



Relation between HIV viral load and infectiousness: a model-based analysis

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Summary

Background A consensus statement released on behalf of the Swiss Federal Commission for HIV/AIDS suggests that people receiving effective antiretroviral therapy—ie, those with undetectable plasma HIV RNA (<40 copies per mL)—are sexually non-infectious. We analysed the implications of this statement at a population level.

Methods We used a simple mathematical model to estimate the cumulative risk of HIV transmission from effectively treated HIV-infected patients (HIV RNA <10 copies per mL) over a prolonged period. We investigated the risk of unprotected sexual transmission per act and cumulatively over many exposures, within couples initially discordant for HIV status.

Findings Assuming that each couple had 100 sexual encounters per year, the cumulative probability of transmission to the serodiscordant partner each year is 0·0022 (uncertainty bounds 0·0008–0·0058) for female-to-male transmission, 0·0043 (0·0016–0·0115) for male-to-female transmission, and 0·043 (0·0159–0·1097) for male-to-male transmission. In a population of 10 000 serodiscordant partnerships, over 10 years the expected number of seroconversions would be 215 (80–564) for female-to-male transmission, 425 (159–1096) for male-to-female transmission, and 3524 (1477–6871) for male-to-male transmission, corresponding to an increase in incidence of four times compared with incidence under current rates of condom use.

Interpretation Our analyses suggest that the risk of HIV transmission in heterosexual partnerships in the presence of effective treatment is low but non-zero and that the transmission risk in male homosexual partnerships is high over repeated exposures. If the claim of non-infectiousness in effectively treated patients was widely accepted, and condom use subsequently declined, then there is the potential for substantial increases in HIV incidence.

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Introduction

A recent consensus statement¹ released on behalf of the Swiss Federal Commission for HIV/AIDS asserted that people with HIV infection receiving effective antiretroviral therapy—ie, those with undetectable plasma HIV viraemia (HIV RNA <40 copies per mL)—and without other genital infections cannot transmit HIV through sexual contact. The statement also stated that “medical and biological data available today do not permit proof that HIV infection during effective antiretroviral therapy is impossible, because the non-occurrence of an improbable event cannot be proven”.

At several levels, evidence exists to provide strong support for the statement. A key study of couples initially discordant for HIV status, from Rakai, Uganda,² showed that there was a strong relation between HIV plasma viral load and heterosexual transmission rates. There were no transmissions from the 51 initially positive partners who had undetectable viral load. A cross-sectional study³ in Spain found no infections among heterosexual partners of people on antiretroviral therapy, compared with 27 (8·6%) among partners of untreated people with HIV infection. Higher viral load has also been shown to be associated with increased levels of mother-to-child transmission.⁴ It is well established that antiretroviral therapy

decreases HIV-RNA levels in blood and semen,^{5–7} strongly suggesting that effective treatment will also lower the risk of transmission from a person infected with HIV.⁸

The Swiss statement has the potential to allay exaggerated fears of transmission when the risk is actually extremely small, and could have particular value in situations such as heterosexual couples with discordant HIV status who are attempting conception.⁹ But although the risk of transmission from people on effective therapy is low, it is unlikely to be zero. Factors such as incomplete adherence to therapy or the presence of other sexually transmitted infections could increase the risk of HIV transmission. Furthermore, a false sense of security might lead to reductions in condom use, as was documented in a behavioural study among men who have sex with men in Australia.¹⁰ HIV incidence in men who have sex with men in a number of countries has been increasing in recent years, despite high treatment rates, coinciding with reductions in condom use and increases in the incidence of other sexually transmitted infections.^{11–16} Our aim was to use a modelling approach, based on an assessment of available data, to estimate the actual risk of transmission from people infected with HIV who are effectively treated.

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Methods

We used the results of the Rakai study of HIV transmission in heterosexual couples² to derive a mathematical relation between viral load and the risk of HIV transmission per unprotected penetrative sexual contact. On the basis of the Rakai data, each ten-fold increment in viral load is associated with a 2·45-fold (95% CI 1·85–3·26) increase in the risk of HIV transmission per sexual contact,² as expressed by the equation:

