Sexually Transmitted Diseases, February 2004, Vol. 31, No. 2, p.100–113
DOI: 10.1097/01.OLQ.0000112721.21285.A2

Changes in the Transmission Dynamics of the HIV Epidemic After the Wide-Scale Use of Antiretroviral Therapy Could Explain Increases in Sexually Transmitted Infections

Results From Mathematical Models

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Background: **Recent increases in bacterial sexually transmitted infections (STI) and risk behavior have coincided with the introduction of antiretroviral therapy (ART) in homosexual communities of industrialized countries. The reasons for these increases are not fully understood.**

Goal: **The goal of this study was to understand the various effects of ART on risk behaviors and STI.**

Objective: **The objective of this study was to assess the independent impact of the change in the transmission dynamics of HIV/AIDS as a result of the wide-scale use of ART on a bacterial STI.**

Study Design: **We developed a mathematical model of bacterial STI and treated/untreated HIV/AIDS infection for an open homosexual population. At the individual level, we assume that susceptible and healthy HIV-positive individuals do not increase their risk behavior as a result of ART over time. However, individuals with AIDS, who are successfully treated with ART, can resume sexual activity. The impact of the wide-scale use of ART on risky behavior, STI, and HIV/AIDS was evaluated over a wide range of assumptions on treatment use, ART efficacy, and population characteristics.**

Results: **Over 10 years, 0% to 55% new bacterial STI could be attributed to the wide-scale use of ART as a result of more modest increases (0–25%) in risky sex occurring at the population level rather than at the individual level. These increases have a negative impact on HIV if coverage is too low. Increasing treatment coverage helps to prevent more HIV infections despite larger increases in risky sex and STI that is predicted to ensue.**

Conclusion: **Taking the differential impact of wide-scale use of ART into account helps to interpret recent behavioral and STI trends. Our results have implications for prevention strategies and for the formulation of public health policies. A better understanding of the differential impact of ART on sexual network over time is required.**

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RECENT INCREASES IN SEXUALLY transmitted infection (STI) and risky behaviors have been observed among different homosexual communities in industrialized countries.[1–6] The precise reasons behind these increases, which coincided with the introduction of antiretroviral therapy (ART) and followed large decreases in the early stage of the epidemic, are still not clearly understood.[7–13] Although increases in HIV incidence have only been reported in a few selected communities,[10] it is feared that similar increases in STI and risk behaviors can occur in other populations in which ART is introduced and eventually enhance the spread of HIV.[14–21] The planning of optimal STI and HIV prevention strategies after ART requires a clear understanding of the different ways by which ART can influence sexual behaviors and then impact on STI and HIV/AIDS. Increases in sexual behavior can occur over time at the individual level or at the population level through changes in the distribution in sexual activity as a result of changes in deaths, migration patterns, and others. Epidemiologic studies have shown that aggregate levels of risk behaviors and STI can decline over time as a result of specific AIDS differential mortality and morbidity of high-risk individuals.[22,23] A recent study estimated that increases in AIDS-associated mortality could have accounted for one third to one half of the decline in syphilis rates among men in the early 1990s.[24] It has also been suggested that the recent declines in AIDS mortality and morbidity as a result of ART could have contributed to the recent outbreaks of bacterial STI in the United States among men who have sex with men (MSM).[24–26]

So far, most epidemiologic studies have investigated the role of ART by assuming that increases in risk behavior occur among individuals who perceive themselves at a lesser risk of HIV acquisition or transmission and/or are more optimistic about the disease as a result of ART.[5,7–13] However, results from surveys on knowledge, attitudes, and sexual behavior are contradictory.[7] Factors such as optimism and complacency toward the risk of AIDS as a result of ART can only explain a limited fraction of the changes. These factors are not consistently associated with high-risk behaviors at the individual level.[7,10,11,19,27–32] Most evidence is based on cross-sectional studies and therefore causality cannot be inferred.[9,10,27,33] Furthermore, when an association is found, only a

MCB acknowledges ATPM for financial support. KD thanks FCAR and WT for financial support. FIB is supported by Fiocruz PAPES grant 250.250.122.

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Received for publication June 30, 2003, revised October 8, 2003, and accepted October 21, 2003.

