

# Supporting on-line information

## Universal HIV Testing with Immediate Antiretroviral Therapy as a Strategy for Eliminating HIV Transmission

Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG

### Initial distribution of CD4<sup>+</sup> cell counts

The initial distribution of CD4<sup>+</sup> cell counts, shown in Figure 1, is taken from a random sample of young adult men in Orange Farm, Gauteng, South Africa.<sup>1</sup> The fitted curve is log-normal with a median at 1116/ $\mu$ L and a standard deviation of 0.303.<sup>1</sup>

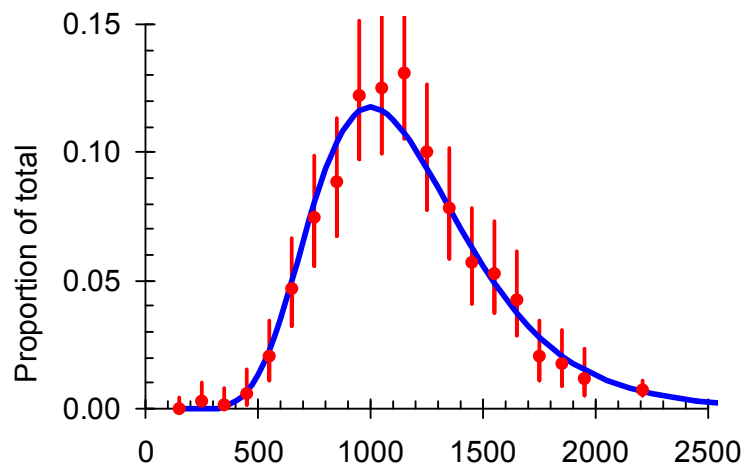


Figure 1. The observed distribution of CD4<sup>+</sup> cells in HIV-negative men in South Africa.<sup>1</sup>

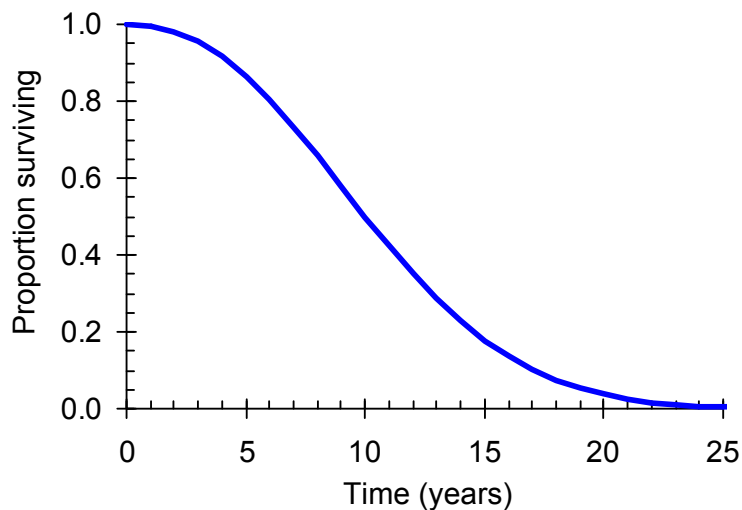


Figure 2. The Weibull survival curve used in the model based on data from the CASCADE study.<sup>2</sup>

## Survival distribution

The models are not age structured. We therefore assume that survival follows a Weibull distribution<sup>3</sup> with a median of 11.0 years and a shape parameter of 2.25<sup>4</sup> as illustrated in Figure 2.

## Stochastic model for estimating $R_0$

### Variation in infectivity with time

For a person with a given survival time, we allow the infectivity to vary with time as illustrated in Figure 3. We consider three phases which we will call acute, chronic and final. The infectivity can be varied in each of three phases as indicated by the letters *a* to *c* in Figure 3, and the duration of the acute and final phases can be varied as indicated by the letters *d* and *e* in Figure 3.

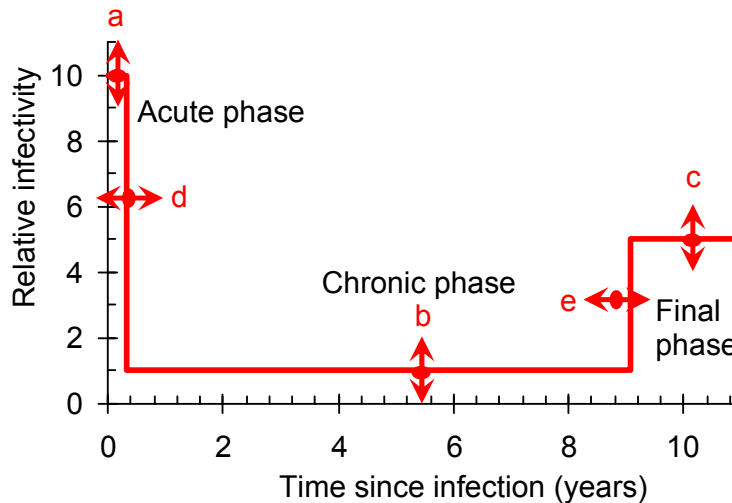


Figure 3. Schematic diagram of the change in infectivity with time in a person who survives for ten years. There is an initial acute phase with high infectivity, a chronic phase when the infectivity is lower and a final phase when the infectivity increases again. The infectivity during each of the three phases (*a*–*c*) can be varied, as can the duration of the acute and final phases (*d* and *e*).

The parameter values in Figure 3 are not known precisely. In a study in Uganda the HIV transmission probability per coital act was measured directly between discordant couples<sup>5,6</sup> and the transmission probability during the first five months after infection and the last three years before death was compared to the transmission probability during the chronic phase. Two other studies used the same data but obtained slightly different rates.<sup>7,8</sup> In a study in the USA viral load in plasma and in semen was measured as a function of time since infection with HIV and the transmission rates during the acute and final phases were compared to the rates during the chronic phase among men who have sex with men.<sup>9</sup> In a study in San Francisco, USA, the transmission probabilities from men with known dates of sero-conversion to their female partners were compared 20 and 54 days after sero-conversion.<sup>10</sup> The results of these studies are given in Figure 4. For our base-line calculations we assume

that the acute phase lasts for two months during which time the probability of transmission is ten times greater than during the chronic phase and that the final phase lasts for 10% of the survival time (1.1 years when survival is eleven years) and during this time the probability of transmission is five times greater than it is during the chronic phase.

