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► **To cite this version:**

Timothy B Hallett, Colette Smit, Geoff P Garnett, Frank de Wolf. Estimating the Risk of HIV Transmission from Homosexual Men on Treatment to their HIV-uninfected partners. *Sexually Transmitted Infections*, 2010, 87 (1), pp.17. 10.1136/sti.2010.042622 . hal-00556863

HAL Id: hal-00556863

<https://hal.science/hal-00556863>

Submitted on 18 Jan 2011

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Estimating the Risk of HIV Transmission from Homosexual Men on Treatment to their HIV-uninfected partners

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Competing Interest: None declared.

Abstract: 248 words, main text: 2169 words, 1 Table and 3 Figures.

A technical appendix accompanies this manuscript.

Abstract

Background: It is not known how the risk of HIV transmission from homosexual men on antiretroviral treatment is related to patterns of patient monitoring and condom use.

Methods: We developed a stochastic mathematical simulation model of cohorts of men who have sex with men (MSM) in the Netherlands, parameterised using observational cohort data. The model incorporates viral load trends during first-line treatment, patient monitoring, and different scenarios for how condom use may depend on recent viral load measurements. The model does not include the effect of sexually transmitted infections on HIV transmission.

Results: For MSM on treatment, the risk of transmitting HIV to their long-term partner is 22% (uncertainty interval: 9-37%) if condoms are never used. With incomplete use (in 30% of sex acts) the risk is reduced slightly, to 17% (7-29%). However, the risk is as low as 3% (0.2-8%) when men on treatment only use condoms six months beyond their last undetectable viral load measurement. The risk is further reduced when three months is the time period beyond which condoms are used.

Conclusions: When condom use by HIV-infected, cART-treated men is based on their last viral load measurement, the transmission risk is much lower than with incomplete condom use. The key message for patients is that although always using condoms during treatment is the best way to protect partners from the risk of HIV transmission, when such use cannot be achieved, the second best strategy is to use condoms whenever the last undetectable viral load was measured more than three months ago.

Key Messages

1. Intermittent use of condoms by men on treatment offers relatively little reduction in the chance of transmission to their partner.
2. In contrast, the chance of HIV transmission can be substantially reduced if condoms are used when the last undetectable viral load measurement was not within the last three months.
3. Frequent viral load measurement can maximize the potential for treatment to reduce HIV transmission.

Introduction

Since the mid-1990s, individuals infected with HIV in industrialized countries have been able to access combination antiretroviral therapy (cART) (1;2), which has substantially decreased HIV-associated mortality in these populations (3). More recently, this trend has been repeated in many developing countries, along with signs of decreasing HIV mortality (4). In both settings, there is a trend for earlier initiation of treatment (5) and increasing debate about whether starting treatment earlier (or even immediately on HIV diagnosis) is advised in order to improve outcomes and reduce HIV transmission (6;7). As the population on treatment grows its potential contribution to HIV epidemic increases. Therefore, we anticipate that the infectiousness and the sexual behavior of those on treatment will become key determinants of the trajectory of the global epidemic in the coming years.

The rate of HIV transmission from infected persons is closely tied to their plasma viral load, which cART can reduce to very low levels (8). On this evidence, in 2008 the Swiss National AIDS Commission (EKAF) suggested that there was effectively no risk of sexual transmission from patients on cART, provided individuals (i) follow antiretroviral therapy strictly to guidelines, (ii) have no detectable viral load when measured in the last 6 months, and (iii) have no other sexually transmitted infection (9;10). The implication that such patients need not use condoms with their sexual partners was warmly welcomed by patient groups and activists (11).

In response, many argued that this was not a helpful public health message. Although the chance of transmission from men on treatment is likely to be low, it is unlikely to be zero, since at least one transmission event from a man on successful cART has occurred (12), and that over many sex acts amongst many men, a small rate of transmission could translate into a large number of new infections (13;14). A simple model was used to argue this point (13), but it did not estimate the absolute risk of transmission from men on treatment; nor did it account for condom use being conditional on a recent viral load measurement, as the EKAF statement recommended (9).

In this paper, using uniquely detailed data on the trends in viral loads among men on treatment (17) and a new stochastic mathematical model, we estimate the risk of HIV transmission from men who have sex with men (MSM) in the Netherlands and determine how this is influenced by various patterns of condom use (including those based on the Swiss recommendations) and schedules of viral load monitoring.

