Projected life expectancy of people with HIV according to timing of diagnosis

Supplementary Material

August 2011

Remarks

The supplementary material is presented in four parts:

- Model details
- Model fit
- Sensitivity analyses
- Supplementary tables to the manuscript

The model details and model fit which follow these remarks were originally put together for the HIV Synthesis V5 model. This stochastic simulation model was originally developed to reconstruct the HIV-infected population in the UK and to predict future trends in key outcomes (1).

For the purposes of this paper, in order to estimate the life expectancy of MSM who were infected age 30 in 2010, the HIV Synthesis model was altered in the following ways:

- We only simulated people to be MSM (i.e. rate of diagnosis was based on those in MSM).
- All MSM are assumed to be living in the UK at the point of infection and are also assumed that they will not emigrate.
- All are infected in 2010, aged 30 and outcomes are simulated until 2090 or until death (whichever occurs earlier).
- All are assumed never to be lost to follow-up throughout their lifetime.

The fitting was by subjective judgement informed by knowledge of the data sources, but not by a formal measurement of goodness of fit. By showing the fit of the model to a wide range of diverse data sources relevant to different parameters, we consider to have demonstrated that we have a reasonably well fitting model. By showing all the fits as we do here, readers (including non-technical readers) can judge for themselves the adequacy of the fit. We acknowledge, however, that the fact that we have not arrived at parameter values through some formal and/or automated fitting procedure is a limitation and we cannot rule out that there are parameter value combinations that would give a better fit.

Model details (Synthesis V5)

Here we describe the details of the model. For each variable we outline how it is generated and what are the factors on which it depends.

All patients - Determination of date of diagnosis

The rate of diagnosis with HIV per 3 month period is 0.045 (under the assumption of a high diagnosis rate). This is consistent with that currently observed in data on MSM in the UK (2). The rate of HIV diagnosis is 0, 0.025 and 0.1 for the low, medium and very high diagnosis rate scenario respectively.

The diagnosis rate is determined by a number of factors. HIV will be diagnosed if AIDS occurs. If CDC B symptoms occur there is a 50% probability that HIV is diagnosed at that point. Subsequently, if CDC B symptoms have occurred there is a 5-fold increased probability of diagnosis, compared with the usual rate of 0.045. Patients who have a general tendency to be non-adherent to care (and to ART if and when they start ART), have a 2-fold reduced rate of diagnosis compared with the usual rate of diagnosis.

This results in the following actual rates of diagnosis for the high diagnosis rate scenario:

End of Year	Number of diagnoses	Follow-up	Diagnosis rate per year	Diagnosis rate per 3 months
2010	2301	9990.25	0.2303	0.0576
2011	1584	9962.5	0.1590	0.0397
2012	1460	9926.5	0.1471	0.0368
2013	1203	9872.75	0.1219	0.0305
2014	925	9821.25	0.0942	0.0235
2015	733	9765.75	0.0751	0.0188
2016	542	9703.75	0.0559	0.0140
2017	406	9648	0.0421	0.0105
2018	267	9588.5	0.0278	0.0070
2019	159	9535.75	0.0167	0.0042
2020	119	9483.25	0.0125	0.0031
2021	72	9419	0.0076	0.0019
2022	52	9351	0.0056	0.0014
2023	39	9280	0.0042	0.0011
2024	23	9211.75	0.0025	0.0006
2025	21	9137.75	0.0023	0.0006
2026	9	9067	0.0010	0.0002
2027	13	8992.75	0.0014	0.0004
2028	3	8912	0.0003	0.0001
2029	2	8826.25	0.0002	0.0001
2030	3	8737.25	0.0003	0.0001

ART-naïve patients - Determination of viral load

v(t) is viral load at time t. vc(t-1) is the change in viral load from t-1 to t

Initial viral load:-

An initial viral load "set point" is defined *vset = 4.0 + Normal(0,0.5)*

Viral load at start of period 1 *v1 = vset*

(no attempt is made to model the dynamic viral load (or CD4) changes in primary infection – viral load and CD4 count are assumed to have reached their settled state right from the first period)

Changes in viral load (v(t)) :-

if vset < 3 *vc(t-1) = 0.02/4 + Normal(0,0.05)*
if 3 ≤ vset < 3.5 *vc(t-1) = 0.06/4 + Normal(0,0 05)*
if 3.5 ≤ vset < 4 *vc(t-1) = 0.10/4 + Normal(0,0.05)*
if 4 ≤ vset < 4.5 *vc(t-1) = 0.11/4 + Normal(0,0.05)*
if 4.5 ≤ vset < 5 *vc(t-1) = 0.12/4 + Normal(0,0.05)*
if 5 ≤ vset < 5.5 *vc(t-1) = 0.12/4 + Normal(0,0.05)*
if 5.5 ≤ vset < 6 *vc(t-1) = 0.12/4 + Normal(0,0.05)*
if 6 ≤ vset *vc(t-1) = 0.12/4 + Normal(0,0.05)*

v(t) = v(t-1) + vc(t-1)
if v(t) gt 6.5 then v(t)=6.5 (so maximum allowable viral load is 6.5 log copies/mL)

These values above determine the underlying viral load. The measured viral load (vm(t) is given by

vm(t) = v(t) + Normal(0,0.2)

Comment: These estimates are derived based on synthesis of evidence from natural history studies (3-9) and were selected in conjunction with other relevant parameter values to provide a good fit to the incubation period distribution (see Table 1 in Model Fit section). Differences that have been found in initial viral load by sex, age and risk group are not currently incorporated in the model.

ART-naïve patients - Determination of CD4 count

CD4 count changes in ART-naïve patients are determined on the square root scale.
csqr(t) is the square root of the CD4 count at time t.
ccsqr(t-1) is the change in root CD4 count between t-1 and t.
c(t) is the CD4 count at time t (c1 is CD4 count at seroconversion).
cc(t-1) is the change in CD4 count between t-1 and t

Initial CD4 count:-

csqr1 = 32 - (2 x vset) + Normal(0,2)

if c1 > 1500 then c1 = 1500

if c1 < 18 then c1 = 18

"usual" CD4 count without HIV (for determination of limit of how high CD4 count can go on ART):-

cmax = Normal(800,150)

