Effect on transmission of HIV-1 resistance of timing of implementation of viral load monitoring to determine switches from first to second line antiretroviral regimens in resource-limited settings.

Supplementary Methods

HIV Synthesis Transmission V1. Model details

1. Demographic model

The intention is to simulate an epidemic similar to those seen in southern Africa. In so far as this is based on data from a single country this is based on the epidemic in South Africa, although the intent was not to mimic the South African situation in all aspects (such as in treatment guidelines). The intent is that variations in sexual risk behaviour patterns (e.g. in the extent of sex between males and female sex workers) and dates of the start of the epidemic can be investigated, and hence generate epidemics with features closer to those seen elsewhere in sub-saharan Africa.

1. 1. General population death rates and determination of age at 1985

The model runs for 40 years from 1985, with variables updated in 3 month periods. Each run of the simulation program creates 100,000 simulated people.

Age specific death rates for uninfected people (based on death rates in South Africa in 1997 – before the significant impact of HIV-related deaths) are as follows:-

Age group	Annual death rate
Males	
15-19	0.00200
20-24	0.00320
25-29	0.00580
30-34	0.00750
35-39	0.00800
40-44	0.01000
45-49	0.01200
50-54	0.01900
55-59	0.02500
60-64	0.03500
65-69	0.04500
70-74	0.05500
75-79	0.06500
80-84	0.10000
≥85	0.40000
Females	
15-19	0.00150
20-24	0.00280
25-29	0.00400
30-34	0.00400
35-39	0.00420
40-44	0.00550
45-49	0.00750
50-54	0.01100
55-59	0.01500
60-64	0.02100
65-69	0.03000
70-74	0.03800
75-79	0.05000
80-84	0.07000
≥85	0.15000

These death rates are modified by a factor 1.5 for smokers and by 0.75 for non-smokers. This is due to the known effects of smoking on all cause mortality (1).

The initial age distribution is determined on the basis of the following distribution.

Age group	Probability of being in age group in 1985*
Males	
-25-14	0.475
15-24	0.120
25-34	0.120
35-44	0.105
45-54	0.095
55-64	0.085
Females	
-25-14	0.465
15-24	0.115
25-34	0.115
35-44	0.105
45-54	0.105
55-64	0.095

* the actual age of a person in a given group in 1985 is determined by sampling from a Uniform distribution.

This distribution is chosen such that in the absence of HIV, given the death rates above, the age distribution in the population would be constant over time.

Thus almost half of simulated people have an age below 15 in 1985. The only variable that is modelled and updated up to reaching the age of 15 (when becoming potentially sexually active) is age itself. The "youngest" person in 1985 is age -25 (i.e. will be born in 2010 and reach age 15 in 2025, when the modelled period ends).

2. Model of sexual risk behaviour and risk of HIV acquisition

Risk behaviour is characterized by two variables representing, respectively, the number of short term unprotected sex partners and whether the person has a current long term *unprotected sex* partner in the 3 month period. The status of long term partners is tracked over time (i.e. if they are infected, diagnosed, on ART, etc). Short term partners are not tracked over time, in that if a person has a short term partner in time period t who is infected with HIV, this is independent of the probability that any short term partner in time t+1 is infected with HIV.

2.1. Determination of number of short term partners at period t

Numbers of short term partners in a given period was generated at random, according to which of four risk behaviour groups the person was in for this period (see also Table 1). Changes in the risk behaviour group from t-t to t were determined by transition probabilities between 4 groups: no short term unprotected partners in 3 month period, 1 short term partner, 2-10 short term partners, and 10 or more short term partners. Transition probabilities p_{gija} of moving from partner group i at t-1 to partner group j at t are given by

$$p_{gija} = f_{gij} / (f_{gi1} + \Sigma_{j=2-4} (f_{gij}. r_{ga}))$$

for j=1

$$p_{gija} = f_{gij}. r_{ga} / (f_{gi1} + \Sigma_{j=2-4} (f_{gij}. r_{ga}))$$

for j=2-4
where g = 0,1 for males, females, respectively, and a = 1-10 for age groups 15-, 20-, 25-, 30-, 35-, 40-, 45-, 50-, 55-, 60-, respectively. Values of f_{gij} and r_{ga} are given in Tables 1 and 2, respectively.

Values of r_{ga} are modified at time t by a factor 0.2 if the subject has a current AIDS defining disease and by a factor 0.75 if the subject is diagnosed with HIV. In addition, there is a person-fixed modification factor. For a random 35% of men and 50% of women, values of r_{ga} are modified by a factor 0.1, to reflect the fact that a proportion of people experience only very low sexual risk activity in their life.

Actual transitions between groups were determined by random sampling. For the first two groups the number of partners in the period is given (i.e. no short term partners, 1 short term partner, respectively). When a person was in the 2-9 short term partners the number of partners was determined by sampling from Poisson(1.5), and when the transition was to $\geq$ 10 short term partners the number of partners was determined by sampling from Poisson(2) and multiplying by 20.

2.2. Determination of having a long term (unprotected sex) partner at period t

At each period people with no current long term partner have age-dependent probabilities of having a short term long term partner: age 15-24, p=0.15; age 25-34, p=0.10; age 35-44, p=0.05; age 45-54, p=0.01; age 55-64, p=0.005.

At the time a long term partnership is started, it is classified into 3 duration groups, each with a different tendency to endure. The percent of people in each group is dependent on age and is shown in Table 3.

At time period, t, for people with a long term partner, the probability of the partnership continuing is 0.75 if duration category is 1, is 0.95 if duration category is 2, and 0.98 if duration category is 3.

Note that only unprotected sex partnerships are modelled. Thus if a person has a long term partner but condoms are used on all occasions of sexual intercourse then this is not counted as having a long term partner.

Note also that levels of risk behaviour, in terms of numbers of short term partners and the probability of a long term partner are essentially determined by the levels of such risk behaviour required in order to produce an epidemic as described, given rates of transmission with unprotected sex partners. Sexual risk behaviour tends to be under-reported particularly in women and higher levels of behaviour have to be assumed both to be consistent with levels of risk behaviour reported in men, and to generate an epidemic of the proportions observed (e.g. 2, 3). Nonetheless, reported risk behaviour, particularly in terms of differences by age in males and females have been referred to (4, 5).

2.3. Determination of number of short term partners who are HIV infected at time t

For each short term partner that a subject has at time t, the probability that the partner is infected is calculated. This is dependent on the prevalence of HIV in those of the opposite gender, taking consideration of age mixing. If the subject is of gender g and age group a, then for each short term partner the first step is to determining by random sampling the age group, a', of the short term partner (in fact, for simplicity, all short term partners at time t are assumed to be in this same age group). The gender and age mixing probabilities (i.e. the proportion of short term partnerships formed by men in age group a_m which are with females of age group a_f ($z_{am,af}$) and the proportion of short term partnerships formed by females in age group a_f which are with men of age group a_m ($z_{af1,am}$)) used to determine this are given by values of in Table 4.

Then, for the given partner (of gender 1-g and age group a'), the risk that the partner is infected is then given by

$$h_{a,g}(t) = \sum_{a',1\text{-}g} L^1(t\text{-}1) / \sum_{a',1\text{-}g} L(t\text{-}1)$$

where $\sum_{a',1\text{-}g}$ is the sum over all subjects of age group a' and gender 1-g, $L^1(t\text{-}1)$ is the number of infected short term partners at time t-1, and $L(t\text{-}1)$ is the number of short term partners at time t-1.

Since we assume that all short term partners at time t are in this same age group, the total number of infected short term partners that the subject has at time t, $L^1(t)$, is then given by

$$L^1(t) = \text{Min} (\text{Poisson} (h_{a,g}(t).\ L(t)) , L(t))$$

The distribution of numbers of short term partners by age and gender, before introduction of HIV, is shown in Table 6.

2.4. Determination of probability that a long term partner is HIV infected at time t

$E^1(t)$ indicates whether the subject has a long term (unprotected sex) partner who is infected ($E^1(t)$ =1 if infected, else $E^1(t)$ = 0). A long term partner at time t can be infected either because (i) a new long term partnership has been formed and the partner was already infected, (ii) because a long term partner at t-1, which has remained a long term partner at time t, has become infected, or (iii) because a long term infected longer partner has remained as a long term partner.

For (i):

$E^1(t) = 1$ if $L^1(t\text{-}1) \geq 1$ (i.e. if the subject had a short term partner at time t-1 who was infected then it is assumed that the new long term partner is infected)

For (ii):

The probability that a long term partner of a subject of age group a and gender g becomes infected is derived from the HIV incidence at t-1 for age group a (i.e. the same age group) and gender 1-g, $i_{a,1\text{-}g}(t\text{-}1)$ (which is given by the number of subjects newly infected in age group at time t-1 / number of HIV-uninfected subjects in age group at t-1)

$E^1(t) = 1$ if a sampled random variable from Uniform(0,1) < $i_{a,1\text{-}g}(t\text{-}1)$, else $E^1(t) = 0$

In order to maintain balance, for each gender, between the number of uninfected people with a long term partner who is infected, and the number of infected people with a long term partner who is uninfected, this incidence $i_{a,1\text{-}g}(t\text{-}1)$ is modified at time t dependent on the degree of balance at time t-1. The balance achieved is illustrated in Figure 4.

