ORIGINAL ARTICLE

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 than 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 RR₉₅₋₅₀ = 4–20. A RMB is as useful as a VMB (ie, break-even) in populations with 5% AI if RR₉₅₋₅₀ = 20 and in populations with 15%-20% AI if RR₉₅₋₅₀ = 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 RR₉₅₋₅₀ = 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 Africa.⁵,⁶ (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.⁶⁻⁹

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.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.²⁵ ²⁶⁻³⁰ However, none have investigated the potential impact of RMB or RVMB in heterosexual population.²¹

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...
Table 1 Summary of CAPRISA-004 trial results—HIV protection after 30-month follow-up\(^5\)

<table>
<thead>
<tr>
<th>Effectiveness (95% CI)</th>
<th>Adherence</th>
<th>Crude efficacy*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intention to treat</td>
<td>39% (6 to 60)</td>
<td>72%</td>
</tr>
<tr>
<td>Per protocol</td>
<td>41% (7 to 63)</td>
<td>NA</td>
</tr>
<tr>
<td>Adjusted</td>
<td>37% (6 to 58)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Subanalysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>43% (5 to 67)</td>
<td>NA</td>
</tr>
<tr>
<td>Urban</td>
<td>26% (1 to 67)</td>
<td>NA</td>
</tr>
<tr>
<td>High gel adherence</td>
<td>54% (4 to 80)</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>Medium gel adherence</td>
<td>38% (1 to 67)</td>
<td>50%–80%</td>
</tr>
<tr>
<td>Low gel adherence</td>
<td>28% (1 to 64)</td>
<td>&lt;50%</td>
</tr>
<tr>
<td>At 12-month follow-up</td>
<td>50%</td>
<td>NA</td>
</tr>
<tr>
<td>At 24-month follow-up</td>
<td>40%</td>
<td>NA</td>
</tr>
</tbody>
</table>

*The observed effectiveness in trials reflects the combination between the real (unmeasured) efficacy of the microbicide and the adherence to the product. Based on the information available, we can crudely estimate the ‘true’ efficacy as the observed effectiveness divided by the observed adherence. The overall adherence during the trial was 72%, which means that the true efficacy could be around 54%, which is similar to the trial effectiveness estimate among high adherers.

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.\(^25\) 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 acquisition, the fraction of all sex acts, which are anal (\(a\)) and vaginal (1−\(a\)), 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 (\(Y_{VMB}\)) or/and anal (\(Y_{RMB}\)) 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 (STI efficacy) during AI or VI.\(^32\) Microbicide use can reduce susceptibility (acquisition) to HIV infection of uninfected women or reduce the infectiousness (transmission) of infected women to their male partners.\(^3\) In the CAPRISA-004 trial, the vaginal use of tenofovir 1% gel significantly reduced HIV incidence among women but did not reduce the viral load of VMB users who seroconverted. No drug resistance due to VMB use was observed during the trial.\(^5\) 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.\(^5\) 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 \(E_{VMB}, E_{RMB} \) and \(E_{RVM}\), 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 \(k_1\) (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 \(k_1\) influences how fast it is achieved. We defined a fast \((k_1=k/2)\) and a slow roll-out \((k_1=k/2)\). 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 35% (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 (\(RR_{RAI}=4\) to 20) (online Appendix C) are based on meta-analyses of observational studies.\(^12\)\(^13\)\(^14\) 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 (\(RR_{IAI}\)) compared with insertive VI. Fewer studies report data on AI frequency than on the fraction of individuals who ever practiced AI.\(^12\) Overall, 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.\(^31\) 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 59%, 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\(^49\) (table 1). Using this information, we predominantly explored efficacy around 30%, 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...
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 epidemic scenarios (CFP) following the start of the intervention. We report the fraction of new HIV infections prevented over the period $[0,T]$. The usefulness of RMB compared with VMB for women practicing AI was assessed by the break-even RMB efficacy ($E^{\text{break-even}}_{\text{RMB}}$) (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$^p$; 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 ($E_{\text{RMB}}$) and VMB ($E_{\text{VMB}}$), the frequency of AI ($a$) and the increase in HIV risk during RAI ($RR_{\text{RAI}}$) compared with the risk during receptive VI

