Sustainable HIV Treatment in Africa through Viral Load-Informed Differentiated Care

Supplementary Material

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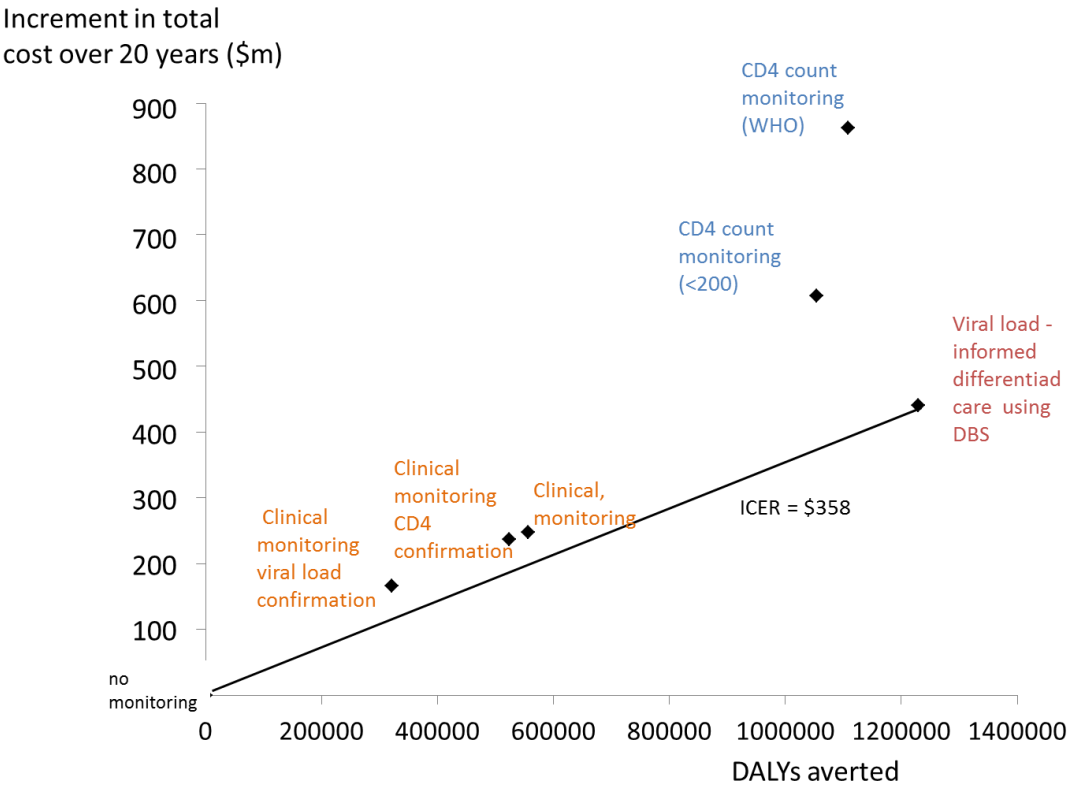
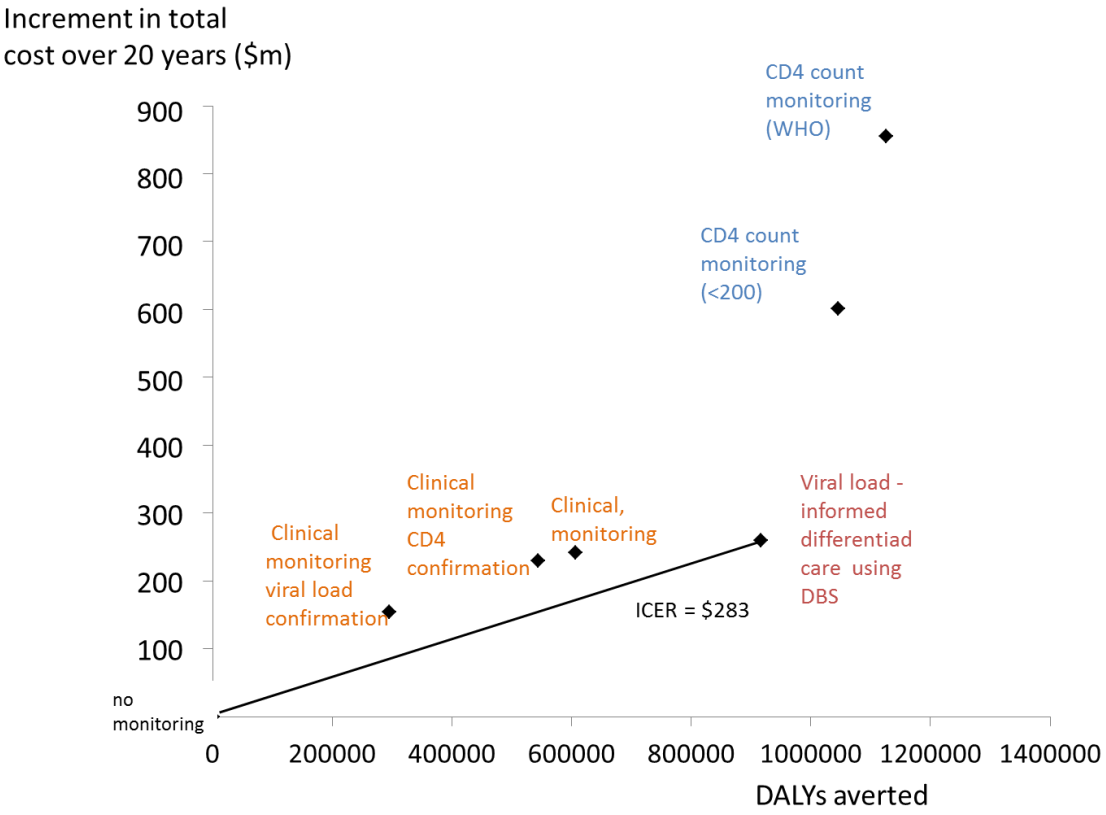
Supplementary Figure 1. Sensitivity analyses showing the cost effectiveness plane corresponding to Figure 2 of the main manuscript after making single changes to the model and assumptions as indicated. These figures correspond to Table 3 of the main manuscript.

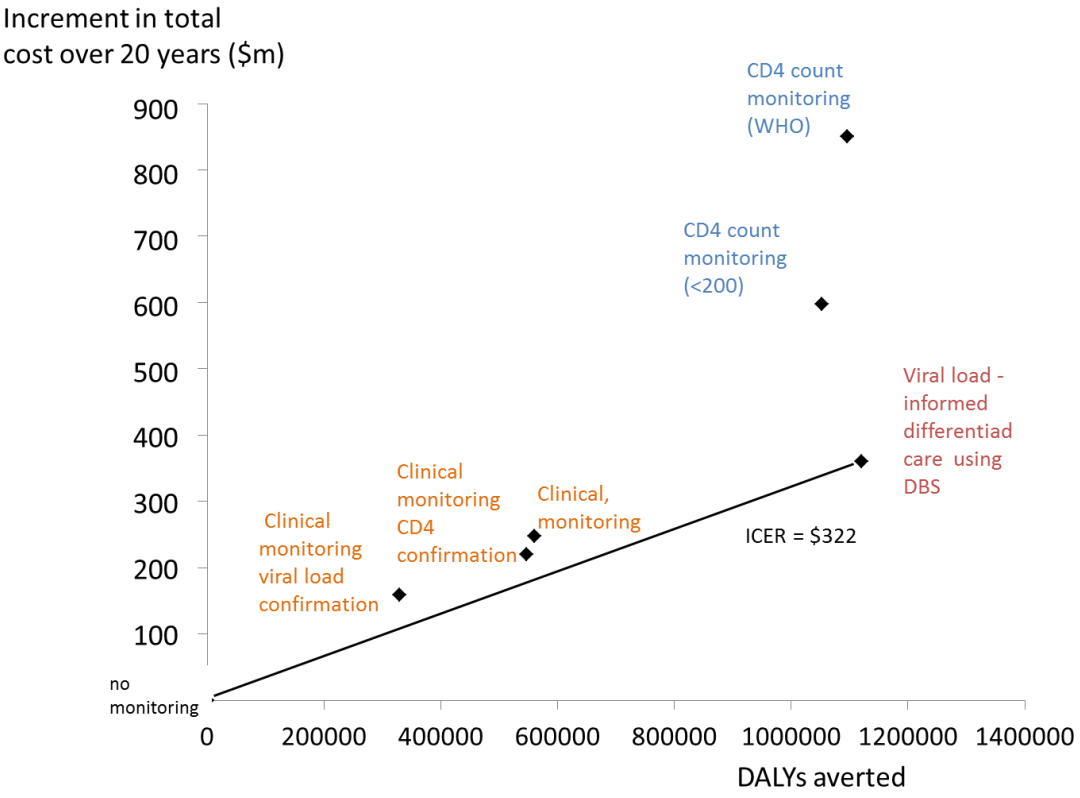
(a) DBS sensitivity 96% and specificity 79% for 1000 cps/mL threshold.



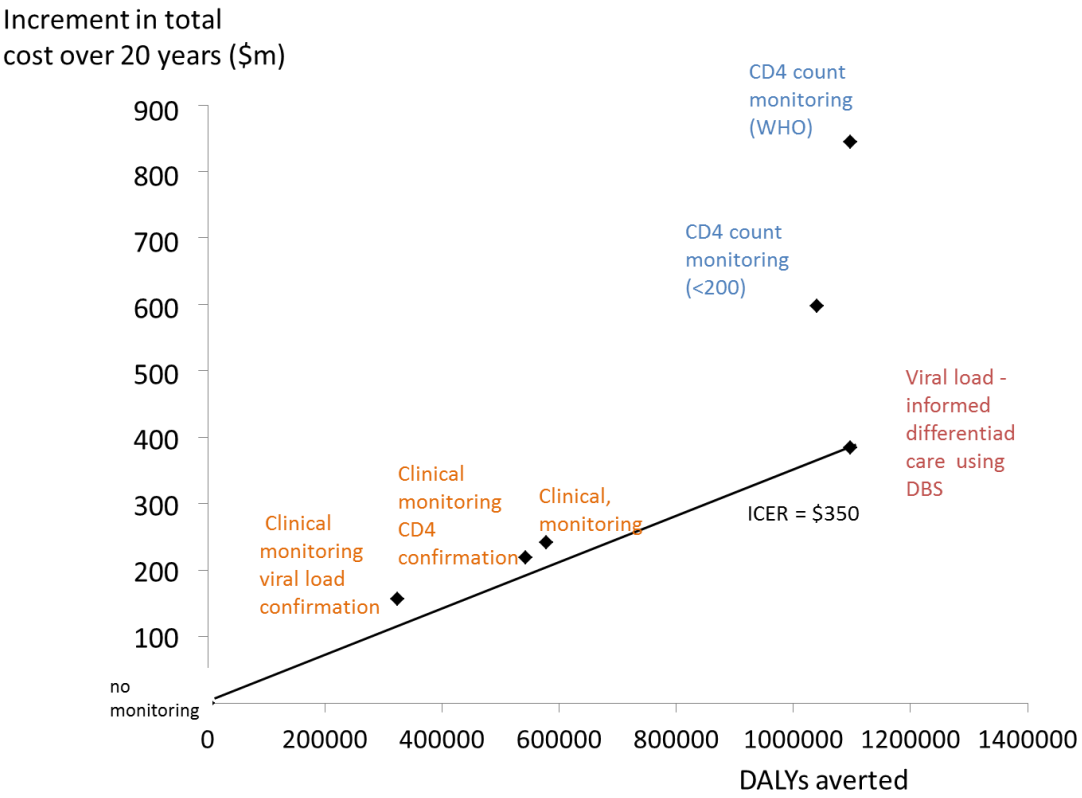
(b) DBS sensitivity 71% and specificity 97% for 1000 cps/mL threshold.