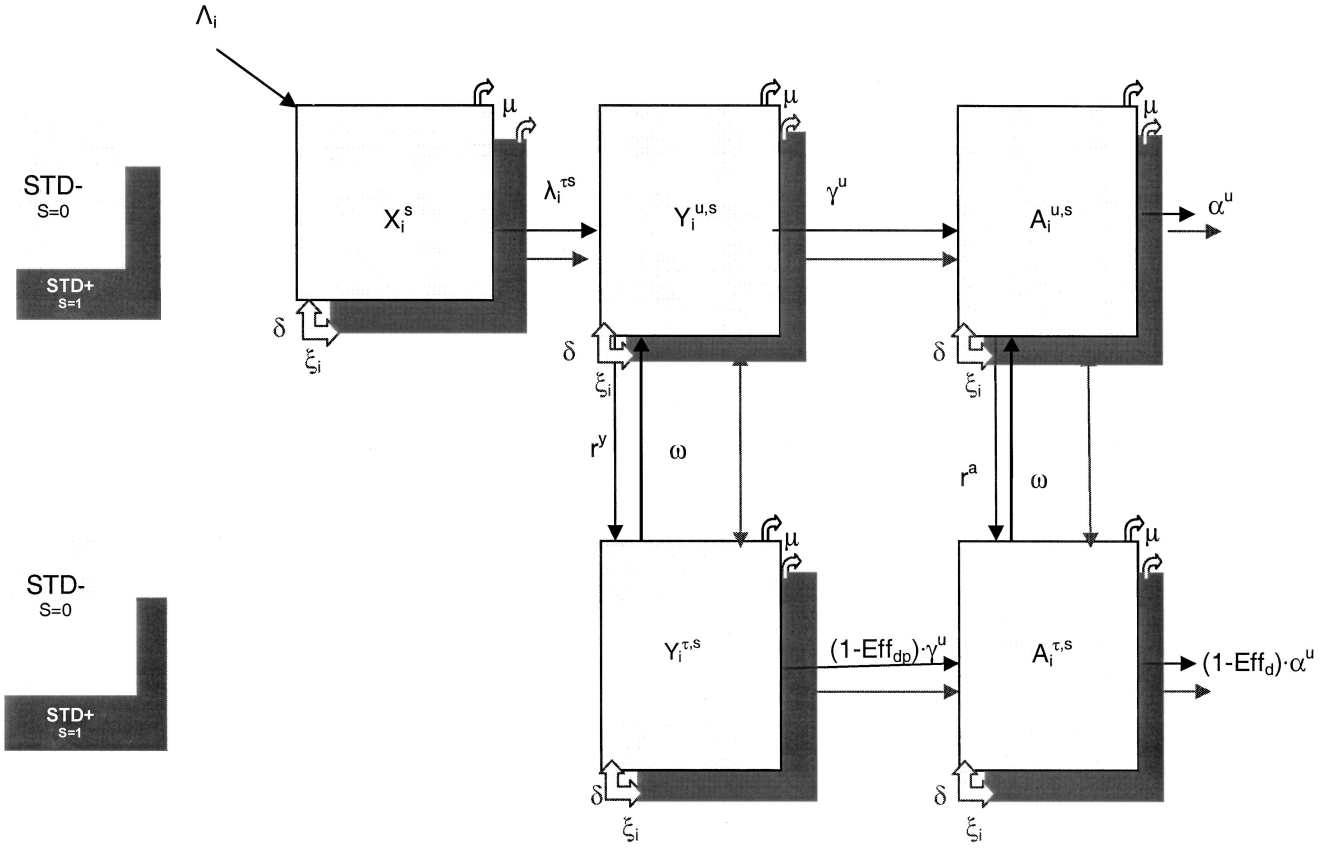

Fig. 1. Flow chart of STI and HIV/AIDS transmission model in the presence of ART (described in "Methods"). X^s_i, $Y^{u,s}_i$, $A^{u,s}_i$, $Y^{\tau,s}_i$, $A^{\tau,s}_i$ represents the number of individuals who are susceptible to HIV infection, untreated HIV+, untreated with AIDS, treated HIV+, and treated with AIDS in risk group i, respectively. Superscript, s = 1 for individuals who are STI+ and s = 0 for individuals who are STI-. Superscripts, u and τ, represent untreated and treated individuals, respectively. The per capita rate of STI and HIV infection of a susceptible individual in risk group i is given by $\xi_i(t)$ and $\lambda_i^{\tau,s}(t)$, respectively. γ^u and α^u are the rate of progression to AIDS and the rate of AIDS mortality, respectively. δ is the recovery rate from the STI infection. Λ_i is the number of new recruits in activity class i ($\Lambda_i = \Lambda \cdot Q_i$). Eff_1, Eff_d, Eff_{dp}, w, and r^a, r^y represents the reduction in HIV infectiousness, reduction in AIDS mortality, reduction in progression to AIDS as a result of ART, withdrawal rate from treatment, and treatment coverage rates of AIDS and HIV-positive individuals, respectively. $1/\mu$ is the average duration of the sexual active life.

small fraction of the population is found to be optimistic or less fearful.[9,11,32]

At the individual level, ART delays disease progression, increases survival, and potentially reduces infectivity by suppressing viral replication among treated HIV-positive individuals.[13–17,34–36] Because ART modifies the natural history of HIV infection, it also modifies the transmission dynamics of HIV/AIDS and therefore has the potential to modify the aggregate level of sexual behavior in an open population. Most studies have studied the impact of individual-level changes in sexual behavior and STI in conjunction with ART on the spread of HIV/AIDS.[16,17,35,36] Instead, we study the impact of the HIV/AIDS epidemic on sexual behavior and STI rates with time after the wide-scale availability of ART. This type of question is very difficult to address directly with epidemiologic studies. Initially, it is best studied with a mathematical model of cocirculating STI and treated/untreated HIV/AIDS infections.

Methods

The mathematical model is specified by a set of differential equations that capture the natural history of a bacterial STI and of untreated and treated HIV/AIDS infection in an open homosexual population with heterogeneous sexual behavior. The bacterial infection modeled is gonorrhea, which was highly prevalent among MSM at the beginning of the HIV epidemic.[2,37–39] There are 2 stages of infection for the bacterial STI (susceptible [STI-], infected [STI+]), 5 stages of infection for HIV/AIDS (susceptible [HIV-], untreated and treated HIV-positive individuals [HIV+], untreated and treated individuals with AIDS [AIDS]) (see Fig. 1 and full mathematical details in Appendix 1). Each year, Λ new uninfected sexually active men (new recruits) join the resident sexually active population. In the absence of AIDS, individuals remain sexually active for an average duration of $1/\mu = 50$ years (from age of sexual debut at 15 years to age 65 when they stop being sexually active).[39–41] The resident sexually active population and new recruits are divided into 6 sexual activity classes i ($i = 1,\ldots,6$) according to a predetermined risky sex distribution, Q_i, assumed constant over time. Each activity class represents a different level of risky sex, m_i (m_i = annual rates of sexual partner acquisition with whom unprotected sex takes place). The mixing between the different sexual activity classes is assumed to be proportionate to the level of sexual activity of each individual (proportionate mixing).

Susceptible individuals get infected with HIV and with the STI

TABLE 1. Biological Parameters in Absence of ART[95–106]

Parameters	Baseline Scenario	References
Duration of STI infectiousness ($1/\delta$ months)	1.7	95–98
STI transmission probabilities per partnership (θ_{ji})	0.90 if i and j = 1,2 0.40 if i or j > 2,. . .,6	95–100
HIV transmission probabilities per partnership (β_{ji})	0.08 if i and j = 1,2 0.02 if i or j >2,. . .,6	50,51,101–103
Duration of HIV infectiousness ($1/\gamma^u$ years)	10	54,56,57,104–106
AIDS survival ($1/\alpha^u$ year)	1	53–57,104–106
Enhancement factors of HIV infectiousness and susceptibility		93,94
With STI (RR^1):	3	
Without STI (RR^0):	1	

STI = sexually transmitted infection.

at a per-capita rate $\lambda_i^{r,s}(t)$ and $\xi_i(t)$, respectively. The rates of infections depend on the level of risky sex (m_i), the mixing between activity classes (ρ_{ij}), the per-partnership HIV (β_{ji}) or STI (θ_{ji}) transmission probability from individual j to partner i, and the prevalence of infection of partners in activity class j (details in Appendix 1). Partnerships involving a higher-risk individual are assumed to be of shorter duration (fewer contacts) than between low-risk individuals. Hence, the per-partnership transmission probabilities β_{ji} and θ_{ji} when one of the partners is from a high-risk class (i or j > 2) are lower than between 2 low-risk partners (i and j = 1 or 2) (see Table 1). The force of HIV infection also depends on the STI status of each partner (s = 1 if STD+ and s = 0 if STD-). Individuals infected with an STI are more susceptible to HIV infection and more likely to transmit HIV infection by a multiplicative factor RR^1. Untreated asymptomatic individuals who are HIV+ progress to AIDS after a long incubation period ($1/\gamma^u$). Untreated individuals with AIDS have a disease-specific mortality rate (α^u) and are assumed to be sexually inactive as a result of the severity of their illness. Individuals who are STI+ recover from their infection at a rate, δ. The values of the biologic parameters are presented in Table 1.

As a result of uncertainty in ART efficacy and variability in treatment practices and diagnostic procedures,[42,43] the impact of ART is assessed for a wide range of parameter values (Table 2). Current Centers for Disease Control and Prevention treatment guidelines recommend treating patients diagnosed with symptomatic HIV disease regardless of plasma viral levels and asymptomatic individuals with <200 CD4+ cells/mm^3. The optimal time to treat asymptomatic patients with >200 CD4+ cells/mm^3 is unknown and also depends on a series of clinical factors.[42] Treatment coverage also depends on diagnostic procedures and access to drugs, which can be difficult even if the drugs are free.[43] Therefore, we assume that treatment can be offered to individuals with AIDS only (AIDS individuals) or to both individuals who are HIV-positive and individuals with AIDS (HIV + AIDS individuals). Here, r^y and r^a represents the treatment coverage rate of individuals who are HIV+ and those with AIDS, respectively. The annual treatment coverage rates (r^a, r^y) of 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, or 0.9 are examined. The effect of ART in treated individuals is modeled by assuming that it slows the rate of disease progression by a fraction, Eff_{dp}.[14–16] It reduces AIDS mortality rate by a fraction, Eff_m, and improves the quality of life of individuals with AIDS to the extent that they resume sexual activity.[7,8,14–16,44,45] It reduces HIV infectiousness by a fraction, Eff_I.[14–16] ART is estimated to reduce seminal plasma HIV-RNA levels by 45% (0.25 log10) to >99% (1.8 log10).[46–49] Each log10 increment in viral load was associated with approximately a 2.0 to 3.5 increase in seroconversion rate.[50,51] However, the exact magnitude of the reduction in infectiousness as a result of ART remains unknown because it has never been shown empirically.[14,15,21,49] Hence, we define pessimistic and optimistic scenarios by assuming that Eff_I = 25% or 99%, respectively, and a moderate one in which Eff_I values of 90%, 80%, 70%, 60%, and 50% are explored. With all 3 scenarios, we look at Eff_m values of 75%, 65%, 55%, 45%, and 35%. Estimates of decreased mortality associated with the use of ART vary between 38% and 75%.[52–56] Estimates of the reduction in disease progression among asymptomatic individuals who are HIV+ vary approximately between 40% to 80%.[52–54,56,57] Therefore, values of Eff_{dp} = 67%, 57%, 47%, 37%, and 27% are explored. Treatment failure and cessation can occur and increases with time as resistance emerges, nontolerance/toxicity develops, and nonadherence increases.[58–63] In a study, antiretroviral-naïve patients had a 22% to 29% and 5% to 10% probability to interrupt current treatment as a result of toxicity