Changes in CD4 count :-

Greater loss with higher viral load: -

if v(t-1) < 3	*ccsqr(t-1) = -0.030 + Normal(0,1.2)*
if 3 ≤ v(t-1) < 3.5	*ccsqr(t-1) = -0.080 + Normal(0,1.2)*
if 3.5 ≤ v(t-1) < 4	*ccsqr(t-1) = -0.015 + Normal(0,1.2)*
if 4 ≤ v(t-1) < 4.5	*ccsqr(t-1) = -0.200 + Normal(0,1.2)*
if 4.5 ≤ v(t-1) < 5	*ccsqr(t-1) = -0.500 + Normal(0,1.2)*
if 5 ≤ v(t-1) < 5.5	*ccsqr(t-1) = -1.000 + Normal(0,1.2)*
if 5.5 ≤ v(t-1) < 6	*ccsqr(t-1) = -2.000 + Normal(0,1.2)*
if 6.0 ≤ v(t-1)	*ccsqr(t-1) = -2.500 + Normal(0,1.2)*

Greater loss at older age: -

if age(t) < 20	*ccsqr(t-1)=ccsqr(t-1) + 0.15*
if 20 ≤ age(t) < 25	*ccsqr(t-1)=ccsqr(t-1) + 0.09*
if 25 ≤ age(t) < 30	*ccsqr(t-1)=ccsqr(t-1) - 0.06*
if 30 ≤ age(t) < 35	*ccsqr(t-1)=ccsqr(t-1) - 0.00*
if 35 ≤ age(t) < 40	*ccsqr(t-1)=ccsqr(t-1) - 0.00*
if 40 ≤ age(t)< 45	*ccsqr(t-1)=ccsqr(t-1) - 0.06*
if 45 ≤ age(t)< 50	*ccsqr(t-1)=ccsqr(t-1) - 0.09*
if 50 ≤ age(t)< 60	*ccsqr(t-1)=ccsqr(t-1) - 0.15*
if 60 ≤ age(t)	*ccsqr(t-1)=ccsqr(t-1) - 0.20*

Greater loss with x4 virus: - *if x4v(t-1) = 1 then ccsqr(t-1) = ccsqr(t-1) - 0.25*

These values above determine the underlying CD4 count. The measured CD4 count (cm(t) is given by

$cm(t) = (sqrt(c(t)) + Normal (0,1.2))^2$

Comment: These estimates are derived based on synthesis of evidence from natural history studies (3-10) and were selected in conjunction with other relevant parameter values to provide a good fit to the incubation period distribution (see Table 1 in Model Fit section).

ART-naïve patients - Shift to X4 virus

Depends on viral load:-
probability of shift at time t is given by $pr\_x4\_shift=10^{v(t-1)} \times 0.0000004$
Whether shift occurs is determined by sampling from Binomial distribution.

Comment: This translates into a rate of 5% per year in a person with viral load 30,000 cps/mL and 16% per year in a person with 100,000 cps/mL, which are broadly consistent with observed data (11).

ART-naïve patients - Presence of resistance acquired at infection

In the following, c_rt184m1 indicates whether the M184V mutation is present in majority virus (1 = yes, 0 =no) at infection, etc. e_rt184m1 indicates whether virus with mutation is present at all, etc. Once e_rt184m{t} takes the value 1 it can never revert to 0.

50% of those infected sexually assumed to be infected from an ART experienced person. Amongst those the following risks are assumed

Reverse transcriptase

12% chance that c_rttams1=1, 5% chance that c_rttams1=2

4% chance that e_rt184m1=1
(unlike all other mutations, m184v is assumed not to persist in majority virus after infection)

0.1% chance that c_rt74m1 = 1

0.3% chance that c_rt65m1 =1

14% chance that c_rtnnm1=1

Protease Inhibitors

2% chance that c_pr30m1=1
2% chance that c_pr33m1=1
2% chance that c_pr46m1=1
2% chance that c_pr48m1=1
2% chance that c_pr50vm1=1
2% chance that c_pr50lm1=1
2% chance that c_pr82m1=1
2% chance that c_pr84m1=1
2% chance that c_pr90m1=1
2% chance that c_prpixm1=1

Other classes

CCR5 antagonist
c_ccrm1=0 (ie assumed negligible risk of acquiring this at infection)

Enfuvirtide
c_enfm1=0 (ie assumed negligible risk of acquiring this at infection)

Integrase inhibitor
c_inin1=0 (ie assumed negligible risk of acquiring this at infection)

ART-naïve patients - Timing of initiation of ART

c = CD4 count

if patient has no CDC B disease and no AIDS:-

if 350 ≤ c < 500	*rate of starting per 3 mth = 0.005*
if 300 ≤ c < 350	*rate of starting per 3 mth = 0.05*
if 250 ≤ c < 300	*rate of starting per 3 mth = 0.35*
if 200 ≤ c < 250	*rate of starting per 3 mth = 0.95*
if 100 ≤ c < 200	*rate of starting per 3 mth = 0.95*
if 0 ≤ c < 100	*rate of starting per 3 mth = 0.95*

if patient has CDC B disease:-

if 350 ≤ c < 500	*rate of starting per 3 mth = 0.02*
if 300 ≤ c < 350	*rate of starting per 3 mth = 0.10*
if 250 ≤ c < 300	*rate of starting per 3 mth = 0.80*
if 200 ≤ c < 250	*rate of starting per 3 mth = 0.95*
if 100 ≤ c < 200	*rate of starting per 3 mth = 0.95*
if 0 ≤ c < 100	*rate of starting per 3 mth = 0.95*

if patient has AIDS then start ART

For patients with average adherence (adhav) = 0.5 (see below), these probabilities are divided by 1.25. If 0.5 < adhav < 0.8 then these probabilities are divided by 1.1.

Comment: The rates are based on knowledge of policy of when to start ART that has been used in the UK (12;13).

Choice of specific drugs

These were made with knowledge of which drugs are available and used (guided by drug sales data and data from UK CHIC).

The following antiretroviral drugs were considered:-
NRTI - zidovudine, d4T, ddi, ddc, 3tc, abacavir, tenofovir, ftc;
NNRTI – nevirapine, efavirenz, etravirine;
PI (ritonavir-boosted) – saquinavir, ritonavir, indinavir, nelfinavir, lopinavir, amprenavir, atazanavir, tipranavir, darunavir;
FI – enfuvirtide;
CCR5I – maraviroc;
II - Raltegravir

Occurrence of AIDS diseases

Rate of AIDS diseases according to CD4 count

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

Independent effect of viral load

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

Independent effect of age

$rate = rate \times (age(t) / 38)^{1.2}$

Independent effect of PJP prophylaxis

If patient on PJP prophylaxis then this rate is multiplied by 0.8

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.

Comment: These estimates are broadly based on references (14-17).

Occurrence of death from HIV / AIDS

Rate of death from HIV/AIDS = rate of AIDS / 4

Comment: The factor 4 was chosen to provide results consistent with observed data, including on the incubation period for death and the time from AIDS to death (in untreated people) (10;18-20) (see Tables 1 and 4 in Model Fit section).

Occurrence of death from other causes

Rates from UK national mortality statistics for 2009 were used (21).