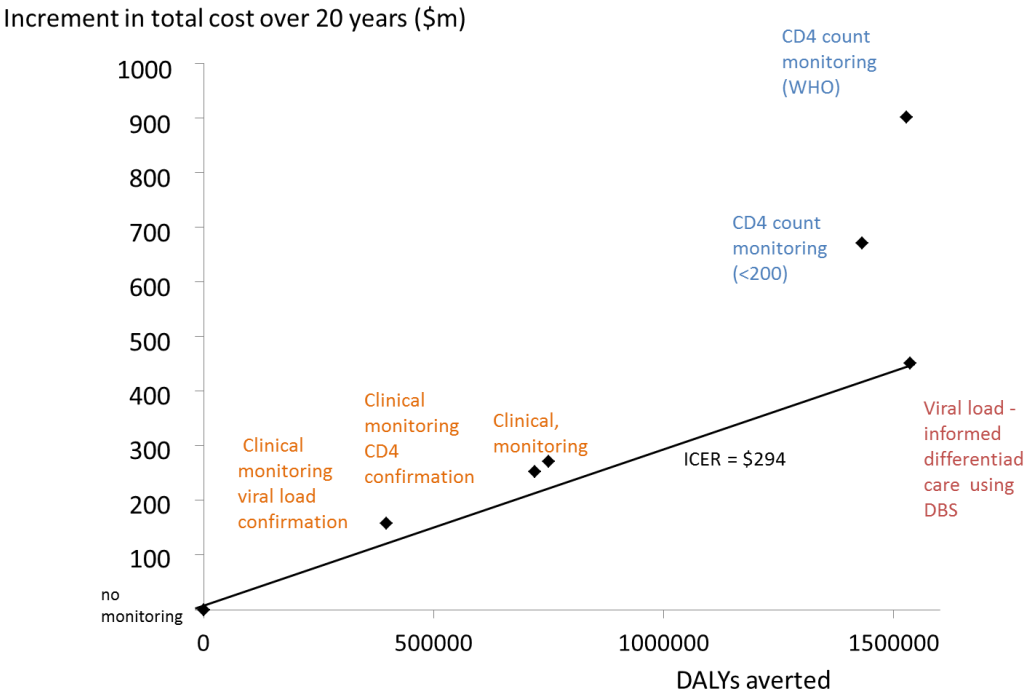
(c) DBS sensitivity 88% and specificity 93% for 1000 cps/mL threshold.



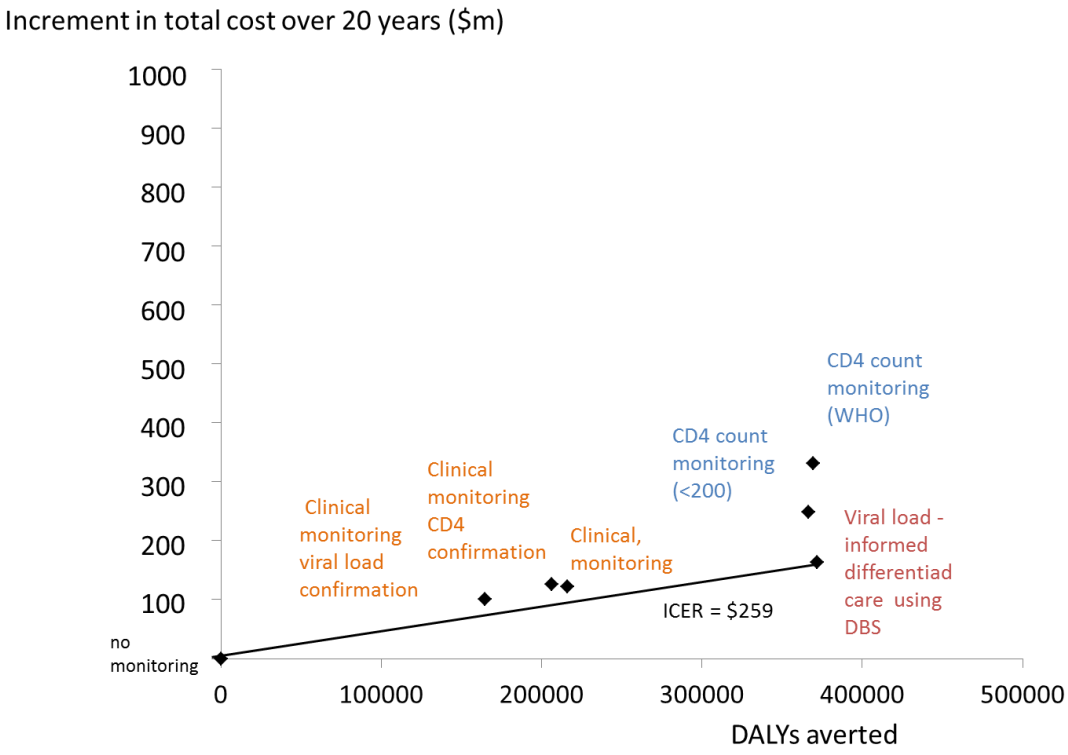
(d) DBS sensitivity 85% and specificity 79% for 1000 cps/mL threshold.



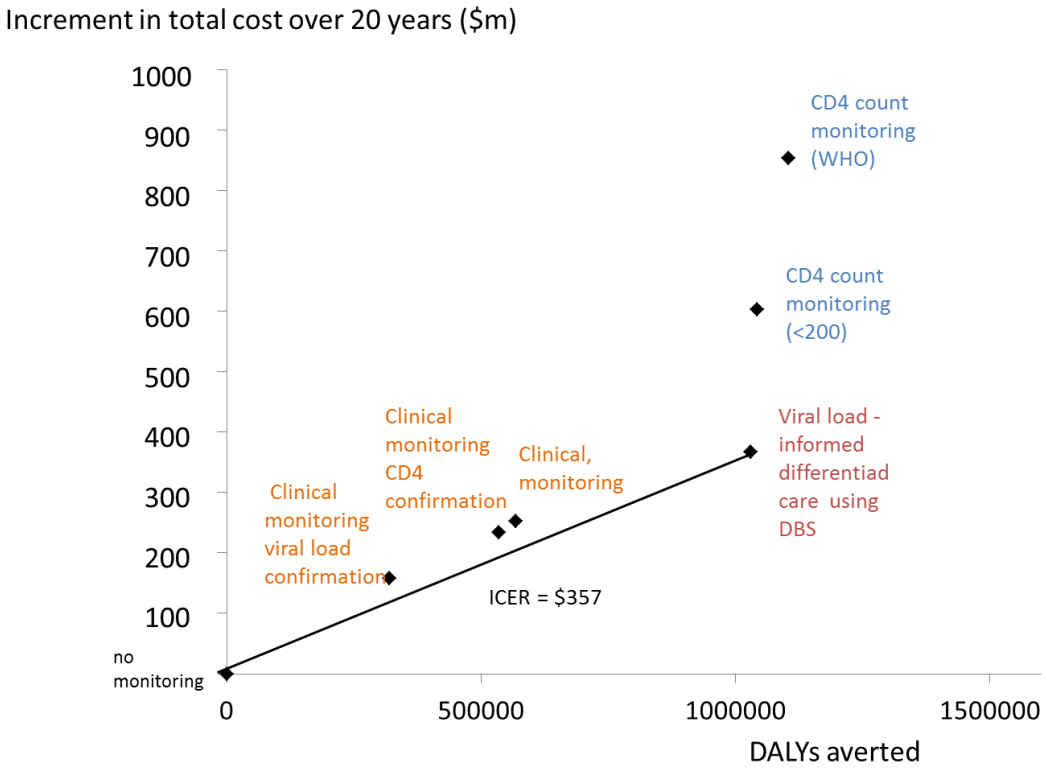
(e) Poorer population ART adherence profile (such that 68% of people on ART are suppressed < 1000 cps/mL - note change in scale)



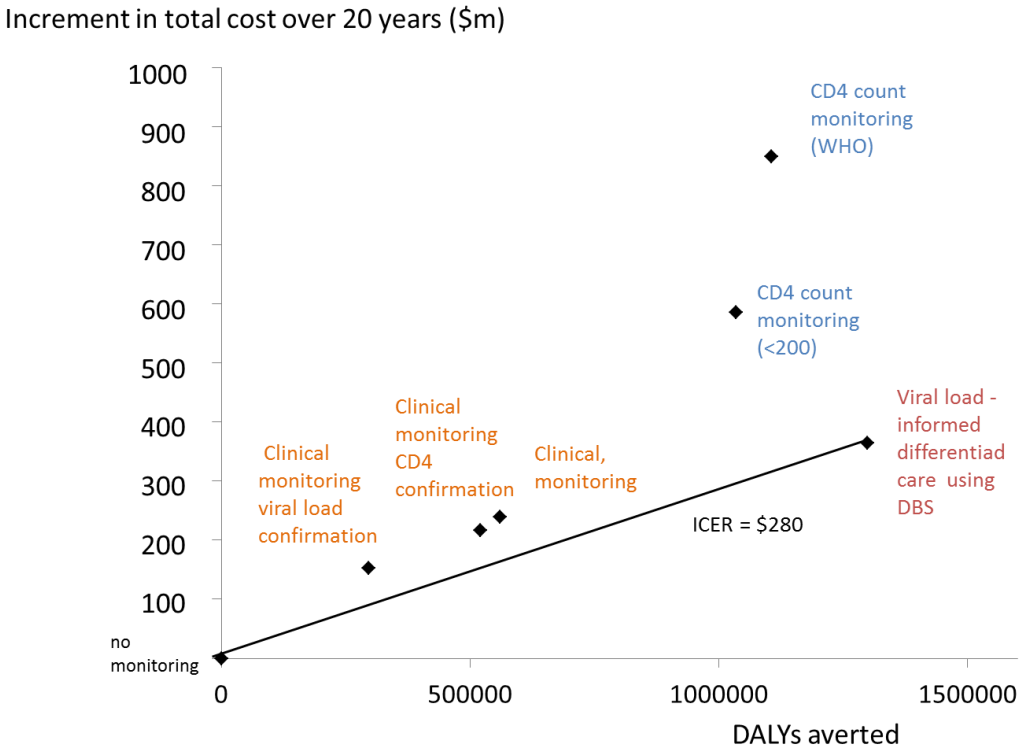
(f) Future greater increase in sexual behaviour in population



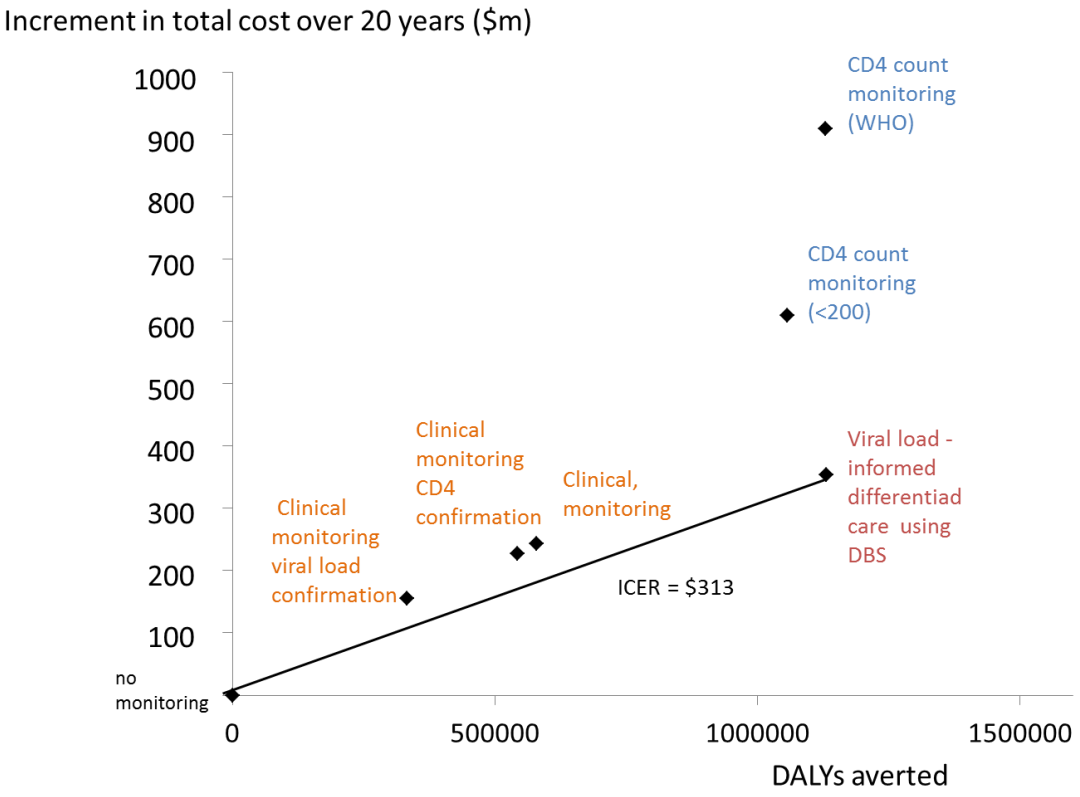
(g) Permanent increase in adherence as a result of viral load measurement alert in none rather than 40%



