The future role of rectal and vaginal microbicides to prevent HIV infection in heterosexual populations: implications for product development and prevention

Marie-Claude Boily,1 Dobromir Dimitrov,2 Salim S Abdool Karim,3 Benoît Mâsse2,4

ABSTRACT

Objectives To compare the potential impact of rectal (RMB), vaginal (VMB) and bi-compartment (RVMB) microbicides to prevent HIV in various heterosexual populations. To understand when a RMB is as useful as a VMB for women practicing anal intercourse (AI).

Methods Mathematical model was used to assess the population-level impact (cumulative fraction of new HIV infections prevented (CFP)) of the three different microbicides in various intervention scenarios and prevalence settings. We derived the break-even RMB efficacy required to reduce a female’s cumulative risk of HIV infection by the same amount than a VMB.

Results Under optimistic coverage (fast roll-out, 100% uptake), a 50% efficacious VMB used in 75% of sex acts in population without AI may prevent ~33% (27, 42%) new total (men and women combined) HIV infections over 25 years. The 25-year CFP reduces to ~25% (20, 32%) and 17% (13, 23%) if uptake decreases to 75% and 50%, respectively. Similar loss of impact (by 25%–50%) is observed if the same VMB is introduced in populations with 5%–10% AI and for RRA = 4–20. A RMB is as useful as a VMB (ie, break-even) in populations with 5% AI if RRA = 20 and in populations with 15%–20% AI if RRA = 4, independently of adherence as long as it is the same with both products. The 10-year CFP with a RVMB is twofold larger than for a VMB or RMB when AI = 10% and RRA = 10.

Conclusions Even low AI frequency can compromise the impact of VMB interventions. RMB and RVMB will be important prevention tools for heterosexual populations.

INTRODUCTION

Research on vaginal microbicide (VMB) to prevent HIV infection is important because it is a biomedical intervention specifically designed to protect women.1 Until July 2010, none of the first generation of microbicide candidates (ie, with non-specific activity against HIV) tested in large clinical trials had shown to protect against HIV.1–4 One clinical trial (CAPRISA-004) has demonstrated the effectiveness of a topical antiretroviral-based vaginal microbicide (ARV-VMB), tenofovir 1% gel, against HIV acquisition among women in South Africa5 6 (table 1). This was the first topical ARV-VMB with specific activity against HIV-1 (suppress viral replication) to be tested. This positive result needs to be confirmed in other trials before it can be licensed and used as a public health prevention tool. Many additional products designed to protect during vaginal and anal intercourse are currently at different stages of development and testing.7 9

The role of anal intercourse (AI) in the overall heterosexual HIV epidemic remains unclear. AI may be an important risk factor because the risk of HIV infection during unprotected receptive AI is much larger than during vaginal intercourse (VI)10–14 and because the fraction of heterosexuals who engaged in AI at least once in their lifetime is substantial in different risk populations, countries and time periods (online Supplement table S1).11 15–17 AI may also be significantly under-reported. For example, in one study, 3.5% of married men in Cotonou reported ever engaging in AI with a woman in face-to-face interviews compared with 17.5% in a pooling booth survey, a method designed to reduce social desirability bias.18

Theoretical studies have also raised the concern that the practice of AI by trial participants may have reduced the effectiveness of VMB in large clinical trials.19 20 VMB use is currently limited to VI due to insufficient safety data on rectal use.19–21 However, data in animal studies indicate that tenofovir gel can protect during rectal challenges.22 23 In theory, it is biologically possible for a vaginally applied ARV-VMB gel to diffuse from the vaginal to the rectal linings and to protect during AI.5 24 Thus, the development of a rectal microbicide (RMB) or bi-compartmental microbicide that protect during vaginal and anal intercourse (RVMB) may eventually be possible and a useful HIV prevention tool for heterosexual populations. Previous mathematical modelling studies have assessed the potential impact of VMB and RMB in heterosexual and homosexual populations, respectively.7 25–30 However, none have investigated the potential impact of RMB or RVMB in heterosexual population.31