For (iii):

If $E^1(t\text{-}1) = 1$ and $E(t) \geq 1$ then we assign $E^1(t) = 1$

2.5. Determination of the risk of infection from a short term partner

For a each HIV infected short term partner of a subject of gender g and age group a the viral load group, v, of the partner is obtained by sampling from the viral load distribution of those of the opposite gender. Thus we sample from Uniform(0,1), where the probability of the partner having viral load in group v is given by

$$\Sigma_v L^1(t\text{-}1) / \Sigma L^1(t\text{-}1)$$

where Σ_v is the sum over all HIV-infected subjects in viral load group v and Σ is the sum over all HIV-infected subjects.

Viral load groups are:

(1) < 2.7 log cps/mL
(2) 2.7-3.7 log cps/mL
(3) 3.7-4.7 log cps/mL
(4) 4.7-5.7 log cps/mL
(5) $\geq$ 5.7 log cps/mL
(6) primary infection.

Once the viral load group, v, of the infected partner is determined, the probability, t_v, of the subject being infected by the partner is then given according to: t_1 = Normal (0.0001,0.000025), t_2 = Normal (0.01,0.0025), t_3 = Normal (0.03,0.0075), t_4 = Normal (0.06,0.015), t_5 = Normal (0.1,0.025), t_6 = Normal (0.2,0.075). These are based on ref 6. These probabilities are increased by 1.5-fold for female subjects aged $\geq$ 20, by 2-fold for female subjects aged < 20, and by 3-fold if the person has an existing STI (risk of a new STI in any one three month period is given by the number of short term unprotected partners / 20 (or 1 if > 20 short term partners)) (7-9).

Realization of whether the subject is infected by each short term partner is determined by sampling from Uniform(0,1).

2.6. Determination of the risk of infection from a long term partner

Infected long term partners at time t are classified by whether they are in primary infection (if infection occurred at t-1), whether they are diagnosed with HIV, whether they are on ART, and whether their current viral load is < 2.7 cps/mL or not. The proportion of long term partners with HIV who have HIV diagnosed at time t, $p^D_e(t)$, is determined with reference to the difference, $d^D_e(t-1)$, in the proportion of subjects with HIV who are diagnosed, $T^D(t-1) / T^1(t-1)$, and $p^D_e(t-1)$; i.e.

$$d^D_e(t-1) = T^D(t-1) / T^1(t-1) - p^D_e(t-1)$$

where $T^D(t-1)$ is the total number of subjects diagnosed with HIV at time t-1and $T^1(t-1)$ is the total number of subjects with HIV (diagnosed and undiagnosed) at time t-1.

If $0.05 \leq d^D_e(t-1) > 0$ then $p^D_e(t) = 0.4$, if $0.10 \leq d^D_e(t-1) > 0.05$ then $p^D_e(t) = 0.5$, if $0.15 \leq d^D_e(t-1) > 0.10$ then $p^D_e(t) = 0.9$, if $d^D_e(t-1) > 0.15$ then $p^D_e(t) = 0.95$.

The proportion of those diagnosed who are on ART, and the proportion of those on ART who have viral load < 2.7 log cps/mL are determined in a similar manner. In this way the proportions diagnosed with HIV, on ART, and with current viral load is < 2.7 cps/mL are kept similar for the long term partners as in the simulated subjects themselves.

Risk of infection from a long term infected partner is determined by Normal (0.2, 0.075) if the existing partner is in primary infection (ie. infected at t-1), Normal (0.0001, 0.000025) if the existing partner has viral load < 2.7 cps/mL, and Normal (0.05, 0.0125) otherwise.

2.7. Transmitted resistance

The viral load group of the person who infected the subject is known, as indicated above (for infection from a short term partner the viral load group of the 6 groups defined in section 2.5. is known, while if infected by a long term partner the viral load is known to be either < 2.7, $\geq$ 2.7 but not primary infection, or primary infection, as described in section 2.6.) . For a subject infected by a person in viral load group v the probability of a resistance mutation being present in the infected person is given by

$$\Sigma_{v,r=1} L^1(t-1) / \Sigma_v L^1(t-1)$$

where $\Sigma_{v, r=1}$ is the sum over all HIV-infected subjects in viral load group v for whom a resistance mutation is present in majority virus and Σ is the sum over all HIV-infected subjects in viral load group v. Again, realization of whether the subject is infected by a person with at least one resistance mutation in majority virus is determined by sampling from Uniform(0,1).

For subjects infected from a source partner with a resistance mutation, the probability that a specific mutation, m, is present in the source is given by

$$\Sigma_{r=1,m=1} L^1(t-1) / \Sigma_{r=1} L^1(t-1)$$

where $\Sigma_{r=1,m=1}$ is the sum over all HIV-infected subjects with mutation m present in majority virus and $\Sigma_{r=1}$ is the sum over all HIV-infected subjects with at least one resistance mutation in majority virus.

If a given resistance mutation, m, is present in the source partner, the probability that the mutation is both transmitted and survives in the subject (ie. that its presence will affect future response to drugs for which the mutation confers reduced sensitivity) is mutation specific, as shown in Table 5.

Table 1. Values of f_{gij} (values determining probability of transitioning between short term partner risk behaviour groups)

Short term partners in period t-1	Short term partners in period t			
	0	1	2-9	≥ 10*
			Poisson mean 1.5	Poisson mean 2 x 20
Males				
0	0.89	0.08	0.03	0.00
1	0.80	0.15	0.05	0.00
2-9	0.37	0.28	0.40	0.00
≥ 10	0.00	0.00	0.00	0.00
Females				
0	0.93	0.05	0.02	0.00025
1	0.86	0.11	0.03	0.0005
2-9	0.53	0.08	0.37	0.001
≥ 10	0.005	0.00	0.00	0.995

Table 2. Values of Γ_{ga} (factor determining relative level of sexual risk activity)

Age group (a=1,10)	Males (g=1)	females (g=2)
15-	0.65	1.50
20-	0.65	1.50
25-	1.00	1.00
30-	0.80	0.80
35-	0.65	0.50
40-	0.50	0.35
45-	0.40	0.10
50-	0.35	0.05
55-	0.25	0.04
60-	0.15	0.02

Table 3. Percent of newly formed long term partnerships classified into each of three duration groups, each of which has a different tendency to endure (higher class, more durable). This results in proportions of people with a long term unprotected sex partner as shown by age and gender in Table 7.

Age	1	2	3
15-44	30%	30%	40%
45-54	30%	50%	20%
55-64	30%	70%	0%

Table 4. The proportion of short term partnerships formed by men in age group a_m which are with females of age group a_f ($Z_{am,af}$) and the proportion of short term partnerships formed by females in age group a_f which are with men of age group a_m ($Z_{af,am}$).

Males Age group (a_m)	Females Age group (a_f) 15-24	25-34	35-44	45-54	55-64
15-24	0.865	0.11	0.025	0.00	0.00
25-34	0.47	0.43	0.10	0.00	0.00
35-44	0.30	0.50	0.20	0.00	0.00
45-54	0.43	0.30	0.23	0.03	0.01
55-64	0.18	0.18	0.27	0.27	0.10

Females Age group (a_f)	Males Age group (a_m) 15-24	25-34	35-44	45-54	55-64
15-24	0.43	0.34	0.12	0.10	0.01
25-34	0.09	0.49	0.30	0.10	0.02
35-44	0.03	0.25	0.34	0.25	0.13
45-54	0.00	0.00	0.05	0.25	0.70
55-64	0.00	0.00	0.00	0.10	0.90

Table 5. Table of probabilities that for a given mutation present in the source partner the mutation is both transmitted and survives in the subject. (based on evidence from studies comparing distribution of resistance mutations between treated and antiretroviral naïve populations; e.g. 10, 11.

M184V	0.2
K65R	0.7
L74V	0.7
Q151M	0.7
Thymidine analogue mutations (TAMS)	0.7
NNRTI mutation	0.8
PI (lopinavir) mutations (46, 82, 84, 90)	0.7

Table 6. Sexual risk behaviour before introduction of HIV. Short term partners in a given 3 month period.

	% with ≥ 1 (≥ 3; ≥ 10) short term partners in a 3 month period	
	Males	Females
Age group		
15-	4.98 (0.28; 0.0)	6.29 (0.69; 0.10)
25-	6.84 (0.44; 0.0)	3.73 (0.19; 0.05)
35-	4.45 (0.32; 0.0)	1.85 (0.19; 0.03)
45-	2.83 (0.15; 0.0)	0.37 (0.03; 0.02)
55-	1.34 (0.07; 0.0)	0.11 (0.01, 0.01)
Total	4.33 (0.26; 0.0)	2.62 (0.20; 0.05)

* This equates over a lifetime to, for example, 40% of women having no more than one unprotected sex partner, and 2.2% ever having more than 10 partners in a 3 month period. In women, 47% of short term unprotected sex partnerships are accounted for by women having 10 or more partners in that three month period. Risk behaviour data for South Africa are given in ref 4 and this allows some broad comparison, although as discussed above there is potential under-reporting in risk behaviour in women and data on the proportion with each number of unprotected sex partners is not presented.