We adjust the chronic phase infectivity to give the appropriate value of  $R_0$ , the mean number of secondary infections that arise from one primary infection, per year. The infectivity in the acute and chronic phases is then calculated as described above.

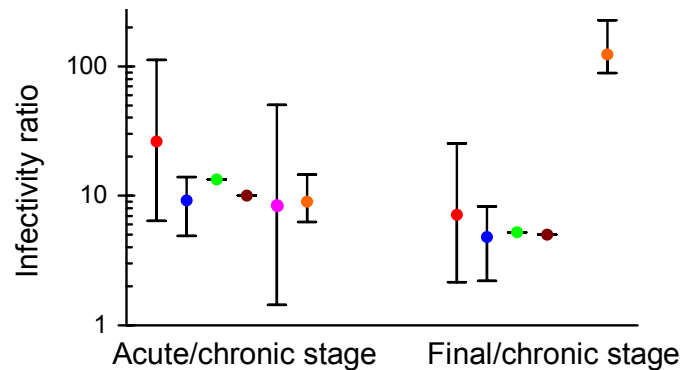


Figure 4. Estimates of the ratio of the infectivity per sexual contact in the acute and final phases to the chronic phase. Red, blue and green points are three different analyses using data from Rakai, Uganda,<sup>6-8</sup> the brown points give the values used in this paper, the pink point is for transmission to the female partners of men with known dates of sero-conversion in the United States<sup>10</sup> and the orange points are for receptive anal intercourse in a study of men in San Francisco.<sup>9</sup>

### Partners and concurrency

For the baseline calculations the number of concurrent partners is four and the mean duration of partnerships is six months so that people have an average of eight partners per year. At each time step any one of the current partners may be changed with a probability calculated to give the preset mean duration of a partnership.

### Model structure

The model runs as follows. Let  $P(C)$  be the log-normal distribution of initial CD4<sup>+</sup> cell counts;  $P(S)$  be the Weibull survival distribution;  $p(a)$ ,  $p(c)$  and  $p(f)$  be the probabilities, per unit time step, that the index case infects any one partner during the acute, chronic or final phase of infection, respectively;  $p(n)$  and  $p(h)$  be the probabilities, per unit time step, that the index case changes any one partner or is tested for HIV, respectively.

- 1 Choose a starting CD4 cell count randomly from  $P(C)$ .
- 2 Choose a survival time randomly from  $P(S)$ .
- 3 During each step:
  - 1.3 Check if the person is in the acute, chronic or final phase of infection;
  - 2.3 Infect another person with probability  $p(a)$ ,  $p(c)$  or  $p(f)$  depending on the phase of infection;

- 3.3 Change one or more partners, each with probability  $p(n)$ ;
- 4.3 Test the person for HIV with probability  $p(h)$ ;
  - 3.4.1 If the person is, or has previously been, tested (and is, by definition, HIV-positive) check the persons CD4 cell count.
    - 3.4.1.1 If it is below the CD4 threshold → Stop
    - 3.4.1.2 If it is above the CD4 threshold increase time, calculate a new CD4 count → 3.
  - 3.4.2 If the person has not been tested check if the CD4 cell count is greater than zero.
    - 3.4.2.1 If the CD4 cell count is less than or equal to zero → Stop
    - 3.4.2.2 If the CD4 count is greater than zero increase time, calculate new CD4 count → 3.

### **Illustration of the model**

The baseline parameter values are given in Table 1. The model, which runs in Excel using Visual Basic, is available from the senior author on request. The model runs with a time step of one month. At each time step other people may be infected, any of the partners may be changed, and the index case may be tested for HIV. Each of these Poisson processes happens with a fixed probability chosen so that the mean rate of infection, duration of partnerships or rate of testing match the values defined by the parameters in Table 1 and the initial CD4<sup>+</sup> cell count and the survival are chosen from the distributions specified. Random numbers are generated using a Mersenne-Twistor.<sup>11,12</sup>

### **Model output**

The output of the model is illustrated in Figure 5 to Figure 7. Figure 5 shows the distribution of the number of secondary cases which ranges from 0 to 25 with a mean of 7.4. Figure 6 shows the distribution of the time  $\bar{\tau}$  between the primary infection and each secondary infection. The mean value of  $\bar{\tau}$  is 7.54 years but note that many more people are infected during the acute phase in months 1 and 2 than in any other month although the acute phase infections are still only 8.9% of all infections. The chronic phase infectivity was chosen to give a doubling time of  $R_0$  of 7.4 and a mean time to each secondary infection of 7.54 years so that the epidemic doubling time is  $\tau_0 \approx \bar{\tau}/(R_0 - 1) = 1.2$  years, close to the observed value for South Africa<sup>13</sup> (see Figure 4B in the main text). Figure 7 provides a check that, if ART is not provided, the stochastic model produces the preset Weibull survival distribution.

Table 1. Parameter values for the log-normal distribution of the initial CD4 cell count (Figure 1); the Weibull survival (Figure 2); the chronic phase is defined in terms of the number of people who are infected each year (on average); the acute phase which is a step function with a defined mean duration and the infectivity set relative to that in the chronic phase; the final phase which is a step function with a preset infectivity and duration set to a fixed proportion of the survival in a particular run; the number of concurrent partners in a given simulation is fixed as is the mean duration of each partnership. Infection is a Poisson process as is the probability of changing any partner with rates set to match the preset mean values. The CD4 count at which ART begins, if the person has been tested is fixed. The last row sets the number of Monte Carlo repeats.

Parameter definition		Value	Dimensions
Initial CD4	Mu	6.98	Log normal location parameter
	Sigma	0.34	Log-normal shape parameter
Survival	Median	10.0	Years
	Shape	2.25	Dimensionless
Acute phase	Duration	2	Integer months
	Infectivity	4.50	Number/year
Chronic phase	Infectivity	0.45	Number/year
Final phase	Infectivity	2.25	Number/year
	Duration	0.15	Proportion of expected life
Concurrency	Number	4	Number
Partnership	Duration	6	Months
Start ART	CD4	0	/micro-litre
Proportion tested	Rate	0	/year
Monte Carlo	Repeats	10,000	Number

