV, since 1995. The DHCS uses the unique civil registration number assigned to all Danes, and immigrants, to identify individuals. This avoids replicate registrations and enables information (for each individual in the study) to be extracted from the Danish National Hospital Registry, the Danish Civil Registration System, and the Danish National Registry of Deaths. The Danish National Hospital Registry contains data on all hospital admission and discharge diagnoses since 1977. The Danish Civil Registration System contains data for immigration, emigration, and death. The Danish National Registry of Deaths documents causes of death. The DHCS dataset includes, for each HIV-infected individual: date of (and CD4 cell count at) diagnosis, complete history of treatment, and viral load and CD4 measurements over time.

We used 20 000 Markov chain-Monte Carlo samples to simulate the back-calculation model, with an initial burn-in of 5000 simulations. MATLAB (version R2014a) was used for implementation. Following the method of Sweeting and colleagues,9 the annual incidence rate was used for implementation. Following the method of Sweeting and colleagues,9 the annual incidence rate was used for implementation. Following the method of Sweeting and colleagues,9 the annual incidence rate was used for implementation. Following the method of Sweeting and colleagues,9 the annual incidence rate was used for implementation. Following the method of Sweeting and colleagues,9 the annual incidence rate was used for implementation.

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the hidden epidemic) was estimated by the back-calculation; the number in groups two and three were calculated from the DHCS data. The total number of potential transmitters has decreased by roughly two-thirds: from 2218 (median, 95% BCI 1955–2381) in 1996 to 819 (463–1065) in 2013. In 2013, most (75% [617/819]) potential transmitters were undiagnosed MSM (figure 4).

Our results show that the annual HIV incidence rate in MSM in Denmark has been decreasing for almost two decades (figure 5A). We calculated the most likely values for the estimates and 95% BCIs using the likelihood function (figure 5A). The rate fell from 117 (median, 95% BCI 94–140) new HIV infections per year in 1996 to a low of 75 (20–117) per year in 2013. Our results provide strong supportive evidence that the annual incidence rate has decreased since the introduction of treatment in 1996 (figure 5B); the 95% BCI for the decrease does not include zero.

In 2009, investigators reported there were approximately 55 000 MSM in Denmark. Using this value, we estimate that there were only 1·4 (median, 95% BCI 0·4–2·1) new HIV infections in men per 1000 MSM in Denmark in 2013. This is very close to the WHO elimination threshold.

The incidence rate (figure 5A) has not decreased in proportion to the reduction in the number of potential transmitters (figure 4). Our data suggest that this finding might be the result of an increase in risky sexual behaviours. There were five new HIV infections (on average) for every 100 potential transmitters in 1996 (figure 5C); by 2013, this had almost doubled (figure 5C).

Of greatest importance, we found a very strong correlation between increasing treatment coverage and decreasing incidence since 1996 (figure 5D). The most likely values for the incidence estimates were determined by the likelihood function. Although this statistical relationship does not demonstrate causality, it provides strong supportive evidence that TasP can reduce epidemics, and it is biologically plausible. We found that the effectiveness of TasP on decreasing incidence is complex and non-linear (figure 5D). Notably, our results show there is a threshold effect: TasP did not have a significant effect on reducing the incidence rate until treatment coverage had reached approximately 35%.

**Discussion**

Our results are the first that show TasP can substantially reduce a country’s HIV epidemic, and has the potential to be an effective elimination tool. Importantly, we have shown that a threshold effect exists, which implies that TasP is not effective in decreasing incidence unless the treatment coverage is moderately high. We have investigated the effect of TasP during the past two decades on an HIV epidemic that UNAIDS has identified as a priority for elimination: the Danish HIV epidemic in MSM. Notably, we have found that TasP has reduced the incidence rate close to the WHO elimination threshold.

Treatment programmes in Denmark have been, and are, outstanding; treatment coverage has been high for almost 20 years, and the viral suppression rate (because of high adherence) has been exceptional. TasP might only be successful in reducing epidemics and eliminating HIV, under these optimal treatment conditions. Under less optimal conditions, TasP (although effective at the individual level), might not be effective in reducing epidemics.

Our results suggest a conceptual framework for understanding how TasP could lead to the global elimination of HIV. They suggest that the introduction of treatment initiates a feedback cycle, but only after a threshold coverage level has been reached. As coverage and viral suppression rates increase, the number of potential transmitters decreases; fewer potential transmitters result in a reduction in the incidence rate. Decreased incidence coupled with increased coverage results in a further decrease in the number of potential transmitters, which in turn, further reduces the incidence rate. If treatment coverage (and the viral suppression rate) is sufficiently high, the incidence rate could be reduced below the WHO elimination threshold.

Our estimates provide explicit targets for Denmark for the number of undiagnosed MSM with HIV that need to be found and provided with treatment, both for their clinical benefit and to eliminate the epidemic. We estimate that this hidden epidemic consists of only several
hundred individuals. Therefore, it seems feasible, potentially through social media and mass testing campaigns, to find almost all of these individuals. Incidence in Denmark will decrease at a faster rate than currently if testing and diagnosis rates increase, risk behaviours decrease, or effective interventions (eg, pre-exposure prophylaxis) are introduced. Biomedical and behavioural interventions, targeting both HIV-infected and HIV-uninfected MSM, should be used. However incidence could rise if there is a substantial in-migration of HIV-infected MSM into Denmark, or risk behaviour increases; temporary visitors could also, potentially, increase transmission. Past immigration of HIV-infected MSM might have increased incidence if sexual networks linked non-nationals with nationals. However, this scenario seems unlikely because very few HIV-infected MSM have immigrated to Denmark; only 5% of the MSM in the DHCS are immigrants who were diagnosed with HIV within 5 years of arriving in Denmark. Recent data indicate that the number of HIV-infected immigrants may be increasing.