Alternative risk behaviour model. Note that an alternative risk behaviour structure has also been developed, in which no woman or man has more than 10 short term partners in a 3 month period. General levels of number of short term partners are higher, in order to generate an epidemic of similar size. For this alternative model, unlike in our base model, a general population reduction in numbers of short term partners is assumed in 1998, in order to prevent the epidemic reaching levels much greater than those observed. Results from using this alternative model are part of sensitivity analyses.

Table 7. Sexual risk behaviour before introduction of HIV. Percent with a long term partner.

	Males	Females
Age group		
15-	62	62
25-	63	62
35-	51	52
45-	37	38
55-	24	21
Total	49	48

Figure 1. Observed and expected total numbers of short term partners per 3 month period. Expected values are based on the number of short term partners for those of opposite sex, accounting for the age mixing patterns shown in Table 4. This illustrates the balance in numbers of unprotected short term partners by age and gender. So, for example, the number of partners of men of age 15-25 matches the number of partners had by women of all ages with men of age 15-25.

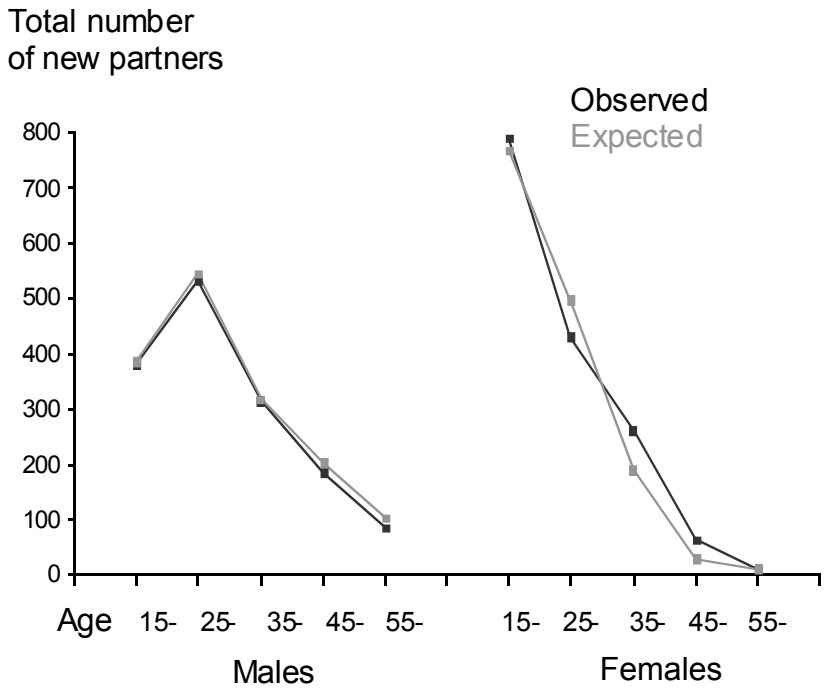
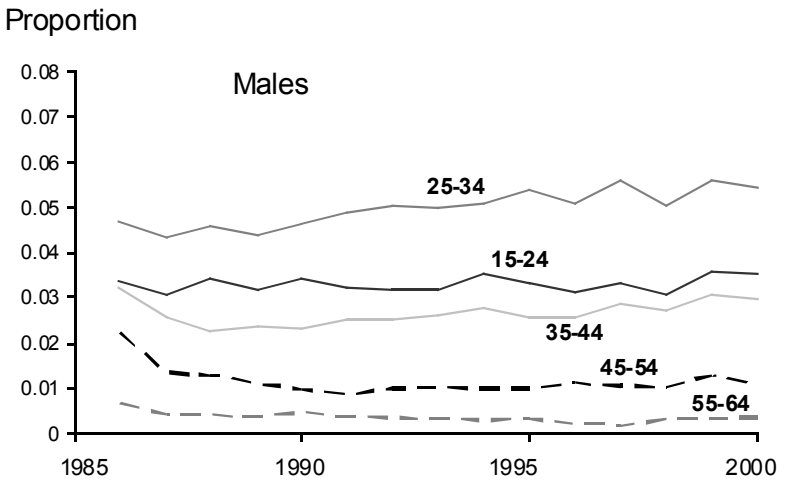


Figure 2. Proportion of people with a long term partner and at least one short term partner by calendar year, age and gender, and by HIV status. The trends by age and gender are consistent with relative differences in risk behaviour described in the Supplementary Methods. Early in the epidemic those infected are people who generally still within the phase of high risk activity that was the cause of their infection. As the epidemic matures, the average level of risk activity among those infected declines. This is due to the fact that the population of infected people is increasingly made up of people who were infected despite not having high risk activity (eg. people infected by a long term partner) and the fact that those who were infected during a period of high risk activity will tend to have reduced levels of sexual activity due to natural variability over time and reductions in risk activity with age.



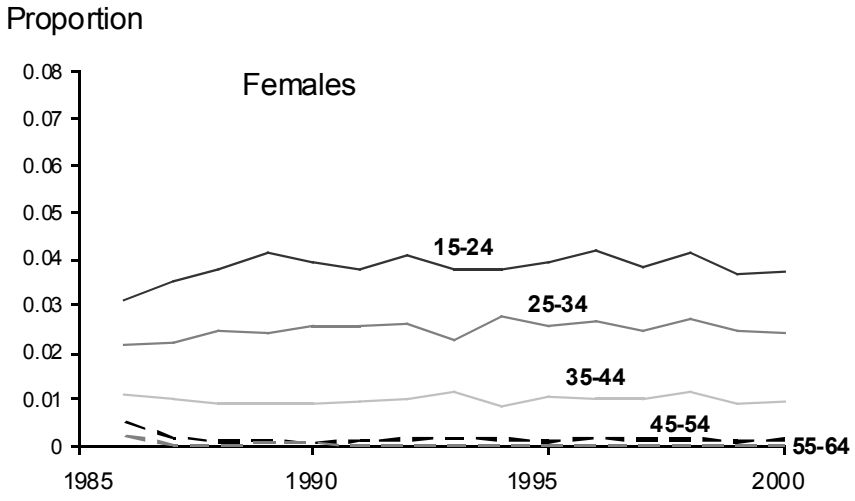


Figure 2 (continued)

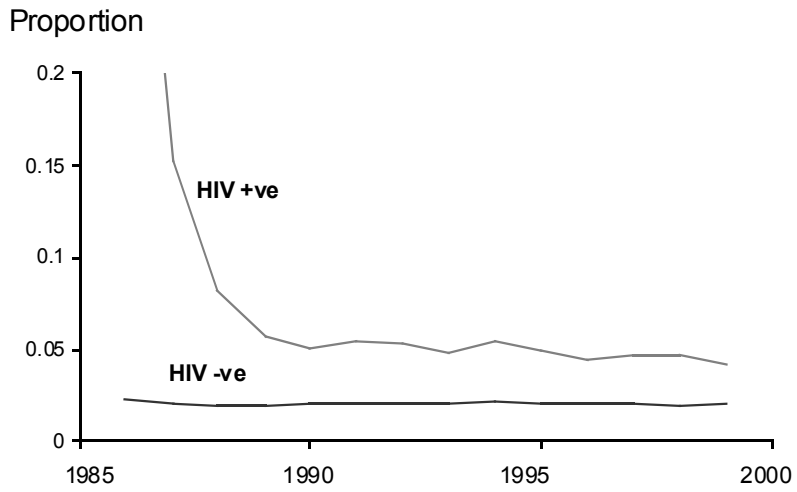
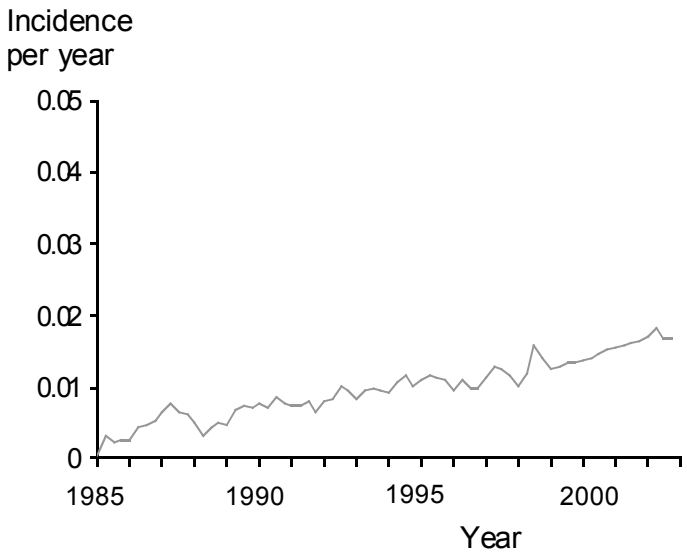


Figure 3 (a). Incidence of HIV (per year in people aged over 15) over the calendar time period from the introduction of HIV to 2003 when ART is introduced. Both genders combined. This curve does not show the classical modelled epidemic curve, where incidence rises and falls as the most susceptible people become infected. The main reason for this is that the dynamics are more complex due to explicit modelling of long term partners. Many people have long term partners (see Table 7 above), so when they have acquired HIV then even if they reduce their risk behaviour and no longer have short term unprotected sex partners they can still infect their long term partner. Thus, any person with a long term partner is potentially at risk of HIV. To illustrate this, we have re-run our model removing long term partners (and increasing the number of short term partners, to generate a similar magnitude of incidence). This is shown in Figure 3(b). This shows a pattern of an early increase in incidence followed by a constant level. However, as shown in Table 9 below, prevalence rises rapidly from 1990 to 2003, showing a similar pattern to that seen in ante-natal clinic attendees (compare, for example, the prevalence in young women with ref. 12) .