TABLE 2. Range of Treatment Parameter Values Explored

Treatment Parameters	Sensitivity Range	References
Reduction in HIV infectiousness (Eff_I)		46–51
Scenarios		
Optimistic	0.99	
Moderate	0.90, 0.80, 0.70, 0.60, 0.50	
Pessimistic	0.25	
Reduction in progression rate to AIDS (Eff_{dp})	0.67, 0.57, 0.47, 0.37, 0.27	52,54,57
Reduction in AIDS death rates (Eff_m)	0.75, 0.65, 0.55, 0.45, 0.35	53–56
Treatment rate (yr^{-1}) of:		
AIDS only	r^a = 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 and r^y = 0.0	
HIV + AIDS	$r^y = r^a$ = 0.1,. . ., 0.9	
Withdrawal rate (ω yr^{-1})	0.0, 0.1, 0.2, 0.3, 0.4, 0.5	59–63

TABLE 3. Range of Population Parameters Used in the Sensitivity Analysis ([40,70–78])

No. of New Recruits per Year (Λ)		400, 800		
Distribution in Risky Sex				
Risk Group	Proportion per Risk Group	Level of Risky Sex (new partners per year)		
i	Q_i	High m_i	Medium m_i	Low m_i
1	10%	0.2	0.1	0.1
2	15%	2.4	0.5	0.3
3	30%	6.6	1.4	1.1
4	25%	10.3	5.6	1.5
5	15%	20.6	15.5	11.9
6	5%	47.0	61.3	43.9
Mean ($m_{rs}^{No\text{-}ART}$ [0])		10.6	7.3	4.7
Standard deviation ($sd_{rs}^{No\text{-}ART}$ [0])		10.3	13.4	9.8
Initial STI prevalence		5.4%	8.7%*	4.4%

*Initial STI prevalence is highest with the medium level of risky sex distribution. The different distribution in sexual activity and its (relatively lower rates in class 1, 2, 3 compared with class 3, 4, 5) influence on the mixing matrix elements (see Appendix) in such a way that STI prevalence among class 3, 4, 5, and overall is higher with the medium activity distribution than the other ones.
STI = sexually transmitted infection.

and failure after a year, respectively.[58] Hence, withdrawal from treatment is allowed to occur at an annual rate, ω, which is varied over a wide range, $\omega = 0$, 0.1, 0.2, 0.3, 0.4, and 0.5 years^{-1}. To isolate the independent population-level impact of ART, no other prevention strategy than ART is modeled. We assume that no individual-level change in risk behavior occurs over time apart from individuals with AIDS who can cease and resume sexual activity depending on their treatment status. This reflects the fact that the evidence on the impact of ART on increases in risky sex among individuals who are HIV+ who experienced a significant improvement in viral load (decline to undetectable level) is more conclusive because ART greatly improves their quality of life.[7,8,44,45]

The first case of HIV infection is introduced in the highest activity class in a population of 20,000 individuals.[39,41] The model simulates the spread of HIV from the beginning of the HIV epidemic until 10 years after the introduction of ART, 30 years ($t_{art} = 30$) into the simulated epidemic, near HIV equilibrium. Most of the results are presented for a mature but relatively small HIV epidemic (initial mean and standard deviation in risky sex is $m_{rs}^{No\text{-}ART}(0) = 4.7$ partners/year and $sd_{rs}^{No\text{-}ART}(0) = 9.8$ partners/year, respectively; initial STI equilibrium prevalence = 4.4%; HIV prevalence at t_{art} approximately 15%). The results are validated for 3 different epidemic sizes (and different risky sex distributions): a low (HIV prevalence at t_{art} approximately 15%), medium (HIV prevalence t_{art} approximately 28%), and large HIV epidemic (HIV prevalence at t_{art} approximately 40%), as observed among some MSM communities in Europe,[9,10,38,64–66] Canada,[67,68] and the United States, respectively,[5,39,69–71] as well as 2 different annual rates of new recruits ($\Lambda = 400$, 800).[39,41] The risky sex distributions are chosen to reflect the level and heterogeneity in risky sex of homosexual populations at the beginning of the HIV epidemic (at $t = 0$) but do not intend to represent a specific cohort.[9,22,38,72–78] The full risky sex distributions are described in Table 3.

The overall impact of ART at the community level is assessed by comparing the overall mean in risky sex and the number of STI and HIV infections after $t_{art} = 30$ between populations with and without the wide-scale use of ART. For each parameter combination, the community-level impact of ART is assessed by 3 measures: the fraction of new STI infections attributable to ART annually ($\Delta t = 1$) and over 10 years ($\Delta t = 10$) ($af^{STI}{}_{\Delta t}(t')$), the fraction of new HIV infections prevented by ART annually ($\Delta t = 1$) and over 10 years ($\Delta t = 10$) ($pf^{HIV}\ \Delta_t(t')$), and the proportion increase in risky sex over 10 years ($\Delta t = 10$) after ART introduction ($ri^{rs}[t_{art}+\Delta t]$) (details in Appendix 2).

Results

Figure 2 highlights the temporal trends in sexual behavior and STI and HIV in a population with ART and without ART for the low HIV epidemic with 800 new recruits per year. As HIV spreads (Fig. 2A), the overall level of STI and risky sex decline over time in absence of ART (Fig. 2B). After the introduction of ART, risky behavior and STI gradually increases over time. Eight and 12 years after the introduction of HIV, AIDS differential mortality and morbidity have induced a 6% (7%) and 19% (26%) reduction in the mean (variance) level of risky sex. These agree with a 21% (33%) reduction in the mean (variance) number of sexual partners estimated from a cohort of MSM in Amsterdam from 1984 to 1992.[22] The impact of the wide-scale use of ART on STI is the result of a mechanism that occurs at the community level because ART modifies the natural history of HIV/AIDS. HIV/AIDS differentially depletes the high-risk population through increased mortality or morbidity. Hence, the overall level of risky sex decreases at the community level even if individuals do not alter their risk behavior. After the introduction of ART, increases in risky sex occur, not only in the short term, because ART restores the quality of life of individuals with AIDS who can resume sexual activity, but also in the long term. Increases continue to occur for 2 main reasons. ART reduces AIDS morbidity and mortality, slowing the depletion of high-risk individuals infected with HIV, and decreases the infectivity of HIV+, which potentially reduces the number of new HIV infections. In an open population, these effects favor the differential renewal of the high-risk population, increasing the overall level of risky sex in the community over time.

