Stochastic simulation of the impact of antiretroviral therapy and HIV vaccines on HIV transmission; Rakai, Uganda

Ronald H. Gray, Xianbin Li, Maria J. Wawer[a], Stephen J. Gange[b], David Serwadda[c], Nelson K. Sewankambo[d], Richard Moore[e], Fred Wabwire-Mangen[c], Tom Lutalo[f], Thomas C. Quinn[g] for The Rakai Project Group*

Objective: To model the effects of antiretroviral therapy (ART) and HIV vaccines on HIV transmission using empirical data from studies in Rakai, Uganda.

Design: A stochastic simulation model estimated HIV incidence, probabilities of transmission per coital act and the reproductive number (R_0) with ART and HIV vaccines. Model inputs included Rakai data on HIV transmission probabilities per coital act by HIV viral load, age and gender, and sexual behaviors. The impacts of therapy were derived from US programs, and vaccine assumptions included preventive efficacies ranging from 25 to 75%. Component projection models estimated the numbers of HIV-infected persons over 20 years.

Results: The model incidence [1.57/100 person years (PY)] closely fitted empirical data (1.5/100 PY). Simulations of ART using DHHS treatment guidelines, predicted declines in HIV incidence, but R_0 remained > 1.0, and the numbers of HIV-positive persons did not change substantially over 20 years. Preventive vaccines with $> 50\%$ efficacy and $> 50\%$ population coverage could reduce R_0 to < 1.0, and substantially reduce the number of HIV-infected persons over 20 years. Concurrent ART and a preventive vaccine can have substantial impact at lower levels of population coverage and would markedly reduce the HIV infected population over 20 years. However, behavioral disinhibition with increased numbers of sexual partners in either ART or vaccine recipients, increased HIV incidence and diminished intervention impact.

Conclusion: ART alone cannot control the HIV epidemic in mature epidemics such as Rakai, and persons in need of therapy will increase over time. ART in combination with a low efficacy vaccine could control the epidemic, if behavioral disinhibition is prevented.

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From the Department of Population and Family Health Sciences, Johns Hopkins University, Bloomberg School of Public Health, Baltimore, Maryland, the [a]Heilbrun Center for Population and Family Health, Columbia University, Joseph L. Mailman School of Public Health, New York, the [b]Department of Epidemiology, Johns Hopkins University, Bloomberg School of Public Health, Baltimore, Maryland, USA, the [c]School of Public Health and the [d]Department of Medicine, Faculty of Medicine, Makerere University, Kampala, Uganda, the [e]Department of Medicine, Johns Hopkins Hospital, Baltimore, Maryland, USA, the [f]Rakai Project, Uganda Virus Research Institute, Entebbe, Uganda, the [g]Department of Medicine, Johns Hopkins University, School of Medicine, Baltimore, and the National Institutes of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA. *See Appendix I.

Correspondence to R. H. Gray, Suite 4030, Johns Hopkins University, School of Hygiene and Public Health, 615 N. Wolfe Street, Baltimore MD 21205, USA.

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Introduction

There is a growing international commitment to the provision of antiretroviral therapy (ART) in developing countries, particularly in Sub-Saharan Africa where the HIV epidemic is most severe [1–3]. Experience in the US and Europe suggests that ART has substantially prolonged survival times and reduced AIDS mortality [4–6] and that therapy can be cost-effective [6–8]. Since HIV transmission is reduced at lower viral loads, [9,10] therapy could theoretically reduce HIV incidence and potentially be used to control the epidemic. Mathematical models suggest that antiretroviral use may have reduced HIV transmission among men who have sex with men, although concomitant increases in high risk sexual behaviors can reduce the magnitude of these benefits [11,12]. There has been less attention to the potential impact of ART on heterosexual HIV transmission, which is the predominant mode of HIV infection globally. Theoretically, widespread treatment could reduce the basic reproduction number (R_0) below unity, resulting in abatement of the epidemic [13]. However, if treatment does not reduce $R_0 < 1.0$, the number of infected persons and the number requiring therapy will continue to grow because of longer survival, [4,6] and because new incident infections will progress to immunodeficiency requiring treatment. This could have important consequences for the ultimate feasibility and costs of antiretroviral care in developing countries. There is debate on the public health utility of HIV preventive vaccines with low efficacy [14,15]. However, little attention has been paid to the possible public health benefit of combining a low efficacy preventive vaccine with ART.

To determine the potential impact of ART or an HIV vaccine on the course of the epidemic, we developed a stochastic simulation model using empirical parameters derived from cohort studies in Rakai District, Uganda which has a mature, generalized HIV epidemic [16].

Methods

Source of empirical data

The model parameters were based on epidemiologic studies in a rural population of Rakai District, southwestern Uganda, where we conducted a community-randomized trial of sexually transmitted disease (STD) control for HIV prevention between 1994 and 1998 [16]. The total population was enumerated by annual censuses of all residents in 56 rural communities, and consenting adults aged 15–59 years were surveyed at 10-month intervals by interview and collection of samples for HIV and STD diagnoses [16,17]. The cohort has been carefully characterized [16,17]. Information was also obtained on the number of sexual partners in the past year, and a sexual networks interview ascertained the frequency of intercourse with each partner. Empirical data were available for 2037 HIV-positive and 13 108 HIV-negative individuals surveyed in 1998, with known distributions of age, gender, number of sexual partners and frequency of intercourse. With regard to the latter parameters, the mean frequency of intercourse was 8.9 acts per month, and declined with increasing age and HIV viral load [10].