(a)



(b)

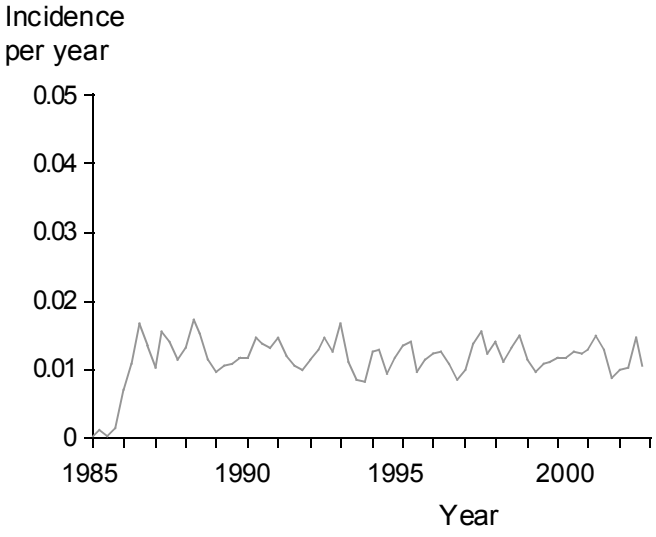


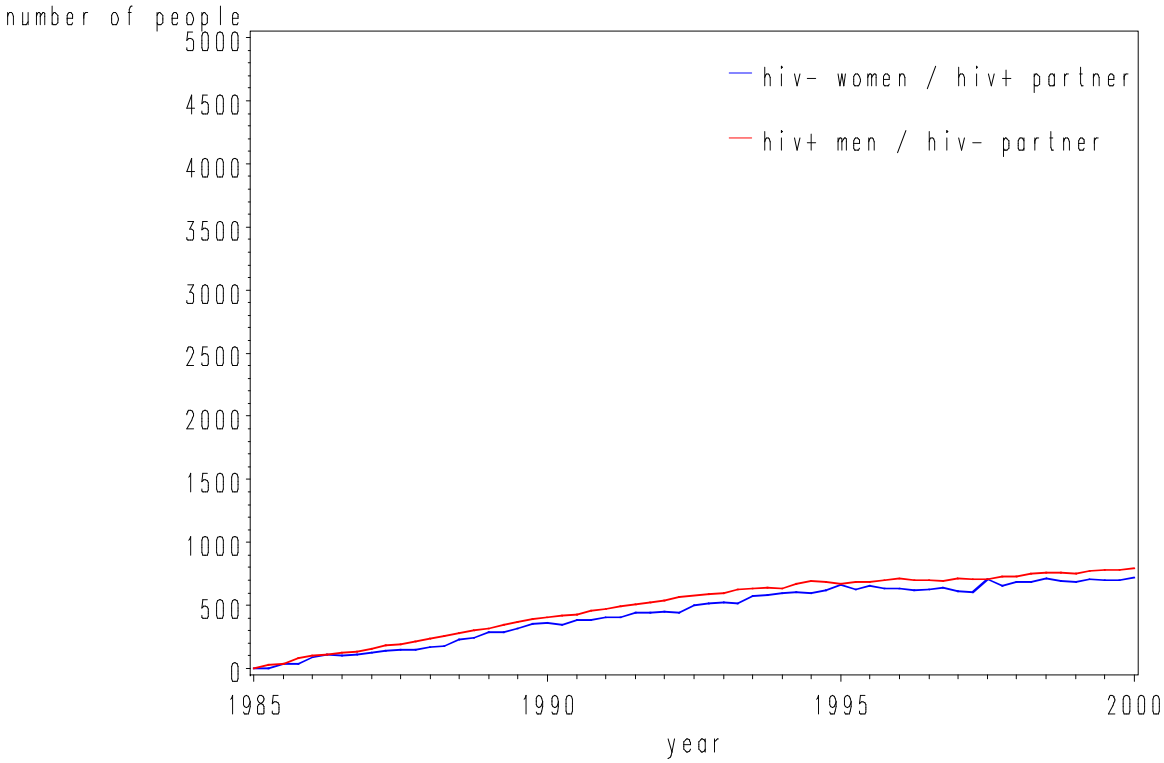
Table 8. Origin of new infections. This shows the proportion of new infections that have been acquired from a person in primary HIV infection by year, and the proportion of new infections that have been acquired from a long term partner by year. For infections from people with primary infection, there are little data from sub-Saharan Africa to our knowledge. Data from men who have sex with men indicate that around one third of new infections may come from people who are themselves in primary infection (13). For proportion of people infected by a long term partner, compare with ref 14.

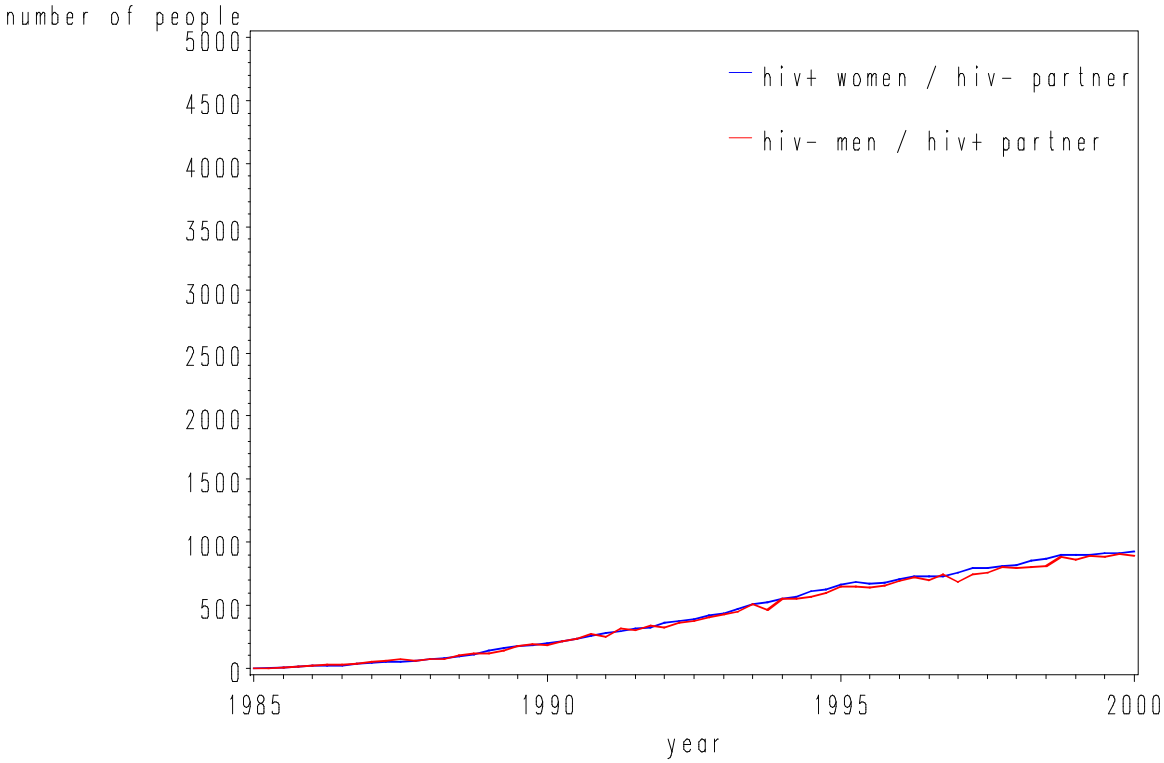
	Status of source partner					
	Primary infection			Long term partner		
	1990	1995	2003	1990	1995	2003
Males	25%	30%	28%	31%	62%	70%
Females	41%	43%	39%	88%	93%	74%