$$\beta_1 = 2 \cdot 45^{\log_{10}(V_1/V_0)} \beta_0 \quad (1)$$

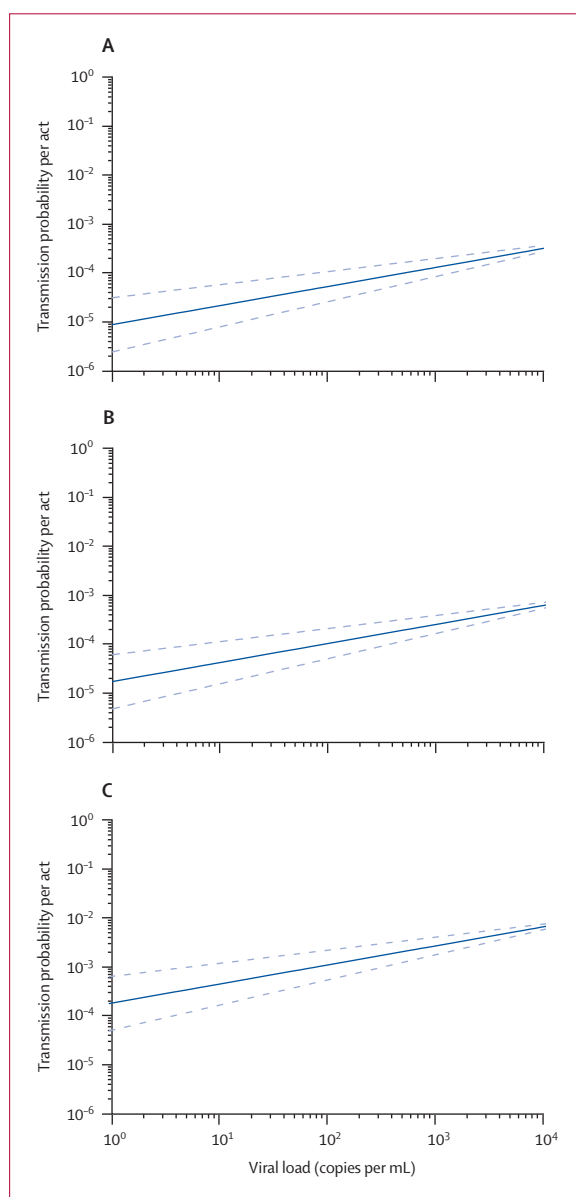


Figure 1: Relation between the transmission probability per act and viral load (A) insertive penile-vaginal transmission, (B) receptive penile-vaginal transmission, and (C) penile-anal transmission. Solid line refers to a rate ratio of 2·45 between transmission probability and viral load; broken lines are uncertainty bounds associated with the 95% CI of the rate ratio.

where β_0 is the probability of HIV transmission from a person with a baseline viral load V_0 , and β_1 is the transmission probability corresponding to any other viral load V_1 , whether above or below the baseline (see webappendix for further details). In the absence of information to the contrary, we assume that this correlation holds for sexual transmission from male to female, female to male, and male to male, and that it applies across the range of viral loads, including those that are below detectable levels, irrespective of whether or not a person is under treatment with antiretroviral therapy. The model can be used to estimate HIV transmission probabilities at any viral load, if the transmission probability at the baseline is known.

Empirical studies of couples have estimated the HIV transmission probability per sexual act in the absence of treatment^{17–21} to be about 0·0005 for receptive penile-vaginal intercourse (ie, transmission to the female partner in vaginal heterosexual intercourse), 0·001 for insertive penile-vaginal intercourse (ie, transmission to the male partner in vaginal heterosexual intercourse), and 0·01 for penile-anal intercourse between men (averaged between the transmission probabilities for insertive and receptive anal intercourse under the simplifying assumption that men who have sex with men engage equally in insertive and receptive sexual acts^{19,22,23}). In general, viral load was not reported from these studies, but other cross-sectional surveys have found that during untreated chronic HIV infection viral load is about 10^4 – 10^5 copies per mL,^{24–26} so we took a viral load of $10^{4.5}$ copies per mL as our baseline, assuming that it applied to the initially infected member of each couple in the studies that were the source of the empirical transmission estimates. We assumed that effective treatment reduced viral load to 10 copies per mL, and then we applied equation 1 to calculate the transmission probability per unprotected sexual act involving effectively treated patients.