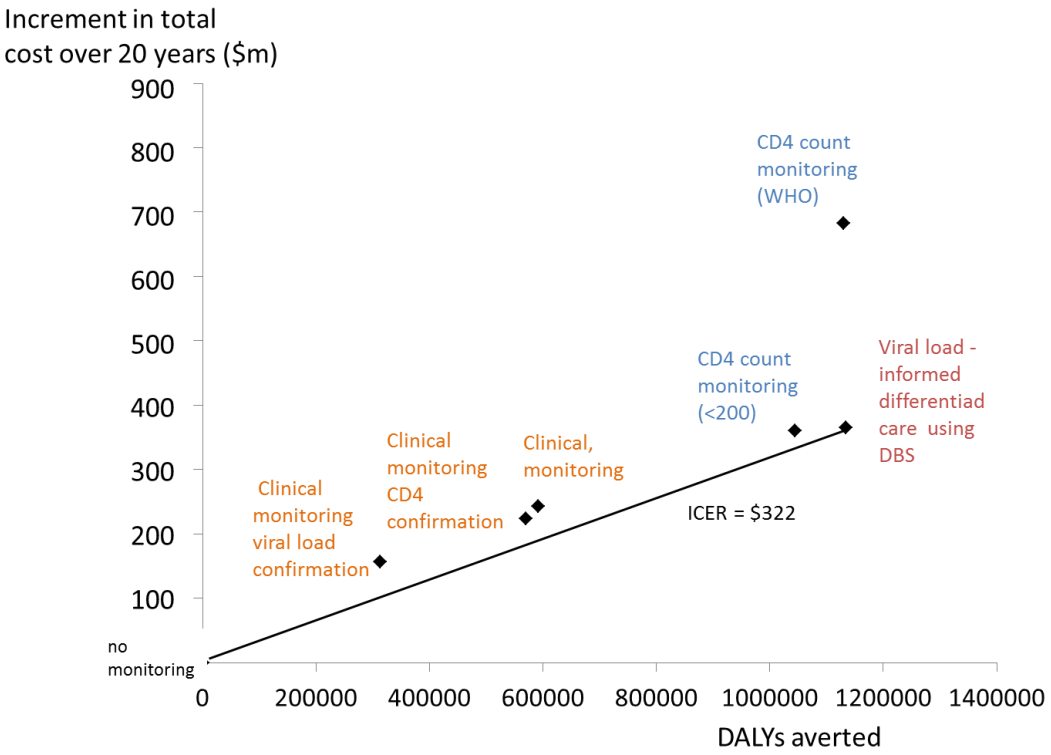
(h) Permanent increase in adherence as a result of viral load measurement alert in 100% rather than 40%



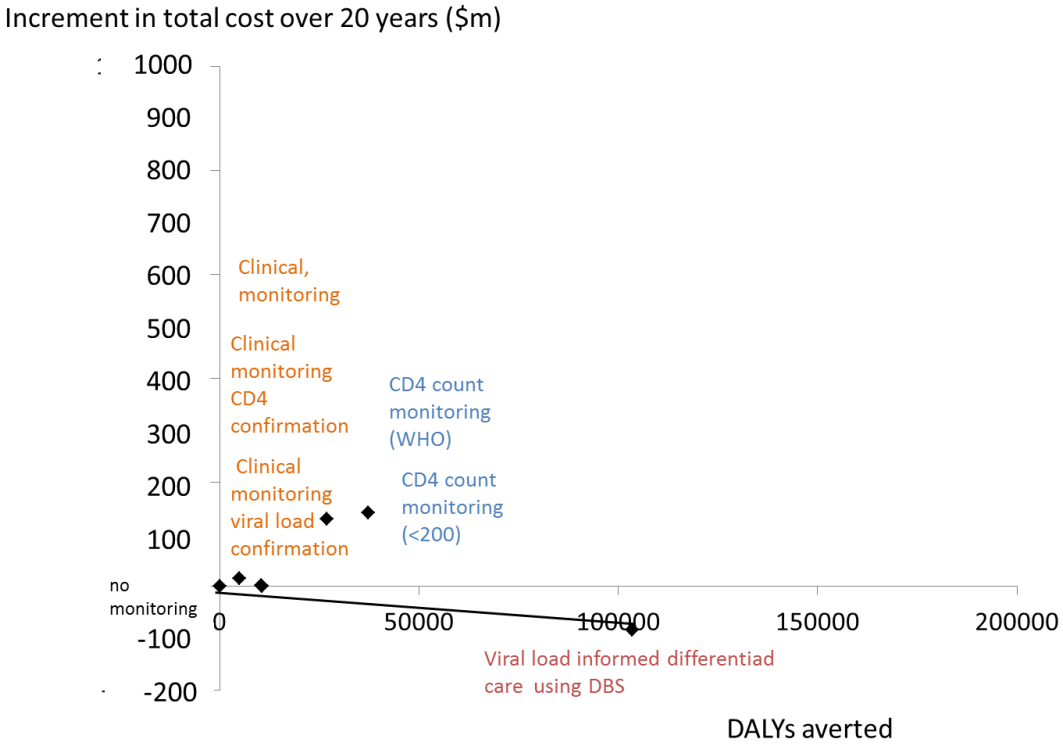
(i) Policy of initiation ofART at diagnosis



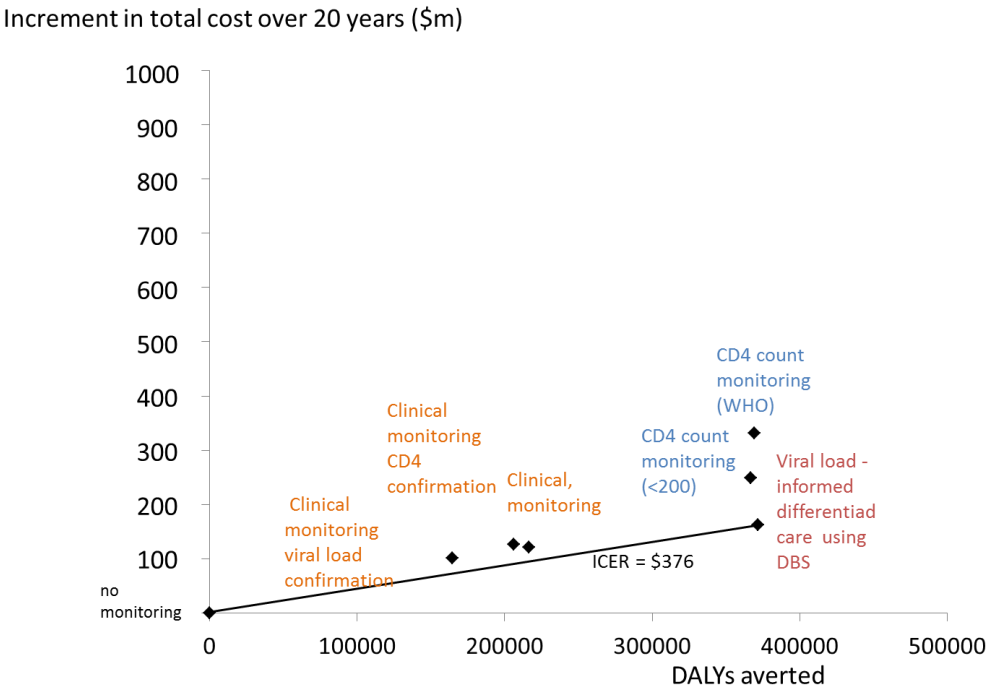
(j) CD4 count monitoring used for differentiated care (reduced visit frequency if CD4 count > 350).



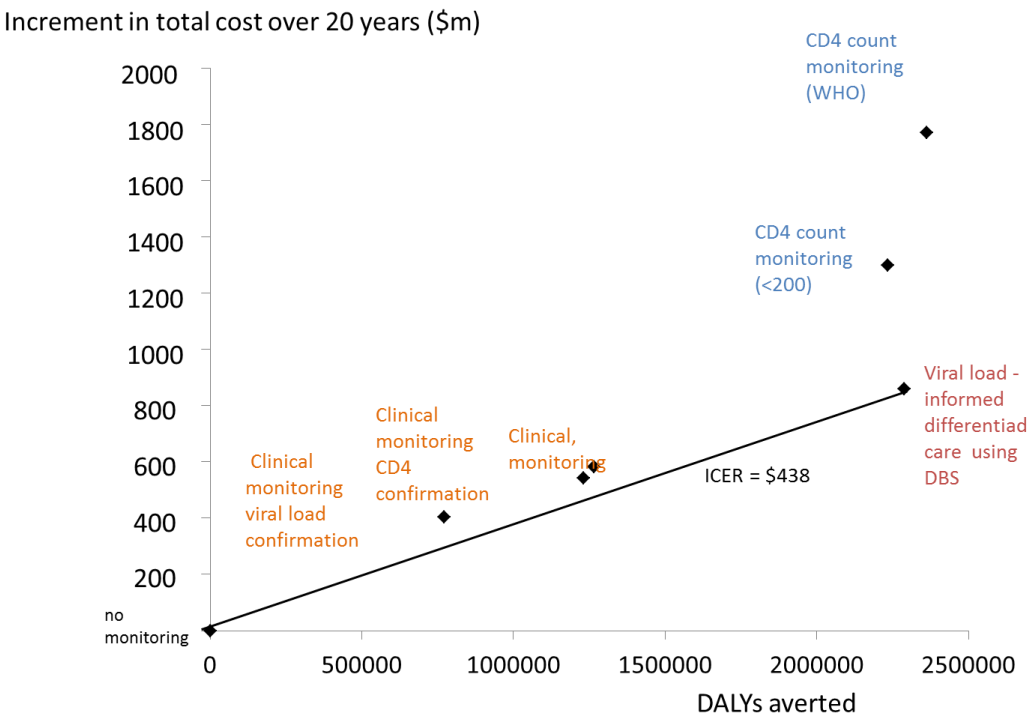
(k) In context of a switch rate of 0 (so only benefit of monitoring is to inform who should be seen less frequently)



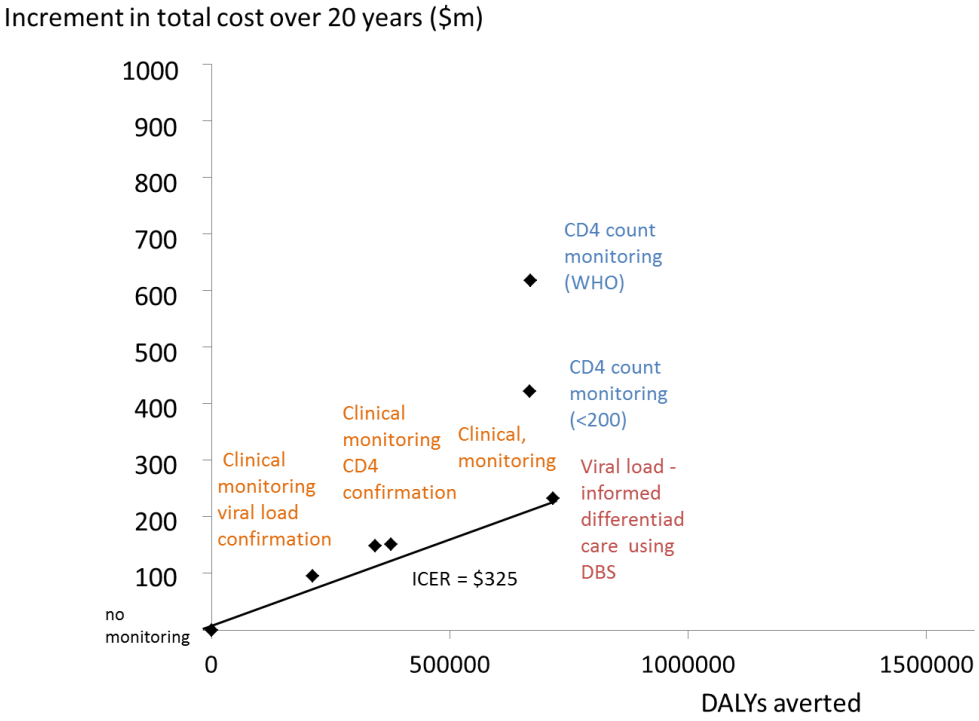
(I) In context of lower prevalence of HIV in 2014 (6% instead of 15% in base case)



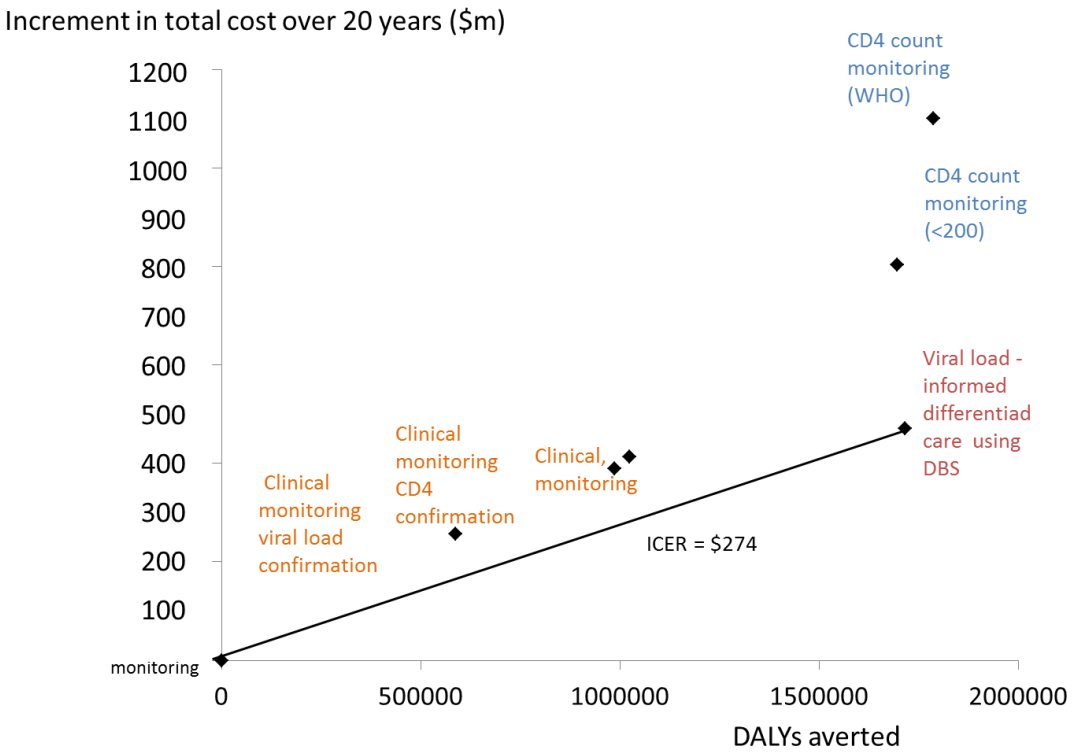
(m) In context of higher prevalence of HIV in 2015 (33% instead of 15% in base case)