Our study aims to fill this gap by comparing the long-term population-level impact of VMB, RMB and RVMB in different heterosexual populations, HIV prevalence settings and intervention scenarios. First, we use a transmission dynamics model to assess the VMB intervention impact in populations without AI under various coverage scenarios. Then, we compare the ‘loss of VMB impact’ due to AI in populations with AI and due to reduced coverage in populations without AI. Third, we assess the
relative and incremental population-level impact of RMB/RVMB compared with VMB under different efficacy, adherence and anal sex assumptions. Finally, we derive the ‘break-even RMB efficacy’ to quantify the usefulness of a RMB, compared with a VMB, at reducing the risk of HIV infection of women practicing AI.

METHODS

Transmission dynamics model
To assess the microbicide population-level impact, we expanded a previously published deterministic model of heterosexually transmitted HIV infection and vaginal microbicide use to include AI, condom use and adherence to a vaginal or rectal microbicide. The model assumes random mixing between susceptible and infectious individuals and divides the population into three major classes: men, women not using and using microbicides, which are further stratified in susceptible, HIV infected and AIDS states (online Appendix A). Men and women who become sexually active join the community at constant rates, which are selected to balance the departure rate in a non-infected population (ie, open but stable population). The gender-specific rates of HIV infection, that is, the forces of infection, for the different classes depend on the annual rate of new partner acquisition, the number of sex acts per partner, the fraction of all sex acts, which are anal (α) and vaginal (1−α), and the HIV transmission probability per anal or vaginal sex act, the fraction of sex acts protected by condoms (c) or by microbicide during vaginal (γVMB) or/and anal (γRMB) intercourse, and the HIV prevalence among the partners of opposite sex.

Microbicide intervention
Theoretically, depending on the product, a microbicide can protect directly against HIV (HIV efficacy) or indirectly by protecting against cofactor STI, tenofovir gel significantly reduced herpes simplex virus-2 incidence in the CAPRISA-004 trial. Although ARV-based microbicides are not necessarily expected to protect against cofactor STI, tenofovir gel significantly reduced herpes simplex virus-2 incidence in the CAPRISA-004 trial. Data from the CAPRISA-004 trial suggest that vaginally applied tenofovir gel may have diffused from the women’s vaginal linings to the rectal linings (thereby explaining the increase in mild diarrhoea seen in CAPRISA-004) opening the interesting, yet unproven, possibility that the gel could also protect during AI.24 It remains unknown if such microbicide would be equally protective during AI than VI, although animal studies suggest that a MB gel could be equally effective during AI and VI.22 23

Based on this information, we modelled three microbicides, which are assumed to reduce the women risk of HIV acquisition during receptive VI only (VMB), during RAI only (RMB) or during both (RVMB) with an efficacy of EVMB, ERMB and ERVMB, respectively. The risks associated with drug resistance and condom substitution were not considered. We modelled the increase in coverage by assuming that the microbicide is immediately adopted by a fraction 1 (speed of roll-out) of women in the population and by an additional fraction k (uptake) of women who newly enter the sexually active population annually. The parameter k determines the maximum long-term achievable coverage, whereas k influences how fast it is achieved. We defined a fast (k=1) and a slow roll-out (k=1/k2). The model is described fully in online Appendix A.