There is increasing evidence that people with HIV infection itself may have a raised risk of common clinical conditions such as non-AIDS cancers, renal and liver disease and cardiovascular diseases (22-27). Data from observational studies suggest that there is a modest increased risk of death for HIV-positive people with CD4 count greater than 500/mm^3, compared to the general population, of the order of approximately 1.5 (28;29). Hence, we assumed that there was a 1.5-fold increased rate of all non-HIV causes of death throughout life.

Smokers experience rate x (1.43). Non smokers experience rate x (0.71). This is based on the knowledge of effect of current smoking on all cause mortality, which is approximately 2-fold (30). It is also based on the assumption that 40% of MSM in the UK are smokers throughout life.

Patients on ART - Adherence

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.

Component which is fixed over time for a given patient

Average adherence (a measure of the patient’s tendency to adhere "adhav") is a fixed value for a patient. "adhvar" is the variance of the adherence from period to period

5% probability	*adhav = 0.49* *adhvar = 0.2*
10% probability	*adhav = 0.79* *adhvar = 0.2*
65% probability	*adhav = 0.90* *adhvar = 0.06*
20% probability	*adhav = 0.95* *adhvar = 0.05*

if adhav lt 0 then adhav=0 *if adhav gt 1 then adhav=1*

Comment: These estimates are based partially on observed adherence data (31-36), but also on adherence levels required to produce observed estimates of rates of resistance development and virologic failure and also data on the proportion of patients at first virologic failure who have no resistance mutations present (37). 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 (38;39). 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.

Actual adherence level in a period

adh(t) is the actual level of adherence between t-1 and t and is determined as follows

adh(t)=adhav

adh(t) = adhav + Normal(0,advar)
if adh(t) > 1 then adh(t)=1
if adh(t) < 0 then adh(t)=0

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. 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.

Comment: Adherence to ART is assumed to have remained stable over time and not decline. There is some recent evidence that this is the case for over ten years (40).

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 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.

Comment: 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 longer 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 (41-48).

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).

	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 (log change from vmax)	≥ 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
	≥ 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
	< 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 change (t-1 to t)	≥ 0.8	+70	+45	+40	+35	+30	+25	+20	+17	+13	+10	+5	-2	-15
	≥ 0.5, < 0.8	+30	+30	+23	+20	+15	+13	+10	+8	+5	+3	+0	-7	-17
	< 0.5	+5	+4	+3	+2	+1	-1	-3	-6	-10	-11	-12	-13	-18
new mutation risk (x log viral load)	≥ 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
	≥ 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
	< 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

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.

Adherence between t-2 & t-1	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

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. This is the mean of a Normal distribution with standard deviation 10, for which the patient's change is sampled. For the new mutation risk, this

Adherence between t-2 & t-1	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	-10.5	-13	-14.5
< 0.5	≥ 0.8	+30	+28	+25	+23	+7.5	+1.5	-4.5	-7.5	-9	-10.5	-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

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).

Adherence between t-2 & t-1	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	0.1	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	0.1	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	0.1	0.1	0.2	0.3	0.4	0.45	0.5	0.5
≥ 0.8	≥ 0.5, < 0.8	0.10	0.15	0.25	0.3	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	0.3	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	0.3	0.3	0.3	0.3	0.35	0.4	0.45	0.5	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, < 0.8	< 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

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).

	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 from vmax)	< 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
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	-17	-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

Patients on ART - Number of active drugs in the regimen

Every drug is treated as being equally potent because virologic efficacy depends only on number of active drugs, not which specific drugs they are that are active. In reality, drugs differ in potency but to our knowledge no reliable estimates are available to use (although further refinements of the model may use early phase data on the short-term (e.g. 2 weeks) effect of drugs on viral load when used as monotherapy, as a measure of efficacy).

The number of active drugs in the regimen at time t (nactive) is the sum of the activity of each component drug (r_zdv for zidovdine, r_d4t for stavudine, etc), where a drug is scored as 1 if no resistance, 0.5 if partial resistance present (whether resistant virus is majority virus or not) and 0 if complete resistance.

```
nres  =
        o_zdv  x  r_zdv
+       o_d4t   x  r_d4t
+       o_ddc  x  r_ddc
+       o_ddi   x  r_ddi
+       o_ten  x  r_ten
+       o_aba  x  r_aba
+       o_3tc  x  r_3tc
+       o_nev  x  r_nev
+       o_efa  x  r_efa
+       o_etr   x  r_etr
+       o_ind  x  r_ind
+       o_rit   x  r_rit
+       o_saq  x  r_saq
+       o_nel  x  r_nel
+       o_lpr  x  r_lpr
+       o_dar  x  r_dar
+       o_enf  x  r_enf
+       o_ccr  x  r_ccr
+       o_ini  x  r_ini
nactive  = nod  - nres  ;
```

where nod is the number of drugs the patient is on, o_zdv means the patient is on zdv at time t, etc. r_zdv is the level of resistance to zdv (0, 0.25, 0.5, 0.75 or 1), etc

Comment: This follows a common approach to reporting drug activity from genotypic (and phenotypic) resistance tests (i.e. this is effectively a genotypic sensitivity score - GSS) (49).

Patients on ART - Accumulation of resistance mutations

The resistance mutations considered are as follows below. Note that the possibility of mutations to anticipated drugs is accounted for. This is necessarily crude (as the new drugs that will be licensed and their resistance profiles are as yet uncertain) but conveys the fact that new drugs are under development for which the virus will have to develop new mutations to evade.

nucleosides: rt184, # tams, rt74, rt65 (rtnucx - specific resistance mutation to a nuc drug yet to appear)

NNRTI's: rtnn (rtnnx - specific resistance mutation to an NNRTI drug yet to appear)

PI: pr30, pr32, pr33, pr46, pr47, pr48, pr50v, pr50l, pr76, pr82, pr84, pr88, pr90

EI: enf mutation

CCR5i: ccr5 mutation

Integrase inhibitor: ii mutation

"newmut" 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.