Methods

Following earlier work (18;19), we developed a stochastic individual-based simulation model of viral load trends, HIV transmission risk, and patient monitoring among cohorts of MSM in the Netherlands. The vast range of possibilities for the evolution of viral load over time was conceptualized as three distinct trajectories (Figure 1). Data from the ATHENA observational cohort of HIV-infected individuals in the Netherlands (17) were used to evaluate the parameters (Table 1, with further detail provided in the technical appendix).

The risk of transmission is characterized as the probability that a man on treatment will infect his uninfected sexual partner over the course of first-line therapy. We examine only the special case where a partnership is maintained over the entire duration of first-line therapy and did not include the effect of sexually transmitted infections on the chance of HIV transmission. In most analyses, the functional relationship between plasma viral load and the chance of transmission in each unprotected sex act was based on a Hill function fitted to observational data on HIV transmission in Zambia by Fraser *et al.* (20). This function is supported by recent review of transmission rates (15;16) and is denoted the ‘Fraser *et al.*’ assumption. The function was rescaled to match the observed approximate transmission risk per sex act for MSM (~ 0.01 for men with log-viral loads of ~ 4.5 log-copies)(13) (Figure S2). An alternative assumption for the relationship (linear trend in log-risk and log-viral load (21): see Figure S2) was used as well in sensitivity analyses: this is denoted the ‘Wilson *et al.*’ assumption. We assumed that there were 100 sex acts per year in the partnership, and that the efficacy of condoms in reducing transmission is 95%. In uncertainty analyses, the model assumption for which there was least directly relevant data were varied independently in a Monte Carlo analysis: specifically, the frequency of sex acts per years (**uniform** between 50 and 150), the efficacy of condoms when used (**uniform** between 85% and 100%) and chance of transmission per sex act without treatment (**uniform** from 0.0075 to 0.0125). **A combined 95% uncertainty interval (the range between the 2.5th and 97.5th percentiles of the resultant distribution) was calculated.**

In the model, reflecting clinical guidelines (22), patients with undetectable viral loads are monitored every 4 months. When viral load is found detectable, the patient returns for another appointment after 8 weeks, and the treatment regimen is then changed if retesting confirms the finding.

Various scenarios for condom use in partnerships were considered: (i) never using condoms; (ii) using condoms in 30% of sex acts (24); (iii) not using condoms if viral load was undetectable at the last measurement in the past 6 months; and, (iv) always using condoms. Scenario (iii) corresponds to the way that the ECAF statement has been interpreted, and we considered two variants whereby the decision not to use condoms is based on the last measurement in the past 3 months (instead of 6 months) or the last viral load measurement ever taken (i.e. irrespective of time).

Results

We find that men on treatment pose a substantial risk of HIV transmission (22% (9-37% in uncertainty analysis)) to their partners if they do not use condoms (Figure 2) and the relationship between viral load and transmission is as described by Fraser *et al.* (20). This risk is generated in three ways: (i) treatment is not sufficient to suppress viral load, so transmission can occur even if the regimen is quickly changed; (ii) the level of virus can rebound quickly and reach high levels before detection and change of regimen; (iii) even with suppressed viral loads, the risk of transmission is non-zero, so that over the many sex acts during treatment, the cumulative chance of transmission becomes relatively non-negligible.

Using condoms 30% of the time reduces the chance of transmission but only marginally (to 17% (7-29% in uncertainty analysis)), since there remains a substantial numbers of unprotected sex acts overall. In contrast, men that always use condoms unless their viral load was undetectable at the last measurement in the past 6 months are much less likely to transmit HIV to their partner (chance of transmission: 3% (0.2-8% in uncertainty analyses)). This is because the risk generated in the first two ways has been largely removed. Men following this strategy, on average, use condoms 10% of the time they are on treatment, while reducing the risk of transmission to 3%. The risk with this strategy is nevertheless greater than always using condoms, in which the chance is 1% (0-7% in uncertainty analysis) (Figure 2). The risk is not zero, because condom efficacy is not perfect.