Parameter assumptions and simulations
We defined ranges of values for the behavioural and biological parameters that are representative of different risk populations in Southern Africa and produced epidemics with HIV equilibrium prevalence between >0% and 55% (table 2A,B).18 35 36 38 39 42 43 The gender-specific HIV transmission probability estimates per vaginal and anal act and the relative increase in HIV acquisition risk during RAI (RRRAI=4 to 20) (online Appendix C) are based on meta-analyses of observational studies.11 12 14 The limited data on HIV risk per insertive anal intercourse (IAI) indicate a lower risk than for RAI.10 11 14 We conservatively assumed a twofold increase in HIV risk during IAI (RRIAI) compared with insertive VI. Fewer studies report data on AI frequency than on the fraction of individuals who ever practiced AI.2 Over 6%–10% of all unprotected sex acts reported by study participants (townships, STI clinics) in Cape Town were AI.12 13 Similarly 10% of all unprotected sex acts reported by female sex workers (FSWs) in Durban were AI.30 31 In previous multicentre VMB trials, 2%–4% low-risk women reported at least one episode of AI in the month prior to enrolment.19 20 36 37 In comparison, between 1.2% and 6.3% of adults in France, Brazil, USA and Australia reported AI at their last sex (online Supplement table S1).44 45 Thus, we explored scenarios with AI frequency of 0%, 2%, 5%, 10%, 15% and 20%. We also allow for a significant variation in the community rate of condom use, annual frequency of sex acts, annual number of sex partners and condom efficacy (table 2A).

In the CAPRISA-004 trial, the true efficacy of tenofovir gel against HIV remains uncertain. It could be over or underestimated since the estimated overall effectiveness (a reflection of the true efficacy and adherence) of tenofovir against HIV was 39%, after 30 months, under imperfect adherence (72% overall), and because tenofovir gel also protected against herpes simplex virus-2 acquisition, which is a cofactor of HIV transmission (table 1). Using this information, we predominantly explored efficacy around 50%, 50%, 75% and adherence around 50% and 75% but also varied them over a wider range (table 2C). We assumed that the RVMB is equally effective during AI and VI. We explored an
Table 2 Parameters and ranges

<table>
<thead>
<tr>
<th>Parameter</th>
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<th>Parameter values</th>
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<td>A. Parameters sampled pre-intervention</td>
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<tr>
<td>$\beta_m$</td>
<td>HIV acquisition risk for men per unprotected vaginal act</td>
<td>0.0021—0.0068*</td>
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<td>$\beta_w$</td>
<td>HIV acquisition risk for women per unprotected vaginal act</td>
<td>0.0019—0.0046*</td>
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<td>$1/\mu$</td>
<td>Average time to remain sexually active</td>
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<td>$d$</td>
<td>HIV-related mortality rates</td>
<td>1/12—1/7</td>
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<td>$n_m$, $n_w$</td>
<td>Average number of sexual acts per year for women and men</td>
<td>50—150</td>
<td>17 28 35—37</td>
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<td>$\rho$</td>
<td>Average number of sexual partners per year for women and men</td>
<td>0.5—2</td>
<td>16 18 28 35 38 39</td>
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<td>$c$</td>
<td>Rate of condom use in general population; fraction of sex acts when a condom is used</td>
<td>0%—60%</td>
<td>17 35 36 40</td>
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<td>$\alpha_c$</td>
<td>Condom efficacy per act</td>
<td>0.80—0.95</td>
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<tr>
<td>$RR_{RAI}$</td>
<td>Relative HIV acquisition risk per receptive anal act compared with receptive vaginal act</td>
<td>2, 4, 10, 20</td>
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<tr>
<td>$RR_{RAI}$</td>
<td>Relative HIV acquisition risk per insertive anal act compared with insertive vaginal act</td>
<td>2</td>
<td>10 11 14</td>
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<td>$a$</td>
<td>Frequency of anal intercourse, fraction of all (unprotected) sex acts which are anal intercourse</td>
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<td>B. Characteristics of epidemics simulated</td>
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<td>Basic reproductive rate</td>
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<td>$y^*$</td>
<td>Overall HIV equilibrium prevalence</td>
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<td>Simulations² 17 42 43</td>
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<td>C. Intervention parameters</td>
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<td>$k$</td>
<td>Uptake: fraction of new sexually active women entering the population using MB</td>
<td>50%, 75%, 100%</td>
<td>Assumed</td>
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<td>$k_1$</td>
<td>Speed of roll-out: initial proportion of women in the population using MB</td>
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<td>$\gamma_{RMB}$, $\gamma_{VMB}$</td>
<td>Adherence: fraction of sex acts protected by microbicide when using or not using condoms</td>
<td>50%, 75% and (0%—30%†, (60%—90%)†</td>
<td>Table 1³</td>
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<td>$E_{VMB}$</td>
<td>VMB efficacy: reduction in susceptibility per vaginal act</td>
<td>30%, 50%, 75% and between 15% and 90%</td>
<td>Table 1⁵</td>
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<td>$E_{RMB}$</td>
<td>RMB efficacy: reduction in susceptibility per anal act</td>
<td>30%, 50%, 75% and between 15% and 90%</td>
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<td>Optimistic coverage (for VMB, RMB, RVMB)</td>
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<td>Uptake and roll-out</td>
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<td>Uptake and roll-out</td>
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<td>Adherence</td>
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Optimistic ($k_1= k=100\%$) and five alternative coverage scenarios with lower uptake (50%, 75%), with slow and fast roll-out (table 2D). The optimistic scenario serves as the reference when comparing the loss of impact due to AI and reduced coverage. Monte Carlo sampling was used to randomly select different pre-intervention parameter sets from their predefined uniform ranges (table 2A). The pre-intervention parameters were filtered to identify 1000 parameter sets that met predefined target criteria of (1) basic reproductive number $R_0>1$ in absence of intervention and (2) equilibrium HIV prevalence below 35% (table 2B). The intervention is introduced in the different mature simulated HIV epidemics. The population-level effectiveness of the intervention is measured as the cumulative fraction of new HIV infections prevented over the period $[0,T]$ (CFP) following the start of the intervention. We report the median and the 90% uncertainty interval (90% UI), derived from the various parameter sets, which reflects the influence of the epidemiological conditions on the impact estimates.