After completion of the trial, we analyzed HIV transmission and acquisition rates in 415 HIV-discordant couples, retrospectively identified in the cohort population [9], and subsequently estimated the risk of HIV transmission per coital act among 174 monogamous couples in which neither partner reported external relationships [10]. HIV RNA viral load was determined by reverse-transcription PCR (Roche Amplicor HIV-1 Monitor 1.5 assay, Roche Molecular Systems, Branchberg, New Jersey, USA).

Stochastic simulation model

Our model simulated HIV transmission from HIV-positive to HIV-negative individuals within HIV-discordant relationships. For each HIV-positive individual, we used the Rakai data to simulate the transmission using three steps: (i) first, we computed a probability of transmission per sex act for the HIV-positive individual. To estimate the transmission probabilities per sex act, a complementary log–log binomial regression model was constructed to model log ($-\log[1-\gamma]$) as a linear function of age (divided into quartiles), gender (i.e., separate male-to-female and female-to-male transmission probabilities), and quartiles of HIV viral load. We assigned a $\log_{10}$ HIV-1 viral load level generated from the normal distribution of $\log_{10}$ viral loads in 415 HIV-discordant couples (male mean $\log_{10}$ viral load $= 4.1 \pm 0.86$, female mean $\log_{10}$ viral load $= 3.9 \pm 0.83$), [9] and randomly assigned by gender to each HIV-infected individual. Details of the model parameters are given in Appendix I; (ii) second, we used the Rakai data to generate sexual contacts of the HIV-positive individual. To estimate sexual contacts with HIV-negative partners, the number of reported sexual partners in the model were randomly reduced by 0.14, as 14% of the infected population is in concordant HIV-positive relationships (Table 1). Rates of partner change and frequencies of intercourse reported by the discordant couples were similar to those observed in the general adult population, as were the rates of STS; (iii) using these two components, we simulated each coital act to determine whether the HIV-negative partner seroconverted based on the transmission probability for each sex act. The simulation was repeated until the HIV-negative partner either seroconverted or remained seronegative at 3 years. Partners who remained uninfected were recycled back into the pool of uninfected persons. New seroconver-

Table 1. Summary of observational data used in stochastic model simulations.

Parameter	Empirical estimates of parameter values	
	Transmission probability/ coital act (γ)	Sex acts/ month (n)
Quartile of HIV viral load copies/ml		
< 1700	0.0001	10.4
1700–12 499	0.0013	9.4
12 500–38 500	0.0014	8.0
⩾ 38 500	0.0023	7.9
Quartile of age (years)		
15–24	0.0013	10.0
24–29	0.0017	9.0
30–34	0.0006	9.1
35–59	0.0009	7.4
Female-to-male	0.0013	9.7
Male-to-female	0.0009	8.3
HIV+ female mean HIV− sex partners/year	1.08	
HIV+ male mean HIV− sex partners/year	1.53	
Mean viral load male seroconverters	4.11 $\log_{10}$ copies/ml	
Mean viral load female seroconverters	3.90 $\log_{10}$ copies/ml	
Antiretroviral treatment effects		
Proportional reduction in HIV viral load		
Johns Hopkins Clinic	43.6% reduction in $\log_{10}$ viral load	
WIHS data	28.6% reduction in $\log_{10}$ viral load	
Average monthly treatment termination rate (%)		
Johns Hopkins Clinic	1.8% per month	
WIHS data	1.6% per month	
Vaccine assumptions		
Efficacy	25%, 50%, 75%	
Assumed treatment or vaccine coverage	0, 25%, 50%, 75%, 100%	

ters generated by this simulation were recycled into the pool of HIV-infected persons, and transmissions to their subsequent HIV-negative partners were simulated as described above. The mean viral load among seroconverters in the Rakai population is 4.64 $\log_{10}$ copies/ml for the first year after infection, and this viral load was ascribed to newly infected incident cases in the model. Simulations were run using SAS (Version 8, SAS Institute, Cary North Carolina, USA) with 1000 replications and were used to estimate the variance of the incidence rates by bootstrap re-sampling [18]. The variance of the parameters was uniformly low (Appendix III).

The total number of seroconversions, total person years (PY) at risk among HIV-negative persons and total number of sexual acts were obtained from the simulation for calculation of average HIV incidence rates per 100 PY in the HIV-negative population, and average transmission probabilities per coital act in discordant couples. To determine the effect of the simulated interventions on the future course of the HIV epidemic we estimated the approximate basic reproductive number (R_0), using the equation $R_0 = \gamma Dc$, [13] where γ is the probability of HIV transmission per sex act, D is the total number of coital acts during the infectious period ($\approx$ 10 years, [14] with an average of 106.8 acts of intercourse per year for one couple), and c is the average number of HIV-negative partners for each infected individual (the mean value of c in Rakai is 1.25 HIV-negative partners per HIV-positive individual per year). Strictly speaking this is an approximation of the effective reproductive number (R_t), but we have retained the notation R_0 because this is familiar to most readers. The mean value for R_0 was estimated to be 1.44 in the Rakai population. If R_0 is reduced below 1.0, each incident HIV-case will be replaced by less than one secondary case, and the epidemic would begin to wane. Therefore, we estimated R_0 over a 10-year period for each simulation scenario, to determine which interventions might control the epidemic.

Modeling the effect of ART and HIV preventive vaccines

The effects of ART or HIV preventive vaccines were simulated as illustrated in Fig. 1. The treatment and vaccine simulations primarily affect incidence and R_0 by reducing the probability of infection per coital act (γ). We also examined the effects of increasing numbers of partners (c) to assess behavioral disinhibition.