We then calculated the probability of transmission within a monogamous couple over n acts, assuming that the risks per act were independent of each other in terms of the chances of HIV transmission, using the standard

	Expected value	Lower bound	Upper bound
Per act			
Female to male	$2 \cdot 2 \times 10^{-5}$	$0 \cdot 8 \times 10^{-5}$	$5 \cdot 8 \times 10^{-5}$
Male to female	$4 \cdot 3 \times 10^{-5}$	$1 \cdot 6 \times 10^{-5}$	$11 \cdot 6 \times 10^{-5}$
Male to male	$4 \cdot 3 \times 10^{-4}$	$1 \cdot 6 \times 10^{-4}$	$11 \cdot 6 \times 10^{-4}$
Over 100 acts			
Female to male	0·0022	0·0008	0·0058
Male to female	0·0043	0·0016	0·0115
Male to male	0·043	0·0159	0·1097

Table 1: Expected transmission probabilities (with lower and upper uncertainty bounds) per sexual act and cumulatively over 100 acts in a serodiscordant partnership, assuming the HIV-infected person has a viral load of 10 copies per mL.

See Online for webappendix

binomial formula to calculate cumulative risk over n exposures (see references by Rottingen and Garnett²⁷ and Kaplan²⁸ and webappendix):

$$1 - (1 - \beta_1)^n \quad (2)$$

Equation 2 was applied to calculate the transmission probability per couple after n sexual acts, for values of n up to 1000, and separately for receptive and insertive penile-vaginal intercourse, and for penile-anal sex between men. These probabilities were assumed to correspond respectively to the risk of female to male, male to female, and male to male transmission over time, within monogamous couples made up of partners who were initially HIV serodiscordant. Upper and lower uncertainty bounds in transmission risk were calculated with the 95% CI in the Rakai study's rate ratio for transmission risk per unit of viral load.²

We also did sensitivity analyses in which the viral load under effective treatment was assumed to be 5, 50, or 400, instead of 10 copies per mL. Lastly, we calculated the extent to which transmission under effective treatment would decrease if condom use among serodiscordant couples was maintained at high rates (80%),²⁹ and assuming that condoms are 95% effective in preventing transmission of HIV.³⁰

Role of the funding source

The funding source had no role in the design or conduct of the study, or in the collection, analysis, or interpretation of the data. DPW had full access to all the data and had final responsibility for the decision to submit for publication.

Results

The relation between the transmission probability per act and viral load is shown in figure 1; table 1 shows the probabilities of HIV transmission from an effectively treated person to a serodiscordant partner per sexual act. The expected probability of HIV transmission per sexual act is small at low viral load, as associated with effective treatment. However, the risk of transmission is expected to magnify over repeated exposures. Figure 2 shows the relation between cumulative risk of HIV transmission with increasing numbers of sexual exposures in a serodiscordant couple when the HIV-positive individual has effectively controlled viral load. The cumulative probability of HIV transmission over 100 acts is shown in table 1. Assuming that the typical couple engages in 100 sexual acts per year,^{31–33} the model-based estimates for annual heterosexual transmission are consistently well within the 95% Poisson CI for the risk of HIV transmission from partners with undetectable viral load in the Rakai study² (calculated to be about 0–2.5 per 100 person-years over all heterosexual couples, and around 0–5 per 100 person-years for male-to-female and for female-to-male transmission). In a larger population,