Break-even efficacy ($E_{break-even}$)
The usefulness of RMB compared with VMB for women practicing AI was assessed by the break-even RMB efficacy ($E_{break-even}$) (equation 1) which was derived from the formula of the cumulative risk of HIV infection over fixed time period, for women using a VMB or RMB during sex (CR$^w_v$; online Appendix B equations B.1—B.2), and is embedded in the expressions for the force of infection of the deterministic model (online Appendix B). Equation 1 determines the minimum RMB efficacy required to reduce a woman’s risk of HIV infection by the same amount as a VMB assuming that 100% of sex acts are with a HIV-positive partner, the same adherence with both products, no condom substitution and no reduction in HIV infectiousness due to microbicides use (online Appendix B). Under these assumptions, the equivalence between a RMB and VMB only depends on the relative efficacy of the RMB ($E_{RMB}$) and VMB ($E_{VMB}$), the frequency of AI ($a$) and the increase in HIV risk during RAI ($R_{RAI}$) compared with the risk during receptive VI.
Coverage decreases ($R_{RRAI}$/b,w) as AI frequency increases independently of the efficacy or adherence assumed. When AI frequency increases from 0% to 5%, 0% to 10% and 0% to 20%, the median 10-year CFP of VMB is reduced by ~18%, ~32% and ~52% if $R_{RRAI}$=4 or ~36%, ~55% and ~75% if $R_{RRAI}$=10, respectively. To produce the same impact in populations practicing AI as in populations not practicing AI, the VMB adherence or efficacy needs to be considerably higher. To prevent a median of 10% new infections over 10 years with a 30% efficacious VMB, requires 50% adherence in absence of AI compared with 75% adherence in populations with 5% AI if $R_{RRAI}$=10 (figure 2D). Alternatively, if $R_{RRAI}$=10, a 75% or 50% efficacious VMB used in populations with 5% AI is not more effective than a 50% or 50% efficacious VMB in absence of AI, independently of the adherence level. Finally, RMB impact increases sharply as AI frequency increases. For example, a RMB which has the same efficacy and adherence level as