Using the alternative ('Wilson *et al.*') assumption about the relationship between plasma viral load and transmissibility, the overall chance of infection if condoms are not used is higher (47% vs. 22%), but the same key result is reproduced: men who use condoms unless their viral load was undetectable in the last six months are much less likely to transmit HIV to their partner than if condoms are used intermittently (Figure S3).

The frequency with which patients on treatment are monitored is a key determinant of the chance of HIV transmission (Figure 3(a)). Patients monitored frequently can be quickly switched to new regimens if first-line fails -- i.e. before viral load increases and they have exposed their partner to an elevated risk of transmission for a long period. The second effect of increased frequency of monitoring is the reduction in overall condom use. This is because with less frequent monitoring, many men with suppressed viral loads would use condoms since they have not had a recent viral load measurement. With monitoring every 18 months, condoms would be used in ~70% of sex acts, but with monitoring every 3 months, condoms are needed in only 9%.

The benefit of patient monitoring is influenced by the proportion of patients lost to follow-up. The probability of infecting a partner increases from 2% when none of the patients are lost to follow-up, to 5% when 20% do not return for care (Figure 3(b)).

Finally, we examined three ways that condom use could be based on viral load measurements (Figure S5). The decision not to use condoms could be based on an undetectable viral load in the last 3 months, the last 6 months or the last measurement ever. With the decision based on a measurement in the last three months, there is reduced transmission compared to a decision based on the last six months, provided that patients are monitored at least every 6-12 months. However, with the decision based only on the last measurement regardless of time, the chance of transmission is higher, especially if monitoring intervals are longer.

Discussion

The debate about the ECAF statement on HIV transmission from patients on cART (13) and earlier modeling work (14) did not consider the way in which deciding not to use condoms could be conditional on the last viral load measurement. There was also little focus on estimating the rate of HIV transmission across the population or exploring how it is influenced by patterns of patient monitoring. In this paper we have shown that basing the decision to use condoms on viral load provides substantially better protection to partners than incomplete condom use, provided that the measurement is within the last 3-6 months. Compared to always using condoms, the viral-load-dependent strategy allows slightly more HIV transmission (2-3% versus 1%). However, as condoms are needed much less of the time (10% vs 100%), adherence to this strategy may be better.

Our results also highlight the importance of monitoring more often and minimizing losses to follow-up. Without such effort, increases in viral load go undetected, exposing partners to higher risks of transmission. With measurement at intervals of 3-12 months, the risk of transmission can be reduced further by basing condom use on measurements taken only three months before. This guards against the risk increases in viral load since the last measurement (25). For this reasons, it is important that decisions are not based on viral load measurements taken more than six months before.

The model used in this paper incorporates more biological realism than earlier work (13;14) by using the functional form of the viral load-transmission relationship that reflects a sophisticated analysis of observational data (20), explicitly tracking viral load monitoring and modeling the course of viral load evolution over time. Nevertheless, a number of simplifying assumptions were made. The risk of transmission per sex act was scaled to match only an approximate observation of the risk, without considering differences in the frequency of being the insertive or receptive partner (26;27). We assumed that, below a certain viral load level, the chance of transmission is low and not actually zero; but evidence is lacking, since observing almost no instances of transmission (15) could be consistent with either possibility. The response of patients to therapy varies widely, and we have attempted to only broadly represent this in the model. However, we believe the key features of viral load evolution have been captured by parameterising the viral load trajectory (its rise, period of stability, and subsequent rise) and its relationship to treatment adherence. An important limitation of the model is that the effects of other STI on HIV transmission is not incorporated. The data available from the cohort do not permit a detailed representation of STI transmission and the influence of STI would depend on many factors about the pattern of STI spread across the populations. If STI were included, the overall estimate of HIV transmission risk would likely be greater, but we would expect the key relationship between risk and patterns of condoms use to hold or be strengthened (since more frequent screening affords greater opportunity for treating STIs). Finally, the model does not include the influence of intermittent viraemia on the chance of HIV transmission, since we assumed its influence on transmission to be relatively small (28).

The implications of this work are that the key message to patients should remain that always using condoms when on treatment is the best way to protect partners from the risk of HIV transmission. However, an additional message is that using condoms is most crucial when patients have not recently (within the last 3 months) had an undetectable viral load

measurement. This message refines the intuitive association between successful treatment and reduced transmission (24;29) and could substantially improve protection for infected partners. This advice must be supported by frequent viral load monitoring (at least every 6 months, but preferably every 3 months) of all patients on treatment.