The consequences of ART on STI transmission for the different combinations of treatment parameters is illustrated in Figure 3A, B. For all scenarios (optimistic, moderate, and pessimistic), the fraction

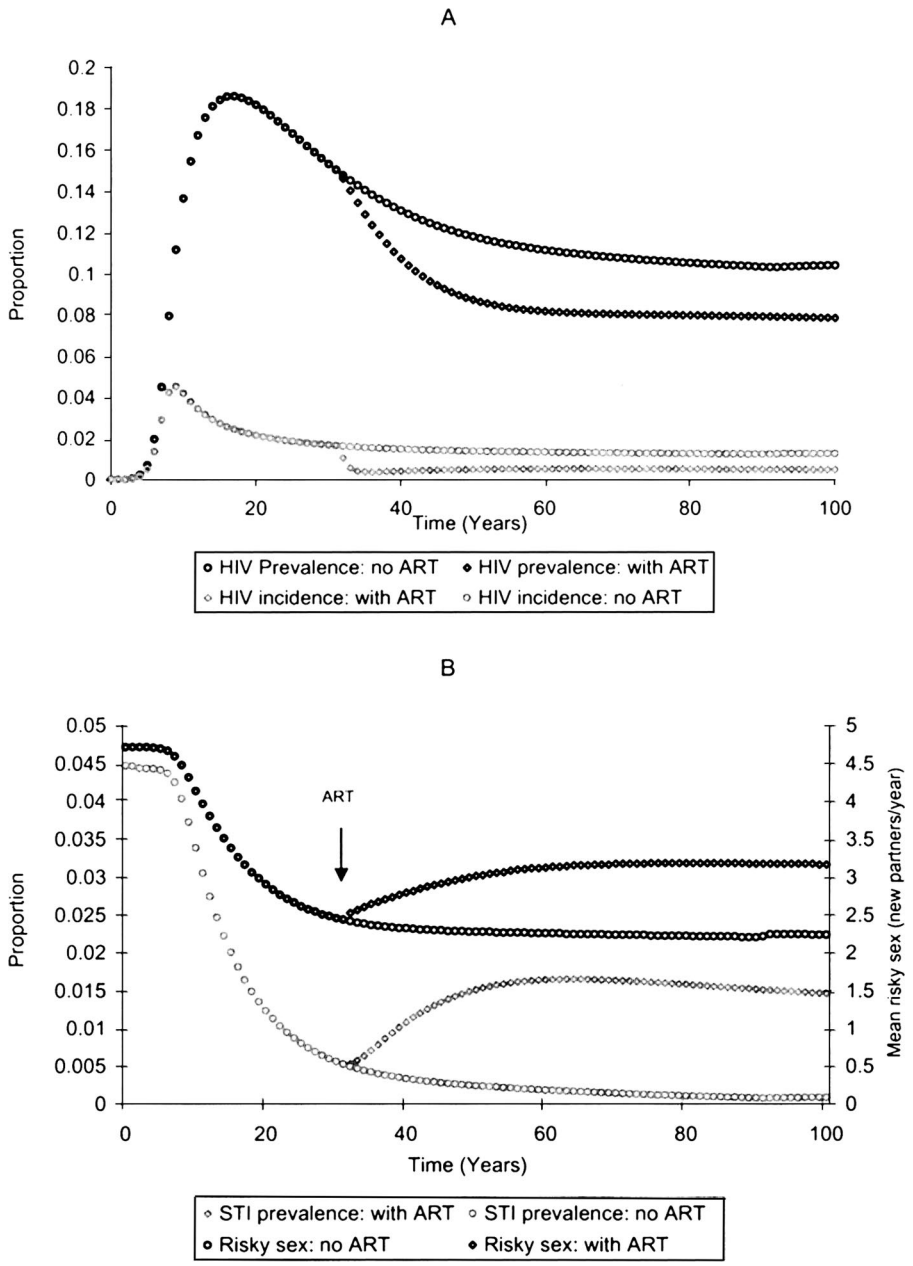

Fig. 2. (**A**) Overall prevalence and incidence (person-year) of HIV infection over time and (**B**) overall Gc prevalence and mean level of risky sex ($m_{rs}^{ART}[t]$) over time in a population with and without the wide-scale use of ART introduced at time $t_{art} = 30$ for the low epidemic population. Treatment parameter values used are: $r^a = 1\ year^{-1}$, $r^y = 1\ year^{-1}$, $Eff_{dp} = 0.65$, $Eff_I = 0.1$, $Eff_m = 0.65$, $w = 0.1$/year. The other parameters are as in Tables 1 and 3.

($\geqslant$0%) of STI cases attributable to the wide-scale use of ART increases rapidly each year, from a maximum of $<$5% in the first year after ART to a maximum of $>$50% and $>$70% in the fifth and tenth years, respectively (Fig. 3A). The annual STI-attributable fraction resulting from ART is smaller, but nonnegligible, when treatment is restricted to individuals with AIDS. Figure 3B shows that the cumulative fraction of STI cases attributable to ART over 10 years after its introduction depends heavily on treatment coverage rate. It is much larger when therapy covers HIV + AIDS individuals. The STI-attributable fraction varies between 10% and 40% even when treatment coverage rates are as low as 0.2/year. On the other hand, when treatment coverage rate is high, the fraction of STI as a result ART over 10 years can reach 20% even if only individuals with AIDS are treated. Figure 3C shows that increases in STI infection result from more modest increases in the average level of risky sex as a result of ART. Understandably, the maximum increase in risky sex and STI-attributable fraction as a result of ART is smaller if only individuals with AIDS are treated. For a given increase in risky sex, the STI-attributable fraction tends to be smaller under the optimistic scenario, which is associated with a larger reduction in HIV infectiousness as a result of ART. Given our model assumptions, a larger fraction of the