Figure 1 (A) Fraction of women using MB over time (coverage) following the intervention start for different uptake and roll-out (fast, slow) assumptions; cumulative fraction of new HIV infections prevented (CFP) over time among men and women not practicing anal intercourse (AI) (AI=0%) and under optimistic coverage (100% uptake, fast roll-out) (B) and among the total population (men and women combined) (C–D) following the introduction of a 50% efficacious VMB ($E_{VMB}$=50%) used in 75% of sex acts (adherence level (adh)=75%). In (C), nobody practice AI (AI=0%), uptake and roll-out are varied; in (D), AI=5%, $R_{RRAI}$ are varied and assumes optimistic coverage. The box plots (median, 5th, 25th, 75th, 95th percentiles) reflect the variation in impact estimates due to the 1000 different parameters sets (ie, epidemiological conditions) explored.
a VMB is expected to prevent the same fraction of infections in populations with 20% AI if $\text{RR}_{\text{RAI}} = 4$ (Figure 2A,C) or in populations with approximately 10% AI if $\text{RR}_{\text{RAI}} = 10$ (Figure 2B,D).

Figure 2 The total (men and women combined) cumulative fraction of new infections prevented by a VMB and RMB over 10 years (10-year CFP) after the MB introduction assuming same adherence to both products, optimistic coverage, and various anal intercourse (AI) frequency and MB efficacy. In (A), adherence level ($\text{adh}$)=50% and $\text{RR}_{\text{RAI}}=4$; in (B), $\text{adh}$=50% and $\text{RR}_{\text{RAI}}=10$; in (C), $\text{adh}$=75% and $\text{RR}_{\text{RAI}}=4$; in (D), $\text{adh}$=75% and $\text{RR}_{\text{RAI}}=10$. Each box plot represents the median (5th, 25th, 75th, 95th percentiles) from 1000 simulations for each of the 36 scenarios per panel.

Incremental benefit of bi-compartmental RVMB

Figure 3 shows the incremental benefit of a bi-compartmental RVMB, which is equally efficacious during VI and AI compared with a VMB only or RMB only. Under optimistic coverage and 60%–90% adherence, the 10-year CFP with a 45%–60% efficacious RVMB is 27% (90% UI: 20–35%). The impact of the RVMB is insensitive to the frequency of AI or $\text{RR}_{\text{RAI}}$. However, the incremental benefit of a RVMB compared with a single VMB (RMB) increases (decreases) with the frequency of AI or $\text{RR}_{\text{RAI}}$. For example, the 10-year CFP of a bi-compartmental RVMB is 1.2- or $\approx 6$-fold larger than a single VMB or a RMB, respectively, in populations with 5% AI if $\text{RR}_{\text{RAI}}=4$ (Figure 3A) but it is twofold larger than for single VMB or RMB in population with 10% AI if $\text{RR}_{\text{RAI}}=10$ (Figure 3D). However, even under optimistic coverage, a 45%–60% efficacious RVMB prevent <10% total new infections over 10 years if adherence is below 30%, independently of AI frequency and $\text{RR}_{\text{RAI}}$ (online Supplement figure S2).