Acknowledgements

TBH thanks the Wellcome Trust for funding support. **We thank two reviewers for their constructive assessment of this work.**

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PARAMETER		VALUE	UNIT
Log ₁₀ viral load at treatment initiation (normal distribution)	Mean	5.1	Log copies per micro-litre
	Variance	0.40	
Fraction achieving suppression [†]		0.70	Fraction
Fraction with good adherence [‡]		0.94	Fraction
Waiting time until viral suppression, if suppression & <u>good</u> adherence (exponential distribution)	Median	5.38	Months
Waiting time until viral suppression, if suppression & <u>not good</u> adherence (exponential distribution)	Median	5.92	Months
Waiting time (months) until viral rebound, if <u>good</u> adherence (double Weibull distribution), assuming <u>Shorted</u> survival times (used unless otherwise stated) or <u>extended</u> survival.	Shape ₁	1.14 (e) 10.23 (s)	Months
	Scale ₁	456.65 (e) 153.25 (s)	
	Shape ₂	1.92 (e) 1.25 (s)	
	Scale ₂	20.70 (e) 41.58 (s)	
	Weighting	0.91 (e) 0.77 (s)	
Waiting time until viral rebound, if <u>not good</u> adherence (Weibull distribution)	Shape ₁	1.14	Months
	Scale ₁	132.86	
Increase in Log ₁₀ viral load, if <u>good</u> adherence [¶]	Rate	0.07 (se=0.002)	Log ₁₀ copies per microliter per month
Rate of increase in Log ₁₀ viral load, if <u>not good</u> adherence [¶]	Rate	0.16 (se=0.01)	Log ₁₀ copies per microliter per month
Maximum survival time with non-suppressed viral load	Max	1	Years
Log ₁₀ viral load if no suppression (normal distribution)	Mean	3.80	Log copies per micro-litre
	Variance	0.84	

Table 1: Natural history parameters for HIV infection on first line treatment (Source: ATHENA cohort data (17)). Refer to the technical appendix for details.

[†]Suppression is defined as at least two consecutive viral load measurement <500 HIV RNA copies per millilitre.

[‡] Adherence is classified as good or poor based on the measurement of plasma drug levels.

[¶]At all times in the simulation, viral load is limited to being less than or equal to the 95th percentile of viral loads at treatment initiation in the ATHENA data (equal to 6 log-copies).

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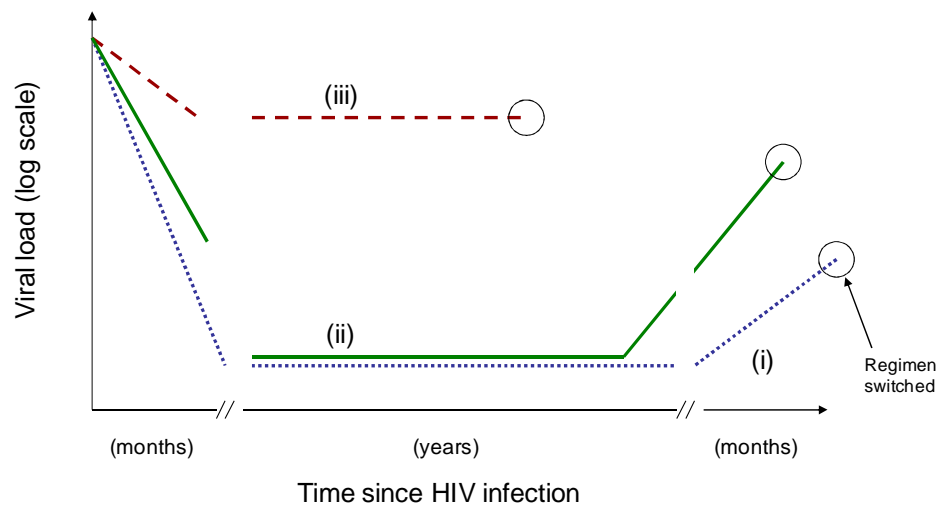


Figure 1: Schematic representation of the three assumed trajectories of (log) viral load following treatment initiation: (i) suppression achieved and adherence good (dotted blue line); (ii) suppression achieved but adherence poor (solid green line); and (iii) suppression not achieved (dashed red line). The circles indicate when the regimen is changed. Parameter values are presented in Table 1 and details are provided in the appendix.