The impact of ART on incident HIV used two scenarios for initiation of therapy. First, we assumed treatment initiation at viral loads > 55 000 copies/ml in

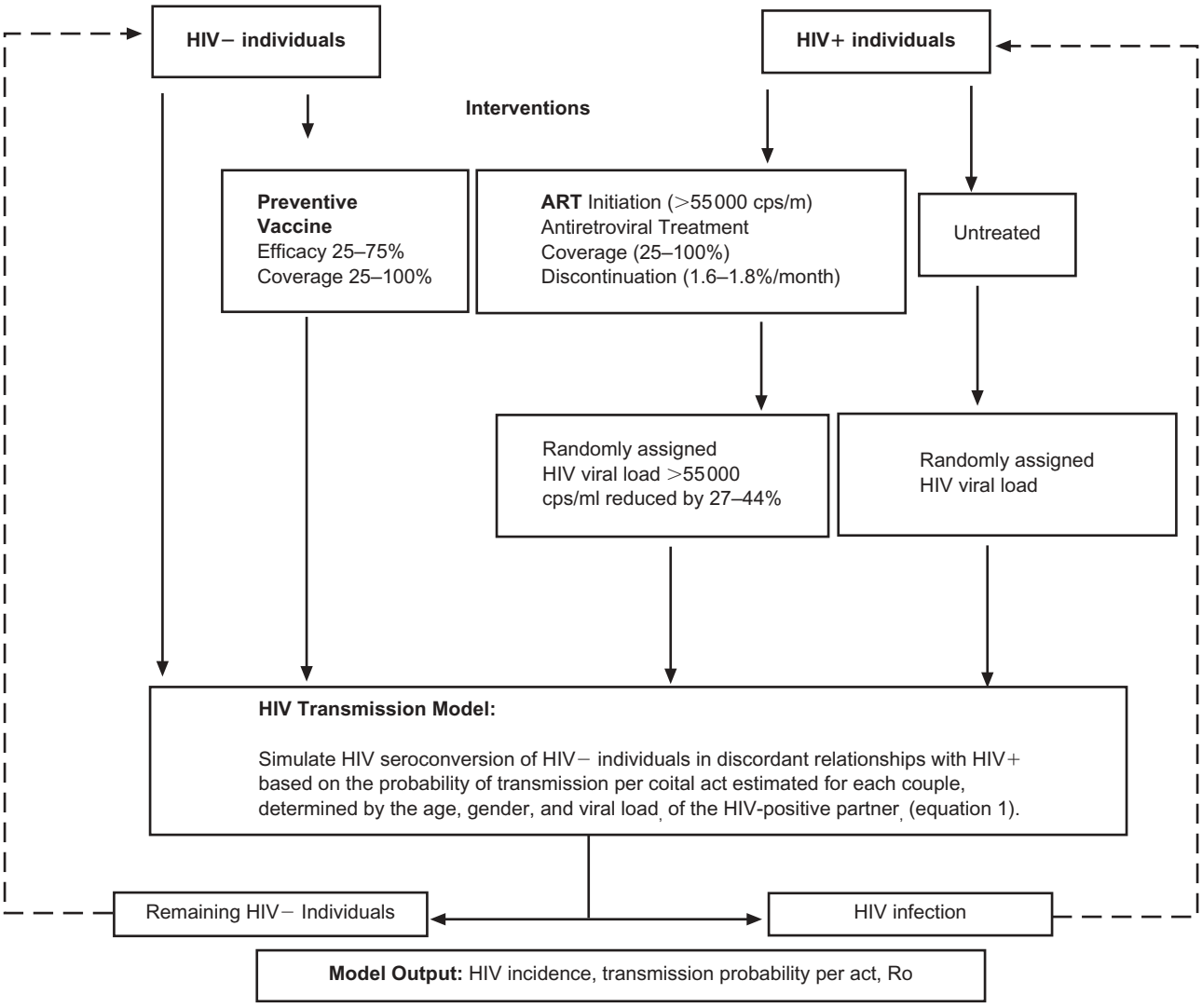

Fig. 1. Structure of the stochastic model.

accordance with current US Department of Health and Human Services (DHHS) guidelines [19]. Second we assumed treatment of all HIV-positive persons, irrespective of HIV-1 viral load. The rationale for this latter strategy is that it would require HIV testing and counseling, but would not entail determination of HIV viral load or CD4 cell counts, which would be difficult in this rural African setting. For each scenario we examined varying levels of program coverage ranging from zero to 100% of persons meeting the criteria for therapy. The criteria for initiation of treatment were then applied to the viral load distribution of the Rakai population, in which 20% of infected persons had viral loads > 55 000 copies/ml [9]. The effects of therapy on HIV viral load were determined from information on 492 patients attending the HIV Clinic at Johns Hopkins Hospital [20] and 999 women enrolled in the Women's Interagency HIV Study (WIHS), [21] as described in Appendix IV.

For the vaccine simulations it was assumed that preventive vaccine efficacies ranged from 25% to 75% in HIV-negative persons, resulting in direct reductions of incident infections (i.e., the model reduced the transmission probability per coital act by 0.25–0.75). We also assessed the impact of a preventive vaccine used in conjunction with ART for HIV-infected persons. Vaccine coverage was assumed to range from zero to 100%.

There is evidence of increased risk behaviors since the availability of highly active antiretroviral therapy (HAART) in the USA, Europe and Australia, potentially due to disinhibition engendered by a sense of security, or because HIV-infected persons become more sexually active as their health improves [11,12,22–25]. Therefore, we constructed models in which we randomly increased number of sexual partners per individual, so that the average number of

partners was increased by 50% or 100% among those receiving treatment, or among all vaccine recipients. The impact on incidence was compared to that estimated from the observed number of partners.

