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Estimating the public health impact of the effect of herpes simplex virus suppressive therapy on HIV-1 plasma viral load

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Abstract

Objective—Trials of herpes simplex virus (HSV) suppressive therapy among HSV-2/HIV-1 infected individuals have reported an impact on plasma HIV-1 viral loads (PVLs). Our aim was to estimate the population-level impact of suppressive therapy on female-to-male HIV-1 sexual transmission.

Design and methods—By comparing prandomization and postrandomization individual-level PVL data from the first two HSV suppressive therapy randomized controlled trials in sub-Saharan Africa, we estimated the effect of treatment on duration of asymptomatic infection and number of HIV-1 transmission events for each trial.

Results—Assuming that a reduction in PVL is accompanied by an increased duration of HIV-1 asymptomatic infection, 4–6 years of HSV suppressive therapy produce a 1-year increase in the duration of this stage. To avert one HIV-1 transmission requires 8.8 [95% confidence interval (CI), 5.9–14.9] and 11.4 (95% CI, 7.8–27.5) women to be treated from halfway through their HIV-1 asymptomatic period, using results from Burkina Faso and South African trials, respectively. Regardless of the timing of treatment initiation, 51.6 (95% CI, 30.4–137.0) and 66.5 (95% CI, 36.7–222.6) treatment-years are required to avert one HIV-1 infection. Distributions of set-point PVL values from sub-Saharan African populations suggest that unintended adverse consequences of therapy at the population level (i.e. increased HIV-1 transmission due to increased duration of infection) are unlikely to occur in these settings.

Conclusion—HSV suppressive therapy may avert relatively few HIV-1 transmission events per person-year of treatment. Its use as a prevention intervention may be limited; however, further research into its effect on rate of CD4 cell count decline and the impact of higher dosing schedules is warranted.

Keywords

acyclovir; HIV; herpes simplex virus type 2; suppressive therapy; transmission; valacyclovir; viral load

Introduction

Epidemiological and biological evidences show that herpes simplex virus type 2 (HSV-2) infection enhances acquisition of HIV-1 and may also increase levels of genital and plasma HIV-1 RNA within coinfecting individuals and hence increase transmission of HIV-1 in populations [1-6]. It is, therefore, reasonable to assume that HSV suppressive therapy may reduce transmission of HIV-1 in populations with high prevalence of both viruses [7].

Recent randomized placebo-controlled trials (RCTs) have quantified the effect of HSV suppressive therapy on the HIV-1 infectiousness of dually HSV-2/HIV-1 positive individuals [8-15]. The first two trials from sub-Saharan Africa reporting the effect of 3-month HSV suppressive therapy on plasma HIV-1 viral loads (PVLs) were parallel-arm RCTs among dually HIV-1/HSV-2 seropositive women ineligible for HAART in Burkina Faso ($n=140$ [9]) and South Africa ($n=300$ [8]). Both reported significant reductions in mean PVL [0.53 $\log_{10}$ copies/ml, 95% confidence interval (CI), 0.35-0.72 using valacyclovir 500 mg twice daily (b.i.d.) [9] and 0.34 $\log_{10}$ copies/ml, 95% CI, 0.15-0.54 using acyclovir 400 mg b.i.d. [8]]. These trials also reported significant reductions in genital HIV-1 and HSV-2 shedding frequency and viral loads [8,9]. Three cross-over trials involving intense follow-up of male and female participants in Peru and Thailand and using valacyclovir or high dose acyclovir (800 mg b.i.d.) also reported significant reductions in PVL (0.26 $\log_{10}$ copies/ml, 95% CI, 0.19-0.33 [14]; 0.43 $\log_{10}$ copies/ml, 95% CI, 0.29-0.56 [15]; and 0.33 $\log_{10}$ copies/ml, 95% CI, 0.23-0.42 [13]) as well as significant reductions in rectal and cervicovaginal HIV-1 RNA concentrations [13-15].

By reducing both genital and plasma HIV-1 viral loads, HSV suppressive therapy is likely to reduce infectiousness of HIV-1, as PVL is highly correlated with risk of HIV-1 transmission [16,17]. In addition, reduced PVL may increase life expectancy by decreasing the rate of CD4 cell count decline during the asymptomatic period of HIV-1 infection [18,19], thus delaying the point at which HAART should be initiated. However, this reduced infectiousness may be offset by an increased duration of infection, providing more opportunity for transmission, although at a lower rate. In this study, we translate results of the first two African HSV therapy trials [8,9] into number of potential HIV infections averted by HSV suppressive therapy.