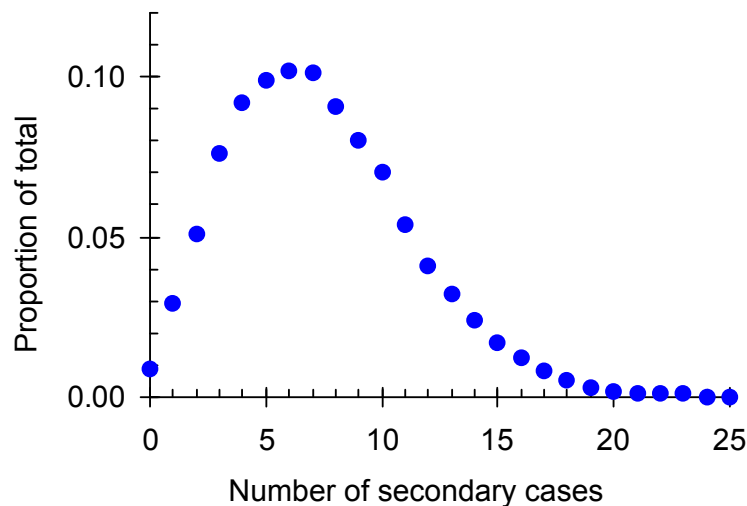


Figure 5. The frequency distribution of the number of secondary cases generated by one primary case. The mean number of secondary cases is 7.4.

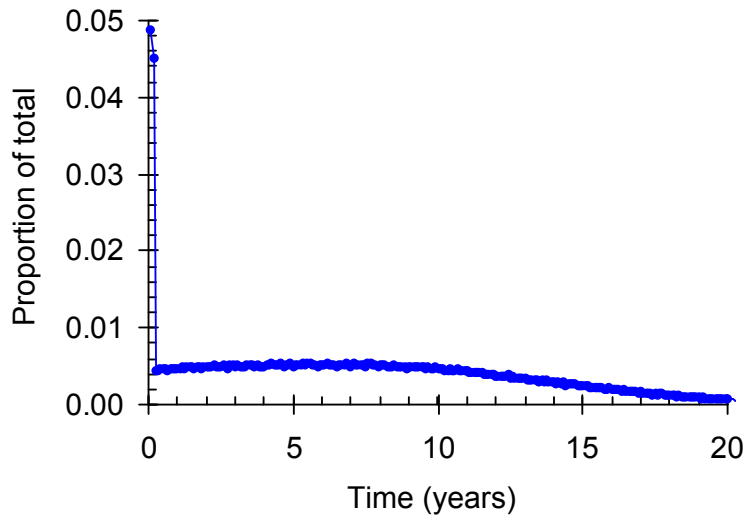


Figure 6. The frequency distribution of the time between the infection of the index case and the infection of each secondary case. Transmission is highest during the first two months but only contributes 8.9% of all secondary infections.

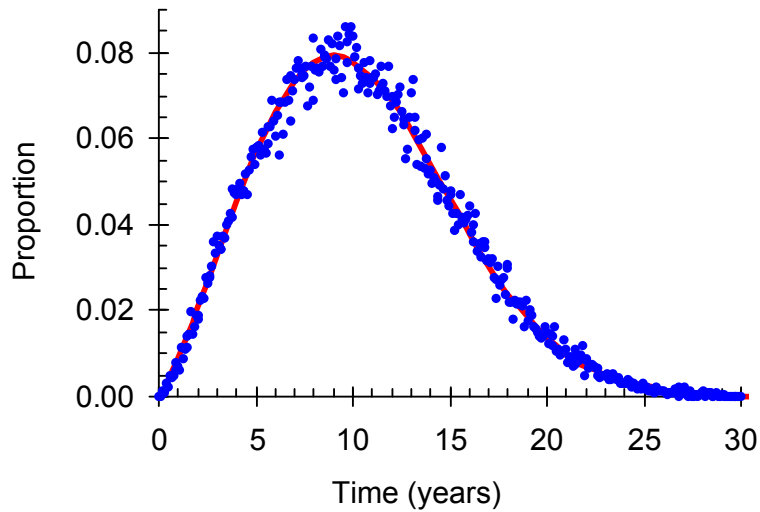


Figure 7. The frequency distribution of the time to death from the simulation (blue dots) compared to the distribution obtained from the Weibull curve if no one is started on ART, as confirmation of the model.

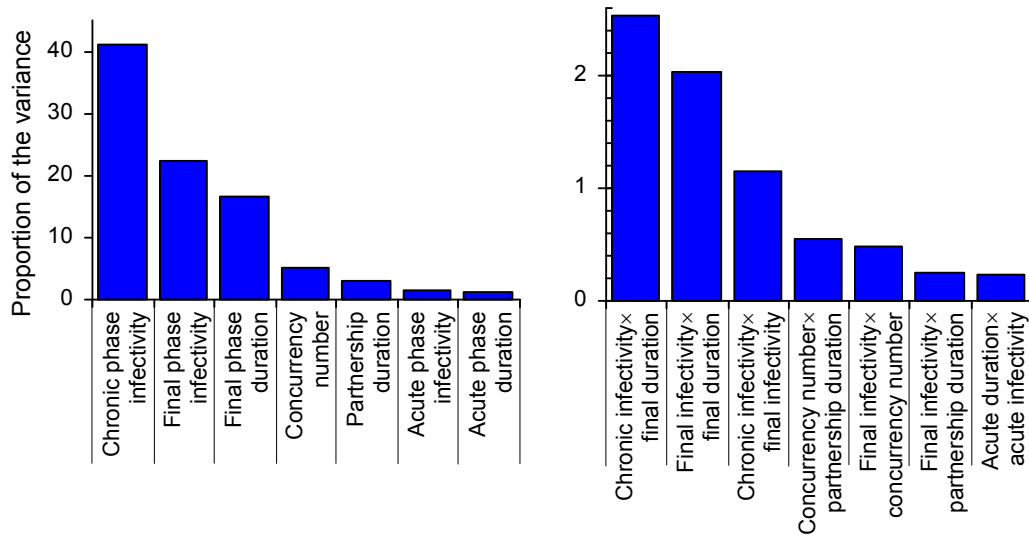


Figure 8. Proportion of the variance in the average value of  $R_0$  explained by the variation in each parameter. Considering the individual terms, 80% of the variance is explained by the chronic and final phase parameters and 11% by the concurrency number, the partnership duration and the acute phase parameters. Considering the interaction terms 5.7% of the variance is explained by the chronic and final phase parameters and 1.5% by the concurrency number, the partnership duration and the acute phase parameters.