Demographic component projection model

To determine the number of HIV infected persons and HIV prevalence over 20 years, we constructed a demographic component projection model [26], using the Rakai population aged 15—59 years in 2000, stratified into 5-year age groups. Five-year age-specific HIV prevalences were used to estimate HIV-infected and uninfected populations. Details are given in Appendix V.

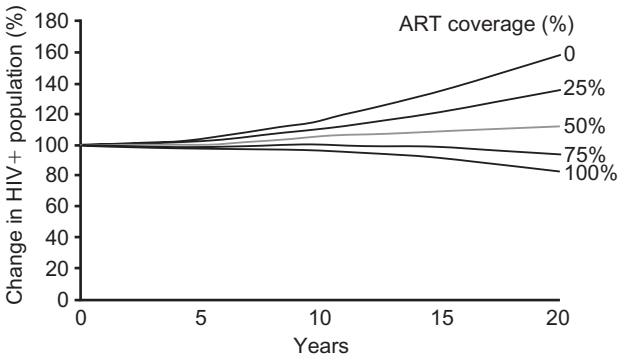

Fig. 2. Percent change in the HIV-positive population and HIV prevalence projected over 20 years, assuming initiation of ART using DHHS criteria and quartiles of treatment coverage among eligible persons.

Results

The HIV incidence rate generated by the model in the absence of treatment or vaccination was 1.57/100 PY, which is close to the observed incidence of 1.5/100 PY in the Rakai population for the period 1994–1998 [16]. Similarly, the simulated HIV transmission probability per coital act was 0.0012, which approximates the empirically estimated transmission probability per act of 0.0011 for the Rakai population [10].

Simulated effects of ART

Table 2 and Fig. 2 show the simulated effects of ART on HIV incidence, assuming the clinical experience of the US studies are applicable to the Rakai context, with respect to treatment induced reductions of HIV viral load and continuity of therapy. The impact of therapy on HIV incidence was more marked in simulations based on the Johns Hopkins Clinic experience than the WIHS data, because of the greater reductions in HIV viral load (Table 1). Using the Johns Hopkins data, if treatment were confined to persons meeting the DHHS criteria (i.e., HIV viral loads $> 55\,000$ copies/ml), even complete coverage of eligible patients could not reduce R_0 to < 1.0, and it is unlikely that control of the epidemic could be achieved by these regimens. The comparable simulations for the WIHS data showed that if DHHS treatment guidelines were applied, even with universal coverage, R_0 would be approximately be 1.27, and the epidemic would continue to grow at a substantial rate. If treatment criteria were extended to include all HIV-infected persons, irrespective of their viral load, the reduction in HIV incidence could be substantial and R_0 could be reduced to < 1.0. Sensitivity analyses examined lower and higher discontinuation rates than those observed in the Johns Hopkins Clinic (Appendix VI).

Fig. 2 shows the projected changes in the HIV-positive population over 20 years. In the absence of therapy,

Table 2. HIV incidence, probabilities of transmission per coital act and R_0, under two scenarios for treatment initiation, and quartiles of program coverage, based on clinical data from Johns Hopkins and the WIHS Study.

	Johns Hopkins clinic data criteria for initiation of therapy[a]				WIHS data criteria for initiation of therapy[a]			
	> 55 000 copies/ml		All HIV-positives		> 55 000 copies/ml		All HIV-positives	
Coverage (%)	HIV Incidence/ 100 PY[b]	Probability transmission/ sex act[c] (R_0)[d]	HIV Incidence/ 100 PY[b]	Probability transmission/ sex act[c] (R_0)[d]	HIV incidence/ 100 PY	Probability transmission/ sex act[c] (R_0)[d]	HIV incidence/ 100 PY	Probability transmission/ sex act[c] (R_0)[d]
0	1.57	0.0012 (1.44)	1.57	0.0012 (1.44)	1.57	0.0012 (1.44)	1.57	0.0012 (1.44)
25%	1.50	0.0011 (1.35)	1.13	0.0009 (1.13)	1.54	0.0012 (1.40)	1.38	0.0010 (1.22)
50%	1.42	0.0010 (1.26)	1.04	0.0007 (0.86)	1.50	0.0011 (1.36)	1.19	0.0008 (1.01)
75%	1.34	0.0010 (1.17)	0.78	0.0005 (0.62)	1.47	0.0011 (1.31)	1.00	0.0007 (0.83)
100%	1.27	0.0009 (1.09)	0.52	0.0003 (0.40)	1.43	0.0010 (1.27)	0.82	0.0005 (0.65)

[a]Observed discontinuation rate 1.8% per month, linear reduction in HIV log viral load 40% within 1 month of initiating therapy for Johns Hopkins data, and discontinuation rates 1.7% per month, linear reduction in HIV log viral load 26.8% within 3 months of initiating therapy for WIHS data. [b]Incidence rate estimated from total seroconversions per 100 person years (PY) for whole HIV-negative population at risk. [c]Probability of HIV transmission per coital act for discordant couples. [d]R_0 is the reproductive number over 10 years, based on the probability of HIV transmission per coital act, number of HIV-negative sex partners and median duration of HIV infection.

the population of HIV-infected persons is projected to rise by 57% over this period, because continued population growth (3.0% per year) and incident infections will offset the effects of HIV-associated mortality. However, ART could result in stabilization or a modest reduction in the number of HIV-infected persons. For example, with 50% ART coverage, the HIV-infected population would increase by 11%, and with 75% ART coverage the HIV-infected population would decrease by 7%.