Usefulness of RMB to protect women practicing AI

Figure 4 shows the minimum, or break-even, efficacy ($E_{\text{break-even}}$) required for a RMB to reduce female HIV risk by the same amount as a 40% efficacious VMB, in function of the AI frequency and $\text{RR}_{\text{RAI}}$, if both products are used as frequently. Understandably, if half of the sex acts are AI, the break-even efficacy is 40% even if $\text{RR}_{\text{RAI}}=1$. When the AI frequency is between 5% and 20%, the break-even efficacy strongly depends on $\text{RR}_{\text{RAI}}$. For example, 40% efficacious RMB and VMB are equally useful in populations with 5% AI if $\text{RR}_{\text{RAI}}=18$, with 10% AI if $\text{RR}_{\text{RAI}}=8$ or with a 20% AI frequency if $\text{RR}_{\text{RAI}}=4$. In many instances (eg, $a=7.5%$ if $\text{RR}_{\text{RAI}}=16$, $a=10%$ if $\text{RR}_{\text{RAI}}=12), a 20%–30% efficacious RMB can even be more useful than a 40% efficacious VMB. However, with <2.5% AI, a RMB is unlikely to be as useful as a 40% efficacious VMB, unless the
show that, for a product of poor to moderate efficacy, or if initial condom use is亚 to a potentially less effective microbicide and assumed the same adherence with RMB and VMB. Condom substitution can worsen the HIV epidemic if it is frequent, especially with product of poor to moderate efficacy, or if initial condom use is high prior to the VMB introduction.27 28 31 56 Given that condom use is sometimes less frequently reported during AI than V1, a RMB may have the additional advantage of minimising the risk of condom substitution especially in populations with high rates of condom use during VI (eg, FSWs with commercial clients).57 58 On the other hand, a coital topical RMB may be used less frequently than a VMB because AI may not always be planned. However, adherence could be improved with slow release RMB and especially with bi-compartmental RVMB since they would only need to be applied vaginally to protect during AI.53 In the CAPRISA-004 trial, the gel needed to be applied 12 h before and after each sex act, which may have protected during multiple sex acts during this 24 h window period.5 The measurable effectiveness of tenofovir in the CAPRISA-004 trial may also be due to the fact that very few women reported AI or perhaps (although premature to conclude) because the gel also protected during AI, despite being vaginally applied.

The precision of our model predictions is limited because available estimates of HIV risk during URAI and UIAI are imprecise and because many studies report the proportion of individuals who ever engaged in AI over fixed time periods but do not report the frequency of unprotected AI and VI, which is required to more precisely assess the future role of RMB and VMB in specific populations.12 Ideally information on AI should
be collected using interviewing techniques to reduce social desirability bias. In our model, we have assumed random mixing between those who practice and do not practice AI. Data on mixing patterns, that is, who is having AI with mixing between those who practice and do not practice AI.

A RMB can prevent more infections than an equally efficacious VMB, despite being used in fewer sex acts under a wide range of plausible assumptions.

Considering realistic level of anal intercourse frequency is as important as considering realistic coverage when assessing the potential impact of microbicide interventions.

More precise data on the frequency of anal intercourse is required to better understand the preventive role of RMB/RVMB against HIV in different heterosexual populations and risk groups.

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Declining interest and the developing world: AIDS post-2000

In the new century, anxieties about AIDS-related stigma moved to the developing world due to the fact that the condition was now relatively treatable in the West. One article sought to explain the reason for this. Why do 95% of the estimated 33 million people infected with HIV live in the developing world? And why are low income (gross domestic product, unequal distribution of wealth [...] and sex inequality strongly associated with HIV prevalence? It may be argued that this confluence is coincidental. The maturity of the epidemic, different sexual practices, or biology explain why sub-Saharan Africa is home to the highest HIV rates. The same article challenged the implicit connection between HIV rates and poverty: ‘clearly there is no simple equation of poverty and HIV prevalence; rather a combination of conditions making a population susceptible to the HIV epidemic and vulnerable to its effects’.

Reporting on AIDS in South Africa sought to investigate the link between stigma towards AIDS and testing for the disease: ‘Results showed that individuals who had not been tested for HIV held significantly greater AIDS related stigmas than individuals who had been tested. People who had not been tested were significantly more likely to agree that people with AIDS are dirty, should feel ashamed, and should feel guilty.’ This showed perhaps that a lack of awareness of the disease fostered a harsher view. This is backed up by the evidence from the article that ‘for people who had been tested, there were no significant differences between those who knew their results and those who did not know their test results on AIDS stigmatising beliefs.’

The viewpoint that AIDS was most prevalent in homosexual relationships continued to decline. A letter from 2008 reported that ‘transmission of HIV is at a record level and heterosexual intercourse is the most commonly reported mode of transmission.’ The same letter also recorded the worry that knowledge about HIV/AIDS had fallen due to the decline in media interest in the subject when compared with the 1990s: ‘Commentators have noted television coverage of AIDS has declined as the progression of the AIDS epidemic has fallen from media interest.’ The paradox is that the more the disease is brought into the public eye for prevention, the more potential there is to fuel stigma.

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