### Sensitivity analysis

In order to explore the sensitivity of the estimated values of  $R_0$  to the various parameters in the model we ran one thousand simulations with the base line set of parameters from which we calculated  $R_0$  and the intrinsic doubling time  $\tau_0$ . We repeated this ten thousand times and on each repeat each parameter was kept the same or multiplied or divided by 2 with equal probability. The ten thousand results were then imported into *Stata* and a multivariate analysis of variance was done with  $\ln(R_0)$  as the dependent variable and the full set of parameters as the independent variables (Figure 7). (A similar analysis was done for  $\ln(\tau_0)$ ; results not shown).

We examined the role of the high levels of infectivity during the acute phase when people have several concurrent partners because the dynamic model, with which we explore trends in prevalence, incidence and mortality as we approach the elimination phase of HIV, does not include a separate acute phase. The analysis-of-variance (Figure 8) shows that the terms in the model involving the chronic phase and the final phase account for 80% of the variance (86% including their interactions). The terms involving concurrency, partnership duration and the acute phase account for 11% of the variance (13% including their interactions). The model output is therefore relatively insensitive to the acute phase parameters as compared to the chronic phase parameters for similar proportional changes in the parameters.

Table 2. The coefficients of the regression of  $\ln(R_0)$  and  $\ln(\tau_0)$  against the various independent variables. The table gives the constant term, the regression coefficients and the change in  $R_0$  or  $\tau_0$  if the parameter is doubled or halved from the based line values given in Table 1. The standard deviations of the estimates of each co-efficient (arising from the Monte Carlo simulation) are all less than 0.002. The base-line value of  $R_0$  is  $e^{2.058} = 7.84$  and of  $\tau_0$  is  $e^{0.073} = 1.08$  yrs.

Variable	Coeff. ( $R_0$ )	$\Delta R_0$ (%)	Coeff. ( $\tau_0$ )	$\Delta \tau_0$ (%)
Constant	2.058	•	0.073	•
Chronic phase infectivity	0.303	35	-0.420	-34
Final phase infectivity	0.226	25	-0.160	-15
Final phase duration	0.192	21	-0.152	-14
Concurrency number	0.108	11	-0.134	-10
Duration of partnerships	-0.082	-8	-0.117	-8
Acute phase infectivity	0.063	6	-0.109	-13
Acute phase duration	0.054	6	0.073	-11

Table 2 shows the proportional change in  $R_0$  when each of the parameters is increased by a factor of two. The value of  $R_0$  is about two to three times less sensitive to changes in the parameters defining the number and duration of partnerships and about four to five times less sensitive to changes in the parameters defining the acute phase than it is to the parameters defining the chronic and final stages of infection. If we were to eliminate the acute phase from the model, by setting the infectivity during this phase and during the chronic phase to be the same, we would have to reduce the acute phase infectivity by a factor of ten. To maintain the value of  $R_0$ , we would need to balance this ten-fold reduction in the relative infectivity of the acute phase by the increasing chronic-phase infectivity by a factor of 1.6. These results show that the overall level of transmission is dominated by the chronic and, to a lesser extent, the final phase, rather than by the acute phase. In a subsequent publication we intend to explore in more detail the affect of each of the parameters in the model to transmission.

We carried out a similar analysis to explore the sensitivity of the doubling time to each of the parameters. The results, also given in Table 2, are similar to those for  $R_0$  except that the result is less sensitive to the final phase infectivity and more sensitive to the acute phase infectivity, as one would expect given the long time scale over which the latter is effective and the short time scale over which the former is effective.

### **Summary**

The stochastic model suggests that the results depend mainly on the overall level of transmission rather than transmission during the acute phase or the number of concurrent partners. In essence, if each HIV-positive person infects one person every one to two years, on average, then even allowing for a ten-fold increase in infectivity during the acute phase they will only infect one person every one to two months during the acute phase no matter

how many concurrent partners they have. Furthermore, if the acute phase was mainly responsible for driving the epidemic then the doubling time would be of the order of months, not years.

## **Dynamical model to assess impact of interventions**

The dynamical model is illustrated and described in Figure 3 in the main text. Here we discuss the assumptions underlying the structure of the model and give details of the estimation of some of the parameters.

### **Survival on and off ART**

The model has four infected classes so that the survival is a gamma-function,  $\Gamma(\tau, 4)$ . A Weibull function with shape parameter 2.25 and mean survival equal to 11 years has a median survival of 10.6 years. The best fit gamma-function has  $\tau = 2.8$  years so that people move between classes at a rate  $\omega = 1/\tau = 0.36/\text{year}$ .<sup>14</sup> If people are tested and found to be positive they move to the equivalent ART stage, at a rate  $\tau$ , and continue to progress from there (Figure 2 in the main text). If people are non-compliant they move back from the ART boxes to the equivalent non-ART boxes at a rate  $\phi$ .

The survival on ART after being found to be HIV-positive in each of the four compartments is important to the model but difficult to determine precisely. A recent paper<sup>15</sup> suggests that survival on HAART is about 6 to 8 years if people start when they are symptomatic and their CD4<sup>+</sup> cell count is less than 100/ $\mu\text{L}$ , and about 15 to 18 years if people start HAART when they are asymptomatic and their CD4<sup>+</sup> cell count is  $> 350/\mu\text{L}$ . Here we let  $\sigma = 2\tau$ . Since the mean survival time without ART is eleven years the mean duration in each of the four compartments for infected people is 2.8 years. Since the mean CD4<sup>+</sup> cell count in Figure 1 is 1179/ $\mu\text{L}$  and there is an initial decline of 25% immediately after seroconversion,<sup>16-19</sup> the mean CD4<sup>+</sup> cell count in each of the compartments is 774/ $\mu\text{L}$ , 553/ $\mu\text{L}$ , 332/ $\mu\text{L}$  and 111/ $\mu\text{L}$ . When HIV-positive people are started on treatment they move from one of the four compartments  $I_i$  to the corresponding compartment  $A_i$ . The average life-expectancies of people who are detected in states  $I_1$  to  $I_4$  and who start ART immediately, are therefore 21, 18, 15 and 12 years, respectively.

### **Adherence to ART**

The conditions for eliminating HIV are sensitive to the level of adherence. We stop transmission by putting everyone who is HIV-positive on ART so that there are a very large number of people living on ART and if a small proportion of them stop taking their drugs they will contribute a significant number of infectious cases to the population.