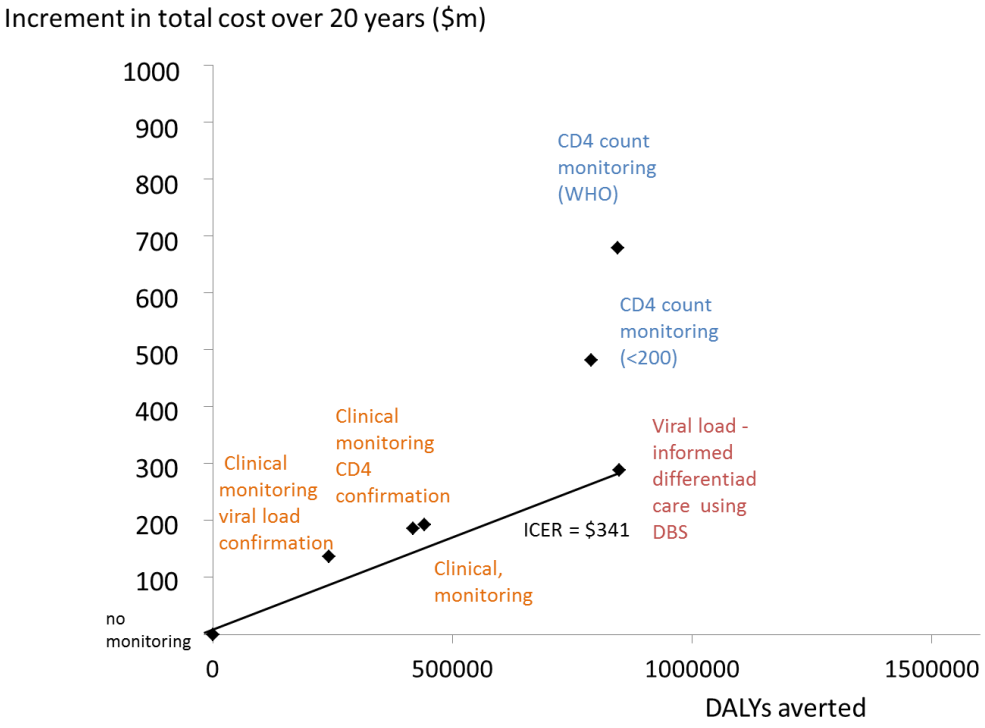
(n) In context of lower proportion on ART in 2015 (33% instead of 56% in base case)



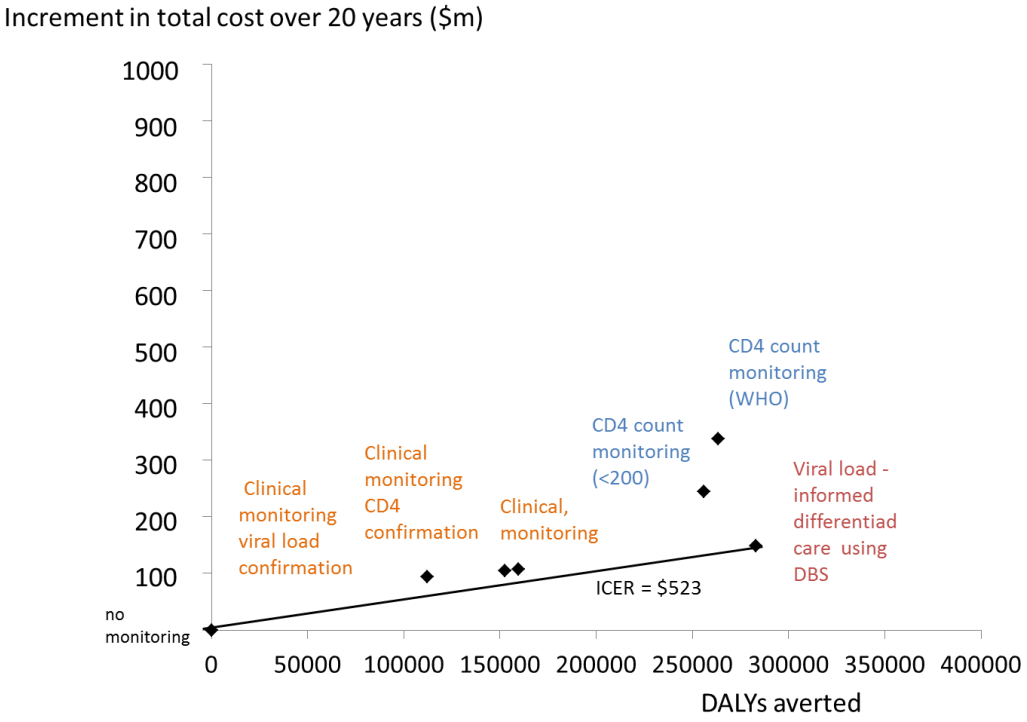
(o) In context of higher proportion on ART in 2015 (70% instead of 56% in base case)



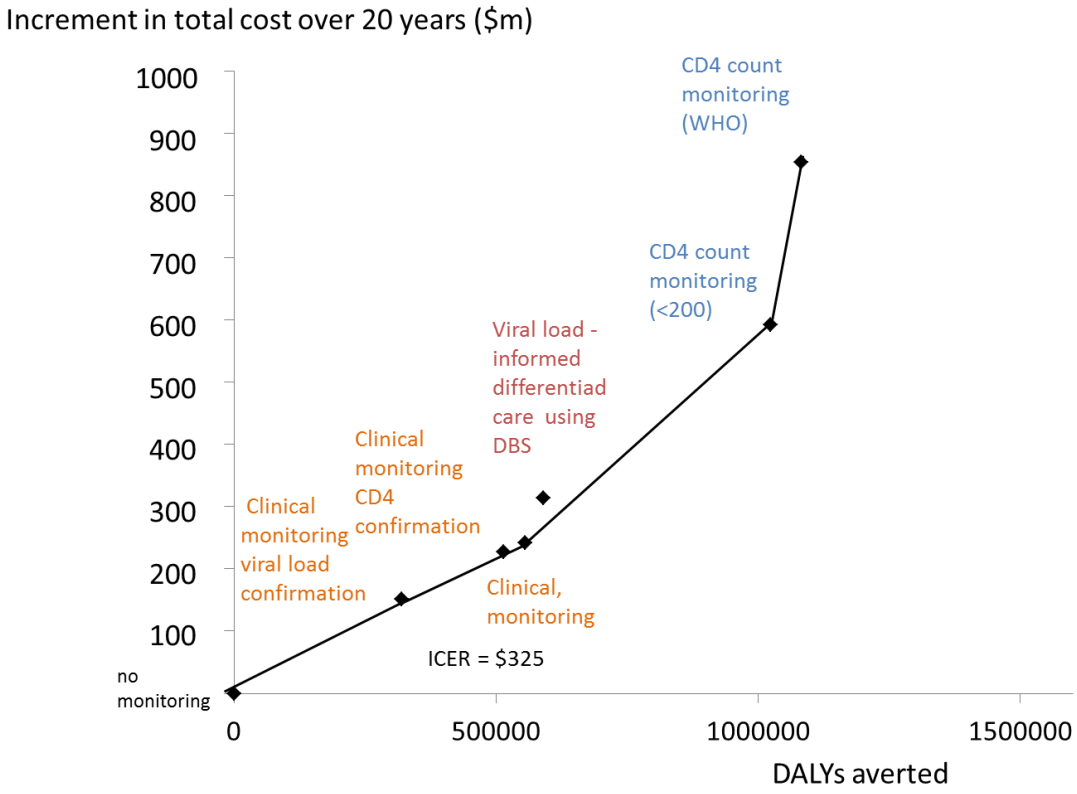
(p) 5% discount rate instead of 3%



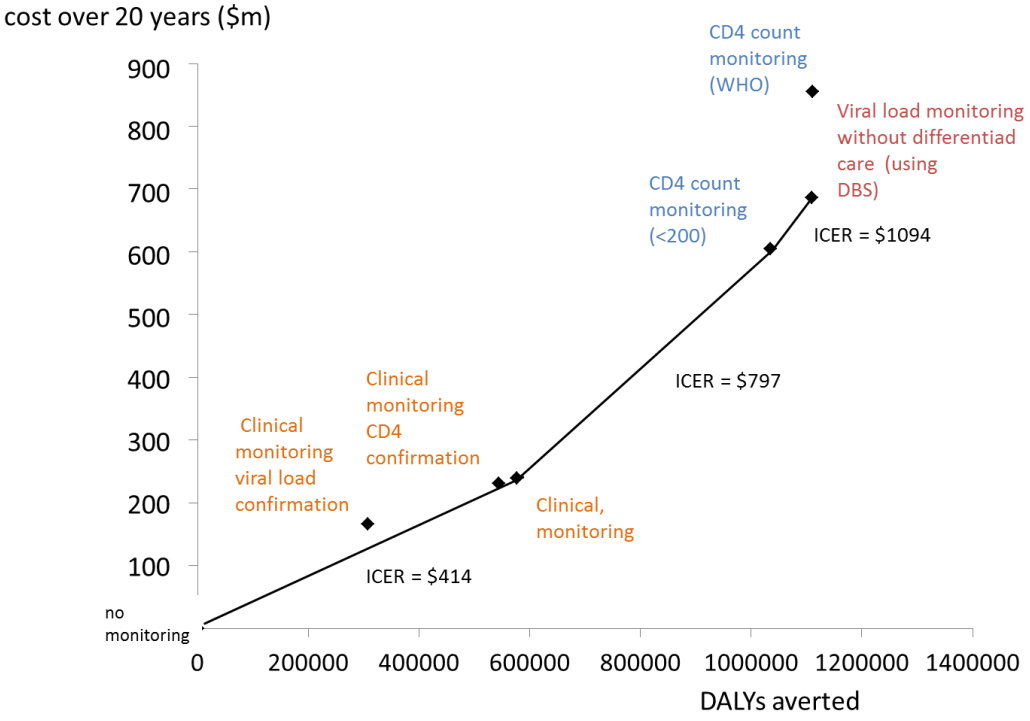
(q) 10 year time horizon instead of 20 year



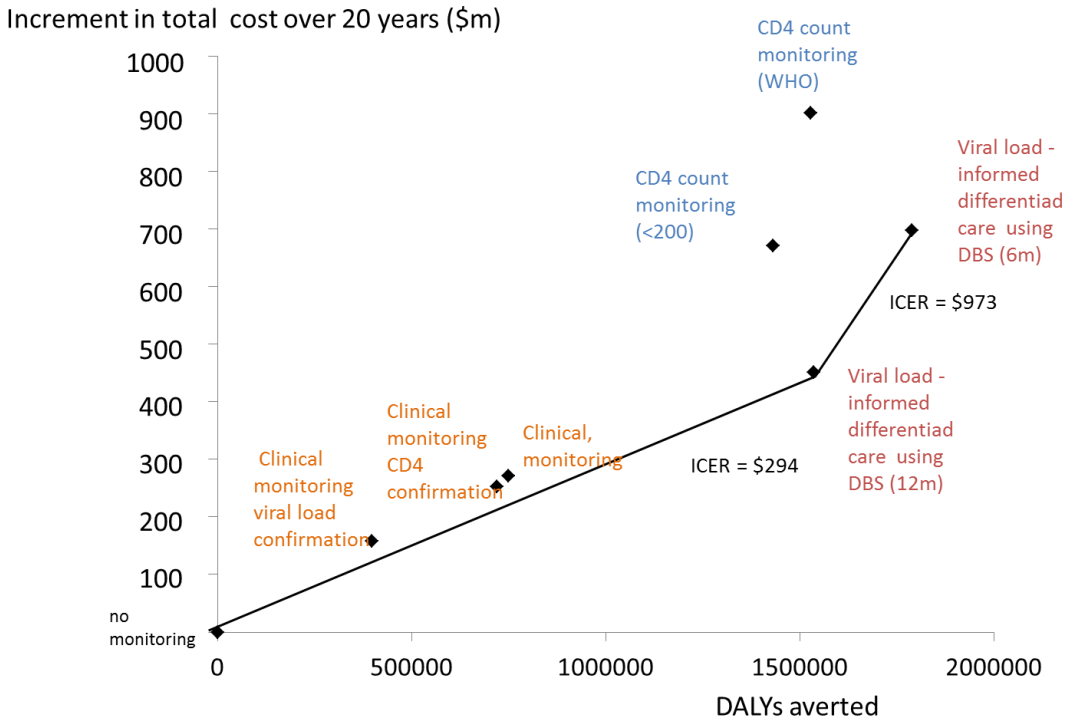
(r) 2 times higher rate of ART interruption if visit frequency has been reduced due to viral load being < 1000 copies/mL