Methods

We assessed the population-level impact of HSV suppressive therapy on HIV transmission by estimating the transmission potential of each HIV-1 infected individual as described by Fraser *et al.* [20]. For the asymptomatic period of HIV-1 infection, the transmission potential is defined as the product of infectiousness and the duration of asymptomatic infection, that is, the mean number of persons that one index case can infect over their whole asymptomatic period, estimated as a function of set-point PVL (defined as the PVL steady state reached after the peak PVL in early infection and before progression to AIDS).

The concepts we explore are illustrated in Fig. 1 that shows duration of asymptomatic HIV infection, HIV transmission rate and HIV transmission potential against set-point PVL (using functions reported by Fraser *et al.* [20]) and changes in these properties for two

illustrative HIV-infected individuals when they start HSV suppressive therapy. At some point during asymptomatic infection, therapy may be initiated and, we hypothesize, be accompanied by a drop in set-point PVL (Fig. 1a). We assume that this drop increases each individual's projected duration of infection (Fig. 1b) and decreases their infectiousness (Fig. 1c). We further assume that HSV-2 infection always precedes HIV-1 infection, as a simplifying assumption and to estimate maximum impact of HSV suppressive therapy. Figure 1d illustrates that the combined effect on transmission potential (i.e. number of onward HIV transmission events over each individual's asymptomatic period) depends on their original set-point PVL. The impact on individuals with high set-point PVL is to increase transmission potential, whereas the opposite is true for those with lower set-point PVL. Therefore, the public health impact of interventions reducing PVL by a moderate amount depends on the distribution of set-point PVL within the population.

Plasma HIV-1 viral load data

There are limited data linking viral load measures to HIV-1 infectiousness. Although a focus of the two African trials was the impact of therapy on genital HIV-1 RNA, to our knowledge, there are no data that quantify the risk of ongoing HIV-1 transmission by frequency or quantity of genital HIV-1 RNA for female-to-male HIV-1 transmission. We, therefore, use PVL data rather than genital viral load to estimate infectiousness.

We used data on PVL preintervention and postintervention from the Burkina Faso and South African trials [8,9] to estimate the potential change in infectiousness and change in duration of asymptomatic infection that each woman may experience if started on indefinite HSV therapy. This analysis is restricted to participants with a measurement available from the end of the study period (12 weeks). Details of the laboratory methods used for quantifying PVL for each study are provided as Supplementary Digital Content (see document and figures, Supplemental Digital Content 1, 2 and 3).

Quantifying reduction in plasma HIV-1 viral loads with herpes simplex virus suppressive therapy

We examined individual-level data from the two trials to investigate whether the reduction in PVL varied with prerandomization (baseline) PVL. Two and three prerandomization PVL measurements were taken from study participants in South Africa and Burkina Faso, respectively. For purposes of comparison between studies, we used the baseline measurement taken closest to the time of randomization. Those with undetectable PVL were assigned a value of half the detection threshold of the assay (detection thresholds of 300 and 50 HIV-1 RNA copies/ml for Burkina Faso and South Africa, respectively). Analysing changes in PVL in the two trials suggested a reduction in PVL among treated participants for all levels of baseline PVL recorded (except very low levels, $<3.0 \log_{10}$ copies/ml, in which any further reduction in PVL is unlikely to be detected) but no such decrease among controls (see document and figures, Supplemental Digital Content 1, 2 and 3). Therefore, we estimate the effect of suppressive therapy on HIV-1 transmission using data from the treatment arms only.

Translating plasma HIV-1 viral loads into estimates of infectiousness and duration of asymptomatic infection

We followed the approach taken by Fraser *et al.* [20]. Briefly, the risk of HIV-1 transmission per year, stratified by PVL of the index case, is quantified using data from a Zambian cohort [16]. To translate PVL data of each RCT participant, V , into an estimate of their infectiousness, defined as the transmission rate (number of HIV-1 transmission events per HIV-1 infected individual per year) $\beta(V)$, the following logistic function is used:

$$\beta(V) = \frac{\beta_{\max} V^{\beta_k}}{V^{\beta_k} + (\beta_{50})^{\beta_k}} \quad (1)$$

where $\beta_{\max}$, the maximum infection rate per annum, is 0.317 per year; β_{50} , the PVL at which infectiousness is half its maximum, is 13 938 copies/ml and β_k , the steepness of the increase in infectiousness as a function of PVL is 1.02.