nucleosides (NRTI's)

if o_3tc(t-1) =1 and c_rt184m(t-1) =0 then
30% chance that rt184 mutation arises

if (o_zdv(t-1)=1 or o_d4t(t-1)=1) and o_3tc(t-1)=0 then
20% chance that # tams increased by 1
1% chance that # tams increased by 2

if (o_zdv(t-1)=1 or o_d4t(t-1)=1) and o_3tc(t-1)=1 then
12% chance that # tams increased by 1
2% chance that # tams increased by 2

if (o_ddi(t-1)=1 or o_ddc(t-1) or o_aba(t-1)=1) and c_rt74m(t-1)=0 then
1% chance rt74 mutation arises

if (o_ten(t-1)=1 or o_aba(t-1)=1 or o_ddi(t-1)=1) and (o_zdv(t-1)=1 or o_d4t(t-1)=1) and c_rt65m(t-1)=0 then
2% chance rt65 mutation arises

if (o_ten(t-1)=1 or o_aba(t-1)=1 or o_ddi(t-1)=1) and (o_zdv(t-1)=0 and o_d4t(t-1)=0) and c_rt65m(t-1)=0 then
10% chance rt65 mutation arises

if on new NRTI then
10% chance mutation rtnucx mutation arises

NNRTI's

if (o_nev(t-1)=1 or o_efa(t-1)) and c_rtnnm(t-1) = 0 then
80% chance rtnn mutation arises

if on etravirine
30% chance rtnnx *mutation* arises

Protease inhibitors

We assume accumulation different on boosted PI (lpr or ind or saq used post 2000.5 or post 1999 respectively)

if o_ind(t-1)=1 then
5% chance pr46 mutation arises
5% chance pr82 mutation arises
5% chance pr84 mutation arises

if o_saq(t-1)=1 then
4% chance pr48 mutation arises
4% chance pr90 mutation arises

if o_rit(t-1)=1 then
12% chance pr46 mutation arises

	12% chance pr82 mutation arises *12% chance pr84 mutation arises*
if o_nel(t-1)=1 then	*15% chance pr30 mutation arises* *15% chance pr90 mutation arises*
if o_amp(t-1)=1 then	*4% chance pr50v mutation arises* *4% chance pr84 mutation arises*
if o_taz(t-1)=1 then	*4% chance pr50l mutation arises* *4% chance pr84 mutation arises* *4% chance pr88 mutation arises*
if o_lpr(t-1)=1 then	*4% chance pr32 mutation arises* *4% chance pr47 mutation arises* *4% chance pr82 mutation arises*
if o_tip(t-1)=1 then	*4% chance pr33 mutation arises* *4% chance pr82 mutation arises* *4% chance pr84 mutation arises*
if o_dar(t-1) then	*4% chance pr50v mutation arises* *4% chance pr54 mutation arises* *4% chance pr76 mutation arises* *4% chance pr84 mutation arises*

Other classes

if o_enf(t-1)=1 then	*8% chance enf mutation arises*
if on ccr5 inhibitor then	*7% chance enf mutation arises*
if on integrase inhibitor then	*7% chance enf mutation arises*

Comment: 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). 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.

Patients on ART - Determination of level of activity for each drug

In what follows, e_rt184m indicates whether the patient has virus with M184V (regardless of whether this virus is the majority virus and detectable on a resistance test, and regardless of whether it ever has been detected on a resistance test), etc, etc.

3tc / ftc

if e_rt184m =1 then r_3tc =0.75
if e_rt184m =1 then r_ftc =0.75

the effect of tams is same regardless of presence of 3tc m - this interaction is factored in earlier, at the level of reduced tam accumulation when on 3tc

zdv, d4t

if 1 <= e_rttams < 3 and o_3tc =0 then	*r_zdv =0.5*	*r_d4t =0.5*
if 3 <= e_rttams < 5 and o_3tc =0 then	*r_zdv =0.75*	*r_d4t =0.75*
if 5 <= e_rttams and o_3tc =0 then	*r_zdv =1.0*	*r_d4t =1.0*
if 1 <= e_rttams < 3 and o_3tc =1 and e_rt184m =1 then	*r_zdv =0.25*	*r_d4t =0.25*
if 3 <= e_rttams < 5 and o_3tc =1 and e_rt184m =1 then	*r_zdv =0.5*	*r_d4t =0.5*
if 5 <= e_rttams and o_3tc =1 and e_rt184m =1 then	*r_zdv =0.75*	*r_d4t =0.75*
if 1 <= e_rttams < 3 and o_3tc =1 and e_rt184m =0 then	*r_zdv =0.5*	*r_d4t =0.5*
if 3 <= e_rttams < 5 and o_3tc =1 and e_rt184m =0 then	*r_zdv =0.75*	*r_d4t =0.75*
if 5 <= e_rttams and o_3tc =1 and e_rt184m =0 then	*r_zdv =0.75*	*r_d4t =0.75*

tenofovir

if e_rt65m =0 and 2 <= e_rttams <= 3 and (o_3tc =0 or (o_3tc =1 and e_rt184m =0)) then
r_ten =0.5
if e_rt65m =0 and 4 <= e_rttams and (o_3tc =0 or (o_3tc =1 and e_rt184m =0)) then
r_ten =0.75
if e_rt65m =0 and 2 <= e_rttams <= 3 and o_3tc =1 and e_rt184m =1 then
r_ten =0.5
if e_rt65m =0 and 4 <= e_rttams and o_3tc =1 and e_rt184m =1 then
r_ten =0.5
if e_rt65m =1 then *r_ten =0.5*

abacavir

x=e_rt74m + e_rt65m + e_rt184m

if x=3 then	*r_aba = 0.75*
if x=2 then	*r_aba = 0.5*
if e_rttams ge 4 then	*r_aba =0.75*

ddc and ddi

if e_rt74m =1 or e_rt65m =1 then	*r_ddi =0.75*	*r_ddc =0.75*
if e_rttams ge 3 then do	*r_ddi =0.5*	*r_ddc =0.5*

new nuc

if e_rtnucxm =1 then	*r_nnu =0.75*

nns

if e_rtnnm =1 then	*r_nev =1.0*	*r_efa =1.0*
if e_rtetrm =1 and e_rtnnm =1 then	*r_etr =1.0*	
if e_rtetrm =1 and e_rtnnm =0 then	*r_etr =0.5*	

protease inhibitors

if 1 <= e_pr46m +e_pr82m + e_pr84m <= 2 then	*r_ind =0.5*
if e_pr46m +e_pr82m + e_pr84m =3 then	*r_ind =0.75*