Our analysis has focused on the HIV epidemic in the major risk group, MSM. There are also individuals in Denmark who have become infected with HIV because of heterosexual transmission; about 25% of these are fairly recent immigrants (within 5 years), many from

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Figure 5: Temporal changes in treatment coverage and HIV incidence rates

MSM=men who have sex with men. (A) Trend in incidence rate in MSM in Denmark since 1994; red lines represent the most likely values (determined by the likelihood function), boxes 95% Bayesian credible intervals (BCIs). (B) Histogram of the estimated decrease in incidence between two timepoints (1996 and 2013): red line shows median, and dashed blue lines the 95% BCI. (C) Temporal relationship between the number of potential transmitters and the average number of new HIV infections. (D) Association between increasing treatment coverage (Danish HIV Cohort Study data) and decreasing incidence: red dots show the most likely values (determined by the likelihood function) of the annual incidence rate between 1996 and 2013.
countries where HIV prevalence is high. This finding suggests these individuals were infected before immigrating. If this is the case, using TasP in Denmark might not be very effective in reducing the number of HIV-infected heterosexuals. In many countries intravenous drug users are a key risk group for acquiring HIV. In Denmark there is minimal HIV transmission in intravenous drug users because effective free needle exchange programmes have been operating for decades.

Our results provide important insights into the effect of increases in risk behaviour on decreasing the effectiveness of TasP. We found that the incidence rate did not decrease to the extent expected in view of the reduction in the number of potential transmitters. Our results suggest this finding can be explained by an increase in risky sexual behaviours, which increased HIV transmission. Notably, a recent study in Denmark documented an increase in gonorrhoea and syphilis in MSM, which suggests an increase in risky sex. However, even with an increase in risky behaviours, incidence continued to fall; this occurred because the number of potential transmitters continued to decrease. TasP would likely have reduced incidence at a faster rate, and to a greater extent, if risk behaviour had not increased. It will be essential to use other interventions with proven efficacy (eg, pre-exposure prophylaxis) in combination with TasP, and to implement effective behavioural interventions that prevent an increase in risky behaviours.

Theoretical studies (published soon after the introduction of effective HIV treatments in 1996) predicted that treatment would act as prevention, decrease incidence, and could (if treatment coverage and viral suppression rates were very high) even eliminate HIV. Since then treatment has been shown to be effective in reducing an individual’s risk of acquiring HIV.5–7 However, before this study, TasP had not been found to be effective in reducing epidemics. Previous studies have shown that incidence rates have remained constant, or increased;8,13–16 notably, these studies were conducted in locations where viral suppression rates are lower than in Denmark. It is possible that TasP was effective in reducing incidence in some locations, but the effect was masked because of an increase in risky behaviours. Early theoretical studies8,17 showed that only a relatively small increase in risky behaviours could counterbalance the effect of TasP on reducing incidence.

Our results have implications for the effectiveness of TasP in reducing concentrated HIV epidemics in other resource-rich countries. Notably, there is universal access to health care in Denmark, with free HIV treatment and many easily accessible community walk-in clinics that provide HIV testing and linkage to care. They have achieved high diagnosis rates (approximately 80% of HIV-infected MSM have been diagnosed), high coverage (about 92% of diagnosed MSM are on treatment), and an exceptionally high viral suppression rate (98%). Additionally, patient retention in care is excellent; only about 2% of patients per year are lost to follow-up. Other resource-rich countries have high treatment coverage, but substantially lower viral suppression rates. In the USA, France, Australia, the UK, and the Netherlands, HIV epidemics in MSM communities have started to resurge. This comparison suggests, that for TasP to be an effective elimination tool, treatment programmes in other countries will have to emulate those in Denmark.

Our findings have important implications for current global health policies, and for the control of the HIV pandemic. Most (approximately 25 million) HIV-infected individuals live in resource-constrained countries in sub-Saharan Africa where treatment coverage is moderate to low. HIV epidemics in sub-Saharan African countries are very different from those in resource-rich countries; they are generalised throughout the population, rather than concentrated in risk groups. Furthermore, incidence rates are substantially higher (eg, about 100 new HIV infections per 1000 per year). It is essential to increase treatment coverage in sub-Saharan Africa because this will provide substantial clinical benefits for millions of HIV-infected individuals. However, for TasP to be effective in reducing HIV epidemics in sub-Saharan Africa, treatment programmes will need to be more successful than many of the current programmes in resource-rich countries. Unless this occurs, the WHO’s global elimination strategy is unlikely to succeed.

Contributors
JTO, DR, LP, JG, NO, and SB designed the project, interpreted the results, and jointly wrote the report. JTO and DR did all statistical analysis and coding of the back-calculation model. LP provided additional technical support. JG and NO provided access to the DHCS data and detailed information about Denmark’s HIV epidemic.

Declaration of interests
We declare no competing interests.

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