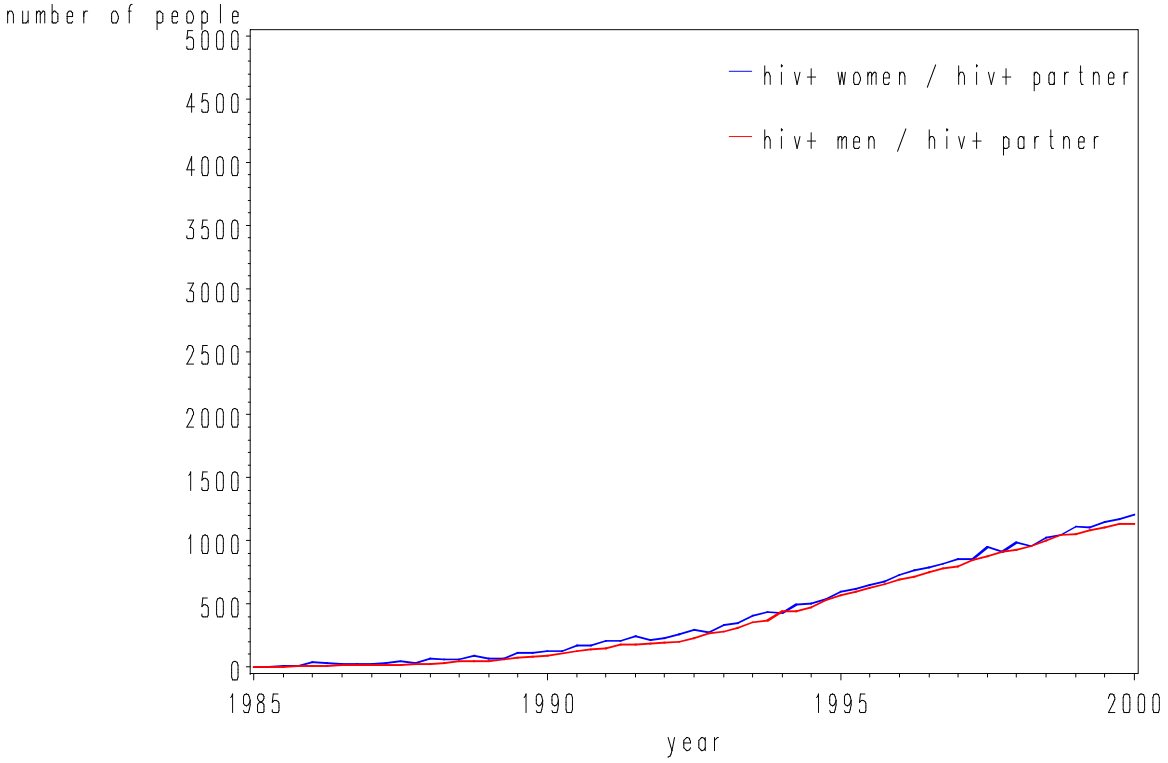
Table 9. HIV prevalence by gender and age. (Compare, for example, with ref. 12 for South Africa)

	Males	Females
1990		
Age group		
15-	2.6	3.0
25-	4.7	4.2
35-	3.2	2.2
45-	2.4	1.6
55-	1.2	0.6
Total	**2.9**	**2.4**
1995		
Age group		
15-	4.6	6.3
25-	10.4	12.9
35-	7.9	7.9
45-	4.2	3.7
55-	2.5	1.7
Total	**6.2**	**6.7**
2003		
Age group		
15-	6.8	8.5
25-	19.9	24.5
35-	19.5	22.1
45-	9.9	10.2
55-	3.1	2.4
Total	**12.4**	**13.9**

Figure 4. Balance between men and women and uninfected and infected long term (unprotected sex) partners. The status of long term partners is tracked in the model so that, for example, if a long term partner has HIV in period t then the long term partner will have HIV at time t+1, so long as that long term unprotected sex partnership remains. This means that it is necessary that there is balance such that, for example, the number of HIV+ subjects who have an HIV- partner should be the same as the number of HIV- subjects who have an HIV+ partner. The first graph shows the number of HIV –ve women subjects who have an HIV+ve long term partner, and the number of HIV+ve male subjects who have an HIV-ve long term partner. This shows the degree of balance over time between these two numbers, which should be the same in a closed population. The converse is shown in the second graph. The third graph shows the number of HIV+ve men with an HIV+ve female partner and vice versa, again showing the balance in these two numbers over time.






number of people
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
1985
1990
1995
2000
year
hiv+ women / hiv+ partner
hiv+ men / hiv+ partner

3. Natural history of HIV infection

The model of the natural history of HIV and the effect of antiretroviral therapy has been derived previously and validated (see refs 15, 16 [and associated Supplementary Methods], and Supplementary Results 1). This model has been incorporated within the larger transmission model.

Below we set out the structure of the model and give parameter values used in our base model. These are the values that we consider provide the best fit to observed data. However, there is uncertainty associated with many of the values. As far as possible we explore the sensitivity of our main findings to potential differences in values of the parameters (See Supplementary Results 1).

3. 1. Determination of changes in viral load and CD4 count

Initial $\log_{10}$ viral load (V_{set}) is sampled from Normal(4.0,0.5)

This viral load (V_{set}) is assumed to be that reached after primary infection. It is not used to determine the risk of transmission in primary infection itself.

Initial CD4 count, modelled on the square root scale, is partially dependent on initial viral load and given by

Square root CD4 count = $32 - (2 \times V_{set}) + \text{Normal}(0,2)$

Initial virus is assumed to be R5-tropic. Shift to presence of X4 virus is assumed to depend on viral load. Probability of a shift per 3 months is given by $10^{v} \times 0.0000004$, where v is the current $\log_{10}$ viral load.

Viral load change (vc) from period t-1 to period t (i.e. in 3 months) is dependent on viral load at t-1 and is given by sampling from a Normal distribution with standard deviation 0.05 and mean as follows

Viral load at t-1	Mean viral load change (per 3 mths)
< 3	0.0050
3-	0.0150
3.5-	0.0250
4.0-	0.0275
4.5-	0.0300
5.0-	0.0300
5.5-	0.0300
6.0-	0.0300

CD4 count changes from period t-1 to t are dependent on the current viral load (i.e. viral load at time t-1) and are given by sampling from a Normal distribution with standard deviation 1.2 and mean as follows

Viral load at t-1	Change in square root CD4 count (per 3 mths)
< 3.0	-0.015
3-0	-0.040
3.5-	-0.075
4.0-	-0.100
4.5-	-0.250
5.0-	-0.500
5.5-	-1.000
6.0-	-1.250

The change additionally is affected by the current age as follows:

Age	Additional change in square root CD4 count
< 20	+0.15
20-	+0.09
25-	+0.06
30-	+0.0
35-	+0.0
40-	-0.06
45-	-0.09
50-	-0.15
60-	-0.20

People with X4 virus present experience an additional change in square root CD4 count of -0.25.

These estimates are derived based on synthesis of evidence from natural history studies (17-25) and were selected in conjunction with other relevant parameter values to provide a good fit to the incubation period distribution. Differences that have been found in initial viral load by sex, age and risk group are not currently incorporated in the model.

Table 10. Incubation period by age. Kaplan-Meier percent with WHO Event. Compare with ref 26.

Age at infection	Years from infection					
	1	3	5	10	15	20
15-	0.5%	2%	7%	36%	70%	88%
25-	1%	4%	11%	46%	77%	93%
35-	1%	6%	15%	56%	85%	95%
45-	1%	7%	21%	66%	89%	98%
55-	2%	10%	26%	74%	93%	99%

4. Diagnosis of HIV infection

The basic rate diagnosis from 2003 when testing is assumed to have started is 0.005 per 3 mths. This was chosen to give approximately realistic proportion of people on ART by 2010.

This basic rate is increased by the following factors in those that have a current WHO 4 diagnosis (10-fold), TB diagnosis (5-fold), WHO 3 diagnosis (3-fold).

5. Use of ART

Initiation of ART

In the base model ART initiation in diagnosed people before 2010 is determined by a CD4 count < 200 or the development of a WHO 4 event.

Interruption of ART

The basic rate of interruption due to patient choice is 0.08 per year, but this rate is greater with current toxicity (2-fold) and greater in patients with a greater tendency to be non-adherent (1.5-fold if adherence average 0.6 – 0.79 and 2-fold if adherence average < 0.60).

if adherence average $\geq$ 0.8 then 30% chance that interruption coincides with interrupting/stopping visits to the clinic (i.e. lost to follow-up), if 0.6 <= adhav < 0.8 then 45% chance, if adhav < 0.6 then 60% chance.

The rate of interruption due to choice is likely to vary by setting. The above rates were derived to be consistent with data from mainly European and US cohorts (27-31). Again, the effect on our main results of varying this estimate is indicated in sensitivity analyses (Supplementary Results 2).

The basic rate of interruption due to interruption of the drug supply is 0.04 per year.

Re-initiation of ART after interrupting in patients still under follow-up

For patients who have interrupted ART due to choice but are still under clinic follow-up, the probability of restarting ART per 3 months in the base model is 0.4. This probability is increased 3-fold if a new WHO 3 condition has occurred at t-1, and 5-fold if a new WHO 4 condition has occurred at t-1.