Simulated effects of HIV vaccines

The simulated effects of a preventive vaccine are shown in Table 3 and Fig. 3. With a preventive vaccine of 25% efficacy and complete population coverage, HIV incidence might be reduced to 1.31/100 PY, and R_0 would be approximately 1.13. Therefore, even a low efficacy vaccine can reduce transmission if coverage is high, but the epidemic would not be curtailed. With higher vaccine efficacies, HIV incidence could be markedly reduced, and R_0 would be substantially below 1.0. For example, with a vaccine of 50% and 75% efficacies, R_0 could be reduced to 0.95 and 0.66, respectively, with 75% coverage of the population. A preventive vaccine could have marked effects on the projected numbers of HIV-persons (Fig. 3). Even a moderately protective preventive vaccine (e.g., 50% efficacy) with broad coverage could reduce the HIV-infected population by as much as 80% over 20 years, and HIV prevalence could fall as low as 1.2%. This would have profound implications for the control of the epidemic, both by reducing HIV incidence and reducing the need for ART over time.

If a preventive vaccine was combined with ART using DHHS criterion for initiation of treatment, the combined impact on HIV incidence is potentially substantial (Table 3). A preventive vaccine with only 25% efficacy, combined with treatment which covered 75% of the population at risk, could reduce R_0 to 0.82, resulting in abatement of the epidemic. Vaccines of greater efficacy could achieve a comparable impact on HIV incidence and R_0 at even lower levels of population coverage. The combination of a preventive vaccine with ART (Fig. 4) has a somewhat lesser impact on the HIV-infected population and HIV prevalence than a vaccine alone (Fig. 3), because of ART-associated improved survival of HIV infected persons.

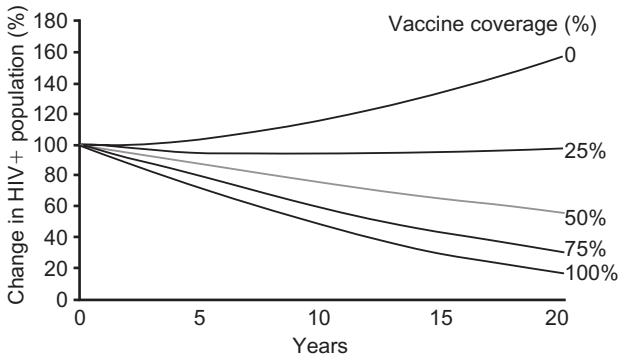

Fig. 3. Percent change in the HIV-positive population and HIV prevalence projected over 20 years, with a 50% efficacious preventive vaccine.

Effects of behavioral disinhibition

To assess behavioral disinhibition, we assumed an increase in the numbers of sexual partners among persons receiving treatment. If patients were treated according to DHHS guidelines, and disinhibition led to an increase in the number of sexual partners among those on therapy, the impact of treatment on HIV

Table 3. HIV incidence, probability of transmission per coital act and R_0, with a preventive vaccine and varying levels of efficacy and population coverage.

Vaccine coverage among HIV− and treatment coverage among HIV+	Vaccine efficacy					
	25%		50%		75%	
	HIV incidence/ 100 PY	Probability of transmission/sex act (R_0)[d]	HIV Incidence/ 100 PY	Probability of transmission/sex act (R_0)	HIV Incidence/ 100 PY	Probability of transmission/sex act (R_0)
Preventive vaccine alone						
No vaccination	1.57	0.0012 (1.44)	1.57	0.0012 (1.44)	1.57	0.0012 (1.44)
25% vaccinated	1.52	0.0011 (1.35)	1.43	0.0010 (1.26)	1.33	0.0009 (1.15)
50% vaccinated	1.45	0.0010 (1.28)	1.28	0.0009 (1.10)	1.07	0.0007 (0.89)
75% vaccinated	1.38	0.0010 (1.20)	1.12	0.0008 (0.95)	0.81	0.0005 (0.66)
100% vaccinated	1.31	0.0009 (1.13)	0.97	0.0007 (0.81)	0.56	0.0004 (0.45)
Preventive vaccine for HIV-negative persons combined with ART for HIV-positive persons using DHHS criteria						
25% vaccinated	1.37	0.0010 (1.20)	1.30	0.0009 (1.12)	1.20	0.0008 (1.02)
50% vaccinated	1.12	0.0008 (1.00)	1.10	0.0007 (0.86)	0.86	0.0006 (0.70)
75% vaccinated	1.00	0.0007 (0.82)	0.80	0.0005 (0.65)	0.56	0.0004 (0.45)
100% vaccinated	0.80	0.0005 (0.66)	0.59	0.0004 (0.46)	0.32	0.0002 (0.25)

PY, Person years; ART, antiretroviral therapy; DHHS, Department of Health and Human Services.