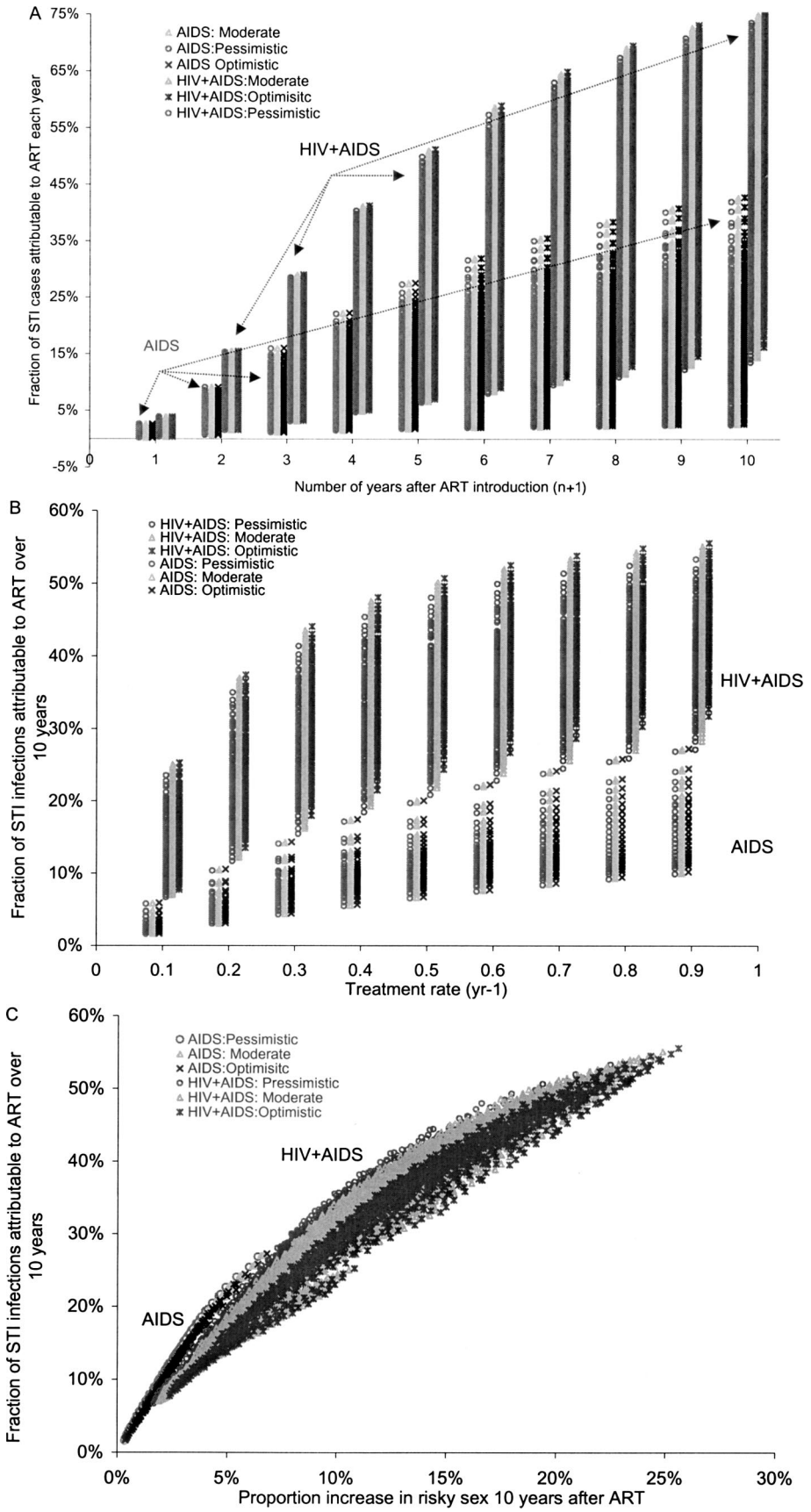

Fig. 3. Fraction of new STI infections attributable to ART between [t', t'+Δt] in the low size epidemic. Treatment is offered to individuals with AIDS only (AIDS) or to asymptomatic individuals with HIV+ and AIDS (HIV + AIDS). (**A**) Annual (Δt = 1) attributable fraction of STI in the (n+1)th year ($af_1^{STI}[t_{art}+n]$, n = 0,. . .,9]) after ART introduction. For each year, the optimistic, moderate, and pessimistic scenarios have 1350, 6750, and 1350 observations, respectively; one observation per parameter combination. (**B**) Cumulative attributable fraction of STI ($af_{10}^{STI}[t_{art}]$), over Δt = 10 years after ART introduction in function of treatment coverage rate (r^a, r^y). Each optimistic, moderate, and pessimistic scenario has 150, 750, and 150 observations at each treatment level, respectively. (**C**) Cumulative attributable fraction of STI ($af_{10}^{STI}[t_{art}]$), over Δt = 10 years in function of the proportion increase in risky sex Δt = 10 years ($ri^{rs}[t_{art}+10]$) after ART introduction. The optimistic, moderate, and pessimistic scenarios have 1350, 6750, and 1350 observations, respectively.

behavioral increase is the result of the recruitment of new sexually active individuals who are not infected with the STI.

The increased level of risky sex and STI infections could, as a result of the synergetic interaction between STI and HIV, have a negative impact on HIV transmission (Fig. 4). When only individuals with AIDS are treated, the cumulative fraction of HIV infections prevented by ART over 10 years is negligible and sometimes negative, indicating that ART enhances HIV transmissions (Fig. 4A). Surprisingly, when individuals with HIV + AIDS are treated, the cumulative HIV-prevented fraction increases as the fraction of STI infections attributable to ART also increases, but more marginally under the pessimistic scenario. The HIV-prevented fraction is always positive and larger under the optimistic scenario. In the most extreme case, a >50% increase in STI as a result of ART is associated with a >80% reduction in HIV infections. The proportional relationship between the HIV infections prevented and the STI-attributable fraction is the result of a positive population-level correlation between increases in risky sex and treatment coverage and/or efficacy. Indeed, by reducing HIV infectiousness and improving prognosis, greater treatment efficacy and better coverage simultaneously reduce the transmission potential of HIV and increase the likelihood of observing increases in risky sex and STI rates over time. The annual fraction of HIV infections prevented by ART is positive each year after its introduction under the optimistic and moderate scenario and when individuals with HIV + AIDS are treated (Fig. 4B). Over time, the upper values on the graph (when treatment is more effective) of the HIV-prevented fraction each year increase whereas the lower values decrease. If HIV infectiousness is insufficiently reduced by ART (by less than 25% under the pessimistic scenario), the HIV-preventive potential of ART is greatly reduced, and sometimes becomes negative, even if individuals with HIV + AIDS are treated. Worse results are obtained under all scenarios when treatment is restricted to individuals with AIDS. When ART has a negative impact on HIV, it does not occur immediately but a few years after ART introduction, especially if more individuals are treated or treatment is more efficacious. The fraction of HIV infections prevented by ART over 10 years rapidly augment (from a maximum of 30% when $r^y = r^a = 0.1$ year^{-1} to a maximum >70% when $r^y = r^y = 0.5$ years^{-1}) if treatment coverage rate increases under the optimistic and moderate scenarios when treatment is offered to individuals with HIV + AIDS (Fig. 4C). Otherwise, increasing the treatment coverage rate only has a marginal impact. When treatment only covers individuals with AIDS, the HIV-prevented fraction under the moderate and pessimistic scenarios decreases as treatment coverage rate increases and sometimes becomes negative even if treatment coverage rates are high.

Table 4 presents the results of the sensitivity analysis. The mean, minimum, and maximum increase in risky sex, STI-attributable fraction, and HIV-prevented fraction as a result of ART show that our results are consistent across the different populations. Increases in risky sex do not strictly depend on larger epidemic size or faster renewal. The magnitude of the increase is more modest for the largest epidemic because its risky sex distribution is less heterogeneous (coefficient of variation [CV] = standard deviation/mean approximately 1) than for the smallest epidemic (CV approximately 2). This reduces the differential impact of AIDS or ART. A faster renewal implies a more pronounced differential renewal of the high-risk population after ART but a less pronounced differential depletion as a result of AIDS. Subsequent changes in STI rates depend on the complex interaction between the baseline level and heterogeneity in risky sex and increases as a result of ART, the renewal of the population, and the local epidemiology of HIV and STI.

Discussion

The objective of the study was not to make precise quantitative projections in any given population. The objective was to gain a better understanding of the independent impact of the changes in the transmission dynamics of HIV/AIDS, on risk behavior and STI, induced by the wide-scale use of ART in sexually heterogeneous populations. Because many communities typically display large heterogeneity in risk behavior, our results could apply to various communities in developed and developing countries.[79,80] The magnitude of the differential impact of ART on risk behavior and STI is difficult to predict and depends on the extent of AIDS differential mortality/morbidity, which in return depends on the size of the HIV epidemic and heterogeneity in sexual behavior. The differential impact of ART could be larger than currently predicted if recruitment rate (eg, immigration, fertility) or risky sex among younger birth cohorts increased with time, instead of being constant, as assumed in the model. On the other hand, a decline in risky sex with age or as a result of effective prevention could limit the differential impact of HIV/AIDS and subsequent increases resulting from ART, whereas a more assortative mixing by risk or age groups and less effective prevention could enhance it.