Field data under programme conditions are available from Malawi (A.J. Harries, person communication). Here we use the results of the Malawi cohort analyses that have been reported for each quarter for the last two years. In these analyses reports were made 6, 12, 18, 24 and 36 months after people started ART (although not all of these time periods were reported in each report). In each quarter we start with the number of people who started treatment the appropriate number of months earlier which ranges from three thousand to

thirteen thousand, the total number of reports in all the cohorts combined being 163 thousand. The possible outcomes were: Alive and on ART; Transferred out; Dead; Lost to follow up; and Stopped treatment.

In the quarterly reports for Malawi 19% of those who started treatment were ‘transferred out’ and, in the reports, are presumed to be still alive. Here, we remove them from the numerator and denominator which is equivalent to assuming, more conservatively, that their outcomes are the same as the outcomes for those who remain in the cohort. A substantial proportion of people die, 16% of all those that started treatment, in part because most people in Malawi start ART with fairly advanced infections. Those who die reduce the total number of people who are on ART so that leaving them out of the model makes the model more conservative. However, in all of the cohorts 11% of people were lost to follow up and 0.7% stopped treatment and we need to decide what proportion of people who were lost to follow up also stopped treatment; they may have died or they may have started treatment elsewhere.

Table 3. Cohort analyses from the ART programme in Malawi. For each quarter the table gives the number of months before that quarter when people started ART. It then gives the number of people who started treatment and the proportion of these that were lost to follow-up the appropriate number of months later.

	2007 Q4		2007 Q3		2007 Q2		2007 Q1		2006 Q4		2006 Q3		2006 Q2	
Mnth.	Start. (k)	Lost (%)	Start. (k)	Lost (%)	Start. (k)	Lost (%)	Start. (k)	Lost (%)	Start. (k)	Lost (%)	Start. (k)	Lost (%)	Start. (k)	Lost (%)
6					11.8	8.6	11.0	8.4	9.8	7.3	8.3	7.9	7.1	9.9
12	11.2	11.6	11.0	10.0	9.7	8.6	8.0	10.9	7.1	13.0	7.1	9.2	4.6	8.6
18					6.6	11.5	6.7	10.7	4.7	10.6	4.0	10.1	2.5	11.6
24	6.8	14.1	6.6	10.9	4.5	10.9	3.9	13.1	2.6	13.7				
36	1.9	16.6	2.0	13.4										

The data in Table 3 are plotted in Figure 9. The fitted line is an off-set exponential of the form:

$$L(t) = \alpha + (\beta - \alpha)(1 - e^{-\gamma t}) \quad 1$$

It is difficult to be certain about the rate of loss in the first six months but the fit in Figure 9 suggests that the initial loss to follow-up is about 7%. After the initial drop-out the loss to follow-up is 2.9% per year falling to 2.2% per year after three years. A recent study in Malawi<sup>20</sup> traced 737 who had transferred out and found that 92% of them had transferred in to another programme with a median delay of 1.3 months. If these numbers apply broadly then the loss to follow up, after the first six months, is about 0.2% per year. To this we need to add the 0.7% per year who are known to have stopped treatment. The initial drop-out rate from ART, excluding those that die, may be as high as 8% and the subsequent drop-out rate is likely to be between 1% and 3% per year. Here we assume a long-term drop out rate (excluding deaths) of 1.5% per year.

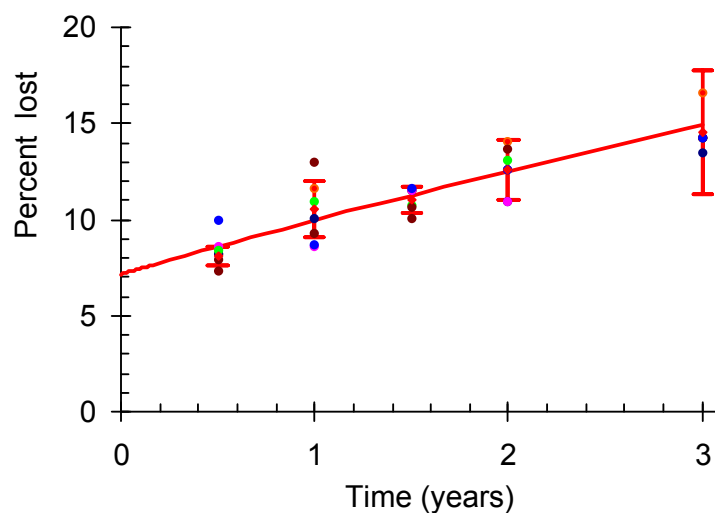


Figure 9. Cumulative loss to follow-up for the Malawi cohort (Anthony Harries, personal communication). Dots are data from particular cohorts. Orange diamonds give average values with 95% error bars. The solid line is an off-set exponential (Equation 1) with  $\alpha = 7.2$ ,  $\beta = 43.1$ ,  $\gamma = 8.1/\text{yr}$ .

### Transmission on ART

We need to consider the residual transmission when people are on ART. We assume people are either completely compliant with their treatment or, if they fail, they return to the untreated state. While people who are fully compliant with respect to their drugs are unlikely to infect others, there may be some residual transmission. A recent study of the reduction in viral load<sup>21</sup> suggests that there is a two-log decline in viral load over the first twenty days after starting ART treatment and a further two- to four-log decline over the next 150 days after starting treatment. The reduction seems to be the same for those starting treatment relatively early, with a median CD4<sup>+</sup> cell count of 444/ $\mu\text{L}$ , as it is for those starting late, with a median CD4<sup>+</sup> cell count of 13/ $\mu\text{L}$ . However, adherence is important and there is viral rebound among those who do not fully comply with their treatment.

Data on the relationship between viral load and transmission are limited. However, a study in Uganda suggests that transmission declines as the viral load to the power of 0.4<sup>22</sup> so that that reducing viral load by between  $10^6$  and  $10^4$  times would reduce transmission to between 0.4% and 2.5% of its value when people are not on ART. Direct data are also limited and the few published studies generally involve people in the late stages of infection or on mono-therapy.<sup>23,24</sup> In a study of discordant couples in Uganda<sup>25</sup> transmission was reduced to 2% (0.05%–11%) of its pre-ART level. Here we assume for our base-line calculations that ART reduces transmission to 1% of the value when people are not on treatment. The extent of residual transmission among people who are on ART is of great importance and this is subject to a sensitivity analysis in Figure 10g (below).