if e_pr48m = 1 then	*r_saq =0.75*
if e_pr90m = 1 then	*r_saq =0.5*
if e_pr82m =1 or e_pr84m =1 then	*r_rit =1.0*
if e_pr30m =1 or e_pr84m=1 or e_pr90m =1 then	*r_nel =1.0*
if e_pr50vm =1 or e_pr84m=1 then	*r_amp =0.75*
if (e_pr82m=1 or e_pr84m =1) and e_pr50vm =0 then	*r_amp =0.25*
if e_pr50lm =1 then	*r_taz =0.75*
if (e_pr84m =1 or e_pr88m =1) and e_pr50lm =0 then	*r_taz =0.5*
if e_pr33m +e_pr82m +e_pr84m = 2 then	*r_tip =0.5*
if e_pr33m +e_pr82m +e_pr84m = 3 then	*r_tip =0.75*
if e_pr32m +e_pr47m +e_pr82m = 1 then	*r_lpr =0.25*
if e_pr32m +e_pr47m +e_pr82m = 2 then	*r_lpr=0.5*
if e_pr32m +e_pr47m +e_pr82m = 3 then	*r_lpr=0.75*
if e_pr50vm+e_pr54m+e_pr76m+e_pr84m = 1 then	*r_dar=0.25*
if e_pr50vm+e_pr54m+e_pr76m+e_pr84m = 2 then	*r_dar=0.5*
if e_pr50vm+e_pr54m+e_pr76m+e_pr84m >= 3 then	*r_dar=0.75*
if e_pr46m +e_pr82m + e_pr84m +e_pr90m = 4 then	*r_saq =max(r_saq ,0.5)* *r_rit =max(r_rit ,0.5)* *r_ind =max(r_ind ,0.5)* *r_nel =max(r_nel ,0.5)* *r_taz =max(r_taz ,0.5)* *r_dar =max(r_dar ,0.5)* *r_amp =max(r_amp ,0.5)* *r_tip =max(r_tip ,0.5)* *r_lpr =max(r_lpr ,0.5)*
if 2 <= e_pr46m +e_pr82m + e_pr84m +e_pr90m < 4 then	*r_saq =max(r_saq ,0.25)* *r_rit =max(r_rit ,0.25)* *r_ind =max(r_ind ,0.25)* *r_nel =max(r_nel ,0.25)* *r_taz =max(r_taz ,0.25)* *r_dar =max(r_dar ,0.25)* *r_amp =max(r_amp ,0.25)* *r_tip =max(r_tip ,0.25)* *r_lpr =max(r_lpr ,0.25)*

ccr5 inhibitor

if e_ccrm =1 then	*r_ccr =1.0*

enfuvirtide

if e_enfm = 1 then	*r_enf=1*

integrase inhibitor

if e_inin = 1 then	*r_inin=1*

Comment: 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). Currently interpretation systems differ in their prediction of activity for some drugs. Over time as more data accumulate and interpretation systems converge it may be possible to refine these rules.

Interruption of ART

The probability of interruption is greater with higher viral load, current toxicity (c_tox is an indicator of whether any of the toxicities are present or not), greater CD4 count and in patients with a greater tendency to be non-adherent (lower value of "adhav").

if v < log10(500) then:
if adhav ≥ 0.8 then if c_tox(t-1) = 1 then prointer = 0.00004 x c(t-1)
if c_tox(t-1) = 0 then prointer = 0.00002 x c(t-1)
if adhav < 0.8 then if c_tox(t-1) = 1 then prointer = 1.5 x 0.00004 x c(t-1)
if c_tox(t-1) = 0 then prointer = 1.5 x 0.00002 x c(t-1)

if v(t-1) >= log10(500) then:
if adhav ≥ 0.8 then if c_tox(t-1) = 1 then prointer = 2 x 0.00004 x c(t-1)
if c_tox(t-1) = 0 then prointer = 2 x 0.00002 x c(t-1)
if adhav < 0.8 then if c_tox(t-1) = 1 then prointer = 2 x 1.5 x 0.00004 x c(t-1)
if c_tox(t-1) = 0 then prointer = 2 x 1.5 x 0.00002 x c(t-1)

interruption 2 fold more likely in first year of ART
interruption 3-fold more likely in those with adhav < 0.5

where prointer is the probability of interruption (so whether interruption occurs is determined by sampling from Binomial distribution) and c_tox(t-1) is toxicity being experienced at time t-1(1=yes, 0=no).

Comment: See references (49-52).

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 (i.e. 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 > 9 months and c(t-1) is > 300 above cmin(t-1):-
v(t) = vmax(t-1)
if v(t) ≥ 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) ≥ 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) ≥ 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)*

Comment: This is broadly based on evidence from a number of analyses of the effects of ART interruption (50;51;53-61).

Loss of mutations (in majority virus, not complete loss) after stopping regimen and starting another, non-cross-resistant, regimen

Note this all relates to those who have started ART - not about persistence of transmitted mutations (which is currently assumed to be indefinite, except for m184v);

In the following, c_rt184m(t) indicates whether the M184V mutation is present in majority virus (1 = yes, 0 =no), etc. e rt184m(t) indicates whether virus with mutation is present at all, etc. tss 3tc indicates the number of time periods since stopping 3TC, p_3tc etc indicates previous use of 3tc, etc..

Note that if a person was infected with virus with a given mutation then this mutation is never lost (e_xxx is always = 1).

Nucleosides

if c_rt184m =1 and (tss_3tc ge 1 or p_3tc =0) and (tss_aba ge 1 or p_aba =0)
then 80% probability that c_rt184m =0

if c_rt74m =1 and (tss_ddi ge 1 or p_ddi =0) and (tss_aba ge 1 or p_aba =0)
and (tss_ddc ge 1 or p_ddc =0)
then 60% probability that c_rt74m =0

if c_rt65m =1 and (tss_ddi ge 1 or p_ddi =0) and (tss_ddc ge 1 or p_ddc =0) and
(tss_ten ge 1 or p_ten =0) and (tss_aba ge 1 or p_aba =0)
then 60% probability that c_rt65m =c_rt65m1

if c_rttams ge 1 and (tss_zdv ge 1 or p_zdv =0) and (tss_ten ge 1 or p_ten =0) and (tss_d4t ge 1 or p_d4t =0) and (tss_ddc ge 1 or p_ddc =0) and (tss_ddi ge 1 or p_ddi =0)
then 40% probability that c_rttams =c_rttams1

if c_rtnucxm =1 and (tss_nnu ge 1 or p_nnu =0)
then 40% probability that c_rtnucxm =c_rtnucxm1

NNRTI's

if c_rtnnm =1 and (tss_efa ge 1 or p_efa =0) and (tss_nev ge 1 or p_nev =0) and (tss_nnn ge 1 or p_nnn =0)
then 20% probability that c_rtnnm =c_rtnnm1

if c_rtetrm =1 and (tss_efa ge 1 or p_efa =0) and (tss_nev ge 1 or p_nev =0) and (tss_nnn ge 1 or p_nnn =0)

then 20% probability that c_rtetrm =c_rtnnxm1

Protease inhibitors

if c_pr30m ge 1 and (tss_nel ge 1 or p_nel =0) then
20% probability that c_pr30m =c_pr30m1

etc (loss of any mutation from majority virus occurs at this rate once the patient is longer taking any drug selecting for the mutation)

CCR5

if c_prpixm ge 1 and (tss_npi ge 1 or p_npi =0) then 20% probability that c_prpixm =c_prpixm1

Enfuvirtide

if c_enfm =1 and (tss_enf ge 1 or p_enf =0) then 60% probability that c_enfm =c_enfm1

Integrase inhibitor

if c_inim ge 1 and (tss_ini ge 1 or p_ini =0) then 20% probability that c_inim =c_inim1

where c_rt184m(t) indicates whether the M184V mutation is present in majority virus (e_rt184m(t) indicates whether virus with mutation is present at all), etc, c_rttams(t) is the number of TAMS present.