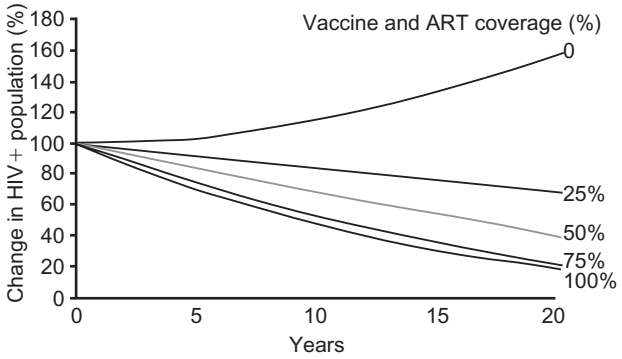

Fig. 4. Percent change in the HIV-positive population and HIV prevalence projected over 20 years, with a 50% efficacious preventive vaccine combined with HAART.

incidence would be attenuated, and it would be impossible to reduce R_0 even close to 1.0 (Fig. 5). If availability of treatment resulted in generalized disinhibition with a 25% increased number of sexual partners in the whole population (treated and untreated), then HIV incidence would rise markedly and the public health benefits of therapy would be lost (results not shown). Analogous simulations of disinhibition among recipients of a preventive vaccine with 50% efficacy suggest that disinhibition could counteract the public health impact, and even result in an increased HIV incidence (Fig. 5). The effects of disinhibition among vaccine recipients on HIV incidence is more marked than the impact of disinhibition among HIV-infected persons receiving therapy, because the population of HIV-negative vaccinees is much larger than the population of HIV-positive persons eligible for treatment.

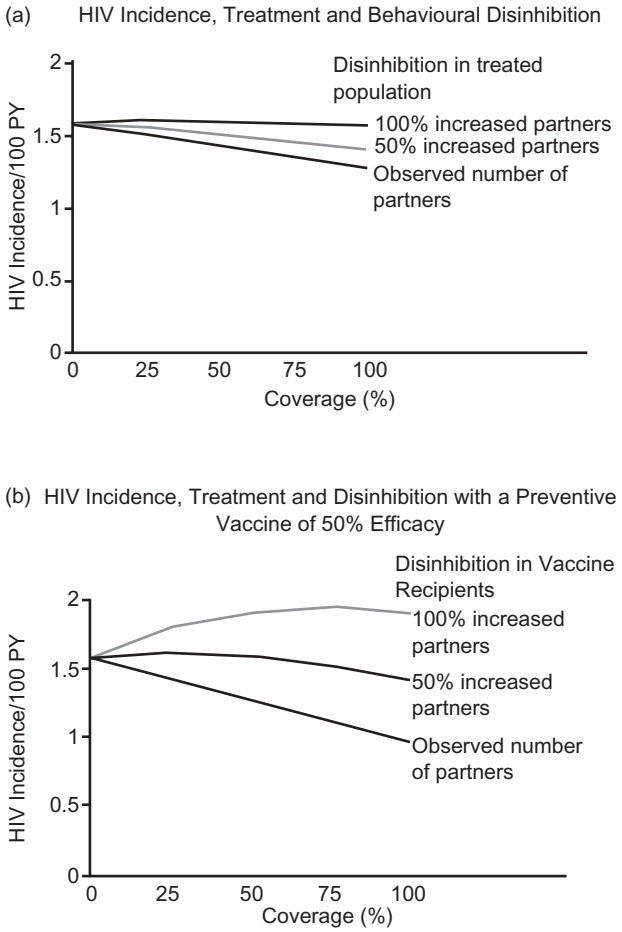

Fig. 5. HIV incidence associated with increased numbers of sexual partners among persons receiving HAART (a) or among recipients of a preventive vaccine with 50% efficacy (b).

Discussion

This simulation model based on empirical data from Rakai required minimal underlying assumptions, and model generated estimates of HIV incidence and transmission probabilities per coital act were similar to the empirically observed estimates [10,17], suggesting that the model closely approximated the HIV epidemic in the Rakai population. Simulations of the effects of ART based on data derived from the two US programs [20,21], also allowed realistic estimates of the effects on HIV incidence that might accrue from reductions of HIV viral load and continuity of treatment. It was assumed that the experience of these US clinics would reasonably reflect the optimal circumstances that might pertain in the Rakai population, if a high quality antiretroviral program were to become available and sustainable.

Of the two scenarios for initiation of ART, the most appropriate and feasible would be adherence to criteria for initiation of treatment compatible with the current DHHS guidelines [19]. As shown in Table 2, an ART program, comparable to that at the Johns Hopkins Clinic, could reduce but not interrupt transmission in Rakai. However, it is unlikely that such high standards of care are feasible in this resource-poor rural setting. A treatment program with viral load reductions comparable to those observed in the WIHS study would, in all likelihood, not be sufficient to control the epidemic. Among HIV infected persons in the Rakai cohort, 20% had HIV viral loads $> 55\,000$ copies/ml, and would thus be eligible for initiation of therapy under DHHS guidelines. It is estimated that 28.3 million people in sub-Saharan Africa are currently HIV infected [3], and assuming viral load distributions similar to those in Rakai, approximately 5.7 million HIV-positive persons would be currently eligible for ART. If, as suggested by these simulation, feasible treatment is insufficient to reduce R_0 to < 1.0, and has minimal effects on the number of HIV-infected persons (Fig. 2), then the

numbers of patients requiring treatment will increase substantially in the future, because currently treated persons will survive longer, persons presently in the latent stage of infection will progress to immunodeficiency, and continued HIV transmission will result in new infections which will progress to a disease stage where therapy is indicated. Thus, the need for treatment and the financial and health service burdens of therapy will increase substantially for the foreseeable future.

Although less stringent criteria for initiation of treatment could potentially control the epidemic (Table 2), and avoid the costs and difficulty of assessing viral load or CD4 cell counts to determine treatment eligibility, such widespread use of antiretroviral drugs would be extremely expensive and logistically difficult. Moreover, universal provision of therapy would be ethically questionable, because early treatment is unlikely to provide significant benefit to patients, and would expose them to risks of drug toxicity and selection of resistant virus [26–30], thus depriving the infected individual of effective therapeutic options during late stage disease [19]. We conclude, therefore, that ART alone is unlikely to curtail the growth of the HIV epidemic in sub-Saharan Africa.