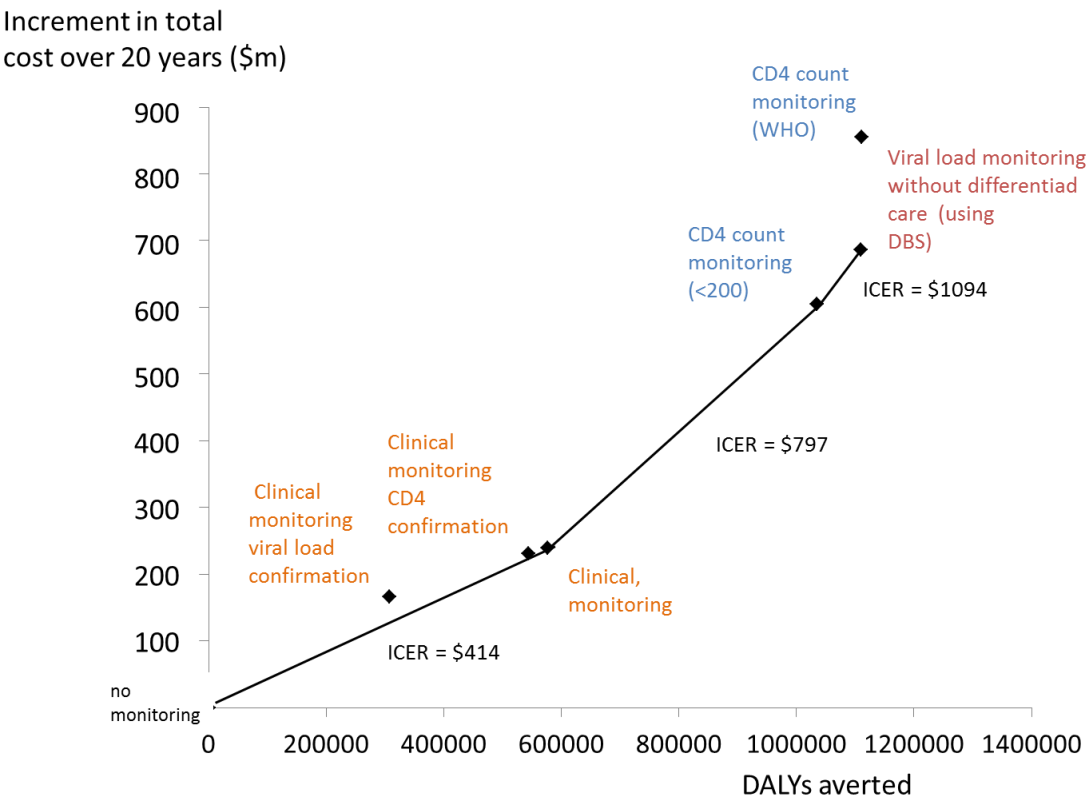
(s) No reduction in non-ART programme costs



(t) Poorer population ART adherence profile (such that 68% of people on ART are suppressed < 1000 cps/mL - note change in scale) - including 6 monthly monitoring



(u) No reduction in non-ART programme costs

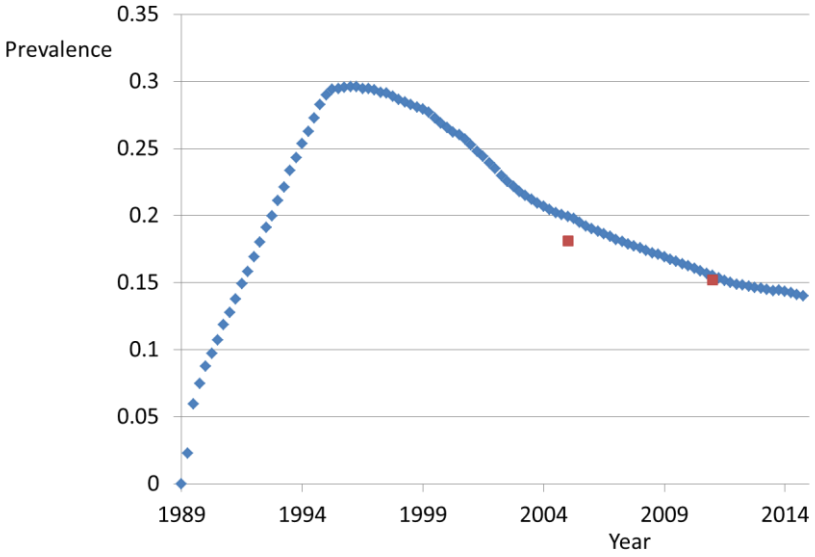


Modelling Methods

1. Summary of calibration to Zimbabwe

The HIV Synthesis Transmission model is an individual-based stochastic model of heterosexual transmission, progression and treatment of HIV infection within a southern African context (Phillips et al 2011, Cambiano et al 2013, Cambiano et al 2014). Details of the model are given in subsequent sections below. For this project we calibrated the model to data on HIV prevalence, testing patterns and ART use from Zimbabwe. Figure S1 shows the calibration to past data on HIV prevalence. Table S1 shows the modelled outputs for the year 2014, together with observed data for some aspects.

Figure S1. Prevalence of HIV in 15-49 year olds. Model output in blue. Data in red are from Demographic Health Surveys*.



*http://dhsprogram.com/Publications/Publication-Search.cfm?ctry_id=48&c=Zimbabwe&Country=Zimbabwe&cn=Zimbabwe

Table S1. Status of the simulated population in 2014. Adults age 15-65 unless otherwise stated

	Model	Observed
Number living with HIV	1,161,000	
Population size age 15-65	8,117,000	8,000,000[&]
Proportion of adult men circumcised	0.27	
Prevalence of HIV age 15-45 women	0.17	0.177[+]
Number of people tested for HIV (per 3 months)	718,000	568,582 in 15-49 year olds
Number of people on ART	655,000	Approx 700,000 adults Jan 2015*
Of people with HIV, proportion on ART	0.56	
Of people diagnosed with HIV, proportion on ART	0.67	
Death rate (per 100 person years) in whole adult population age 15-65	1.85	1.15 age 15-49[+]
Death rate (per 100 person years) in people with HIV age 15-65	5.22	
Death rate (per 100 person years) in people on ART age 15-65	3.21	
Of people on ART, proportion with VL below 500 copies/mL	0.82	0.78**
Proportion of ART experienced people who have started 2nd line	0.06	0.015*

& CIA world factbook; + DHS 2011; *Zimbabwe MoHCC (personal communication);
** baseline results SAPPH-IRe trial;

2. Demographic model

General population death rates and determination of age in 1989

The model runs to from 1989 (the start of the epidemic) to 2039 (although in our results we concentrate on the 20 year period to 2035), with variables updated in 3 month periods. Each run of the simulation program creates 100,000 simulated people who will be age 15 or above at some point between 1989 and 2035, of whom approximately 50,000 are alive and age over 15 at any one point in time. In order to scale up from the simulated population to the actual population in Zimbabwe we use a scale factor of 228.

In the absence of data on death rates considerd reliable for Zimbabwe, age specific death rates for uninfected people are based on death rates in South Africa in 1997 (Table S2) – before the significant impact of HIV-related deaths. These rates were modified by a factor 2-fold in order to mimic the population pyramid in Zimbabwe (Table S3).

Table S2. Age specific death rates (per year)

Age group	Annual death rate
Males	
15-19	0.00400
20-24	0.00640
25-29	0.01160
30-34	0.01500
35-39	0.01600
40-44	0.02000
45-49	0.02400
50-54	0.03800
55-59	0.05000
60-64	0.07000
65-69	0.09000
70-74	0.11000
75-79	0.13000
80-84	0.20000
≥85	0.80000
Females	
15-19	0.00300
20-24	0.00560
25-29	0.00800
30-34	0.00800
35-39	0.00840
40-44	0.01100
45-49	0.01500
50-54	0.02200
55-59	0.03000
60-64	0.04200
65-69	0.06000
70-74	0.07600
75-79	0.10000
80-84	0.14000
≥85	0.30000

Table S3. Observed and modelled populationsize by age in 2014.

	Male		Female	
	Observed	Model	Observed	Model
15-24 years:	1.55m	1.56m	1.53m	1.54m
25-54 years:	2.48m	2.25m	2.27m	2.66m
55-64 years:	1.85m	0.22m	3.24m	0.41m
65 years and over:	0.19m	0.13m	0.30m	0.37m

Observed data from CIA world factbook (2014) https://www.cia.gov/library/publications/the-world-factbook/geos/zi.html

The initial age distribution for both males and females is determined on the basis of the distribution in Table S4.

Table S4. Distribution of ages of simulated individuals in 1989

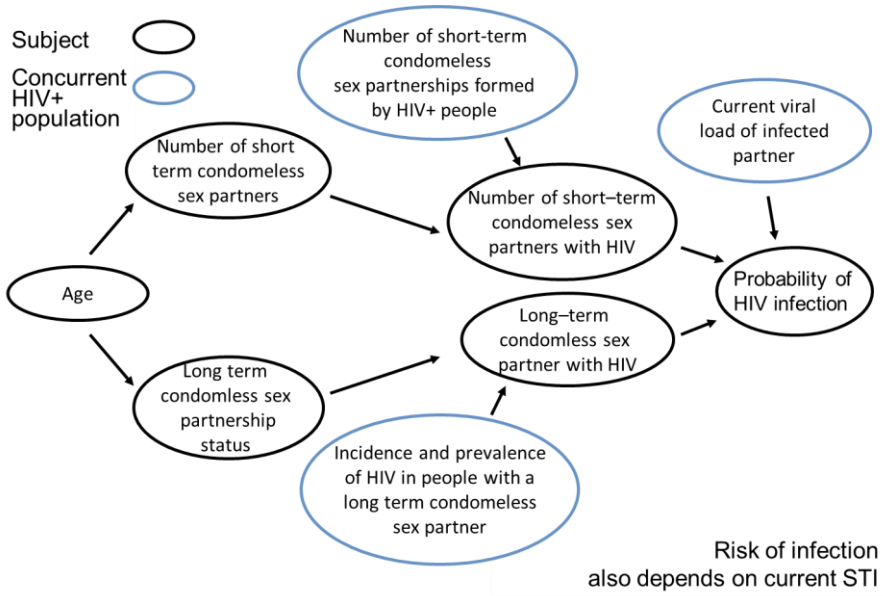
Age group	Probability of being in age group in 1989*
-35-14	0.720
15-24	0.091
25-34	0.075
35-44	0.062
45-54	0.033
55-64	0.021

This distribution is chosen such that in the absence of HIV, given the death rates above, the population size increases over time. Thus around 72% of simulated people have an age below 15 in 1989. 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 1989 is age -35 (i.e. will be born in 2024 and reach age 15 in 2039, when the modelled period ends.

3. Sexual behaviour and risk of HIV acquisition

Here we describe the approach to modelling sexual behaviour and HIV acquisition. The basic approach is summarized in Figure S2. The parameter values related to sexual behaviour were chosen such that they lead to a modelled HIV prevalence level over time as observed (Figure S1). Sexual behaviour is characterized by two variables representing, respectively, the number of short term condomless sex partners and whether the person has a current long term condomless *sex* partners in the 3 month period. The status of long term partners is tracked over time (i.e. if they are infected, diagnosed, on ART). 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.

Figure S2. Summary of modelling of sexual behaviour and HIV acquisition



Determination of number of short term (condomless sex) partners at period t

Numbers of short term partners in a given period was generated at random, according to which of four sexual behaviour groups the person was in for this period. Changes in the sexual behaviour group from t-1 to t were determined by transition probabilities between 4 groups: (i) no short term condomless partners in 3 month period, (ii) 1 short term partner, (iii) medium number of short term partners, and (iv) high number of 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

$$p_{gija} = \frac{f_{gij} \times r_{ga}}{\left(f_{gi1} + \sum_{j=2}^{4} (f_{gij} \cdot r_{ga})\right)}$$

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 S5 and S6, respectively, and if j=1 then r_{ga}=1.