### Rate of spread of programme coverage

We assume that coverage increases logistically as shown in Figure 10. In 2007 UNAIDS estimates were that about 5% of all those living with HIV were on ART (250k out of 5.3M). We also assume that coverage reaches 50% in 2011 and that it reaches 95% in 2016.

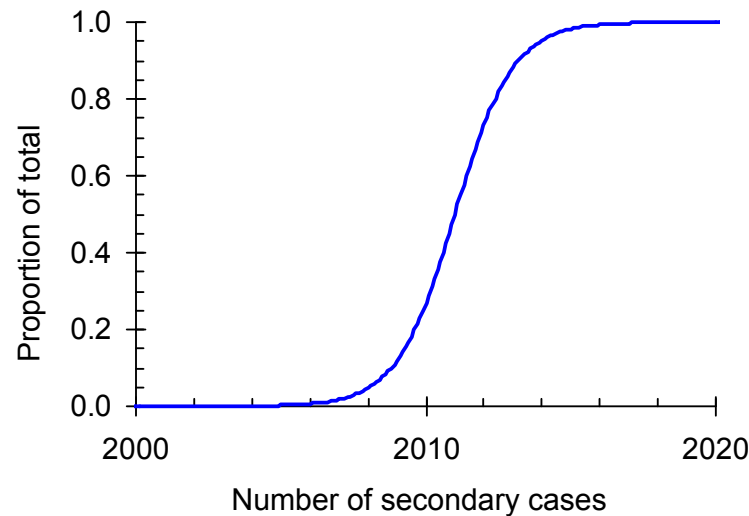


Figure 10. The coverage or extent of the intervention as a function of time. We assume that at full coverage 90% of the population is reached.

### Comparison with other control methods

We compare the impact of the proposed strategy with the impact of other methods of reducing transmission which might include partner reduction, condom use, treatment of curable sexually transmitted infections, male circumcision and so on.

Figure 11 shows the impact on the epidemic if transmission is reduced by 20%, 40%, 80% and 95%. If transmission is reduced by 40% over the next ten years this will only reduce the incidence in 2030 to 1.2% per year (Figure 11B). To achieve a reduction equivalent to that of the proposed strategy (Figure 4A in the main text) would need a reduction in transmission of 95% over the next ten years (Figure 11D).

### Sensitivity analysis

It is important to examine the sensitivity of the results to the various parameters in the model. Since we are concerned mainly with the conditions under which we can eliminate transmission we focus the sensitivity analysis on the effect that varying the model parameter has on the incidence, prevalence and mortality among people not on ART in 2030.

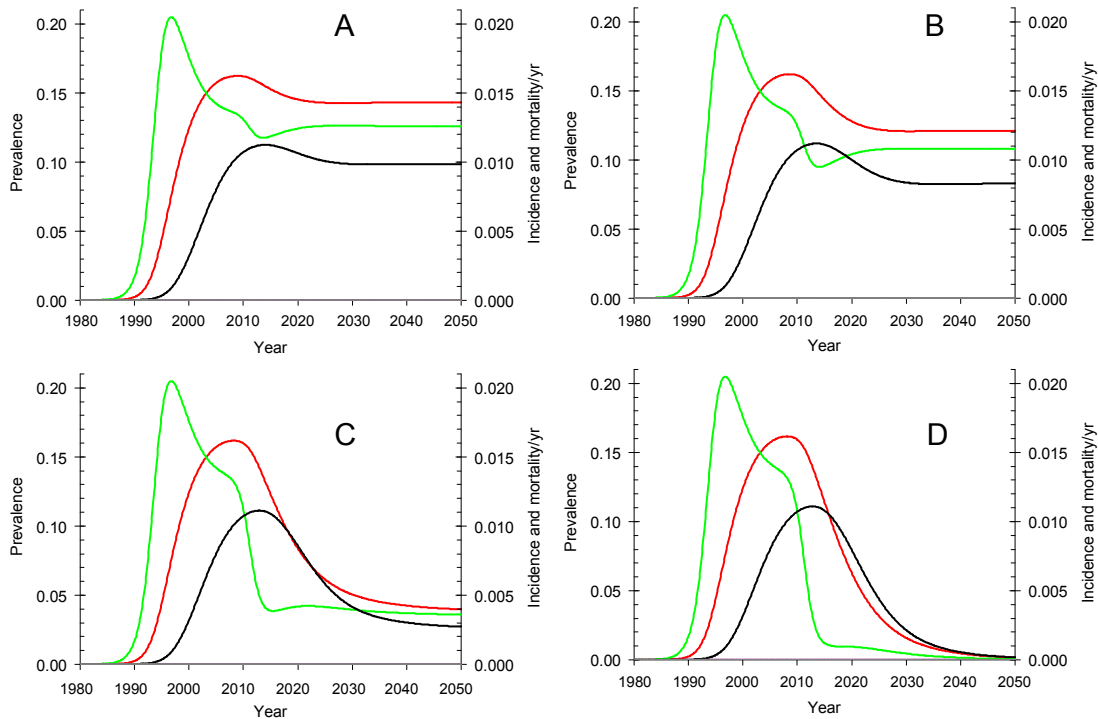


Figure 11. The impact of interventions that reduce transmission on the prevalence (red), incidence (green) and mortality (black) of HIV in South Africa. The reduction in transmission follows the curve shown in Figure 10 and the final reduction is A 20%, B 40%, C 80% and D 95%. The 95% reduction in transmission shown in D is the reduction needed to match the impact of the proposed strategy on incidence in 2030 as shown in Figure 4A of the main text.

Figure 12 shows a univariate sensitivity analysis in which the parameter values are varied about their default values given in Table 4. We plot the prevalence, incidence and mortality among those that are not on ART in 2030 against each parameter. Among adults, at the default values, the prevalence is 0.10%, the incidence is 0.042% per year, and the mortality is 0.002% per year as indicated by the large dots in Figure 12.

Figure 12A shows that the impact is insensitive to the rate at which the intervention is implemented bearing in mind that we assume that the intervention reaches halfway at the same year so that if it takes longer it also starts earlier. Starting the intervention later would simply delay the impact.

Figure 12B shows that if we also ensure that people with low CD4<sup>+</sup> cell counts are identified and started on ART, then we reduce mortality by a further factor of ten but have little additional impact on incidence or prevalence, as expected on the basis of the Monte Carlo model.

Figure 12C shows that the results are very sensitive to the average testing interval. To keep the incidence of new infection below 0.1% per year we need to ensure that people are tested at least once a year, on average.