Comment: This is based on evidence from studies in people interrupting ART (62-67).

"Regaining" mutations (in majority virus) after restarting ART

Mutations previously present are regained when one of the corresponding drugs listed above is restarted.

Re-initiation of ART after interruption

If c < 50 then 95% chance of re-starting in a given 3 month period
If 50 ≤ c < 100 then 90% chance of restarting
If 100 ≤ c < 200 then 80% chance of restarting
If 200 ≤ c < 300 then 3% chance of restarting
If 300 ≤ c then 1% chance of restarting

if an AIDS disease occurs then ART is restarted

For those on triple therapy at the time of interruption, the regimen restarted is same as that at time of interruption (because have not virologically failed it or stopped drugs due to toxicities).

Comment: This is based on a perception of clinical decisions made in recent years (58;60).

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. Further refinement will be possible as more data accumulate.

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.

Switching off PI therapy when viral load < 50 copies/mL

Those patients with viral load < 50 copies/mL who have never previously failed an NNRTI have a certain probability of being switched from a PI to an NNRTI or abacavir.

Use of PCP prophylaxis

If a person is present at time t and c(t-1) < 200 then there is a 90% chance of being on PCP prophylaxis.

Comment: This is based on recent guidelines on use of prophylaxis for opportunistic infections (68).

Model fit

The following provides some further details of the comparisons of the fit of the model to observed data.

Table 1. Incubation period to AIDS and death from seroconversion (no ART)

Year from s/c	% with AIDS Observed[69]	model	% died Observed[69]	model
1	0.6	0.7	0.3	0.7
2	2.0	2.0	1.4	1.5
3	4.3	4.8	3.1	3.0
4	8.1	9.0	5.8	5.8
5	13.4	15.2	9.8	10.2
6	19.8	22.5	14.8	16.2
7	25.9	30.4	20.5	23.5
8	32.3	38.4	27.0	31.6
9	38.8	46.8	33.8	40.2
10	46.1	54.4	40.5	48.6
11	53.0	61.5	48.3	56.6
12	58.1	68.0	55.4	63.4
13	63.0	73.8	62.4	70.7

Table 2. Incubation period to CD4 <200, <350, <500 (no ART)

Year from s/c	% CD4 < 200 Observed[70]	model	% CD4 < 350 Observed[70]	model	% CD4 < 500 Observed[70]	model
1	8.8	0.8	26.1	10.8	48.0	43.7
2	12.2	5.0	33.2	24.5	55.9	58.8
5	32.3	33.2	55.0	57.7	72.7	79.3

Table 3. Viral load set point and initial CD4 count (after primary infection)

	Observed[71]	Model
Median VL set point:	4.5	4.0
Median CD4:	570	576

Table 4. Incubation period AIDS to death (pre-ART era)

Years from AIDS diagnosis	% died Observed[20]	model
1	40%	40%
3	84%	77%
median	17 mths	18 mths

Table 5. Association between viral load measured close to seroconversion (between 6-24 months) and risk of AIDS, adjusting for CD4 count and age.

	Adjusted Relative Hazard	
	Observed[5] (95% confidence interval)	Model
Viral load (Per 0.5 log higher)	1.87 (1.58 – 2.20)	2.56
CD4 count (Per 100 cells/mm^3 higher)	1.12 (1.02 – 1.24)	1.20
Age (Per 10 years older)	1.19 (0.96 – 1.47)	1.34

Table 6. Risk of AIDS by CD4 count and viral load and age over 6 years (pre-HAART)

		Observed[10]	Model
CD4 < 350			
Viral load	≤ 1500 - (low n)		
	1501- 7000	19	41
	7001- 20000	42	65
	20001- 55000	73	85
	> 55000	92	96
CD4 350-500			
Viral load	≤ 1500 - (low n)		
	1501- 7000	22	17
	7001- 20000	40	34
	20001- 55000	57	64
	> 55000	78	83
CD4 > 500			
Viral load	≤ 1500 - (low n)	5	4
	1501- 7000	15	6
	7001- 20000	26	16
	20001- 55000	48	37
	> 55000	67	62

***** Viral load values used in MACS may need to be multiplied by ~ 2 to approximate to more commonly used Roche assay levels.

Table 7. Median CD4 count at diagnosis of AIDS and at death (pre-HAART era)

	AIDS	death
Observed[19]:	~ 40	~ 0
Model:	42 IQR 13 - 112	5 IQR 1 - 30

Table 8. 3 year percent risk of AIDS after start of ART by baseline CD4 / viral load (age < 50, non-IDU, AIDS-free)

		Observed[72]	Model
Baseline viral load < 100,000			
Baseline CD4 count	< 50	16	17
	50 - 99	12	9
	100 - 199	9	5
	200- 349	5	5
	≥ 350	3	0
Baseline viral load ≥ 100,000			
Baseline CD4 count	< 50	20	22
	50 - 99	16	12
	100 - 199	12	9
	200- 349	6	5
	≥ 350	4	0

Table 9. Effect of HAART vs no therapy on risk of AIDS and death

Simulated trial with 5 years follow up Relative hazard of AIDS (HAART vs no therapy)	
Observed[73]	model
0.10	0.16

Table 10. % with virologic failure (viral load > 500 copies/mL / on ART) by time from start of HAART (patients starting with PI/r or NNRTI regimen). Observed data from ref (74).

Years from start of HAART

1		2		3		4		5		6		7	
obs	mod	obs	mod	obs	mod	obs	mod	obs	mod	obs	mod	obs	mod
7%	10%	13%	15%	17%	19%	20%	23%	22%	25%	24%	29%	27%	32%

*Observed data may be overestimates due to some unrecognised stopping of ART

8	
obs	mod
29%	34%

Table 11. Rate of viral rebound in people on 1st line HAART and with viral load < 50 copies/mL

	Rate per 100 person-years
Observed[75]:	3-6
Model:	5.6

Table 12. Median CD4 count change at 3 years from start of HAART

Observed[47]:	273
Model:	268

Table 13. Discontinuation of drugs in initial HAART regimen

Time from start of ART to discontinuation of at least one drug in initial regimen (discontinuation for any reason)

Years from start of HAART (observed data from ref (76). - modelled data for 1996-2001 inclusive)

1		2		3		4	
obs	mod	obs	mod	obs	mod	obs	mod
30%	31%	45%	45%	62%	55%	73%	63%

Table 14. Risk of resistance mutations (and virologic failure) after start of ART (patients starting with PI/r or NNRTI regimen)

% with at least one resistance mutation (and virologic failure)
observed data from ref (77).