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 *ch_risk_diag_newp* (with a value 0.83, informed by (Fonner et al 2012) if the subject is diagnosed with HIV (sqrt(*ch_risk_diag_newp* from 6 months after diagnosis). In addition, there is a person-fixed modification factor (*p_rred_p = 0.2*). For a proportion *p_rred_p* of men and 1.5.*p_rred_p* 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 medium short term partners group the number of partners was determined by sampling from a Poisson(*highsa*), where *highsa* (= 4.4). When in the high short term partners group the number of partners was determined by sampling from a Poisson(2) distribution and multiplied by the parameter *swn (= 7*).

Determination of having a long term (condomless sex) partner at period t

Note that only condomless 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 condomless sex partner.

At each period, people with no current long term partner have age-dependent probabilities of having a new long term partner is dependent on parameter *eprate* and given by: age 15-24, p= *eprate*; age 25-34, p= *eprate*; age 35-44, p= *eprate/2*; age 45-54, p= *eprate/3*; age 55-64, p= *eprate/5* (*eprate* = 0.1).

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 S7.

At time period, t, for people with a long term partner, the probability of the condomless sex partnership continuing is (1-(0.25 / *ch_risk_beh_ep*)) if duration category is 1, is (1-(0.05 / *ch_risk_beh_ep*)) if duration category is 2, and (1-(0.02 / *ch_risk_beh_ep*)) if duration category is 3, where *ch_risk_beh_ep* is a parameter conveying the population level change in sexual behaviour with long term partners that occurs in 1995 (*ch_risk_beh_ep* = 0.4*).* Further, this probability is reduced by a factor *ch_risk_diag* in the 3 month period after a partner's diagnosis, if a partner has HIV and is diagnosed. (*ch_risk_diag* = 0.7).

Note also that levels of sexual 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 sexual behaviour required in order to produce an epidemic as described, given rates of transmission with condomless sex partners. Sexual 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. Gregson 20022, Johnson 2009). Nonetheless, reported sexual behaviour, particularly in terms of differences by age in males and females have been referred to (e.g. Zimbabwe DHS 2004, Zimbabwe DHS 2011).

Population level change in sexual behaviour

There is assumed to be a general average reduction in condomless sex after 1995, reflecting the reductions observed over the period from around this date (Gregson 2010, Halperin 2011).

Determination of number of short term (condomless sex) 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 determine by sampling at random, the age group of the short term partner, a^{newp} (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 used are given by values in Table S8.

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

$$h_{gat} = \frac{\sum_{a^{\text{newp}},(g-1)} L^{\text{inf}}_{(t-1)}}{\sum_{a^{\text{newp}},(g-1)} L_{(t-1)}}$$

where $L^{\text{inf}}_{(t-1)}$ is the total number of infected short term partners at time (t-1), and $L_{(t-1)}$ is the total number of short term partners at time t-1. The numerator is therefore the total number of infected short term partnerships of the opposite gender in age group a^{newp}.

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^{inf}_t, is then given by

$$L^{\text{inf}}_t = \text{Min}(\text{Poisson}(h_t \cdot L_t), L_t)$$

The distribution of numbers of partners by age and gender is shown in Table S9.

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

E_t^{inf} indicates whether the subject has a long term (condomless sex) partner who is infected ($E_t^{\text{inf}} = 1$ if infected, else $E_t^{\text{inf}} = 0$). 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 an infected long term partner has remained as a long term partner.

For (i):

$E_t^{\text{inf}} = 1$ if $L_{(t-1)}^{\text{inf}} \geq 1$ (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, $i_{a(1-g)(t-1)}$ among the sexually active population, either with a long term partner or at least one short term partner (which is given by the number of subjects newly infected in age group at time *t-1* divided by the number of HIV-uninfected subjects in age group at *t-1*, who had condom-less relationships, either long or short term)

$$\begin{cases} E_t^{\text{inf}} = 1, & U < i_{a(1-g)(t-1)} \text{ where } U \text{ randomly sampled from } Uniform(0,1) \\ E_t^{\text{inf}} = 0, & \text{otherwise} \end{cases}$$

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 $i_{a(1-g)(t-1)}$ is modified at time t dependent on the degree of balance at time t-1.

For (iii):

If $E_{(t-1)}^{\text{inf}} = 1$ and $E_t \geq 1$ then assign $E_t^{\text{inf}} = 1$

Determination of the risk of infection from a short term partner

For 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

$$\frac{\sum_v L_{(t-1)}^{\text{inf}}}{\sum L_{(t-1)}^{\text{inf}}}$$

where the numerator is the total number of short-term partnerships had by infected people in viral load group v and the denominator is the total number of short-term partnerships had by infected people (in any viral load group).

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) ≥ 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 (*tr_rate_undetec_vl*,0.000025^2), t_2 = Normal ($0.01,0.0025^2$), t_3 = Normal ($0.03,0.0075^2$), t_4 = Normal ($0.06,0.015^2$), t_5 = Normal ($0.1,0.025^2$), t_6 = Normal (*tr_rate_primary*,0.075^2). These are based on Hollingsworth et al (2008) and are the rates for a longer term partner. The transmission rate for a short term partner is multipled by fold_tr_newp (0.35) due to the assumed lower number of sex acts. These probabilities are increased by *fold_change_w*-fold (= 1.5) for female subjects aged $\geq$ 20, by 2-fold for female subjects aged < 20, and by *fold_change_sti*-fold (= 3.0) 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 condomless partners / 20 (or 1 if > 20 short term partners)) (Cohen et al 1998, Nicolosia 1994).

We assume that super-infection can occur(i.e. a person can be reinfected with HIV with consequent risk of acquiring new mutations).

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

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, $p_t^{\text{e,diag}}$, is determined with reference to the difference, $d_{(t-1)}^{\text{e,diag}}$, in the proportion of subjects with HIV who are diagnosed, $\frac{T_{(t-1)}^{\text{diag}}}{T_{(t-1)}^{\text{inf}}}$ and $p_{(t-1)}^{\text{e,diag}}$;

i.e. $d_{(t-1)}^{\text{e,diag}} = \frac{T_{(t-1)}^{\text{diag}}}{T_{(t-1)}^{\text{inf}}} - p_{(t-1)}^{\text{e,diag}}$

where $T_{(t-1)}^{\text{diag}}$ is the total number of subjects diagnosed with HIV at time t-1and $T_{(t-1)}^{\text{inf}}$ is the total number of subjects with HIV (diagnosed and undiagnosed) at time t-1.

$$\begin{cases} \text{if } 0 < d_{(t-1)}^{\text{e,diag}} \leq 0.05 \text{ then } p_t^{\text{e,diag}} = 0.4 \\ \text{if } 0.05 < d_{(t-1)}^{\text{e,diag}} \leq 0.10 \text{ then } p_t^{\text{e,diag}} = 0.5 \\ \text{if } 0.10 < d_{(t-1)}^{\text{e,diag}} \leq 0.15 \text{ then } p_t^{\text{e,diag}} = 0.9 \\ \text{if } 0.15 < d_{(t-1)}^{\text{e,diag}} \text{ then } p_t^{\text{e,diag}} = 0.95 \end{cases}$$

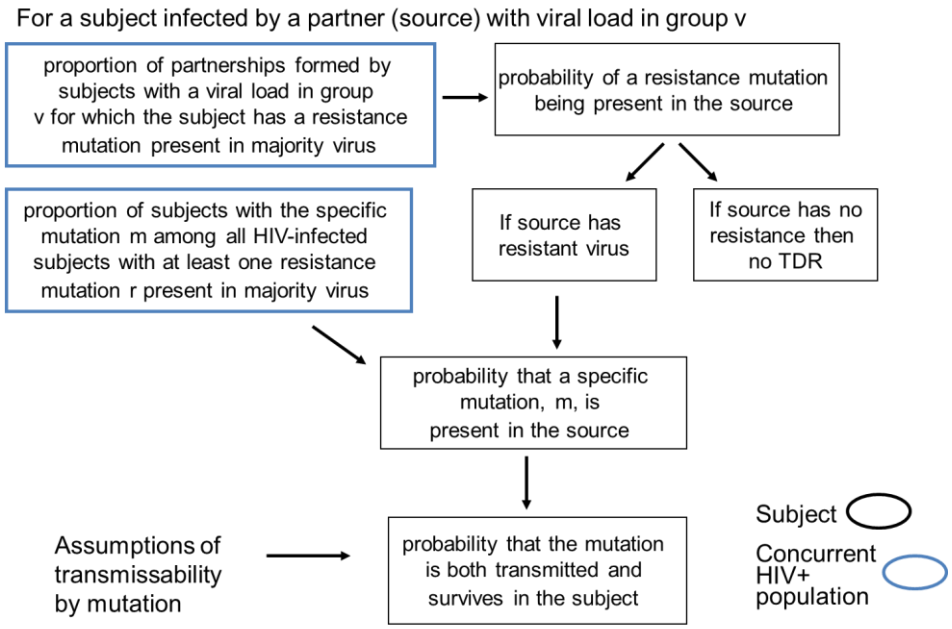
The proportion of those diagnosed who are on ART, and the proportion of those on ART who have viral load < 2.7 log cps/mL are determined in a similar manner. In this way the proportions diagnosed with HIV, on ART, and with current viral load is < 2.7 log cps/mL are kept similar for the long term partners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

Risk of infection from a long term infected partner is determined by Normal (*tr_rate_primary*, 0.075^2) if the existing partner is in primary infection (ie. infected at t-1), Normal (*tr_rate_undetec_vl*, 0.000025^2) if the existing partner has viral load < 2.7 log cps/mL, and Normal (0.05, 0.0125^2) otherwise.

Transmitted resistance: overview

The modelling of transmission of drug resistance is summarized in Figure S3. The presence or not of resistance mutations does not influence the risk of transmission (i.e. virus with resistance mutations present is assumed equally transmissible as virus without such mutations, for a given viral load). Resistance is modelled in terms of the presence or absence of mutations specific to the drugs in use. Distinction is made for each mutation as to whether it is only present in minority virus (if the patient has a mutation present but has stopped drugs that select for that mutation), so the mutation is assumed not transmissible, or if it is present in majority virus, and hence the mutation is assumed transmissible. The probability that resistance mutations present in majority virus of the source partner are transmitted to the newly infected person is dependent on the specific mutation. Once a resistance mutation is transmitted to the new host it is assumed to have a certain probability of being lost from majority virus over time (Castro 2013). Even after being lost from majority virus, it is assumed to remain in minority virus and is selected back as majority virus if an antiretroviral drug selecting for that mutation is initiated. We also consider the possibility of a person who is already infected become super-infected, including with drug resistant HIV (Smith 2005), although there is assumed to be at most a 20% chance that a person super-infected by a person with HIV resistance then has virus with those resistance mutations as a result.

Figure S3. Overview of modelling of transmission of drug resistance.



Transmitted resistance: details

The viral load group of the person who infected the subject is known, as indicated above. 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

$$\frac{\sum_{v,\text{ and mutation present}} L^{\text{inf}}_{(t-1)}}{\sum_{v} L^{\text{inf}}_{(t-1)}}$$

where $\sum_{v,\text{ and mutation present}}$ is the sum over all partnerships had by HIV-infected people in viral load group v for whom a resistance mutation is present in majority virus and $\sum_{v}$ 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

$$\frac{\sum_{\text{mutation } m \text{ present}} L^{\text{inf}}_{(t-1)}}{\sum_{\text{mutation present } v} L^{\text{inf}}_{(t-1)}}$$

Where $\sum_{\text{mutation } m \text{ present}}$ is the sum over all HIV-infected subjects with mutation m present in majority virus and $\sum_{\text{mutation present}}$ 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 (i.e. that its presence will affect future response to drugs for which the mutation confers reduced sensitivity) is mutation specific, as shown in Table S10.

We consider uncertainty in the extent to which transmitted resistance mutations are effectively immediately lost (even from minority virus) by sampling from a distribution for parameter *res_trans_factor* (= 0.6, informed by fitting of a model of HIV in MSM to UK data (Phillips et al PLOS ONE 2013).

Loss from majority virus of transmitted mutations

There is a probability per 3 months of loss of persistence of transmitetd mutations from majority virus to minority virus (same for each mutation) *rate_loss_persistence* 0.04, again informed by fitting of a model of HIV in MSM to UK data (Phillips et al PLOS ONE 2013).

Model outputs relating to sexual behaviour and transmission

Table S9 shows the proportion of people with at least one (at least two) condomless sex partner in the past year by HIV status and year. Table S11 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. Table S13 shows HIV prevalence by age and gender and calendar year.