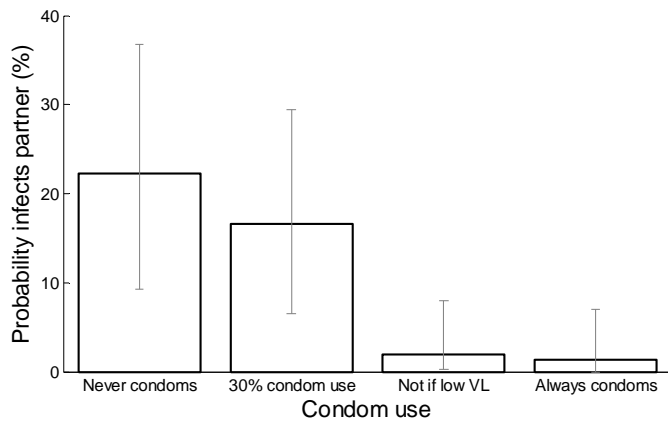


Figure 2: Probability of transmission to partner during first-line therapy, if (i) condoms are never used; (ii) condoms are used 30% of the time; (iii) condoms are used unless last viral load measurement in last 6 months was undetectable, or (iv) always using condoms. **Error-bars show the 95% uncertainty interval, as described in the text.** It is assumed that the partnership is maintained over the entire course of first-line therapy and that viral load is related to transmission rate as Fraser *et al.* (20) have described.

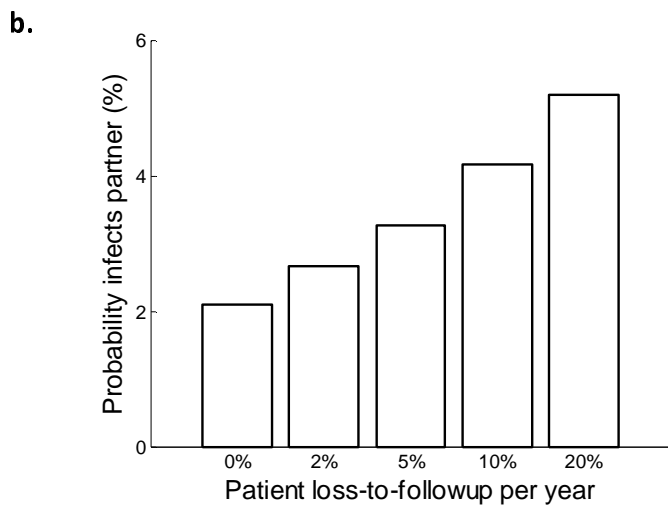
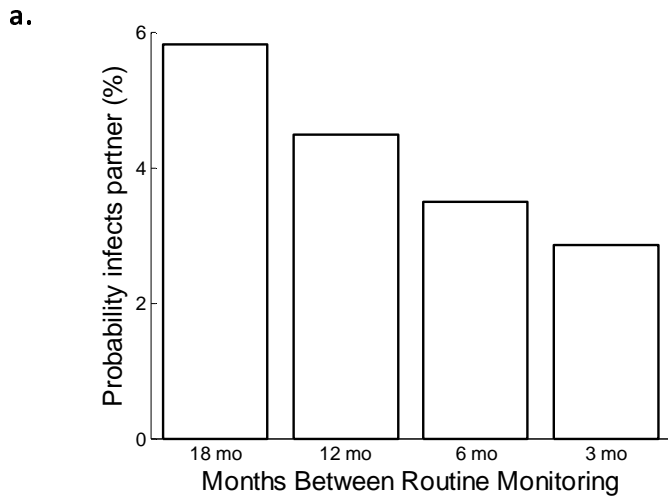


Figure 3: The influence of (a) monitoring frequency and (b) loss to follow-up on the probability of HIV transmission, assuming condoms are used unless last viral load measurement in last 6 months was undetectable. It is assumed that the partnership is maintained over the entire course of first-line therapy and that viral load is related to transmission rate as Fraser *et al.* (20) have described.