Little data are available on the differential impact of AIDS in developing countries. Nevertheless, in deprived communities, such as in sub-Saharan Africa, where the HIV/AIDS epidemic is pronounced and prevention among youths might not be adequate,[81] increases in STI could occur as a result of the wide-scale use of ART, even if individuals do not increase risk behavior. Note that, in the absence of AIDS differential mortality and morbidity, similar results are expected to occur after ART introduction if risky behavior among younger birth cohorts and in migrants increases over time. In developed countries, some empiric evidence supports the plausible impact of AIDS mortality/morbidity on risky sex and STI, particularly for homosexual populations.[22,24,39] Given that a large fraction of HIV-infected homosexual men (approximately 50%) in developed countries are estimated to be treated,[16,35,39,82] our results suggest that the differential impact of ART could help explain a nonnegligible fraction of new STI infections among homosexual men since ART became widely available. It is unlikely that the recent increases in risky sex and STI will be only the result of one factor. Nevertheless, our results could help explain why the recent increases have been larger among homosexual than heterosexual populations. The expected HIV/AIDS mortality/morbidity should be less pronounced among heterosexuals because the HIV epidemic is much smaller than among homosexuals. Increases in STI and risk behaviors reported among MSM have also been slower than the declines observed at the beginning of the HIV epidemic,[2–4,22,38,76,83,84] which sometimes began even before the start of the first mass media prevention campaign.[38,76,84] Indeed, our results predict that differential replenishment of the high-risk population after ART is much slower than the initial depletion of high-risk individuals as a result of the differential impact of AIDS. The reduced mortality as a result of ART could also account for a fraction of the increased reporting of male-to-male sexual activity since 1996 in a national survey in the United States.[85] Our results are more likely to apply to bacterial STI with a relatively short infectious period because their transmission is very sensitive to behavioral changes in the high-risk population.[84,86] This is supported by the fact that recent increases have mostly been reported for gonorrhea, syphilis, and chlamydia.[2,6,87] Our results predict relatively modest population-level increases in risk behavior compared with those of STI. Nevertheless, the differential impact of ART could partly explain why individual-level factors (eg, optimism, complacency toward AIDS) are not consistently associated with increases in high-risk behavior.[7,11,14,28] This has led some

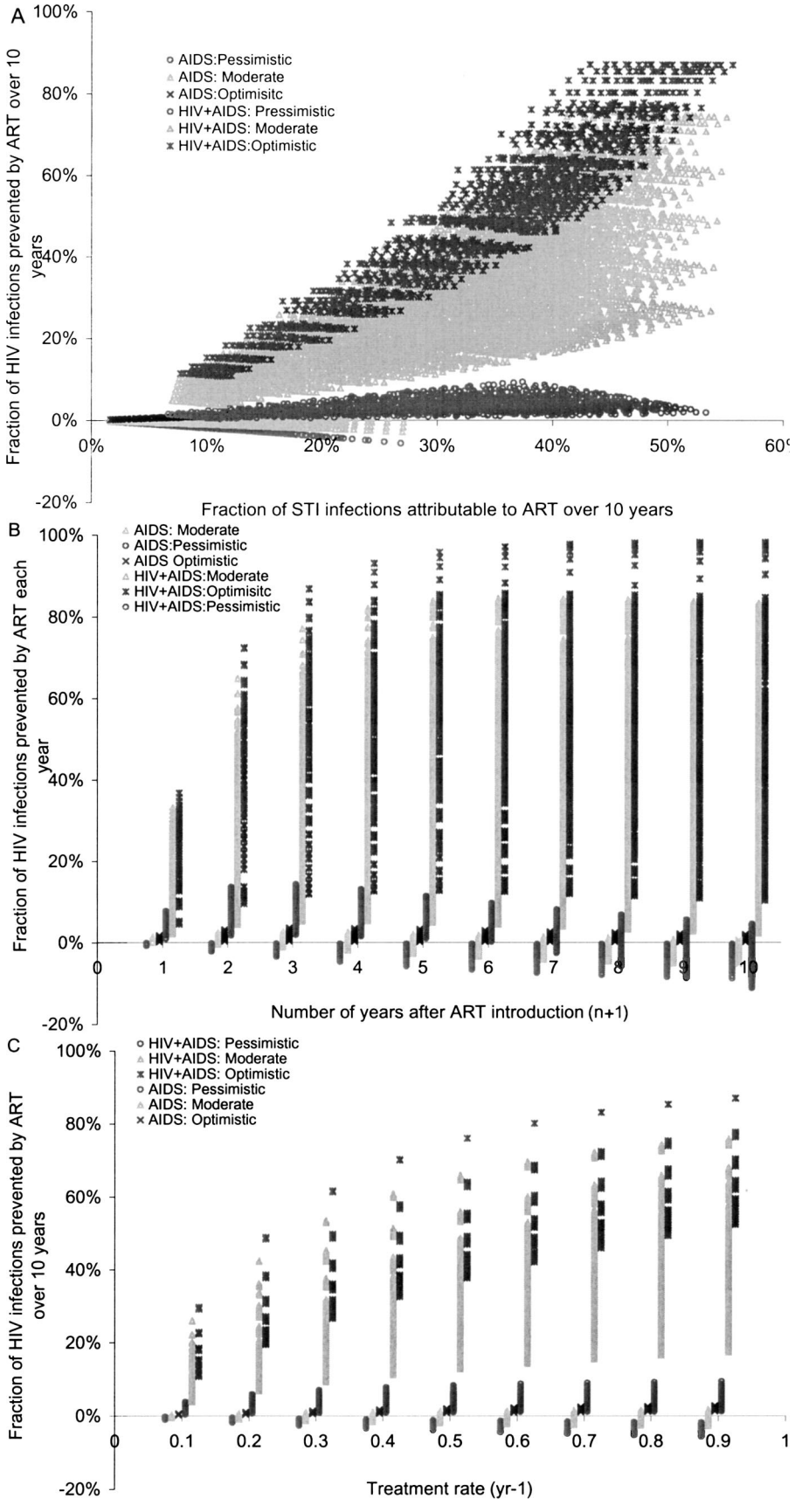

Fig. 4. Fraction of new HIV infections prevented by ART between [t', t'+Δt] in the low size epidemic. Treatment is offered to individuals with AIDS only (AIDS) or to asymptomatic individuals with HIV+ and AIDS (HIV + AIDS). (**A**) Cumulative HIV-prevented fraction ($pf_{10}^{HIV}(t_{art})$) in function of the fraction of STI attributable to ART ($af_{10}^{STI}[t_{art}]$) over Δt = 10 years after ART introduction. The optimistic, moderate, and pessimistic scenarios have 1350, 6750, and 1350 observations, respectively; one observation per parameter combination. (**B**) Annual (Δt = 1) HIV prevented fraction in the (n+1)th year ($pf^{1HIV}(t_{art}+n)$, n = 0,. . .,9) after ART introduction. For each year, the optimistic, moderate, and pessimist scenarios also have 1350, 6750, and 1350 observations, respectively. (**C**) Cumulative HIV prevented fraction ($pf_{10}^{HIV}[t_{art}]$) over Δt = 10 years after ART introduction in function of treatment coverage rate (r^a, r^y),. The optimistic, moderate, and pessimistic scenarios have 150, 750, and 150 observations, respectively, for each treatment level.

TABLE 4. Sensitivity Analysis*

	Λ = 800 New Recruits per Year			Λ = 400 New Recruits per Year		
At t_{art} = 30 years	Epidemic Size			Epidemic Size		
	Small	Medium	Large	Small	Medium	Large
HIV prevalence	15%	28%	40%	15%	27%	44%
STI prevalence	0.5%	3.1%	0.4%	0.2%	2.5%	0.2%
Risky sex (partners/year):						
Mean ($m_{rs}^{No\text{-}ART}(t_{art})$):	2.4	3.9	7.7	2.2	3.5	7.4
Standard deviation ($sd_{rs}^{No\text{-}ART}(t_{art})$):	6.3	9.1	8.5	5.9	8.5	8.3
Percent increase in risky sex ($ri^{rs}(t_{art}+10)$)						
HIV + AIDS treated						
Mean [minimum, maximum]	11.5 [1.9, 2.5]	12.6 [2.1, 27.0]	8.6 [1.7, 16.5]	11.2 [1.9, 24.1]	12.9 [2.2, 27.6]	9.2 [1.8, 17.9]
AIDS only treated						
Mean [minimum, maximum]	2.2 [0.3, 6.8]	2.9 [0.5, 8.2]	2.1 [0.4, 5.7]	2.2 [0.3, 6.6]	2.9 [0.5, 8.3]	2.3 [0.4, 6.2]
STI Attributable fraction ($af_{10}^{STI}(t_{art})$) (%)						
HIV + AIDS treated						
Mean [minimum, maximum]	32.4 [7.0, 55.1]	15.1 [2.9, 29.2]	24.0 [4.1,49.3]	41.5 [8.6, 69.8]	16.0 [3.1, 30.8]	18.3 [2.9, 39.9]
AIDS						
Mean [minimum, maximum]	10.6 [1.6, 27.2]	4.7 [0.7, 12.4]	6.4 [0.7, 19.2]	13.9 [2.1, 35.7]	5.0 [0.8, 13.3]	4.9 [0.4, 15.0]
Fraction of HIV prevented($pf_{10}^{HIV}(t_{art})$) (%)						
HIV + AIDS treated						
Mean [minimum, maximum]	30.4 [3.9, 75.6]	27.1 [3.8, 69.7]	31.8 [4.6, 76.4]	32.3 [4.5, 77.0]	27.9 [3.9, 70.8]	31.7 [4.6, 75.9]
AIDS						
Mean [minimum, maximum]	0.3 [−1.9, 2.9]	0.8 [0.0, 3.7]	1.1 [0.0, 4.9]	0.3 [−1.9, 2.9]	0.8 [−0.0, 3.6]	1.2 [0.1, 5.2]