This was derived from consideration of estimates of the proportion of people who had started ART who were on ART (e.g. 31). This will likewise vary by setting and is investigated in sensitivity analyses.

For patients who have interrupted ART due interruption of supply the probability of restarting ART per 3 months in the base model is 0.8.

Switch to second line after failure of first line ART

Whatever the criterion for the need to switch to second line ART is determined, the probability of switching per 3 month period after the criterion is met is 0.8, in the base model.

Loss to follow-up while off ART

The probability per 3 months of interrupting/stopping clinic visits (i.e. being lost to follow-up) is 0.03 if adherence average $\geq$ 0.8. This is increased by 1.5 fold if 0.6 $\leq$ adherence average < 0.8 and by 2-fold if adherence average < 0.6.

For people lost to follow-up who are asymptomatic, the probability of returning to clinic per 3 months is 0.10 if adherence average $\geq$ 0.8. This is decreased by 2-fold if 0.6 $\leq$ adherence average < 0.8 and by 3-fold if adherence average < 0.6. If a person develops a new WHO 3 or 4 event then they are assumed to return to the clinic with probability 1.

These will vary by setting (32-35) and its effect is estimated in sensitivity analyses.

Adherence to ART

There are two components, each patient has a fixed “tendency to adhere” but their actual adherence varies from period to period, both at random and according to the presence of symptoms. Adherence is measured on a scale of 0 to 1.

Component which is fixed over time for a given patient

Adherence average (adhav) is a measure of the patient's tendency to adhere, a fixed value for a patient.

5% probability	*adherence average*	= 0.50
	adherence variability	= 0.2
10% probability	*adherence average*	= 0.80
	adherence variability	= 0.2
25% probability	*adherence average*	= 0.90
	adherence variability	= 0.06
60% probability	*adherence average*	= 0.95
	adherence variability	= 0.05

Adherence at any one period is determined as follows (although with modifications explained below):- adh(t) = adhav + Normal(0,advar)

if adh(t) > 1 then adh(t)=1

These estimates are based partially on observed adherence data (36, 37), but also on adherence levels required to produce observed estimates of rates of resistance development and virologic failure (see Supplementary Results 1) and also data on the proportion of patients at first virologic failure who have no resistance mutations present (38). It is clear from such data in more recent years that the great majority of patients who started ART with 3 or more drugs are sufficiently adherent that virologic failure rates (and so resistance accumulation is likely to have been slow also) are low (39-41). Note that absolute values of adherence are not crucial to the model estimates, the crucial issue is whether the adherence level is within a range within which the risk of resistance development is raised (here 0.5 - 0.8). Recent work on this issue, including differences by drug class, will allow refinement of this in future.

Effective adherence

We also considered the concept of effective adherence, which reflects predicted adequacy of drug levels, whereby for those on regimens that do not include an NNRTI the effective adherence is as the adherence, but for those on NNRTI-containing regimens the effective adherence is the adherence + 0.05, reflecting the long half life of these drugs (42) . Additionally, it is assumed that patients on ART are susceptible to occasional (rate 0.02 per year) severe temporary drops in drug level (i.e. effective adherence level), leaving them susceptible to viral rebound (but with low risk of resistance as the effective adherence drop is so profound). This phenomenon is assumed to be 3 times more frequent among those on protease inhibitor regimens. This latter assumption is the only plausible means (at least within our model framework) to explain why virologic failure occurring on boosted protease inhibitor regimens often occurs in the absence of resistance.

6. Effect of ART on viral load, CD4 count, resistance development and drug toxicity

Patients on ART - Determination of viral load, CD4 count, acquisition of new resistance mutations between t-1 and t (variable "newmut(t)")

These depend on the effective adherence between t-1 and t, number of active drugs (nactive(t-1)), time on the current regimen and the current viral load itself. The way the values are generated is detailed on the following pages. For those on NNRTI regimens the new mutations risk is assumed to be that for the effective adherence category of 0.5 – 0.8 (i.e. maximal) even if the effective adherence is below 0.5, reflecting the fact that NNRTI resistance develops easily, even when drug exposure is very low.

The changes in viral load and CD4 count are based on observed data and observational studies (and to some extent randomized trials, although responses tend to be better in trial participants), and provide long term estimates of virologic failure rates and CD4 count increases in ART which are broadly consistent with observed. Values of the “new mutation risk” parameter have been chosen in conjunction with the translation of presence of mutations into reduce drug activity to provide estimates of resistance accumulation consistent with those observed in clinical practice (41,43-50)

Table 11a. Viral load (mean change from viral load max), CD4 count change (mean change between t-1 and t), and new mutation risk in first 3 months. For 0 active drugs, these are the changes regardless of time from start of regimen. For viral load this is the mean of a Normal distribution with standard deviation 0.2, from which the patient's value/change is sampled. For the CD4 count patients vary in their underlying propensity for CD4 rise on ART (given by sampling from exp(0.5*normal(0)) and the CD4 count change given here is multiplied by this factor. For the new mutation risk, this is a number that is multiplied by the viral load (mean of values at t-1 and t). The resulting number ("newmut") is used when assessing whether a new mutation or mutations have arisen (see below).

	Effective adherence between t-1 & t	Number of active drugs 3	2.75	2.5	2.25	2.0	1.75	1.5	1.25	1	0.75	0.5	0.25	0
Viral load	≥ 0.8	-3.0	-2.6	-2.2	-1.8	-1.5	-1.25	-0.9	-0.8	-0.7	-0.55	-0.4	-0.3	-0.3
(log change	≥ 0.5, < 0.8	-2.0	-1.6	-1.2	-1.1	-0.9	-0.8	-0.6	-0.5	-0.4	-0.25	-0.1	-0.05	-0.1
from vmax)	< 0.5	-0.5	-0.4	-0.3	-0.25	-0.2	-0.15	-0.0	+0.05	+0.1	+0.1	+0.1	+0.1	-0.0
CD4 count	≥ 0.8	+50	+45	+40	+35	+30	+25	+20	+17	+13	+10	+5	-2	-15
change	≥ 0.5, < 0.8	+30	+30	+23	+20	+15	+13	+10	+8	+5	+3	+0	-7	-17
(t-1 to t)	< 0.5	+5	+4	+3	+2	+1	-1	-3	-6	-10	-11	-12	-13	-18
new mutation	≥ 0.8	0.002	0.01	0.03	0.05	0.1	0.15	0.2	0.3	0.4	0.45	0.5	0.5	0.5
risk	≥ 0.5, < 0.8	0.15	0.15	0.2	0.25	0.3	0.3	0.3	0.35	0.4	0.45	0.5	0.5	0.5
(x log viral load)	< 0.5	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05

Table 11b. Summary of viral load (mean absolute value or mean change from viral load max) between 3-6 months, and after 6 months if viral load at t-1 > 4 logs. This is the mean of a Normal distribution with standard deviation 0.2, from which the patient's value/change is sampled.

Effective adherence between t-2 & t-1	Effective adherence between t-1 & t	Number of active drugs 3	2.75	2.5	2.25	2.0	1.75	1.5	1.25	1	0.75	0.5	0.25
≥ 0.8	≥ 0.8	0.5	0.8	1.2	1.4	2.0	2.7	-1.7	-1.15	-0.9	-0.75	-0.6	-0.4
≥ 0.5, < 0.8	≥ 0.8	1.2	1.2	1.2	1.4	-2.0	-1.6	-1.2	-1.05	-0.9	-0.7	-0.5	-0.35
< 0.5	≥ 0.8	1.2	1.2	1.2	1.4	-2.0	-1.6	-1.2	-1.0	-0.9	-0.7	-0.5	-0.2
≥ 0.8	≥ 0.5, < 0.8	1.2	1.6	1.8	2.2	2.4	-2.4	-1.5	-0.9	-0.7	-0.55	-0.4	-0.3
≥ 0.5, < 0.8	≥ 0.5, < 0.8	2.5	2.5	2.5	2.5	-1.2	-1.1	-0.8	-0.65	-0.5	-0.35	-0.2	-0.05
< 0.5	≥ 0.5, < 0.8	-2.0	-1.8	-1.5	-1.35	-1.2	-1.1	-0.8	-0.65	-0.5	-0.2	-0.2	-0.05
≥ 0.8	< 0.5	-0.5	-0.4	-0.3	-0.25	-0.2	-0.15	-0.10	-0.05	+0.0	+0.0	+0.0	+0.0
≥ 0.5, < 0.8	< 0.5	-0.5	-0.4	-0.3	-0.25	-0.2	-0.15	-0.10	-0.05	+0.0	+0.0	+0.0	+0.0
< 0.5	< 0.5	-0.5	-0.4	-0.3	-0.25	-0.2	-0.15	-0.10	-0.05	+0.0	+0.0	+0.0	+0.0

Table 11c. Summary of CD4 count change (mean change between t-1 and t) between 3-6 months, and after 6 months if viral load at t-1 > 4 logs. For the CD4 count patients vary in their underlying propensity for CD4 rise on ART (given by sampling from exp(0.5*normal(0)) and the CD4 count change given here is multiplied by this factor. Once the mean of the underlying CD4 count is obtained, to obtain the (underlying) CD4 count, variability (SD = 1.2) is added on the square root scale