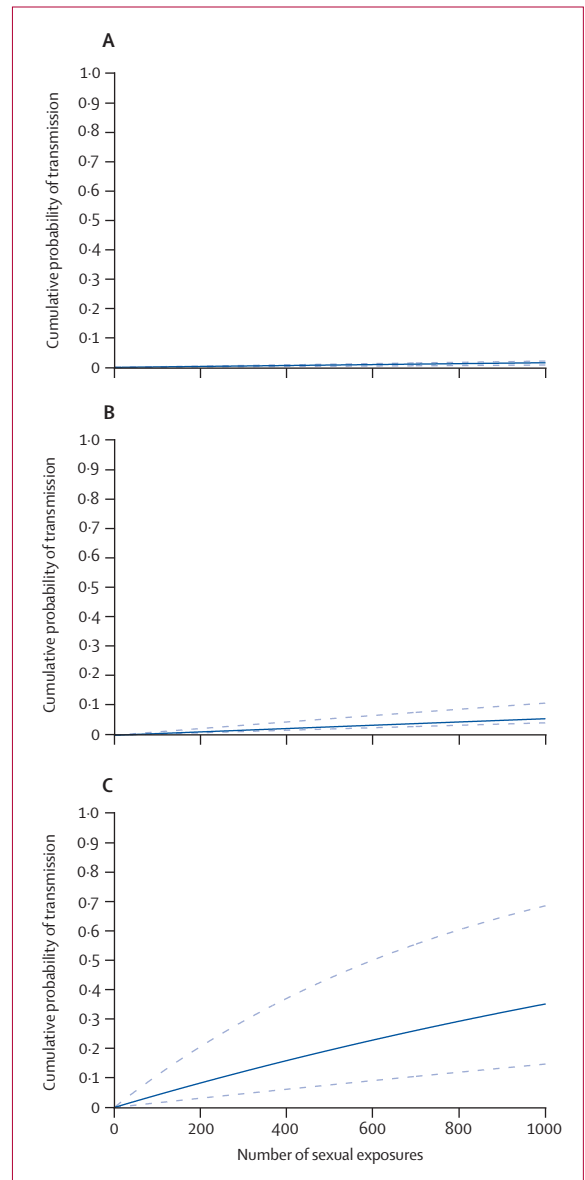


Figure 2: Relation between the cumulative risk of HIV transmission and the number of sexual exposures to HIV-infected partner who is effectively treated (viral load of 10 copies per mL)

(A) Insertive penile-vaginal transmission, (B) receptive penile-vaginal transmission, and (C) penile-anal transmission. Solid line refers to a rate ratio of 2.45 between transmission probability and viral load; broken lines are uncertainty bounds associated with the 95% CI of the rate ratio.

over a longer duration, the number of HIV transmissions is likely to be of substantial public-health importance. The number of seroconversions over 1000 acts (ie, an average of about 10 years of regular exposure) among 10 000 initially serodiscordant partnerships in which the person infected with HIV is effectively treated is expected to be fairly high for all exposure routes, especially among men who have sex with men (table 2).

Figure 3 shows the relation between the cumulative probability of transmission with number of sexual

Viral load in infected partner	Sexual exposure route	Expected value	Lower bound	Upper bound
5 copies per mL	Female-to-male	164	56	471
	Male-to-female	326	111	920
	Male-to-male	2823	1060	6191
10 copies per mL	Female-to-male	215	80	564
	Male-to-female	425	159	1096
	Male-to-male	3524	1477	6871
50 copies per mL	Female-to-male	398	181	854
	Male-to-female	781	359	1635
	Male-to-male	5565	3059	8325
400 copies per mL	Female-to-male	872	517	1441
	Male-to-female	1669	1007	2674
	Male-to-male	8391	6543	9557

Table 2: Expected number of HIV seroconversions out of 10 000 serodiscordant couples in a hypothetical population over 1000 acts per partnership, with lower and upper uncertainty bounds

exposures when viral load is suppressed to different levels and the corresponding number of seroconversions out of 10 000 serodiscordant couples, after 1000 sexual acts per couple, at varying levels of viral load is shown in table 2. These data indicate that the degree to which the viral load has been suppressed below detectable levels by effective therapy can have a substantial effect on the rate of HIV transmission.

Condom use is the main method for reducing HIV transmission in serodiscordant couples. If condoms were abandoned altogether among serodiscordant couples in whom the HIV-positive partner was effectively treated, incidence rates could be expected to increase substantially. In 10 000 serodiscordant couples where the HIV-infected partner is effectively treated (with a viral load of 10 copies per mL) and condom use is maintained at 80%, assuming that condoms are 95% efficacious per act, after 10 years the expected number of seroconversions is 52 (uncertainty bounds 19–138) for female-to-male transmission, 104 (38–275) for male-to-female transmission, and 990 (376–2433) for male-to-male transmission. These results suggest that if condoms are not used as a result of a perceived small risk of transmission then incidence could increase by four times.

The efficacy of effective treatment depends on the absolute drop in viral load: if viraemia drops by 3–4 log₁₀ then the efficacy in reducing infectiousness is about 95%. For Australian men who have sex with men on antiretroviral therapy, viral suppression is achieved in about 85% of cases.³⁴ Thus, if 15% of treated cases had an inflated average viral load of 1000 copies per mL, then 4385 (uncertainty bounds 2482–7312) seroconversions could be expected after 10 years.