A logistic function is also used to estimate the mean duration of the asymptomatic period of HIV-1 infection as a function of PVL using data from the Amsterdam Seroconverters Cohort and allows for variability in the duration, given set-point PVL [20]. The Amsterdam Seroconverters Cohort prospectively recruited homosexual men from 1982 onwards; the cohort has been described elsewhere [19]. The PVL of each RCT participant, V , is translated into an estimate of their duration of asymptomatic infection, $D(V)$, using:

$$D(V) = \frac{D_{\max} (D_{50})^{D_k}}{V^{D_k} + (D_{50})^{D_k}} \quad (2)$$

where $D_{\max}$, the maximum duration of asymptomatic infection, is 25.4 years; D_{50} , the PVL at which the duration is half its maximum, is 3058 copies/ml and D_k , the steepness of the decrease in duration as a function of PVL, is 0.41.

Calculating HIV-1 infections averted

Each intervention arm participant's transmission potential (number of transmission events during their entire duration of asymptomatic infection) was calculated as the product of their transmission rate and duration [from equations (1) and (2)] for their baseline PVL and similarly for their PVL at the end of the trial. The number of infections averted is the difference between them. This assumes that suppressive therapy starts at the beginning of asymptomatic infection; therefore, alternative scenarios in which treatment starts at different points during the incubation period were also explored. A bootstrap sampling method was used to derive 95% confidence bounds for each outcome [21].

Results

The number of study participants randomized to the intervention and control arms was 68 and 68 for Burkina Faso and 152 and 148 for South Africa, respectively. For the Burkina Faso (South Africa) trial, 62 (132) from the treatment and 63 (135) from the control arm had PVL measurements recorded at the end of the 3-month follow-up and were included in our analysis. For Burkina Faso, 61 intervention and 60 control arm participants had a baseline PVL measurement at the time point closest to randomization. The remaining four participants in the trial (one in treatment, three in control arms) had measurements recorded at 3 weeks prerandomization. For South Africa, one control arm participant with a PVL measurement at study end had no measurement at the time point closest to randomization; her measurement recorded at her previous baseline visit (1 week before) was used.

Figure 2 shows distribution of PVL among women in the Zambian study that links PVL to infectiousness (Fig. 2a, [16]), transmission potential by set-point PVL (Fig. 2b) and the distribution of PVL for study participants in the two African trials (Figs. 2c-f, [8,9]). The Zambian data show women only to make it comparable with the trials because there may be differences in PVL distributions between women and men [22,23]. This distribution is skewed because of the selection of nontransmitting partners for this discordant couple study. Burkina Faso study participants at baseline had a similar PVL distribution to those from

Zambia (mean PVL 4.4 and 4.5 $\log_{10}$ copies/ml, respectively), whereas those from South Africa were slightly lower (mean 3.9 $\log_{10}$ copies/ml). However, both trials recorded more frequent undetectable PVL measurements than the Zambian study (Figs. 2a,c,e). This may partly be due to greater immunosuppression among the Zambian cohort [$>80\%$ of participants had CD4 cell count <400 cells/ μ l compared with a median 446 (range 334-628) cells/ μ l for Burkina Faso and 475 (251-1382) cells/ μ l for South Africa]. Figures 2d and f illustrate the shift in distribution of PVL for the treatment arms after 3 months, with no such shift apparent for the control arms (Figs. 2c and e). The highest frequency PVL group for the controls before and at study end is close to the level at which transmission potential is predicted to peak.

Impact of treatment on infection duration and transmission: results for study participants

Table 1 shows estimated benefits of HSV suppressive therapy based on the duration of asymptomatic infection in the two trial populations. Greater benefits are produced the earlier that therapy is initiated in HIV-1 infection. A maximum increase in duration of asymptomatic infection of 2.8 years using Burkina Faso data and 1.9 years using South African data was estimated if therapy was initiated at the beginning of asymptomatic infection. The duration of therapy required to gain one HAART-free year extension to the asymptomatic period was independent of time at which therapy was initiated and was estimated as 4.2 years (95% CI, 2.5-8.6) using Burkina Faso data and 6.2 years (95% CI, 3.4-14.6) using South African data.