STI = sexually transmitted infections, ART = antiretroviral therapy.
*Mean [minimum, maximum] percent increase in risky sex after Δt = 10 year, fraction of new STI attributable to ART, and fraction of new HIV infections prevented by ART, over Δt = 10 years after ART introduction for different population characteristics for the moderate scenario. Each mean and range is calculated from 6750 observations (one observation for each parameter combination).

authors to suggest that optimism toward ART could be a justification of high-risk behavior rather than a cause[27,33,88] or that a more social explanation could be required understanding recent trends.[30] We provide an ecologic explanation.

The impact of the wide-scale use of ART on HIV transmission, as a result of the increases in aggregate measure of risky sex and STI, depends on treatment coverage and efficacy. HIV transmission is predicted to increase if treatment coverage is inadequate (ie, restricted to individuals at a critical stage of HIV infection) or if the reduction in infectiousness as a result of ART is less than what could be expected based on the reduction in viral load observed among treated individuals. If HIV transmission does increase, it will likely be a few years after ART introduction. If ART efficacy is high, more HIV infections will be prevented as treatment coverage increases (HIV + AIDS individuals treated), yet the level of risky sex and STI could easily be increased by more than 10% and 25% over 10 years, respectively. These results have implications for many parts of the developing world where optimizing treatment coverage and minimizing treatment interruption, 2 key factors in the model, could prove particularly challenging. Our results contrast slightly with previous theoretical studies that showed that a 10% increase in risk behavior could counterbalance the positive effect of ART in the first year after treatment[16] and that HIV incidence would initially rise before falling after increases in risk behavior.[16] Increases in HIV incidence have only recently been reported in few communities[89–92] where STI and risk behavior started to rise a few years ago.[1,8,89,90] The difference in the model predictions can in most part be explained by the difference in the basic behavioral hypotheses that were formulated to address different questions. In former theoretical studies, increases in risk behavior after the introduction of ART are assumed to occur instantaneously, at the individual level, and independently of treatment effectiveness and coverage.[16,17,35,36] In our model, we assumed that individuals did not change their level of risky sex over time, apart from patients with AIDS who can resume sexual activity when treated. Therefore, increases in risk behavior occur gradually over time, at the community level rather than at the individual level, and are positively correlated with treatment coverage and efficacy. Our results agree with former analysis, which show that a large fraction of HIV infections could be prevented by increasing use of ART,[16,35] despite the predicted population-level increase in STI and risk behavior that will ensue. This is not a reason for complacency that the predicted impact on HIV will be worse than predicted if risky sex also increases at the individual level.

The new insights gained with our mathematical analysis are difficult to verify empirically. To distinguish the differential impact of AIDS and ART from other possible factors, it would ideally require comparing changes in risky behavior (and STI) at the population and individual level (over a relatively long period of time) before and after the introduction of ART in comparable communities receiving and not receiving ART. Clearly, this ideal type of data is difficult to obtain. However, empiric validation could be possible in developing countries as ART is phased in or by comparing the differential impacts of AIDS and ART among heterosexual and homosexual populations. Despite their limitations, ecologic and qualitative studies could be used as a first step to address this question. Our hypothesis could also be validated in a modeled population where the more complex local and global structure of the network is represented.

Clearly, ART should be made available to any individuals in need in the world. However, it is important to bear in mind that maximizing treatment coverage and minimizing treatment interruption, in implementing an ART program, could have a positive impact (reduce) on HIV incidence yet a negative impact (increase) on STI rates. The impact of the wide-scale use of ART and the cause of the observed increases in risk behaviors and STI should be well understood, at the community level as well as the individual level, to tailor effective concomitant prevention programs and formulate ap-

propriate public health policies. It is very important to consider the differential impact of HIV/AIDS on sexual behavior, otherwise the effect of intervention (pre-ART) could be overestimated. Similarly, ignoring the differential impact of ART could lead to overestimation of change in behavior among individuals and relapse to risky sex. Our results support the fact that prevention should be emphasized among young sexually active individuals and the migrant population. Our results highlight the needs, frequently neglected, not only to study the impact of sexual networks on HIV/AIDS, but also to analyze the impact of HIV/AIDS and ART (acting by changes in morbidity and mortality patterns) on the very structure of sexual networks. The interaction between the biologic and behavioral process needs to be understood more clearly.

Appendix 1

System of Differential Equations for the General Model

$$\frac{dX_i^s(t)}{dt} = \Lambda_i - (\lambda_i^{\tau,s}(t) + \mu)\cdot X_i^s(t) + (1-s)(-\xi_i(t)\cdot X_i^0(t) + \delta\cdot X_i^1(t)) + (s)(\xi_i(t)\cdot X_i^0(t) - \delta\cdot X_i^1(t)) \quad (A.1)$$

$$\frac{dY_i^{u,s}(t)}{dt} = \lambda_i^{\tau,s}(t)\cdot X_i^s(t) - (\gamma^u + \mu + r^y)\cdot Y_i^{u,s}(t) + \omega\cdot Y_i^{\tau,s}(t) + (1-s)(-\xi_i(t)\cdot Y_i^{u,0}(t) + \delta\cdot Y_i^{u,1}(t)) + (s)(\xi_i(t)\cdot Y_i^{u,0}(t) - \delta\cdot Y_i^{u,1}(t)) \quad (A.2)$$

$$\frac{dY_i^{\tau,s}(t)}{dt} = r^y\cdot Y_i^{u,s}(t) - (\gamma^\tau + \mu + \omega)\cdot Y_i^{\tau,s}(t) + (1-s) \times (-\xi_i(t)\cdot Y_i^{\tau,0}(t) + \delta\cdot Y_i^{\tau,1}(t)) + (s)(\xi_i(t)\cdot Y_i^{\tau,0}(t) - \delta\cdot Y_i^{\tau,1}(t)) \quad (A.3)$$

$$\frac{dA_i^{u,s}(t)}{dt} = \gamma^u\cdot Y_i^{u,s}(t) - (\alpha^u + \mu + r^a)\cdot A_i^{u,s}(t) + \omega\cdot A_i^{\tau,s}(t) + (1-s)(\delta\cdot A_i^{u,1}(t)) + (s)(-\delta\cdot A_i^{u,1}(t)) \quad (A.4)$$

$$\frac{dA_i^{\tau,s}(t)}{dt} = \gamma^t\cdot Y_i^{\tau,s}(t) - (\alpha^\tau + \mu + \omega)\cdot A_i^{\tau,s}(t) + r^a\cdot A_i^{u,s}(t) + (1-s)(-\xi_i(t)\cdot A_i^{\tau,0}(t) + \delta\cdot A_i^{\tau,1}(t)) + (s)(\xi_i(t)\cdot A_i^{\tau,0}(t) - \delta\cdot A_i^{\tau,1}(t)) \quad (A.5)$$

$dX^s{}_i(t)/dt$, $dY^{u,s}{}_i(t)/dt$, $dA^{u,s}{}_i(t)/dt$, $dY^{\tau,s}{}_i(t)/dt$, $dA^{\tau,s}{}_i(t)/dt$ represents the change in the number of susceptible to HIV infection of untreated HIV$^+$, untreated HIV+ with full-blown AIDS, treated HIV+, individuals with AIDS treated over time for individual infected (s = 1) and not infected with the STD (s = 0), respectively. Superscripts, u and τ, represent untreated and treated individuals, respectively. The per capita rate of STI infection, $\xi_i(t)$, of a susceptible individual in risk group i is:

$$\xi_i(t) = m_i\sum_j \rho_{ij}(t)\cdot\theta_{ji}\cdot\left(\frac{NA\cdot{}^1_j(t)}{\sum_s NA\cdot{}^s_j(t)}\right)$$

.