Effective adherence between t-2 & t-1	Effective adherence between t-1 & t	Number of active drugs 3	2.75	2.5	2.25	2.0	1.75	1.5	1.25	1	0.75	0.5	0.25
≥ 0.8	≥ 0.8	+30	+28	+25	+23	+21	+19	+3	-5	-9	-10.5	-12	-14
≥ 0.5, < 0.8	≥ 0.8	+30	+28	+25	+23	+7.5	+1.5	-4.5	-7	-9	-11	-13	-14.5
< 0.5	≥ 0.8	+30	+28	+25	+23	+7.5	+1.5	-4.5	-7.5	-9	-11	-13	-16
≥ 0.8	≥ 0.5, < 0.8	+15	+13	+10	+8	+7	+13.5	+0	-9	-11	-12.5	-14	-15
≥ 0.5, < 0.8	0.5, < 0.8	+15	+13	+10	+8	-4.5	-6	-10	-11.5	-13	-14.5	-16	-17.5
< 0.5	≥ 0.5, < 0.8	+7.5	+4.5	+0	-2	-4.5	-6	-10	-11.5	-13	-16	-16	-17.5
≥ 0.8	< 0.5	-13	-14	-15	-15.5	-16	-1	-17	-17.5	-18	-18	-18	-18
≥ 0.5, < 0.8	< 0.5	-13	-14	-15	-15.5	-16	-16.5	-17	-17.5	-18	-18	-18	-18
< 0.5	< 0.5	-13	-14	-15	-15.5	-16	-16.5	-17	-17.5	-18	-18	-18	-18

Table 11d. Summary of new mutation risk between 3-6 months, and after 6 months if viral load at t-1 > 4 logs. This is a number that is multiplied by the viral load (mean of values at t-1 and t). The resulting number ("newmut") is used when assessing whether a new mutation or mutations have arisen (below).

Effective adherence between t-2 & t-1	Effective adherence between t-1 & t	Number of active drugs											
		3	2.75	2.5	2.25	2.0	1.75	1.5	1.25	1	0.75	0.5	0.25
≥ 0.8	≥ 0.8	0.002	0.01	0.03	0.05	0.05	0.1	0.2	0.3	0.4	0.45	0.5	0.5
≥ 0.5, < 0.8	≥ 0.8	0.002	0.01	0.03	0.05	0.05	0.1	0.2	0.3	0.4	0.45	0.5	0.5
< 0.5	≥ 0.8	0.05	0.05	0.03	0.05	0.05	0.1	0.2	0.3	0.4	0.45	0.5	0.25
≥ 0.8	≥ 0.5, < 0.8	0.10	0.15	0.2	0.2	0.3	0.3	0.3	0.35	0.4	0.45	0.5	0.5
≥ 0.5, < 0.8	≥ 0.5, < 0.8	0.10	0.15	0.2	0.2	0.3	0.3	0.3	0.35	0.4	0.45	0.5	0.5
< 0.5	≥ 0.5, < 0.8	0.10	0.15	0.2	0.2	0.3	0.3	0.3	0.35	0.4	0.45	0.5	0.25
≥ 0.8	< 0.5	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
≥ 0.5, < 0.8	< 0.5	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
< 0.5	< 0.5	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05

Table 11e. Summary of viral load (mean change from viral load max), CD4 count change (mean change between t-1 and t), and new mutation risk after 6 months, where viral load at t-1 < 4 logs. For viral load this is the mean of a Normal distribution with standard deviation 0.2, from which the patient's value/change is sampled. For the CD4 count patients vary in their underlying propensity for CD4 rise on ART (given by sampling from exp(0.5*normal(0)) and the CD4 count change given here is multiplied by this factor. For the new mutation number, this is a number that is multiplied by the viral load (mean of values at t-1 and t). The resulting probability ("newmut") is used when assessing whether a new mutation or mutations have arisen (see below).

	Effective adherence between t-1 & t	Number of active drugs 3	2.75	2.5	2.25	2.0	1.75	1.5	1.25	1	0.75	0.5	0.25
Viral load	≥ 0.8	0.5	0.9	1.2	1.6	-2.5	-2.0	-1.4	-1.15	-0.9	-0.75	-0.6	-0.3
(absolute value	≥ 0.5, < 0.8	1.2	1.2	1.2	1.4	-1.2	-1.0	-0.7	-0.6	-0.5	-0.4	-0.3	-0.1
or log change	< 0.5	-0.5	-0.4	-0.3	-0.25	-0.2	-0.2	-0.1	-0.1	-0.1	-0.1	-0.1	-0.0
from vmax)													
CD4 count	≥ 0.8	+30	+28	+25	+23	+21	+19	+3	-5	-9	-10.5	-12	-12
change	≥ 0.5, < 0.8	+15	+13	+10	+8	-4.5	-7.5	-10	-12	-13	-14	-15	-15
(t-1 to t)	< 0.5	-13	-14	-15	-15.5	-16	-16.5	-17	-17	-18	-17	-17	-17
new mutation	≥ 0.8	0.002	0.01	0.03	0.08	0.10	0.15	0.2	0.3	0.4	0.45	0.5	0.5
(x viral load)	≥ 0.5, < 0.8	0.15	0.18	0.2	0.25	0.3	0.3	0.3	0.35	0.4	0.45	0.5	0.5
	< 0.5	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05

Variable patient-specific tendency for CD4 count rise on ART

There is variability in the tendency for the CD4 count to rise on ART, for a given level of viral load suppression. For scenarios in the above table in which the CD4 count change is positive the CD4 count change is modified by this patient-specific factor (i.e. it is fixed for each patient), which is given by sampling for each patient from

Exp (N(0,0.5))

Reduced CD4 count rise for faster CD4 count risers after 2 continuously years on ART

To reflect the fact that the rate of CD4 count increase on ART tends to diminish with time (51), for those with patient-specific factor determining the CD4 count rise on ART > 1, this factor is modified by a factor 0.25 after 2 years of continuous treatment.

Accelerated rate of CD4 count loss if PI not present in regimen

The rate of change in CD4 count in people on failing regimens is largely based on data from the PLATO collaboration, for which patients were mainly on regimens containing a PI. If the regimen does not contain a PI the change in CD4 count per 3 months is modified (in the base model) by -10 cells/mm^3. This applies regardless of viral load level, so PIs are assumed to lead to a more beneficial CD4 count change than NNRTIs (52).

Variability in individual (underlying) CD4 counts for people on ART

Once the mean of the underlying CD4 count is obtained as described above for people on ART, to obtain the CD4 count, variability (SD = 1.2) is added on the square root scale. The estimate was based on unpublished analyses.

Viral load and CD4 count changes during ART interruption

Viral load returns to previous maximum viral load (vmax) in 3 months and adopts natural history changes thereafter.

CD4 rate of decline returns to natural history changes (ie those in ART naïve patients) after 9 months, unless the count remains > 200 above the CD4 nadir
Rate of CD4 count decline depends on current viral load.

if time off ART = 3 or if time off ART > 3 months and CD4 in previous period is > 300 above the minimum CD4 count to date

v(t) = vmax(t-1)

if v(t) $\geq$ 5	then cc(t-1) = Normal (-200,10)
if 4.5 <= v(t) < 5	then cc(t-1) = Normal (-160,10)
if v(t) < 4.5	then cc(t-1) = Normal (-120,10)

If this leads to c(t) < cmin(t) (CD4 nadir) then c(t) is set to cmin(t)

if time off ART = 6 months:-

if v(t) $\geq$ 5	then cc(t-1) = Normal (-100,10)
if 4.5 <= v(t) < 5	then cc(t-1) = Normal (-90,10)
if v(t) < 4.5	then cc(t-1) = Normal (-80,10)

if time off ART = 9 months:-

if v(t) $\geq$ 5	then cc(t-1) = Normal (-80,10)
if 4.5 <= v(t) < 5	then cc(t-1) = Normal (-70,10)
if v(t) < 4.5	then cc(t-1) = Normal (-60,10)

This is broadly based on evidence from a number of analyses of the effects of ART interruption (53-63).

Incidence of new current toxicity and continuation of existing toxicity

Toxicities including gastrointestinal symptoms, rash, hepatoxicity, CNS toxicity, lipodystrophy, hypersensitvity reaction, peripheral neuropathy and nephrolithiasis can occur with certain probability on certain specific drugs. These probabilities are based broadly on evidence from trials and cohort studies, although there are no common definitions for some conditions which complicates this.

Table 12.