Table 1 also shows the impact of HSV suppressive therapy on number of infections averted. Unless therapy was initiated very early in infection and continued throughout the asymptomatic period, that is, for more than a decade, relatively few HIV-1 infections could be averted per woman treated. To avert one HIV-1 transmission to a sexual partner of an HSV-treated woman requires 8.8 (95% CI, 5.9-14.9) and 11.4 (95% CI, 7.8-27.5) women to be treated from halfway through their HIV-1 asymptomatic period, predicted using Burkina Faso and South African data, respectively. If therapy can be initiated at the beginning of asymptomatic infection, these figures reduce to 4.4 (95% CI, 3.0-7.5) and 5.7 (95% CI, 3.9-13.8), respectively. There was a linear relationship between time on treatment and benefits achieved; therefore, regardless of the timing of treatment initiation, 51.6 (95% CI, 30.4-137.0) and 66.5 (95% CI, 36.7-222.6) treatment-years are required to avert one HIV-1 infection using Burkina Faso and South African data, respectively.

Impact of herpes simplex virus suppressive therapy on HIV-1 transmission: generalized results

Figure 3 illustrates the effect on number of onward HIV-1 transmission events if therapy was administered to a hypothetical population of 1000 HSV-2/HIV-1 dually seropositive individuals, by mean set-point PVL (assumed normal distribution, SD, $n=1$) if the reduction in PVL through suppressive therapy was as predicted for Burkina Faso or South African trial data, respectively. All populations with a mean set-point PVL less than about 4.75 $\log_{10}$ copies/ml are likely to experience a net beneficial effect of an intervention such as this, which produces a modest reduction in PVL. Mean PVL for the trials' data and Zambian dataset, as well as data from Uganda for HSV-2-seropositive individuals [24], illustrates that HSV-2-infected populations in Africa are likely to have distributions in PVL that would result in a positive impact of HSV suppressive therapy. The largest relative benefit of HSV suppression would occur among populations with modestly low (around median 3.5 $\log_{10}$ copies/ml, Fig. 3) mean PVLs because it is at this point that changes in PVL have the greatest impact on transmission potential (shown by the steepest gradient of the curve in Fig. 2b).

Discussion

Our analysis suggests that if HSV suppressive therapy reduces PVL of HIV-1/HSV-2-positive individuals as demonstrated by the first two African trials, it would reduce HIV-1 transmissions and increase the duration of asymptomatic HIV-1 infection, although by modest amounts. We estimate that treating between nine and 11 HSV-2/HIV-1-infected individuals, starting therapy halfway through asymptomatic HIV-1 infection, would avert one HIV-1 infection. This compares favourably with the impact of male circumcision, in which an estimated five to 15 surgeries would avert one HIV-1 infection over 10 years (Hankins *et al.* manuscript in preparation). This is partly due to the use of suppressive therapy to prevent transmission rather than acquisition: there is no 'wastage' of the intervention on those who will never be exposed to HIV-1 (the effect of HSV suppressive therapy on reducing acquisition of HIV-1 among HSV-2-positive/HIV-1-negative women has recently been investigated by two RCTs but no effect was observed [25,26]). Results of the partners in prevention (PiP) study, following over 3400 HIV-1-discordant couples, will provide the first empirical data examining whether HSV suppressive therapy reduces HIV-1 transmission (www.clinicaltrials.gov NCT00194519).

Although time from HIV-1 acquisition to symptomatic infection is longer for individuals with lower PVL [27], an intervention decreasing PVL in order to increase the duration of asymptomatic infection has not been previously assessed. Historical studies [28] using high-dose acyclovir suggested moderate improvements in survival, although these typically treated patients with late stage rather than asymptomatic infection. The potential of HSV therapy to reduce the rate of CD4 cell count decline and thus increase the time before starting HAART has important implications for HIV-1 patient management. PiP may have sufficient power to detect such an effect, which is also currently being investigated in Rakai, Uganda (www.clinicaltrials.gov NCT00405821), although many study participants started therapy while already at relatively late stage infection. To investigate impact for early HIV-1 infections, an ancillary study [25] to the recent HPTN039 HSV suppressive therapy HIV-1 acquisition RCT is maintaining HIV-1 seroconverters on their trial regimens (acyclovir or placebo) to investigate whether treatment alters HIV-1 set-point up to 6 months.