There is a concern that poor compliance with use of HAART may result in treatment failures due to selection of resistant virus [19,29,30]. We did not formally simulate such a reduction in treatment efficacy because we cannot predict compliance in African populations. However, the majority of patients who discontinued therapy at the Johns Hopkins Clinic, did so as a result drug resistance and the absence of alternative therapeutic options [20]. Thus, the empirical data on discontinuation of treatment incorporated in our models implicitly accounts for emergence of resistant virus or toxicity as the main reasons for therapeutic termination.

The simulations of the potential impact of an HIV vaccine lack empirical data on efficacy, since no phase III trial had been completed at the time of waiting [23]. We therefore assumed a range of vaccine efficacies from a weakly protective (25% efficacy) to a highly protective vaccine (75% efficacy), based on animal studies or preliminary trial data. A vaccine of low preventive efficacy could not, by itself, control the epidemic (Table 3). However, if there was concomitant provision of ART to reduce viral load in HIV-positive individuals, there could be substantial reductions in HIV incidence and R_0 could be reduced well below 1.0, even with incomplete coverage (Table 3). Therefore, consideration should be given to combined strategies of treatment and vaccination, even if future vaccines have relatively low preventive efficacy. As illustrated in Fig. 3, a 50% efficacious vaccine could markedly reduce the numbers of HIV-infected persons in the population, and this will diminish the need for ART over time, thus potentially saving substantial resources. More efficacious vaccines would obviously have the maximum impact, but unfortunately no vaccine of proven efficacy is currently available.

Other models have simulated the impact of HAART on HIV incidence among homosexual men in San Francisco [11], and Australia [12], and suggest that treatment could have a substantial impact on incident HIV, but these models did not initiate treatment using current DHHS guidelines. There is growing evidence that homosexual men in Europe and North America are adopting higher risk practices since HAART became widely available, and that such disinhibition is occurring both among the HIV-positive treated patients and among HIV-negative individuals [24,25]. If behavioral disinhibition were to occur in response to treatment or a vaccine in the Rakai population, it could markedly offset the public health benefits (Fig. 5). Moreover, the adverse effects of disinhibition are dependent on the size of the population adopting high-risk behaviors. For example, disinhibition among recipients of ART results in moderate increases in incidence because the number of persons receiving ART constitute a small proportion of the total population. However, if disinhibition occurred among vaccine recipients, who constitute a potentially large proportion of the total population, then the increase in HIV incidence with higher risk behaviors is much more marked and results in rising HIV incidence, abolishing all benefits of vaccination. Thus, the promotion of safe sex is critical to the public health benefits that might accrue from ART or vaccines.

In conclusion, improved access to ART is needed for eligible HIV-infected persons in developing and developed countries to improve survival and quality of life. However, there is also a need to consider the societal benefits of therapy in terms of control of the HIV epidemic. ART initiated only for persons with advanced disease is unlikely to reduce HIV transmission sufficiently to control the epidemic. Moreover, benefits of therapy could be markedly offset by behavioral disinhibition. A preventive vaccine, were it to become available, offers the best hope of controlling the epidemic in the long-term, particularly if there was a concurrent ART program, or if the vaccine itself could reduce viral load in HIV-infected persons.

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Appendix I

Rakai Project Group Kalisizo, Uganda

N. Kiwanuka, G. Kigozi, F. Nalugoda.

Data by the Women's Interagency HIV Study (WIHS) Collaborative Study Group with centers (Principal Investigators) at New York City/Bronx Consortium (K. Anastos); Brooklyn, NY (H. Minkoff); Washington DC Metropolitan Consortium (M. Young); The Connie Wofsy Study Consortium of Northern California (Ruth Greenblatt, Herminia Palacio); Los Angeles County/Southern California Consortium (A. Levine); Chicago Consortium (M. Cohen); Data Coordinating Center (A. Munoz, S. J. Gange).

Appendix II

Parameters for model estimates of the probabilities of HIV transmission per coital act

Rakai data from HIV-discordant couples were used to

estimate the model parameters, with frequencies of intercourse reported by HIV-infected persons in the population as an offset term [10]. The analyses showed that the HIV-1 viral load in the HIV-positive partner was the main determinant of transmission risk, and the probabilities of transmission per coital act decreased with older age, and differed by gender. The likelihood ratio test of nested models indicated an improved fit with linear, quadratic and cubic $\log_{10}$ viral load terms (χ^2, 7.01; $P = 0.0081$). The parameter estimates for the latter model were as follows: log $(-\log [1-\gamma]) = -97.5 + 61.1[\log_{10}$ viral load$] + 13.7 [\log_{10}$ viral load$]^2 + 1.02 [\log_{10}$ viral load$]^3 + 0.35$ I [age 25–29] $+ 0.59$ I [age 30–34] $- 0.65$ I [age 35–59] $+ 0.56$ I [female] where I is an indicator function. It was assumed that the probabilities of transmission per coital act derived from studies of HIV-discordant couples applied to all HIV-infected persons, and that the distribution of viral loads in the discordant couples were representative of those in the general population of HIV-infected persons.

Appendix III

Variance of simulation models

The simulated probability of transmission per coital act was 0.0012 (SD, 0.000055, coefficient of variation 4.6%), and the mean HIV incidence was 1.57 per 100 PY (SD, 0.061, coefficient of variation 3.9%). Because of this precision in our estimates we have not included variance statistics in the results presented.