Years from start of HAART													
1		2		3		4		5		6		7	
obs	mod	obs	mod	obs	mod	obs	mod	obs	mod	obs	mod	obs	mod
4%	12%	8%	15%	10%	19%	11%	21%	12%	23%	14%	25%	16%	27%

8	
obs	mod
17%	30%

Observed data underestimates because resistance tests not always performed at virologic failure.

Table 15. % with at least one resistance mutation for all three main classes (and virologic failure)

Years from start of HAART
(observed data from ref. (78)).

1		2		3		4		5		6	
obs	mod	obs	mod	obs	mod	obs	mod	obs	mod	obs	mod
		1.0%	0.5%			2.7%	2.1%			4.1%	4.8%

Table 16. Risk of resistance mutations after start of ART *

% with at least one resistance mutation

	Years from start of HAART					
	2		4		6	
	obs	mod[41]	obs	mod[41]	obs	mod[41]
M184V mutation (in those starting with 3TC)	6%	9%	13%	14%	18%	18%
TAM (in those starting with zdv or d4T)	4%	6%	9%	10%	13%	12%
PI mutation (in those starting with boosted PI regimen)	3%	6%	7%	9%	--	
NNRTI mutation (in those starting with NNRTI regimen)	8%	14%	14%	19%	21%	23%

*Observed data are likely to be under-estimates as resistance testing is not always performed at virologic failure

Table 17. Risk of death after triple class resistance

% dead by 3 years (for people with TCR up to 2004.5)

Observed[79]	model
12%	**19%**

Table 18. Percent with triple class virologic failure by years from start of HAART (patients naïve before HAART)

Observed data from ref (80). Modelled estimates based on ART start years 1998-2008 inclusive

Years from start of HAART			
5		9	
obs	mod	obs	mod
3.4%	**6.8%**	8.6%	**12.6%**

Sensitivity Analyses

Here we describe the details of the multivariable sensitivity analyses that were performed.

Sensitivity Analyses

The effects (on life expectancy) of varying key assumptions were explored in sensitivity analyses.

We performed both univariable sensitivity analyses and multivariable sensitivity analysis. In the multivariable sensitivity analysis, the values of multiple parameters were changed simultaneously.

Univariable sensitivity analyses

Several sensitivity analyses were performed to assess the effects of varying key assumptions on life expectancy. These are all described in the main manuscript (Table 1). The assumptions that were varied include the rate of diagnosis, rate of interruption, the rate of ART uptake and adherence.

Multivariable sensitivity analysis

In the multivariable sensitivity analysis, a total of 10,000 runs of the model were made, each time sampling at random, values for a number of different key parameters in order to generate the distribution of life expectancy. The parameters which were varied, along with the probability distributions which were given in the sensitivity analysis and resulting 95% uncertainty bounds, are shown in Table S1.

The probability distributions and thus the uncertainty bounds for each parameter were chosen such that even at the boundary values, the parameter was thought to be just plausible. The parameters in Table S1 were chosen on the basis that there is some uncertainty regarding the assumed value, i.e. some have only limited evidence supporting the choice of value for the parameter and some are purely best guess estimates as, to our knowledge, there is no good quality supporting data.

Probability distributions were selected depending on the nature of the variable concerned. Parameters which correspond to probabilities were given Beta distributions, such that the outcomes were restricted to between 0 and 1 inclusive. Parameters which correspond to ratios were given log-normal distributions, such that they are additive on the log scale (and thus multiplicative on the normal scale).

Further to the parameters in Table S1, we also varied the adherence pattern for each of the 10,000 runs such that in 80% of the runs, individuals had an underlying tendency to adhere as found in the Model details section above (which is what we estimated from observed data), in 10% of the runs they had worse adherence in general and in the remaining 10% of the runs, they had better adherence in general.

The median life expectancy from this multivariable sensitivity analysis was 73.8 years and the 95% uncertainty bound was (68.0,77.3) years, i.e. Of the 10,000 runs, the estimated life expectancy was between 68.0 and 77.3 years in 95% of the runs.

Table S1: Parameters varied in multivariable sensitivity analyses

Parameter	Value in model	Distribution given in sensitivity analysis	2.5th and 97.5th percentile of given distribution
Probability of willingness to take enfuvirtide	0.85	Beta(15,59/17)	0.65,0.93
Mean of viral load set point (log copies/ml)	4	Normal(4,0.2)	3.67,4.33
Standard deviation of viral load set point (log copies/ml)	0.5	Normal(0.5,0.1)	0.33,0.67
Standard deviation of viral load change when ART-naïve (log copies/ml)	0.05	Normal(0.05,0.01)	0.033,0.067
Maximum value that the viral load set point can take (log copies/ml)	6.5	Normal(6,0.2)	5.67,6.33
Maximum value that actual viral load can take (log copies/ml)	6.5	Normal(6,0.2)	5.67,6.33
Standard deviation of the measured CD4 count (cells/mm^3)	1.2	Normal(1.2,0.2)	0.87,1.53
Standard deviation of the actual CD4 cell count (cells/mm^3)	1.2	Normal(1.2,0.2)	0.87,1.53
Maximum value that the actual CD4 count can take (cells/mm^3)	800	Normal(800,20)	767,834
Additional variability given to change in CD4 count whilst on ART (cells/mm^3)	0	Normal(0,5)	-8.23,8.24
Probability that initiation of ART depends on the underlying tendency to adhere	1	Beta(10,52)	0.09,0.24
Probability of initiating ART given that, 350 ≤ measured CD4 count < 500 (cells/mm^3)	0.02	Beta(10,442)	0.012,0.034
Probability of initiating ART given that, 300 ≤ measured CD4 count < 350 (cells/mm^3)	0.95	Beta(20,2)	0.80,0.98
Probability of initiating ART given that, 250 ≤ measured CD4 count < 300 (cells/mm^3)	0.95	Beta(20,2)	0.80,0.98
Probability of initiating ART given that, 200 ≤ measured CD4 count < 250 (cells/mm^3)	0.95	Beta(20,2)	0.80,0.98
Probability of initiating ART given that, 100 ≤ measured CD4 count < 200 (cells/mm^3)	0.95	Beta(20,2)	0.80,0.98
Probability of initiating ART given that, 0 ≤ measured CD4 count < 100 (cells/mm^3)	0.95	Beta(20,2)	0.80,0.98
Value used to calculate individual's underlying propensity for CD4 rise on ART[1]	0.5	Normal(0.5,0.1)	0.33,0.67
Change in reduction of underlying propensity of CD4 rise after 4 years[2]	4	6 + Uniform(0,4)	6.2,9.8
Multiplicative factor given to rate of interruption in those with low tendency to adhere	1.5	0.5 + exp{Normal(0,0.5log2.5)}	0.98,2.60
Multiplicative factor given to overall rate of interruption	1	Normal(1,0.1)	0.83,1.16
Probability of re-initiating ART given that, 300 ≤ measured CD4 count (cells/mm^3)	0.01	Beta(5,397)	0.005,0.022
Probability of re-initiating ART given that, 200 ≤ measured CD4 count < 300 (cells/mm^3)	0.03	Beta(5,391/3)	0.014,0.067
Probability of re-initiating ART given that, 100 ≤ measured CD4 count < 200 (cells/mm^3)	0.8	Beta(20,23/4)	0.63,0.89
Probability of re-initiating ART given that, 50 ≤ measured CD4 count < 100 (cells/mm^3)	0.9	Beta(20,28/9)	0.74,0.96