Drug	Toxicity	Risk of development per 3 months	Probability of continuation if pre-existing
lopinavir ddI zidovudine	nausea	0.1 (1.5-fold higher in 1st year)	0.5
lopinavir ddI	diarrhoea	0.03 (1.5-fold higher in 1st year) 0.05	0.2 0.2
efavirenz nevirapine	rash	0.03 (this is a one-off risk in 1st 3 mths) 0.1 (ditto)	
efavirenz	CNS	0.1 (in 1st year, 0 after)	0.8 (in 1st year) 0.9 (after 1 year)
d4T zdv	lipodystrophy	0.05 0.015	1.0 1.0
d4T ddI	peripheral neuropathy	0.02 (1.5 fold higher in 1st year) 0.01 (1.5 fold higher in 1st year)	1.0 (if remain on d4T) 1.0 (if remain on ddI)
nevirapine	acute hepatitis	0.05 (one off risk in first and 2nd 3 month periods)	
zidovudine	anaemia	0.03 (1.5 fold higher in 1st year)	0.2
zidovudine	headache	0.1 (1.5 fold higher in 1st year)	0.4
ddI d4T	pancreatitis	0.001 0.001	
zidovudine ddI d4T	lactic acidosis	0.001	

Switching of drugs due to toxicity

If toxicity is present then individual drugs may be switched due to toxicity. In most cases, the switch is to another in the same class, if such a drug (that has not been previously failed nor stopped due to toxicity) is available. This will vary by setting and availability of alternative drugs.

Table 13. Kaplan-Meier estimates of percent with viral load failure (> 500 after > 6 months on ART), resistance (predicted susceptibility < 50%) to at least one drug, and a CD4 count rise of > 100/mm^3 by time from start of ART. Compare, for example, with ref 64.

	Years from start of ART					
	1	3	5	10	15	20
Viral load failure	13%	21%	25%	38%	49%	60%
Resistance	11%	17%	22%	35%	47%	60%
CD4 count rise of > 100/mm^3	54%	73%	77%	81%	82%	83%

7. Emergence of specific resistance mutations and their effect on drug activity

Accumulation of resistance mutations

"newmut" (see section 6, Table 11 above) is a probability used to indicate the level of risk of new mutations arising in a given 3 month period. If this chance comes up in a given 3 month period (determined by sampling from the binomial distribution) then the following criteria operate.

Table 14.

Drug on	Mutation	Probability of arising (given newmut=1)
3TC	M184V	0.80
d4t or zidovudine	new TAM	if not on 3TC increase by 1: 0.20 increase by 2: 0.01 if on 3TC increase by 1: 0.12 increase by 2: 0.01
ddI	L74V	0.01
ddI or d4t	65R	if on zidovudine 0.01 If not on zidovudine 0.04
ddI or d4t or zidovudine	Q151M	0.02
nevirapine efavirenz	NNRTI mutation	0.80
lopinavir/r	32 47 82	0.04 0.04 0.04

These values are chosen, in conjunction with values of the “new mutation risk” (newmut), to provide estimates of accumulation of specific classes of mutation consistent with those observed in clinical practice (41, 65, 66). They reflect a greater propensity for some mutations to arise than others. This probably relates to the ability of the virus to replicate without the mutations (e.g. probably very low in the presence of 3TC for virus without M184V) as well as the replicative capacity of virus with the mutations. Over time as more data accumulate it may be possible improve these estimates of rates of accumulation of specific mutations.

New resistance to NNRTI arising as a result of ART interruption

It is assumed that due to the long half life of NNRTIs nevirapine and efavirenz, stopping of a regimen containing one of these drugs is associated with a 5% risk (in base model) of an NNRTI resistance mutation arising (see, for example, ref 67).

Loss of acquired mutations from majority virus

It is assumed that mutations tend to be lost from majority virus with a certain probability from 3 months after stopping to take a drug that selects for that mutation. The probability of losing mutations per 3 months (from 3 months after stopping) is as follows (ref 68-74).

Table 15.

M184V		0.8
L74V		0.6
Q151M		0.6
K65R		0.6
TAMS (lose all)		0.4
NNRTImutation		0.2
Protease	32	0.2
codon	47	0.2
	82	0.2

Mutations are regained in majority virus if a drug selecting for the mutation is again started.

Determination of level of resistance to each drug

Table 16.

Mutation	Drug	Level of resistance (1 = full resistance)
M184V	3TC	0.75
1-2 TAMS	zidovudine or d4t (no 3TC in regimen)	0.5
3-4 TAMS	zidovudine or d4t (no 3TC in regimen)	0.75
5-6 TAMS	zidovudine or d4t (no 3TC in regimen)	1.00
1-2 TAMS	zidovudine or d4t (3TC in regimen - no M184V ever)	0.5
3-4 TAMS	zidovudine or d4t (3TC in regimen - no M184V ever)	0.75
5-6 TAMS	zidovudine or d4t (3TC in regimen - no M184V ever)	0.75
1-2 TAMS	zidovudine or d4t (3TC in regimen - M184V ever)	0.25
3-4 TAMS	zidovudine or d4t (3TC in regimen - M184V ever)	0.5
5-6 TAMS	zidovudine or d4t (3TC in regimen - M184V ever)	0.75

Q151M	zidovudine or d4t	0.75
K65R	d4t	0.5
≥ 3 TAMS	ddI	0.5
L74V	ddI	0.75
K65R	ddI	0.75
Q151M	ddI	0.75
NNRTI mutation	nevirapine or efavirenz	1.00
1 from Pr 32,47,82	lopinavir/r	0.25
2 from Pr 32,47,82	lopinavir/r	0.5
3 from Pr 32,47,82	lopinavir/r	0.75
4 from Pr 46, 82, 84, 90	lopinavir/r	max(r_lpr, 0.5)
2 or 3 from Pr 46, 82, 84, 90	lopinavir/r	max(r_lpr, 0.25)

These rules approximately follow the interpretation systems for conversion of mutations present on genotypic resistance test into a predicted level of drug activity (or, equivalently, of resistance; e.g. 75-77). Currently interpretation systems differ to some degree in their prediction of activity for some drugs.

Calculation of activity level of each drug

This is given by 1-level of resistance. For lopinavir/r (in base model) it is given by 2 – (2 x level of resistance); i.e. assumed higher potency. Activity levels of each drug in the regimen are summed to give the total number of active drugs.

8. Risk of clinical disease and death in HIV infected people

Occurrence of WHO 4 diseases

(see ref 52, 78-79)

Rate of WHO 4 diseases according to CD4 count

If c{t} > 650	rate=0.002		
if 500 ≤ cd4 < 650	rate=0.010	if 450 ≤ cd4 < 500	rate=0.013
if 400 ≤ cd4 < 450	rate=0.016	if 375 ≤ cd4 < 400	rate=0.020
if 350 ≤ cd4 < 375	rate=0.022	if 325 ≤ cd4 < 350	rate=0.025
if 300 ≤ cd4 < 325	rate=0.030	if 275 ≤ cd4 < 300	rate=0.037
if 250 ≤ cd4 < 275	rate=0.045	if 225 ≤ cd4 < 250	rate=0.055
if 200 ≤ cd4 < 225	rate=0.065	if 175 ≤ cd4 < 200	rate=0.080
if 150 ≤ cd4 < 175	rate=0.10	if 125 ≤ cd4 < 150	rate=0.13
if 100 ≤ cd4 < 125	rate=0.17	if 90 ≤ cd4 < 100	rate=0.20
if 80 ≤ cd4 < 90	rate=0.23	if 70 ≤ cd4 < 80	rate=0.28
if 60 ≤ cd4 < 70	rate=0.32	if 50 ≤ cd4 < 60	rate=0.40
if 40 ≤ cd4 < 50	rate=0.50	if 30 ≤ cd4 < 40	rate=0.80
if 20 ≤ cd4 < 30	rate=1.10	if 10 ≤ cd4 < 20	rate=1.80
if 0 ≤ cd4 < 10	rate=2.50		

Independent effect of viral load

if v < 3	rate = rate x 0.2
if 3 <= v < 4	rate = rate x 0.3
if 4 <= v < 4.5	rate = rate x 0.6
if 4.5 <= v < 5	rate = rate x 0.9
if 5 <= v < 5.5	rate = rate x 1.2
if 5.5 <= v	rate = rate x 1.6

Independent effect of age

rate = rate x $(age / 38)^{1.2}$

Independent effect of PJP prophylaxis

If patient on PJP prophylaxis then this rate is multiplied by 0.8 (PJP prophylaxis assumed to be used with 90% probability in diagnosed patients if WHO 3 or 4 disease is present or CD4 count < 200 /mm3).

Independent effect of being on ART

For patients on a single drug regimen this risk is multiplied by 0.9, for patients on a two drug regimen it is multiplied by 0.85 and for patients on a 3 drug regimen it is multiplied by 0.8, to reflect that being on HAART has a positive effect on risk of AIDS and death independent of latest CD4 count and viral load.

Occurrence of WHO 3 diseases

As for WHO 4 except risk is 5-fold higher.

Risk of HIV-related death

As for WHO 4 except risk 2-fold lower. (CD4-, viral load- age-specific) death rate raised 2-fold if current TB and 5-fold if current WHO 4 disease. Assume 15% of deaths are classified as non-HIV-related (despite actually being HIV-related). The effects of varying these assumptions is explored in sensitivity analyses (Supplementary Results 2).

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