Discussion

Our model suggests that although the individual risk of HIV transmission per act is fairly small, the rate of transmission over large numbers of acts might be

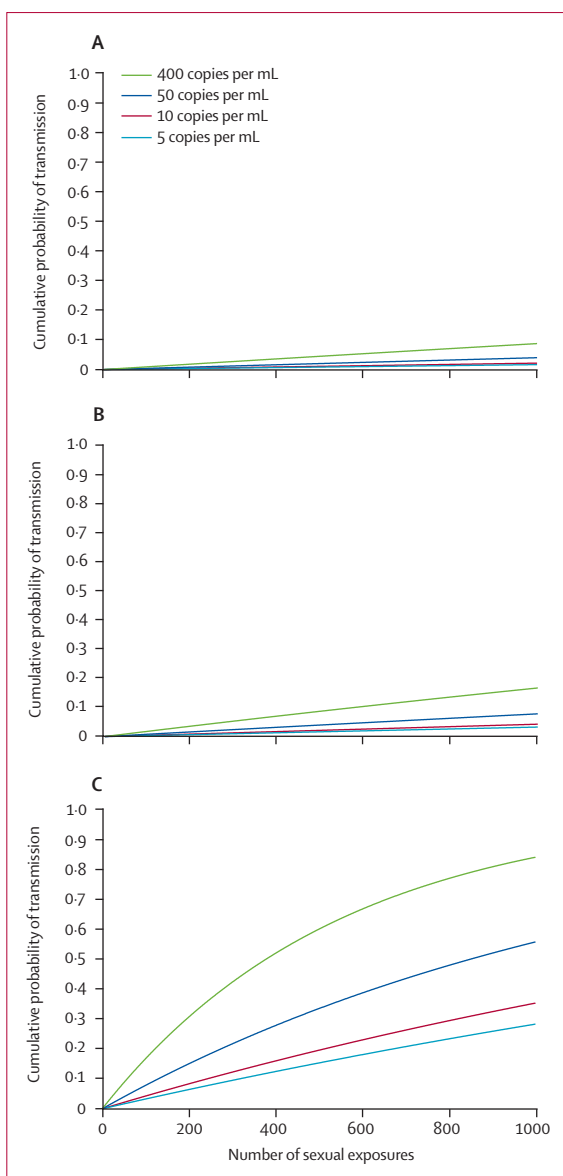


Figure 3: Effect of viral load on the relation between cumulative risk of HIV transmission and the number of sexual exposures for (A) insertive penile-vaginal transmission, (B) receptive penile-vaginal, and (C) penile-anal transmission

substantial and could be further exacerbated by viral rebounds. Viral rebound after achieving viral suppression is common in previously treatment-naive individuals and higher rates are observed in treatment-experienced patients.^{35,36} Although the primary purpose of antiretroviral therapy is to slow disease progression in people with HIV infection, it is likely to have the secondary benefit of reducing the risk of new transmission to HIV-negative sexual partners.³⁷ Under our assumptions, the effectiveness of treatment in reducing the risk of HIV transmission per sexual act was about the same as has been reported for condoms.^{38–42}

Although we agree that effective antiretroviral treatment which leads to undetectable viral load is likely to have a substantial effect on reducing infectiousness,¹¹ our analyses suggest that it should not replace condoms.

The authors of the Swiss statement acknowledge that HIV-negative individuals at risk of HIV acquisition should not refrain from protecting themselves, and that they should verify whether their partner really is effectively treated. They also concede that the decision to continue or stop using condoms must be made by the HIV-negative partner, as the person bearing the risk of seroconversion.¹ However, on the basis of the data presented here, we believe that the Swiss statement is not a sensible public-health message, because its logical outcome would be the abandonment of condoms by people with effectively treated HIV infection. The use of therapy as a prevention strategy does not represent an improvement over condom use, and there are reasons to believe that it could be worse. For example, there is evidence that as well as increasing their condom use, people who are diagnosed with HIV infection tend to reduce their number of new sexual partners;^{34,43–48} diagnosis may no longer have this effect if people with HIV believe themselves to be non-infectious. The adverse effect could be even worse because serodiscordant couples could agree to engage in what they believe is safer unprotected sex.⁴⁹ In addition to its potential public-health consequences, a literal interpretation of the Swiss statement could have legal implications in the many jurisdictions where so called “reckless endangerment” legislation requires people with HIV infection to disclose the potential risk of transmission to sexual partners.^{50–52} Furthermore, it is likely that many people would not be certain that their viral load was below detection, but would assume they are non-infectious; this could be further complicated if drug regimens are switched or if there is incomplete adherence to therapy. There are currently no empirical data available to quantify the likelihood or scale of these effects, but it is plausible that the abandonment of condoms by effectively treated people could cause substantial increases in HIV transmission.