Appendix IV

Data on the impact of anitretroviral therapy on HIV viral load

The effects of therapy on HIV viral load were determined from information on 492 patients attending the HIV Clinic at Johns Hopkins Hospital [20] and 999 women enrolled in the Women's Interagency HIV Study (WIHS) [21]. The HIV Clinic at Johns Hopkins Hospital specializes in management of HIV infection; 79% of eligible patients received (HAART) between 1996 and 2000 [20]. Among 275 treatment-naive patients with viral loads $> 55\,000$ copies/ml attending the Johns Hopkins Clinic, the mean viral load declined from 5.32 to 3.06 $\log_{10}$ copies/ml, a 43.6% reduction within 1 month of therapy, and remained low thereafter (3.21 $\log_{10}$ copies/ml at 12 months). We therefore assumed a linear decrease in HIV viral load by 44% within 1 month of initiating therapy and an approximately constant viral load while on therapy. The participants in the WIHS study obtained care from a variety of service providers, 35% had received treatment prior to enrollment and 65.3% received HAART during follow up [21]. In 316 women with initial viral loads $> 55\,000$ copies/ml in the WIHS population, the mean $\log_{10}$ HIV viral load declined from 5.23 to 3.82 copies/ml within 3 months of initiation of HAART (a 27.0% reduction), and the viral load remained relatively stable thereafter (3.75 $\log_{10}$ copies/ml at 15 months). The differences in the viral load response to HAART in these two clinic populations probably reflects the more specialized management of the Johns Hopkins Clinic patients, compared with patients receiving care from diverse service providers in the WIHS data. These proportionate declines in HIV viral load were used to adjust the HIV-1 viral load distributions in the simulated populations receiving treatment.

Discontinuation of HAART, defined as interruption of therapy for more than 6 months for all reasons (drug toxicity, treatment failure and personal choice) was available from both studies for up to 3 years. At the Johns Hopkins Clinic, the mean discontinuation rate per month was 1.8%, and the cumulative proportion discontinuing treatment was 56.2% over 3 years. In the WIHS data, the mean discontinuation rate was 1.6% per month, with a cumulative discontinuation of therapy of 55.2% at 3 years. Thus, sensitivity analyses were conducted to assess the effects of better compliance assuming no terminations over 3 years, or half the observed Johns Hopkins termination rates (i.e., 0.9% per month). The effects of poorer compliance were assessed by assuming monthly discontinuation rates of 3.6% and 7.2% (i.e., a two- and fourfold increase in discontinuation rates). The reductions in viral load and continuity of treatment can be considered as measures of use-effectiveness of HAART in the USA, and these were applied to persons entering therapy in the model. It was assumed that the viral load returned to baseline levels within 1 month of termination of treatment [22], recursively returning terminating individuals to their baseline transmission risk. Persons continuing therapy could contribute to ongoing transmission, depending on their estimated HIV-1 viral loads. Treatment of acute seroconverters, as recommended by DHHS [19] was not simulated, because it is not feasible to identify newly infected persons during or shortly after the acute seroconversion illness in the rural Rakai setting. Seroconverters could become eligible for treatment if they met the criterion for initiation of therapy specified by the models.

Appendix V

Component projection model

In the model, HIV-negative individuals could remain uninfected when moving to next 5-year age group,

become HIV infected within a 5-year age interval, or be removed from the population by death. For the HIV-positive populations, persons could progress to the next older 5-year age group with or without receiving treatment (depending on eligibility and assumed treatment coverage levels). Among those receiving therapy, we projected continuation or termination of treatment over 5-year age intervals, using data from the Johns Hopkins Clinic. The cumulative 5-year continuation of therapy was 34%, implying that 66% of patients would terminate therapy either because of drug toxicity or treatment failure, and would return to the untreated HIV-positive population or die. Five-year age-specific mortality rates by HIV status were obtained from Rakai data [27] to calculate 5-year survival probabilities using exponential assumptions. For treated patients, we assumed that the relative mortality risk was 0.51 compared to untreated patients, based on reductions in mortality due to AIDS observed in the USA [4]. HIV-positive persons who discontinued treatment were assumed to have the same mortality rates as untreated individuals. Population growth rates were derived from Rakai data and we estimate that the population aged 15–19 years will increase by 3% per annum. HIV incidence estimated from the stochastic models was used as an input to calculate the HIV incidence over 5-year age intervals for the HIV-negative population. The age-specific probabilities of seroconversion over 5 years were obtained from the model derived incidence rates by an exponential distribution (seroconversion probability = 1−exp (−incidences within 5-year age group), allowing for declines in incidence, but assuming constant rate ratios of age-specific incidence rates. The proportional changes in the HIV-infected population estimated from the component projection model are presented.

Appendix VI

Sensitivity analyses for ART

Sensitivity analyses examined lower and higher discontinuation rates than those observed in the Johns Hopkins Clinic. Using DHHS guidelines for therapy and the Johns Hopkins clinic data, if no patients discontinued treatment, the incidence would be 1.15 per 100 PY, approximately 10% lower than the simulations for complete coverage shown in Table 2. Thus, improved continuation of therapy beyond that currently observed at Johns Hopkins does not appear to yield substantially greater public health impact. However, if discontinuation rates were substantially higher than those observed in the Johns Hopkins Clinic, the impact on HIV incidence would be markedly attenuated. For example, if the termination rate was four-fold higher (i.e., 7.2% per month), HIV incidence would be approximately1.45 per 100 PY with complete coverage of eligible patients, which is only 7.6% less than the estimated incidence in the absence of treatment (1.57 per 100 PY). Thus, poor continuity of therapy could undermine the public health impact of HAART.