Table S5. Values of f_{gij} (values determining probability of transitioning between short term partner risk behaviour groups)

Short term partners group in period t-1	Short term partners group in period t			
	0	1	medium (Poisson mean *highsa**)	high (Poisson mean 2 x *swn**)
Males				
0	0.89	0.08	0.03	0.00
1	0.80	0.15	0.05	0.00
medium	0.35	0.27	0.38	0.00
high	---	---	---	---
Females				
0	0.93	0.05	0.02	0.00025
1	0.86	0.11	0.03	0.0005
medium	0.54	0.08	0.38	0.001
high	0.05	0.05	0.10	0.800

* *highsa* = 4.4, *swn* = 7

Table S6. Values of r_{ga} (factor determining relative level of sexual risk activity)

Age group (a=1,10)	Males (g=1)	females (g=2)
15-	0.60	1.60
20-	0.60	1.60
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 S7. 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).

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

Table S8. Sexual mixing by age and gender. The proportion of short term partnerships formed by men in age group a_m which are with females of age group a_f and the proportion of short term partnerships formed by females in age group a_f which are with men of age group a_m.

	Females Age group (a_f)				
Males Age group (a_m)	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
	Males Age group (a_m)				
Females Age group (a_f)	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 S9. Sexual risk behaviour in 1990 and 2000 (after behaviour change)

1990 (start of epidemic)	% with ≥ 1 (≥2; ≥ 10; ≥50) condomless sex partners (short or long term) in past year	
Age group	Males	Females
15-	85% (66%;10%;0%)	87% (77%;21%;0.5%)
25-	96% (84%;17%;0%)	94% (77%;18%;0.2%)
35-	94% (77%;12%;0%)	88% (60%;9%;0.2%)
45-	91% (68%;9%;0%)	70% (23%;1%;0.05%)
55-	85% (57%;6%;0%)	64% (19%;1%;0%)

2000	% with ≥ 1 (≥2; ≥ 10; ≥50) condomless sex partners (short or long term) in past year	
Age group	Males	Females
15-	48% (55%;2%;0%)	55% (17%;5%;0.15%)
25-	71% (64%;4%;0%)	64% (36%;58%;0.05%)
35-	58% (47%;4%;0%)	47% (25%;2%;0.07%)
45-	52% (25%;2%;0%)	25% (21%;0.05%;0%)
55-	40% (17%;2%;0%)	17% (15%;0%;0%)

Table S10. 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. Corvasce et al 2006, Turner et al 2004) and modelling of HIV in MSM in the UK (Phillips PLOS ONE 2013).

M184V	0.52
K65R	0.52
L74V	0.70
Q151M	0.70
Thymidine analogue mutations (TAMS)	0.70
NNRTI mutations (K103N, G190A, Y181C)	0.88
PI mutations	0.70

Table S11. Proportion of people with at least one (at least two) condomless sex partner (including long term partner) in the past year by HIV status and year using modal values for parameters.

	1990	1995	2000	2005	2010	2014
HIV+	98% (89%)	87% (56%)	64% (29%)	60% (29%)	55% (27%)	63% (37%)
HIV + diagnosed	---	---	53% (23%)	54% (23%)	51% (24%)	60% (33%)
HIV-	86% (64%)	71% (38%)	46% (18%)	46% (19%)	49% (21%)	59% (32%)

Table S12. Origin of new infections for one example epidemic, based on using modal values for parameters. 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. For proportion of people infected by a long term partner, compare with Dunkle et al 2008.

	Status of source partner					
	Primary infection			Long term partner		
	1990	2000	2010	1990	2000	2010
Males	87%	39%	28%	27%	50%	47%
Females	88%	44%	36%	25%	45%	42%

Table S13. HIV prevalence age 15-49 by gender and prevalence by age and gender 2015

	Males	Females
1990	12.3%	13.2%
1995	26.4%	34.4%
2000	21.5%	30.1%
2005	15.4%	23.9%
2010	11.8%	20.2%
2014	10.1%	17.6%

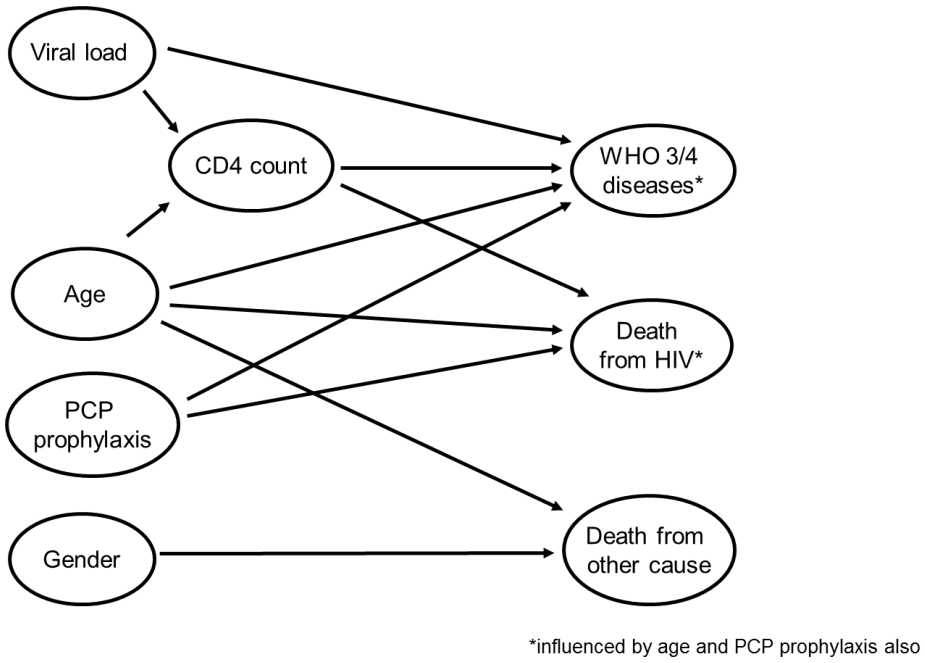
Prevalence by age 2014

15-25	2.8%
25-35	13.8%
35-45	33.5%
45-55	28.2%
55-65	10.9%

4. Natural history of HIV infection

Figure S4 gives an overview of the modelling of HIV natural history. The model of the natural history of HIV and the effect of antiretroviral therapy has been derived previously and compared with a range of observed data (see Phillips et al Lancet 2008, AIDS 2011, Nakagawa et al 2012, 2015 and associated supplementary material). Below we set out the structure of the model and explain what parameters represent.

Figure S4. Overview of modelling of natural history of HIV infection.



Determination of changes in viral load and CD4 count

Initial $\log_{10}$ viral load (V_{set}) is sampled from Normal(4.0,0.5^2)

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 = *mean_sqrtcd4_inf* (= 27.5) - (1.5 x V_{set}) + Normal(0,2^2) – ((age – 35) x 0.05)

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 x 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 given by

Vc(t-1(= (gx x 0.02275 + Normal(0, 0.05^2) + ((age(t-1) - 35) x 0.00075)

gx=1 viral load at t (v(t)) = v(t-1)+ vc(t-1)

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 *sd_cd4* and mean *fx* (= 1.0) times the values as follows

Viral load at t-1	Change in square root CD4 count (per 3 mths)
< 3.0	+0.000
3-0	+0.022
3.5-	+0.085
4.0-	- 0.400
4.5-	- 0.400
5.0-	- 0.850
5.5-	- 1.300
6.0-	- 1.750

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

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

These estimates were derived based on consideration of evidence from natural history studies (Pantazis 2005, Sabin JAIDS 2000, Hubert J-B 2000, O'Brien 1998, Henrard 1995, Lyles 2000, Touloumi 2004, Mellors 1997, Koot 1993) 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 S14. Incubation period by age. Kaplan-Meier percent with WHO 4 Event. Compare with Darby et al 1996.

Age at infection	Years from infection					
	1	3	5	10	15	20
15-	0.6%	4%	14%	50%	75%	89%
25-	1.1%	2%	23%	67%	88%	97%
35-	2.1%	13%	34%	82%	97%	100%
45-	3.7%	21%	54%	93%	100%	100%
55-	1.4%	24%	59%	96%	100%	100%

5. HIV testing and diagnosis of HIV infection

HIV testing was assumed introduced in 1996. At that time we assumed 20% of the population were resistant to be tested for HIV unless symptomatic and this decreased linearly to 5% by the end of 2010. In the model this group has no possibility of getting tested for HIV unless symptomatic. Limited data are available to inform this parameter (proxy variables are the proportion who reported never being tested for HIV and, more precisely, the proportion who refuse HIV testing), nevertheless we considered it important to take this into account, given the evidence that not everyone accepts HIV testing for various reasons. The level of acceptability of provider initiated HIV testing and counselling (PITC) in resource limited settings is extremely variable from levels of 99%, observed in inpatients in Uganda (Wanyenze 2011) to 31% among outpatients in South Africa (Bassett 2007). Among pregnant women the level of acceptability of PITC seems to be higher, varying from 76 to 99.9% (Hensen 2012), while the estimated acceptability of home-based counselling and testing has been estimated in a meta-analysis to be 83% (Sabapathy 2012). This variability seems to be related mainly to the quality of the intervention delivered and calendar time. Acceptability seems to have increased over time due to the reduction in stigma and higher availability of ART, therefore we thought it was reasonable to assume a decline in the proportion resistant to be tested for HIV down to 5% in 2010.

For the remainder of the population (non-resistant to HIV testing), increasing gender and age-specific rates of HIV testing (for the 1st time and for repeat testing) since 1996 were assumed, to reflect the level of testing observed in the DHS (DHS Zimbabwe). Pregnant women experience an additional probability of being tested in the ANC, which increases over calendar year (DHS Zimbwabwe).

For people who have never had condomless sex, a 3-fold reduction in the rate of testing was assumed. This has been observed in the Zimbabwe DHS where people who reported never having had sex (whether with or without condom) are less likely to test for HIV. Comparisons of modelled output with data from DHS are shown in Figures S5 and S6.

People with acute symptoms (WHO stage 4, 3 or active TB) are assumed to have a higher chance of testing for HIV in that 3 month period and a higher chance of being linked to care once diagnosed. In 2015 the probability of testing as a result of symptoms was 0.8, 0.48 and 0.12, respectively, for people with a WHO stage 4 event, tuberculosis and WHO stage 3 event.

In this application the model does not distinguish between how HIV testing is delivered. Further details of calibration of testing rates to Zimbawe and of modelling of self-testing are given in Cambiano et al 2015.

Figure S5. Gender and age-specific proportion ever tested for HIV predicted by the model and observed in DHS surveys