### Table 2 Parameters and ranges

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Parameter values</th>
<th>Ranges</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_m$</td>
<td>HIV acquisition risk for men per unprotected vaginal act</td>
<td>0.0021–0.0068*</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>$\beta_w$</td>
<td>HIV acquisition risk for women per unprotected vaginal act</td>
<td>0.0019–0.0046*</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>$1/\mu$</td>
<td>Average time to remain sexually active</td>
<td>30–40 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$d$</td>
<td>HIV-related mortality rates</td>
<td>1/12–1/7</td>
<td>33 34</td>
<td></td>
</tr>
<tr>
<td>$n_{sw}, n_{sm}$</td>
<td>Average number of sexual acts per year for women and men</td>
<td>50–150</td>
<td>17 28 35–37</td>
<td></td>
</tr>
<tr>
<td>$\rho$</td>
<td>Average number of sexual partners per year for women and men</td>
<td>0.5–2</td>
<td>16 18 26 35 38 39</td>
<td></td>
</tr>
<tr>
<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>
<td></td>
</tr>
<tr>
<td>$\alpha_c$</td>
<td>Condom efficacy per act</td>
<td>0.80–0.95</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>$RR_{\text{RAI}}$</td>
<td>Relative HIV acquisition risk per receptive anal act compared with receptive vaginal act</td>
<td>2, 4, 10, 20</td>
<td>10–14</td>
<td></td>
</tr>
<tr>
<td>$\gamma_{\text{VMB}}, \gamma_{\text{RMB}}$</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 1†</td>
<td></td>
</tr>
<tr>
<td>$E_{\text{VMB}}$</td>
<td>VMB efficacy: reduction in susceptibility per vaginal act</td>
<td>30%, 50%, 75% and between 15% and 90%</td>
<td>Table 1†</td>
<td></td>
</tr>
<tr>
<td>$E_{\text{RMB}}$</td>
<td>RMB efficacy: reduction in susceptibility per anal act</td>
<td>30%, 50%, 75% and between 15% and 90%</td>
<td>Table 1†</td>
<td></td>
</tr>
</tbody>
</table>

### Notes

*80% CI of the pooled estimate.13†Ranges uniformly sampled.

*subscript w, women; subscript m, men; superscript p, microbicide user; RAI, receptive anal intercourse; IAI, insertive anal intercourse.

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**Break-even efficacy ($E^{\text{break-even}}_{\text{RMB}}$)**

The usefulness of RMB compared with VMB for women practicing AI was assessed by the break-even RMB efficacy ($E^{\text{break-even}}_{\text{RMB}}$) (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$^p$; 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 ($E_{\text{RMB}}$) and VMB ($E_{\text{VMB}}$), the frequency of AI ($a$) and the increase in HIV risk during RAI ($RR_{\text{RAI}}$) compared with the risk during receptive VI.
(βw); it is independent of the men increased in HIV risk during IAI (RRRAI), coverage and adherence as long as it is equal for both products.

\[
E_{\text{break-even}} = \left[ 1 + \frac{E_{\text{VMB}}\beta_w}{1 - \beta_w} \right] \frac{1}{(1 - \beta_w)^d - 1}\left( \frac{1}{RRRAI\beta_w} - 1 \right)
\]

Equation 1

RESULTS

Population-level impact of VMB by coverage level

Figure 1A shows the fraction of female MB user (coverage) under different uptake and roll-out assumptions. With 50% uptake and slow roll-out, 25% and 40% of women use the MB after 1 and 25 years, respectively (low coverage). With 100% uptake and fast roll-out, all women immediately use MB (optimistic coverage). Figure 1B–D shows the cumulative fraction of new HIV infections prevented (CFP) over time following the MB introduction. Under optimistic coverage, a 50% efficacious VMB, used in 75% of sex acts in populations without AI, is expected to prevent 35% (90% UI: 33–36%) and <3% new HIV infections in the first year among women and men, respectively (figure 1B). However, the difference between men and women reduces over time solely due to ‘herd effects’ (ie, men are indirectly protected by female users) since the microbicide does not reduce the infectiousness of HIV-positive females. As expected, the VMB impact is reduced if coverage decreases (figure 1C). With fast roll-out, the 25-year total (men and women combined) CFP reduces from 33% (90% UI: 27–42) to 25% (90% UI: 20–32) and to 17% (90% UI: 13–23), respectively, when uptake decreases from 100% to 75% and to 50% (figure 1C). Over 10 years, only 8% (90% UI: 7–9%) total HIV infections are prevented with low coverage (slow roll-out, 50% uptake).

Loss in VMB population-level impact due to AI

Under optimistic coverage, the median total 25-year CFP reduces from 35% in populations without AI to 27%, 21% and 15% in populations with 5% AI if RRRAI=4, 10 and 20, respectively (figure 1D). Thus, levels of only 5% AI could produce the same loss in VMB impact than a 25%–50% reduction in uptake (figure 1C).