In contrast to the positive results from the two trials used in this analysis, a subsequent RCT among women in Tanzania reported no effect of acyclovir 400 mg b.i.d. on genital HIV-1 RNA and HSV-2 DNA [10] at 6 or 12 months, whereas an RCT in Zimbabwe found no effect on genital HIV-1 RNA but an impact on genital HSV-2 DNA [odds ratio (OR), 0.24; 95% CI, 0.12-0.48] at 3 months [11]. Possible explanations for the varied findings include different durations of follow-up, drug regimens and levels of adherence achieved within these high-risk study populations, with lower adherence reported in the Tanzanian and Zimbabwean trials. Our estimate of averting one infection by treating nine to 11 individuals, starting therapy halfway through asymptomatic infection, requires individuals to be treated for approximately 6 years, with adherence continuing at the high levels maintained in the trials, which could be challenging. However, suppressive therapy offers the additional benefits of reducing HSV-2 symptoms and would keep HIV-1-infected individuals within the healthcare system, allowing appropriate timing of HAART initiation, whereas loss of contact and delayed start of HAART would result in poorer prognoses.

Our analysis has a number of limitations. We assume that all partners of the participants are HIV uninfected, so this will overestimate the impact of therapy. Transmission potential was derived from data from discordant couples, which may underestimate infectiousness relating to more casual partnerships. Transmission potential is estimated for a scenario assuming random mixing between partners, which corresponds to a very high partner change rate. Mixing is seldom random, yet random mixing may be more appropriate for estimating

transmission potential for these high-risk women than the other extreme of serial monogamous partnerships. A sensitivity analysis exploring the impact of these assumptions shows that modelling serially monogamous relationships would avert fewer HIV-1 infections with suppressive therapy because the transmission potential of each woman is reduced (see document and figures, Supplemental Digital Content 1, 2 and 3).

We have made the simplifying assumption that by the end of each 3-month trial, the maximum impact of suppressive therapy has been reached, but there was a slight incremental benefit over time in Burkina Faso, which would increase the number of infections averted. However, such an effect may be mitigated if accompanied by waning adherence or if the effectiveness of HSV therapy actually decreases over time (there has been concern over the selection of resistant HIV mutants under the selective pressure of acyclovir *in vitro* [29]).

A recent review of serodiscordant couple studies estimated that the probability of transmitting HIV would increase by 20 and 40% for 0.3 and 0.5 $\log_{10}$ copies/ml increases in PVL, respectively, with a 25 and 44% increased risk of progression to AIDS or death [30]. We believe that the estimated changes in infectiousness and duration of asymptomatic infection used in our analysis are more reliable because x units change in either of these parameters does not change linearly with y units of $\log_{10}$ PVL, as assumed in the review. Our estimates depend not only on the change in PVL but also on the original set-point because a small change in PVL when at high or low levels has less impact than at intermediate PVL (Fig. 1). However, for comparison, using a 'typical' viral set-point value of 4.5 $\log_{10}$ copies/ml (as used by others [31]) and formulas (1) and (2), infectiousness would increase by 18 and 26% and duration of infection before AIDS would decrease by 24 and 44% for 0.3 and 0.5 $\log_{10}$ copies/ml increases in PVL, respectively using our methods, yet these values change substantially for different baseline viral set-points.

Our analysis suggests that although in theory, interventions to reduce PVL could risk the unintended consequence of increasing rather than decreasing overall HIV-1 transmission; this is unlikely to occur among sub-Saharan African target populations. This is because the distribution of set-point PVL is sufficiently low that any reduction in PVL likely moves the population to a lower mean transmission potential. Although the benefits of HSV suppressive therapy as a public health measure are predicted as modest using standard regimens, investigating the effect of higher dosing schedules may be important. Delaying the need to initiate HAART would be of particular value in resource-limited settings, in which demand for HAART will likely continue to outstrip supply.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Schematic diagram illustrating the predicted impact of herpes simplex virus suppressive therapy on duration of asymptomatic HIV-1 infection, HIV-1 transmission rate (hazard of transmission: probability of HIV-1 transmission per year) and HIV-1 transmission potential (product of hazard of transmission and duration of asymptomatic infection) for two hypothetical patients (red and blue). gr1 Time starts at the beginning of each individual's asymptomatic period (i.e. after high PVL accompanying primary infection). The figure shows that all patients experiencing a drop in PVL with therapy would experience increases in duration of asymptomatic infection and infectiousness, but direction of change to transmission potential depends on baseline set-point PVL and reduction in PVL with therapy. HSV, herpes simplex virus; PVL, plasma HIV-1 viral load.