Figure 12D shows that the results are insensitive to the proportion refusing treatment essentially because they do not start ART and do not contribute to the build up of people on ART whose breakdown leads to the residual transmission in 2030. Once the elimination phase

has been reached there are few new incident cases and the refusal rate does not have a major impact on transmission.

Table 4. Base-line parameter values. The demographic, transmission, progression, drop-out and testing rates refer to the parameters in Figure 3 of the main text. The intervention parameters define the logistic curve which gives the rate at which the interventions are rolled out. ‘Testing refusal’ gives the proportion of people who refuse testing so that the actual testing rate is  $\tau(1-\xi)$ . The ‘CD4 failure rate’ gives the proportion of people who, having been tested at a low CD4 cell count, fail treatment and die. The parameter for ‘other interventions’ gives the reduction in transmission due to condom use, behaviour change or any other complementary intervention. We assume that these are rolled out following the same logistic curve defined in the table.

Parameter		Value	Units
Birth rate	$\beta$	0.029	/yr
Background mortality rate	$\mu$	0.018	/yr
Transmission parameter	Initial value $\lambda$	0.767	/yr
	Location $\alpha$	0.055	0
	Shape $n$	0.996	0
	Relative transmission on ART $\varepsilon$	0.010	
Progression	Untreated $\rho$	0.303	/yr
	Treated $\sigma$	0.165	/yr
Intervention	Timing $t$	2011	yr
	Rate $r$	1.00	/yr
	Maximum $m$	0.90	
Testing	Rate $\tau$	1.00	/yr
	Refusal $\xi$	0.08	
Drop-out	$\phi$	0.015	/yr
CD4	On/Off	Off	
	Failure rate $\eta$	0.10	/yr
Other interventions	Reduction in transmission $\gamma$	0.40	

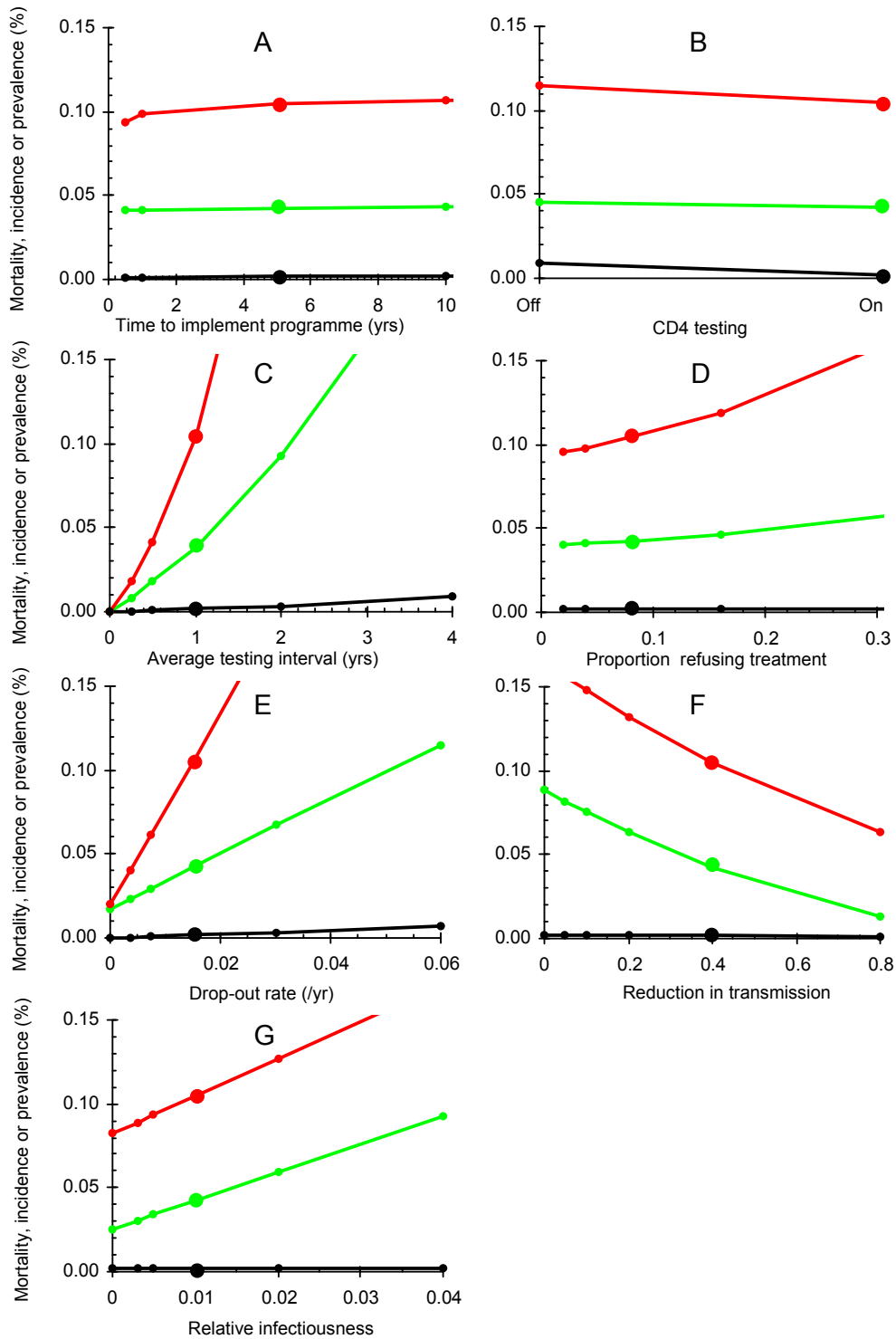


Figure 12. Sensitivity analysis. Red: prevalence; green incidence; black mortality, in 2030. A The time it takes to implement the programme; B The effect of introducing testing at low CD4 cell counts, C The rate of testing; D The proportion of people that refuse treatment; E The rate of drop-out from the ART programme (excluding deaths); F The reduction in transmission if a complementary intervention is introduced at the same time. Large dots give the values for the base-line parameter values.

Figure 12E shows that the results are sensitive to the rate at which people drop-out of the ART programme and return to an infectious state. To ensure that the incidence is less than 0.1% per year in 2030 fewer than 5% of people should drop-out of the ART programme each year. The reason for this is that when the elimination phase has been reached there are very many HIV-positive people living on ART and if only a small percentage of them drop-out this has a big impact on transmission.