Relative population-level impact of RMB and VMB

Figure 2A–D compares the total 10-year CFP of a VMB and RMB for different efficacy, adherence, AI frequency and RRRAI, under optimistic coverage. VMB impact reduces rapidly 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 RRRAI=4 or ~36%, ~55% and ~75% if RRRAI=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 RRRAI=10 (figure 2D) or 10% AI if RRRAI=4 (figure 2C). Alternatively, if RRRAI=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
A VMB is expected to prevent the same fraction of infections in populations with 20% AI if RR RAI = 4 (figure 2A,C) or in populations with approximately 10% AI if RR RAI = 10 (figure 2B,D).

**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 RR RAI. However, the incremental benefit of a RVMB compared with a single VMB (RMB) increases (decreases) with the frequency of AI or RR RAI. For example, the 10-year CFP of a bi-compartmental RVMB is 1.2- or ∼6-fold larger than a single VMB or a RMB, respectively, in populations with 5% AI if RR RAI = 4 (figure 3A) but it is twofold larger than for single VMB or RMB in population with 10% AI if RR 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 RR RAI (online Supplement figure S2).

**Usefulness of RMB to protect women practicing AI**

Figure 4 shows the minimum, or break-even, efficacy (E_{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 RR 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 RR RAI = 1. When the AI frequency is between 5% and 20%, the break-even efficacy strongly depends on RR RAI. For example, 40% efficacious RMB and VMB are equally useful in populations with 5% AI if RR RAI = 18, with 10% AI if RR RAI = 8 or with a 20% AI frequency if RR RAI = 4. In many instances (eg, a = 7.5% if RR RAI > 16, a = 10% if RR 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 dynamical model (A), where we assume an adherence of 75% efficacious than the VMB (ie, $R_{RVMB}$), without AI, under the same conditions of use, a VMB would have to be 75% efficacious in populations with 5% AI if $R_{RAI}$ = 10 (figure 2). A RVMB may be approximately twofold more effective than a RMB or VMB in populations with >10% AI and $R_{RAI}$ = 10 (figure 3). Thus, a dual protection seems a desirable MB characteristic.

We showed that AI can reduce the impact of VMB to the extent that RMB can become as useful as VMB, for a wide range of plausible AI and $R_{RAI}$—despite being used in much fewer sex acts overall than a VMB (figures 2 and 4). Our break-even efficacy analysis suggested that, in many instances when both products are used as frequently, even a slightly less efficacious RMB could be more useful than a VMB, especially in populations with >15%–20% AI. Below this, the relative (incremental) benefit of RMB (RVMB) compared with VMB strongly depends on the $R_{RAI}$ assumed.

In this analysis, we explored various VMB coverage and adherence scenarios. Although the optimistic coverage will likely overestimate the potential impact of a microbicide intervention, especially on the short to medium term, they are unlikely to influence the relative comparison between RMB, VMB, and RVMB. The optimistic scenario helps to appreciate the maximum impact that a MB with fixed efficacy can have and to determine the very minimum MB efficacy required to be useful. For example, a 50%–45% RVMB would have a modest impact if adherence was <50% even under optimistic coverage (online Supplement figure S2). Adherence is an important determinant of the potential success of microbicide interventions. Although overall gel adherence in the CAPRISA-004 trial was high at 72%, this may overestimate the potential achievable adherence level in populations in real-life setting. How often a microbicide will be used will depend, among others things, on the delivery system (eg, coital or daily gel or slow release ring), individual preferences, availability, acceptability and cost of the product.

We did not investigate the potential impact of condom substitution, where women switch from more effective condom 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. Given that condom use is sometimes less frequently reported during AI than VI, 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). 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. 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. 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. 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 those who do not practice AI. Data on mixing patterns, that is, who is having AI with whom, would also be valuable to better understand the contribution of this high-risk practice to heterosexual HIV epidemic.

Our results suggest that even low AI frequency can seriously compromise the impact of VMB interventions. The development of RMB and bi-compartmental RVM is essential HIV prevention among heterosexual populations.

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**Competing interests** None.

**Contributors** M-CD and DD designed the analysis. DD developed the model and performed the simulations. D-CD and M-CD analysed the results. M-CD drafted the first version of the manuscript. BM and SS provided input on different MB trial results. All authors helped with the parameterisation of the model, interpretation of the results and revised all drafts.

**Provenance and peer review** Commissioned; externally peer reviewed.

**REFERENCES**


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

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