Fig. 2. Distribution of plasma HIV-1 viral loads among women in the Zambian study that links plasma HIV-1 viral load to infectiousness, transmission potential by set-point plasma HIV-1 viral load and the distribution of plasma HIV-1 viral loads for study participants in the two African trials gr2 Comparison of (a) distribution of HIV-1 PVL for female study participants from Zambia participating in an HIV serodiscordant couple study from which transmission rate estimates were calculated ($n=134$) [16]; and (b) transmission potential (onward HIV transmission events during asymptomatic infection) by PVL estimated by Fraser *et al.* [20], with distributions of PVL for the HSV suppressive therapy trials; (c) Burkina Faso control arm ($n=63$); (d) Burkina Faso treatment arm ($n=62$) [9]; (e) South Africa control arm ($n=135$); and (f) South Africa treatment arm ($n=132$) [8]. Mean PVL for women from the Zambian study was $4.51 \log_{10}$ copies/ml [16]. Mean PVL was 4.22 and $4.61 \log_{10}$ copies/ml at baseline and 3.70 and $4.65 \log_{10}$ copies/ml at study end for the Burkina Faso treatment and control arms, respectively. For the South African study, these values were 4.01 and $3.87 \log_{10}$ copies/ml at baseline and 3.66 and $3.92 \log_{10}$ copies/ml at study end, respectively. HSV, herpes simplex virus; PVL, plasma HIV-1 viral load.

Fig. 3.

Change in total number of onward HIV-1 transmission events if herpes simplex virus suppressive therapy was administered to hypothetical populations of 1000 herpes simplex virus type 2/HIV-1 dually seropositive individuals by mean set-point plasma HIV-1 viral load of the population (assumed normal distribution, SD 1). gr3 Estimates for the impact of therapy assuming they effect a 0.53 $\log_{10}$ copies/ml reduction in PVL (Burkina Faso data) or 0.34 $\log_{10}$ copies/ml reduction (South Africa data). For each mean viral set-point value (x-axis), a hypothetical population of PVL values is generated ($n=1000$, drawn from a normal distribution). The reduction in PVL with therapy for each individual is drawn from a normal distribution with the mean reduction in PVL and SD calculated using 95% CIs reported from the two trials. From the two sets of PVLs, transmission potentials were calculated. Plotted are mean HIV-1 PVLs for the study participants of the Burkina Faso and South African trials (both arms, all HSV-2 positive: mean 4.4 $\log_{10}$ copies/ml, SD 0.97 and mean 3.9 $\log_{10}$ copies/ml, SD 1.10, respectively); for women from the Zambia transmission study (HSV-2 prevalence not stated: mean 4.5 $\log_{10}$ copies/ml, SD 0.82); and for a study from Uganda comparing PVL for HSV-2 infected and uninfected individuals (HSV-2 positives only: mean 4.6 $\log_{10}$ copies/ml, SD 0.94). CIs, confidence intervals; HSV, herpes simplex virus; PVL, plasma HIV-1 viral load. [24].

Table 1

Impact of herpes simplex virus suppressive therapy based on results of the two treatment trials in terms of extending the duration of asymptomatic infection and number of HIV-1 infections averted

Point of asymptomatic period at which treatment initiated	[0,2-3]Mean duration on HSV therapy (years)	[0,4-5]Mean increase in duration of asymptomatic infection (years)	[0,6-7]Infections averted ^a	[0,8-9]Number to treat to avert one HIV-1 transmission event
[0,1-9]Burkina Faso trial (95% CI)				
■ Start	11.7	2.8	14.0	4.4
■ 1/4 way	8.8	2.1	10.5	5.9
■ 1/3 way	7.8	1.9	9.3	6.6
■ 1/2 way	5.8	1.4	7.0	8.8
■ 2/3 way	3.9	0.9	4.7	13.3
■ 3/4 way	2.9	0.7	3.5	17.7
[0,1-9]South African trial (95% CI)				
■ Start	11.7	1.9	23.2	5.7
■ 1/3 way	8.8	1.4	17.4	7.6
■ 1/3 way	7.8	1.3	15.5	8.5
■ 1/2 way	5.9	0.9	11.6	11.4
■ 2/3 way	3.9	0.6	7.7	17.0
■ 3/4 way	2.9	0.5	5.8	22.7

CI, confidence interval; HSV, herpes simplex virus.

^a Predicted number of infections averted by treating all 62 (132) women in the intervention arm for the Burkina Faso (South Africa) study.