Figure 12F shows that while other complementary interventions have an impact on prevalence and incidence they have much less impact on mortality as this depends on people who are already infected progressing to death over a period of ten years.

Finally, Figure 12G shows that incidence and prevalence are sensitive to the relative infectiousness of people on ART compared to those not on ART. To keep the incidence of new infections below 0.1% per year the infectiousness of those on ART should be less than 5% of that of those not on ART.

### ***Summary***

The key parameters are the testing rate, the drop out rate and the relative infectiousness of people on and off ART. If the intention is to ensure that there is less than one new infection per thousand people per year in the elimination phase, then we need to test people at least once a year on average, ensure that the drop-out rate from ART is less than 5% per year and ensure that the viral-load suppression is sufficient to the infectiousness of those on ART to less than 5% of that of people not on ART.

### **References**

1. Williams BG, Korenromp EL, Gouws E, Schmid GP, Auvert B, Dye C. HIV Infection, Antiretroviral Therapy, and CD4+ Cell Count Distributions in African Populations. *J Infect Dis.* 2006;**194**:1450-8.
2. CASCADE Collaboration. Time from HIV-1 seroconversion to AIDS and death before widespread use of highly-active anti-retroviral therapy. A collaborative analysis. *Lancet.* 2000;**355**:1131-7.
3. Cox DR, Oakes D. *Analysis of Survival Data.* First ed. Boca Raton: Chapman and Hall; 1998.
4. Williams BG, Dye C. Antiretroviral drugs for tuberculosis control in the era of HIV/AIDS. *Science.* 2003;**301**:1535-7.
5. Gray RH, Wawer MJ, Brookmeyer R, Sewankambo NK, Serwadda D, Wabwire-Mangen F, et al. Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda. *Lancet.* 2001;**357**:1149-53.
6. Wawer MJ, Gray RH, Sewankambo NK, Serwadda D, Li X, Laeyendecker O, et al. Rates of HIV-1 Transmission per Coital Act, by Stage of HIV-1 Infection, in Rakai, Uganda. *J Infect Dis.* 2005;**191**:1403-9.

7. Hollingsworth TD, Anderson RM, Fraser C. HIV-1 Transmission, by Stage of Infection. *J Infect Dis.* 2008;**198**:687-93.
8. Abu-Raddad L, Longini IM, Jr. No HIV stage is dominant in driving the HIV epidemic in sub-Saharan Africa. *AIDS.* 2008.
9. Rapatski BL, Suppe F, Yorke JA. HIV epidemics driven by late disease stage transmission. *J Acquir Immune Defic Syndr.* 2005;**38**:241-53.
10. Pilcher CD, Tien HC, Eron JJ, Jr., Vernazza PL, Leu SY, Stewart PW, et al. Brief but efficient: acute HIV infection and the sexual transmission of HIV. *J Infect Dis.* 2004;**189**:1785-92.
11. Matsumoto M, Nishimura T. Mersenne Twister: A 623-dimensionally equidistributed uniform pseudorandom number generator. *Association for Computer Machinery Transactions Modeling and Computer Simulation (TOMACS).* 1998;**8**:3-30.
12. Marsaglia G, Zaman A. Some portable very-long-period random number generators. *Computers in Physics.* 1994;**8**:117-21.
13. Williams BG, Gouws E. The epidemiology of human immunodeficiency virus in South Africa. *Philos Trans R Soc Lond B Biol Sci.* 2001;**356**:1077-86.
14. Williams BG, Lloyd-Smith JO, Gouws E, Hankins C, Getz WM, Hargrove J, et al. The Potential Impact of Male Circumcision on HIV in Sub-Saharan Africa. *PLoS Medicine.* 2006;**3**.
15. Hallett TB, Gregson S, Dube S, Garnett GP. The Impact of Monitoring HIV Patients Prior to Treatment in Resource-Poor Settings: Insights from Mathematical Modelling. *PLOS Medicine.* 2008;**5**:e53.
16. Detels R, English PA, Giorgi JV, Visscher BR, Fahey JL, Taylor JM, et al. Patterns of CD4+ cell changes after HIV-1 infection indicate the existence of a codeterminant of AIDS. *J Acquir Immune Defic Syndr.* 1988;**1**:390-5.
17. Katubulushi M, Zulu I, Yavwa F, Kelly P. Slow decline in CD4 cell count in a cohort of HIV-infected adults living in Lusaka, Zambia. *AIDS.* 2005;**19**:102-3.
18. Lang W, Perkins H, Anderson RE, Royce R, Jewell N, Winkelstein W, Jr. Patterns of T lymphocyte changes with human immunodeficiency virus infection: from seroconversion to the development of AIDS. *J Acquir Immune Defic Syndr.* 1989;**2**:63-9.
19. Lyles RH, Munoz A, Yamashita TE, Bazmi H, Detels R, Rinaldo CR, et al. Natural history of human immunodeficiency virus type 1 viremia after seroconversion and proximal to AIDS in a large cohort of homosexual men. Multicenter AIDS Cohort Study. *J Infect Dis.* 2000;**181**:872-80.
20. Joseph Kwong-Leung Yu JK-L, Tok T-S, Tsai J-J, Chang W-S, Dzimadzi RK, Yen P-H, et al. What happens to patients on antiretroviral therapy who transfer out to another facility? *PLoS ONE.* 2008.

21. Kilby JM, Lee HY, Hazelwood JD, Bansal A, Bucy RP, Saag MS, et al. Treatment response in acute/early infection versus advanced AIDS: equivalent first and second phases of HIV RNA decline. *AIDS*. 2008;**22**:957-62.
22. Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med*. 2000;**342**:921-9.
23. Cohen MS, Gay C, Kashuba AD, Blower S, Paxton L. Narrative review: antiretroviral therapy to prevent the sexual transmission of HIV-1. *Ann Intern Med*. 2007;**146**:591-601.
24. Montaner JS, Hogg R, Wood E, Kerr T, Tyndall M, Levy AR, et al. The case for expanding access to highly active antiretroviral therapy to curb the growth of the HIV epidemic. *Lancet*. 2006;**368**:531-6.
25. Bunnell R, Ekwaru JP, Solberg P, Wamai N, Bikaako-Kajura W, Were W, et al. Changes in sexual behavior and risk of HIV transmission after antiretroviral therapy and prevention interventions in rural Uganda. *AIDS*. 2006;**20**:85-92.