The per capita rate of HIV infection, $\lambda_i^{\tau,s}(t)$, of a susceptible individual in risk group i depends on the STI status and is:

$$\lambda_i^{\tau,s}(t) = m_i\cdot RR^s\cdot\sum_j\left(\rho_{ij}(t)\cdot\frac{\sum_s RR^s(\beta_{ji}\cdot Y_j^{u,s}(t) + (1-Eff_I)\cdot\beta_{ji}\cdot(Y_j^{\tau,s}(t) + A_j^{\tau,s}(t))}{\sum_s NA\cdot{}^s_j(t)}\right)$$

with:

$$NA\cdot{}^s_i(t) = X_i^s(t) + Y_i^{u,s}(t) + Y_i^{\tau,s}(t) + A_i^{\tau,s}(t)$$

We define m_i as the annual number of new partners with who unprotected sex takes place. Sexual mixing between individuals i and j ($\rho_{ij}[t]$) is assumed to be proportionate to the level of risky sex of each individual such that

$$\rho_{ij}(t) = \frac{\sum_s (N\cdot{}^s_j(t)\cdot m_j)}{\sum_j(\sum_s N\cdot{}^s_j(t)\cdot m_j)}$$

As can be seen by the equation, the mixing matrix elements will be different for the different distribution in sexual activity used, which will influence STI and HIV prevalence levels. $RR^1 = 3$ and $RR^0 = 1$ are the increase in HIV susceptibility and in infectiousness among STI+ (*s* = 1) and STI- (*s* = 0) individuals, respectively.[93,94] β_{ji} (θ_{ji}) is the per-partnership HIV (STI) transmission probability between 2 low-risk partners (i and j = 1 or 2). γ^u and α^u are the annual rate of progression to AIDS and of AIDS mortality. Λ_i ($\Lambda_i = \Lambda\cdot Q_i$), Eff_I, Eff_d, Eff_{dp}, r^a, r^y, w, and δ are defined in the main text. Before ART introduction, $r^y = r^a = w = 0$ and $Y_j^{\tau,s}(t) = A_j^{\tau,s}(t) = 0$. The rate of exit from the sexual active population is μ ($1/\mu$ = sexually active life duration in absence of AIDS). At time t = 0, the initial HIV size of HIV-susceptible population is ,[39,41] the HIV epidemic is seeded with $Y^{u,0}{}_6(0) = 1$, whereas the STI is already at its equilibrium prevalence. The other HIV state variables equal zero.

Appendix 2

Impact Measures

The community-level impact of ART is assessed by 3 measures: the fraction of new STI infections attributable to ART between t' to t'+Δt years ($af^{STI}{}_{\Delta t}(t')$), the fraction of new HIV infections prevented by ART between t' to t'+Δt years ($pf^{HIV}{}_{\Delta t}(t')$), and the proportion increase in risky sex Δt years after ART introduction ($ri^{rs}[t_{art}+\Delta t]$).

The fraction of new STI infections attributable to ART between year t' to t'+Δt is:

$$af_{\Delta t}^{STI}(t') = \left(\frac{IN_{\Delta t}^{STI/ART}(t') - IN_{\Delta t}^{STI/No\text{-}ART}(t')}{IN_{\Delta t}^{STI/ART}(t')}\right) \quad (S1)$$

The fraction of new HIV infections prevented by ART between year t' to t'+Δt is

$$pf_{\Delta t}^{HIV}(t') = \left(\frac{IN_{\Delta t}^{HIV/No\text{-}ART}(t') - IN_{\Delta t}^{HIV/ART}(t')}{IN_{\Delta t}^{HIV/No\text{-}ART}(t')}\right) \quad (S2)$$

$$IN_{\Delta t}^{STI/ART}(t^1) = \sum_i\int_{t'}^{t'+\Delta t}\xi_i(t)\cdot\left(X_i^0(t) + Y_i^{u,0}(t) + Y_i^{\tau,0}(t) + A_i^{\tau,0}(t)\right)dt$$

and

$$IN_{\Delta t}^{STI/No\text{-}ART}(t') = \sum_i \int_{t'}^{t'+\Delta t} \xi_i(t) \cdot (X_i^0(t) + Y_i^{u,0}(t))dt$$

are the cumulative number of incident cases of STI infection between year t' and t'+Δt in a population with ART and without ART, respectively.

$$IN_{\Delta t}^{HIV/ART}(t') = \sum_i \int_{t'}^{t'+\Delta t} (\lambda_i^{\tau,0}(t) \cdot (X_i^0(t) + \lambda_i^{\tau,1}(t))dt$$

and

$$IN_{\Delta t}^{HIV/No\text{-}ART}(t') = \sum_i \int_{t'}^{t'+\Delta t} (\lambda_i^{u,0}(t) \cdot X_i^0(t) + \lambda_i^{u,1}(t) \cdot X_i^1(t))dt$$

are the cumulative number of incident cases of HIV infection between year t' and t'+Δt in a population in presence and in the absence of ART, respectively.

The proportion increase in risky sex Δt years after ART introduction is given by $ri^{rs}[t_{art}+\Delta t])$.

$$ri^{rs}(t_{art} + \Delta t) = \left(\frac{m_{rs}^{ART}(t_{art} + \Delta t) - m_{rs}^{No\text{-}ART}(t_{art} + \Delta t)}{m_{rs}^{No\text{-}ART}(t_{art} + \Delta t)}\right)$$

$$m_{rs}{}^{ART}(t_{art} + \Delta t) = \frac{\sum_i (NA_i^{ART}(t_{art} + \Delta t) \cdot m_i)}{\sum_i NA_i^{ART}(t_{art} + \Delta t)}$$

and

$$m_{rs}{}^{No\text{-}ART}(t_{art} + \Delta t) = \frac{\sum_i (NA_i^{No\text{-}ART}(t_{art} + \Delta t) \cdot m_i)}{\sum_i NA_i^{No\text{-}ART}(t_{art} + \Delta t)}$$

are the overall mean in risky sex in a population in the presence and in the absence of ART, respectively.

$$NA_i^{ART}(t_{art} + \Delta t) = \sum_{i,s} (X_i^s(t_{art} + \Delta t) + Y_i^{u,s}(t_{art} + \Delta t) + Y_i^{\tau,s}(t_{art} + \Delta t) + A_i^{\tau,s}(t_{art} + \Delta t))$$

and

$$NA_i^{No\text{-}ART}(t_{art} + \Delta t) = \sum_{i,s} (X_i^s(t_{art} + \Delta t) + Y_i^{u,s}(t_{art} + \Delta t))$$

are the numbers of sexually active individuals in the resident population in the presence and in the absence of ART, respectively. [95–106]

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