Probability of re-initiating ART given that, measured CD4 count < 50 (cells/mm^3)	0.95	Beta(20,2)	0.79,0.98
Multiplicative factor given to probability of new mutations arising	1	0.5 + exp{Normal(0,0.5log2)}	0.57,1.78
Virological failure threshold[3] (log copies/ml)	500	Normal(500,50)	418,583
Probability of use of PCP prophylaxis[4]	0.9	Beta(25,5)	0.71,0.93
Multiplicative factor given to rate used to calculate occurrence of AIDS and death	1	0.5 + exp{Normal(0,0.5log2)}	0.57,1.77
Raised risk of AIDS occurring at HIV diagnosis	3	3 x exp{Normal(0,0.5log1.5)}	2.15,4.19
Raised risk of all-cause mortality due to HIV infection	1.5	Normal(1.5,0.2)	1.17,1.82
Decreased risk of death for non-smokers[5]	5/7	Normal(5/7,0.04)	0.65,0.78

1) As seen in the model details section, 'Patients on ART – Determination of viral load, CD4 count, acquisition of new resistance mutations between t-1 and t' (variable "newmut(t)"), the patients vary in their underlying propensity for CD4 rise on ART, which is given by sampling from exp{Normal(0,0.5)}. So in the sensitivity analyses, we are varying the standard deviation of the Normal distribution, 0.5.
2) If a patient has been on their current regimen for longer than 2 years, their underlying propensity for CD4 count rise reduces 4-fold to reflect the fact that the rate of CD4 count increase decreases over time. So in the sensitivity analyses, we have reduced the rise by (6+uniform(0,4))-fold if a patients has been on their current regimen for longer than 4 years.
3) The viral failure threshold is varied for each 3-month period for each individual, rather than for each simulation.
4) Given that the person has a CD4<200.
5) Given that in this model we are assuming that 40% of MSM are smokers for life. The risk of death for smokers is calculated according to the value sampled from Normal(5/7,0.04) using the formula: risk of death for smokers = {1 – (risk of death for non-smokers x 0.6)} / 0.4, such that the risk of smoking on all cause mortality is 2-fold.

Supplementary tables to the manuscript

Table S2: Values used in order to plot projected range of outcomes in terms of mortality and diagnosis status in Figures 2a and 2b.

Table S3: Values used in order to plot projected range of outcomes in terms of mortality status and CD4 cell counts in Figures 3a and 3b.

Table S2:

High diagnosis rate

	Age (years)																
	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110
Undiagnosed	9034	2195	310	35	5	2	1	0	0	0	0	0	0	0	0	0	0
Diagnosed and off ART	962	3049	2142	1587	1201	1006	872	721	628	463	327	168	82	19	6	1	0
Diagnosed and on ART	0	4524	7033	7572	7660	7384	6973	6376	5536	4489	3213	1805	729	220	55	18	0
Dead from AIDS	2	136	266	396	537	676	803	923	1031	1158	1239	1322	1360	1369	1373	1374	1374
Dead from non-AIDS	2	96	249	410	597	932	1351	1980	2805	3890	5221	6705	7829	8392	8566	8608	8617

Low diagnosis rate

	Age (years)																
	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110
Undiagnosed	9035	6263	2646	802	254	108	53	27	14	6	2	0	0	0	0	0	0
Diagnosed and off ART	960	958	854	798	778	723	658	547	455	364	257	148	48	22	6	2	0
Diagnosed and on ART	0	2403	5244	6477	6614	6439	6055	5575	4842	3881	2731	1544	669	171	51	17	0
Dead from AIDS	3	256	942	1401	1646	1773	1904	2047	2165	2282	2363	2427	2462	2474	2478	2480	2480
Dead from non-AIDS	2	120	314	522	708	957	1330	1804	2524	3467	4647	5881	6821	7333	7465	7501	7514

Table S3:

High diagnosis rate

	Age (years)																
	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110
CD4 <200/mm³	0	748	545	600	552	468	416	386	332	265	187	106	42	8	4	0	0
CD4 200-349/mm³	86	1815	1546	1482	1305	1207	1054	934	783	593	417	237	103	34	7	1	0
CD4 350-499/mm³	2226	2590	2101	1791	1657	1556	1339	1213	979	803	581	268	123	29	6	3	0
CD4 ≥500/mm³	7684	4615	5290	5244	5125	4768	4507	3919	3409	2660	1850	1013	377	115	31	11	0
Dead from AIDS	2	136	266	396	537	676	803	923	1031	1158	1239	1322	1360	1369	1373	1374	1374
Dead from non-AIDS	2	96	249	410	597	932	1351	1980	2805	3890	5221	6705	7829	8392	8566	8608	8617

Low diagnosis rate

	Age (years)																
	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110
CD4 <200/mm³	0	1659	1621	972	588	483	436	364	303	229	171	102	36	7	1	1	0
CD4 200-349/mm³	107	2297	1812	1451	1173	1054	938	767	635	506	346	204	84	25	10	1	0
CD4 350-499/mm³	2224	2239	1800	1602	1460	1291	1131	1012	823	674	470	250	109	26	6	1	0
CD4 ≥500/mm³	7664	3429	3507	4004	4273	4164	3876	3537	3042	2361	1618	843	359	95	24	8	0
Dead from AIDS	3	256	942	1401	1646	1773	1904	2047	2165	2282	2363	2427	2462	2474	2478	2480	2480
Dead from non-AIDS	2	120	314	522	708	957	1330	1804	2524	3467	4647	5881	6821	7333	7465	7501	7514

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