The studies done to date that have reported no transmission from virally suppressed people have been roughly of the size of 100 serodiscordant couples and duration of about 1 year, and have only assessed heterosexual transmission. Our analysis has shown that it is not surprising from a probabilistic sense that no transmission events were seen in these cohorts because of the fairly small samples. On the basis of the Rakai data, we have estimated that over a larger number of exposures and with a larger number of people there could be significant levels of transmission via all sexual exposure routes and particularly among men who have sex with men. In the absence of studies involving large numbers of serodiscordant couples in whom the person with HIV infection is receiving effective therapy, it is not

possible to empirically confirm the validity of the model-based estimates.

Although the empirical studies of transmission probabilities report variation in values with wide CIs, the estimates we use in our analysis are consistent across these studies and are widely accepted in the HIV modelling literature.^{53–57} Our model has used estimates of HIV transmission probabilities that represent averages, whereas the risk in fact varies considerably among couples according to a number of factors apart from viral load and condom use. For example, gay men practise insertive and receptive anal sex to differing degrees; those who mainly practise insertive sex are at significantly lower risk than those who engage primarily in receptive sex. Our quantitative estimates are not applicable to men who do not engage equally in both roles, such as those who practise so called strategic positioning to reduce HIV transmission risk.¹⁰ For simplicity we also assumed that heterosexual couples do not engage in penile-anal intercourse. The presence of genital infections in either partner can also increase the risk of HIV transmission in couples. One must also note that although there are strong associations,^{5–7} undetectable plasma viral load does not necessarily translate to undetectable viral load in semen, cervicovaginal, or rectal fluids.⁵⁸

Our key, but ultimately unverifiable, assumption is that transmission risk follows a specific and known log-linear relationship with viral load which holds in the range of undetectable viral loads and in the presence of highly active antiretroviral therapy. We used the 95% CI of the original association to assess the sensitivity of our results. It is possible that there is a threshold level for plasma HIV RNA below which sexual transmission is indeed very difficult. If effective treatment reduces viral load below such a threshold then our quantitative results would overestimate the risk of transmission. However, we have been conservative in assuming that effective therapy generally results in a constant, suppressed viral load, without the presence of viral blips or rebounds, and we ignored the potential effect on transmission of other sexually transmitted infections, such as herpes simplex virus, which are fairly common.^{59,60}

Our model has also ignored the possibility that average viral loads at baseline may differ across populations and that a different non-linear relationship exists between viral load and transmission risk. We explored sensitivity in the effect of viral load on transmission (figure 3). Additionally, we assumed that every unprotected sexual encounter between serodiscordant people is independent of other encounters and carries equal risk of transmission. It has been postulated that not every act has the same transmission risk and that after a certain point in time if transmission has not occurred then it is unlikely to do so.⁶¹ The statistical relation we used in this analysis was based on the Rakai data² on untreated heterosexual couples. In the absence of other data, we have also assumed that this relation can be applied to the

transmission risk associated with both heterosexual and male homosexual contact. No prospective studies have investigated the risk of transmission when viral load is undetectable due to treatment.

In its most favourable light, the Swiss statement can be viewed as guidance that individual serodiscordant couples, in consultation with their physicians and depending on their circumstances, may wish to consider as a basis for reducing the risk of HIV transmission from the positive to the negative partner—ie, by using treatment to prevent transmission. By contrast, our calculations have shown that as a population strategy, the use of treatment as prevention has the potential to reduce HIV epidemics only if consistent condom use is maintained. Indeed, our analysis suggests that there is a large potential for doing more harm than good. In practice, there may be some degree of trade off between condom usage rates and viral suppression through effective therapy, which could be elucidated through further modelling. However, with HIV incidence having already risen in a number of populations of men who have sex with men since effective treatment became widely available,⁶² even in the absence of a general recommendation that condoms can be abandoned by those who are effectively treated, it seems far too early to promote treatment as a public-health strategy to prevent transmission.

Contributors

DPW conceived and designed the study, did the analyses, and was involved in the writing of the manuscript. MGL was involved in the design and analysis of the model, and in the editing of the manuscript. AEG provided advice on empirical models and behavioural insights, and participated in the editing of the manuscript. DAC provided advice on clinical and biological aspects of the project, and took part in the editing of the manuscript. JMK provided epidemiological advice and took part in the writing of the manuscript. All authors saw and approved the final version of the manuscript.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

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