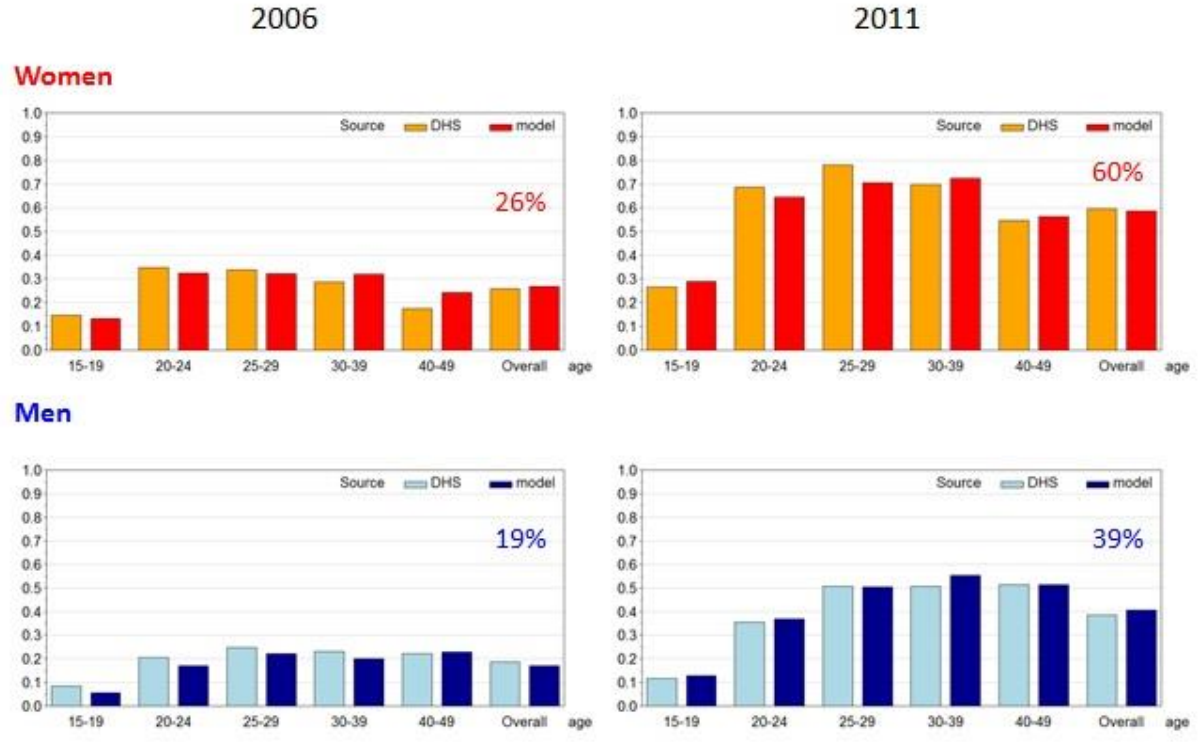
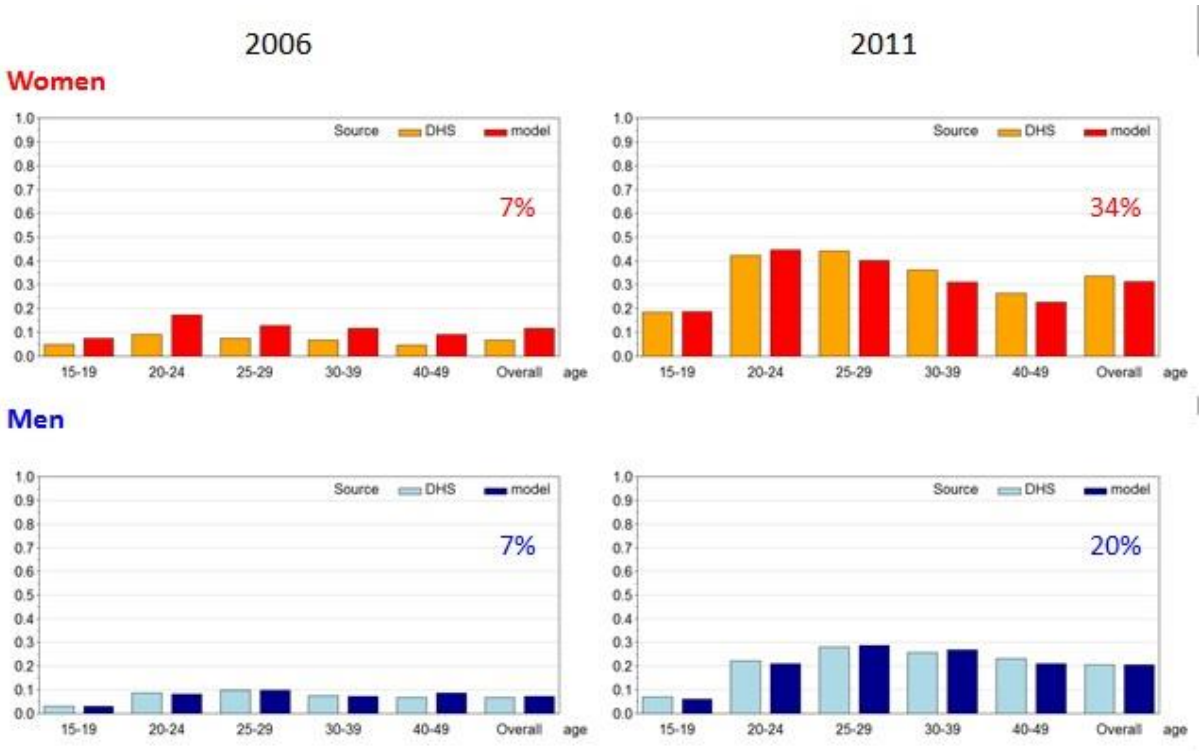


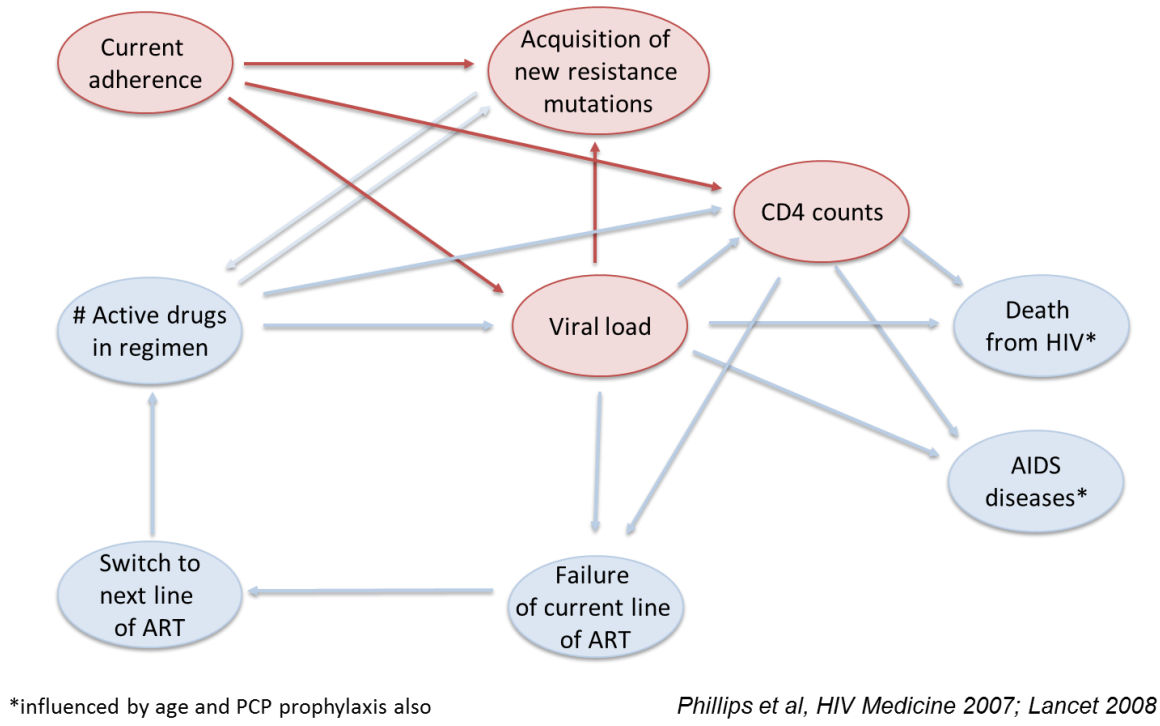
Figure S6. Gender and age-specific proportion tested in the last year, predicted by the model and observed in the DHS surveys



6. Modelling the effect of ART

The structure of the relationship between ART adherence, viral load, development of resistance, CD4 count and risk of death is modelled is illustrated in Figure S7 below. The adherence level - the determination of which is described in detail below - influences the risk of acquisition of new mutations as well as having a direct effect on the viral load and CD4 count. Acquisition of resistance mutations impacts on the number of fully active drugs in the current regimen. This, in turn, is a further determinant of the risk of new mutations arising. Failure of the current line of ART is determined by CD4 count or viral load or clinical disease, depending on the monitoring strategy, and this triggers a switch to the next line of ART (if assumed available, and often with a delay), which leads to the number of active drugs again returning to 3 or more if on boosted PIs. The following sections provide further details, including how adherence levels are determined and how they influence the viral load, risk of resistance and the CD4 count. We also explain the modelling of ART interruption and loss to follow-up. We provide references to papers that have been used to inform the approach. It should be noted though that parameter values used in the model are rarely extracted directly from any one paper, they are values that are arrived at based on their ability to generally reproduce outputs that are consistent with observed estimates, as illustrated below.

Figure S7. Overview of the modelling of the effect of ART, highlighting the role of adherence.



Initiation of ART

ART initiation in diagnosed people before 2010 is determined by a measured CD4 count < 200 or the development of a WHO 4 event. From 2011 this is determined by a CD4 count < 350 and from 2015 by a CD4 count < 500 or pregancy (option B+). We assume that CD4 counts are monitored at 6 monthly intervals for those who are in pre-ART care.

Switch to second line after failure of first line ART

Whichever 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 *pr_switch*_line (0.001 before 2015, increasing after 2015 as described in main manuscript). The switch rate is likely to vary substantially by setting (Fox 2012; Johnston 2012). In several settings, including Zimbabwe, the proportion of people who have started second line ART is consistent

with a value for *pr_switch*_line of below 0.1 (e.g. Lesotho, Malawi) (personal communications Zimbabwe MoHCC; Government of Malawi Ministry of Health, Integrated HIV Program Report, Oct-Dec 2014).

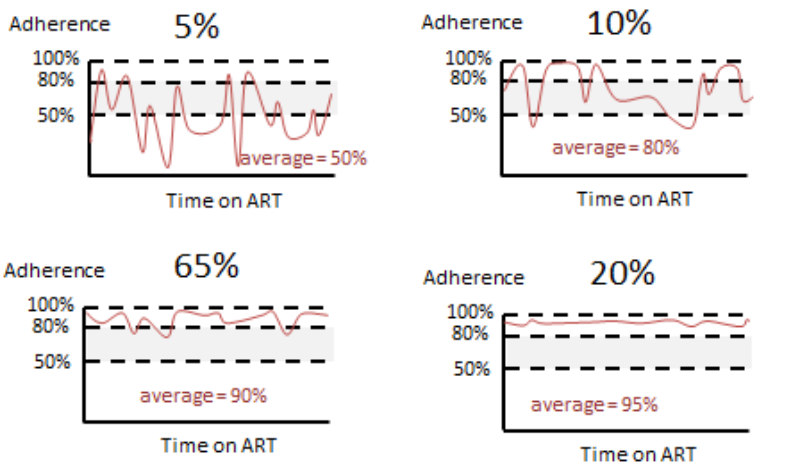
Adherence pattern

The model specifies a current adherence level (i.e. for the current 3 month period) for people on ART. Given that the model updates in 3 month time periods the adherence level in a given 3 month period has to effectively be considered as the average adherence over the period. The determination of this is described below. Interruption of ART for periods of duration 3 months is considered separately (and explained in subsequent sections below).

Consistent with evidence that people tend to have different tendencies to adhere (Cambiano 2010a;Carrieri 2001;El-Khatib 2011;Genberg 2012;Glass 2010;Kleeberger 2004;Lazo 2007;Levine 2005;Mannheimer 2002;Meresse 2014;Osterberg 2005), adherence is modelled using two components. Each patient has a certain greater or lesser tendency to adhere (*adhav,* measured on a scale of 0-100%) but their actual adherence in a given period varies over time, both at random and according to the presence of symptoms (with drug toxicity or presence of WHO stage 4 disease leading to a decrease in adherence) and there is an effect of a tendency for increasing adherence with age. Adherence in a given 3 month period (*adh{t}*) is measured on a scale of 0 to 100%. *adhvar* is the standard deviation representing the within-person period-to-period variability over time. Thus, adherence at any one period (*adh{t}*) is determined as follows (although with modifications explained below):- adh(t) = *adhav* + Normal(0,$adhvar^2$). The distribution of the values of *adhav* and *adhvar* is specified as follows and as illustrated in Figure S8:

5% probability	*adhav* = 50%	*adhvar* = 0.2
10% probability	*adhav* = 80%	*adhvar* = 0.2
65% probability	*adhav* = 90%	*adhvar* = 0.05
20% probability	*adhav* = 95%	*adhvar* = 0.05

Figure S8. Illustration of adherence pattern assumptions. 5% of the population have the adherence as shown in the top left, 10% as shown in the top right, etc. While adherence is generally high in the majority of people on ART (hence the high proportion of people on ART with viral suppression), most probably experience at least some periods of poorer adherence (e.g. see (Muyingo 2008)).



Adherence also influenced by (i) current toxicity (current ADC) (ii) start second line (iii) viral load measurement

This distribution of adherence is primarily determined by the adherence levels required for the model outputs to mimic observed data. This includes data on 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 (Bangsberg 2004;Bangsberg 2006b;Hamers 2011;Hassan 2014;Hoffmann 2014;Kobin 2011;Li 2014;Mackie 2010;Mannheimer 2002;Meresse 2014;Rosenblum 2009;Tran 2014;Usitalo 2014;von, V 2013). 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 are low (and so resistance accumulation is also likely to be low) (El-Khatib 2011;Johannessen 2009).

Figure S9: Risk of virologic failure while on ART according to adherence level

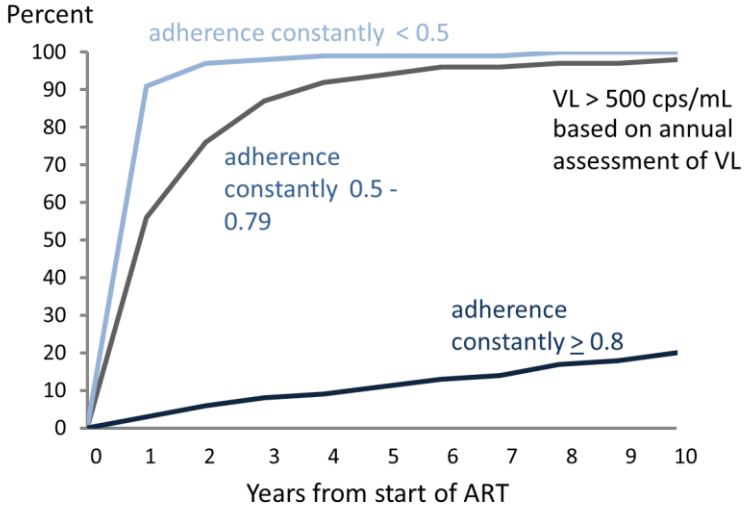
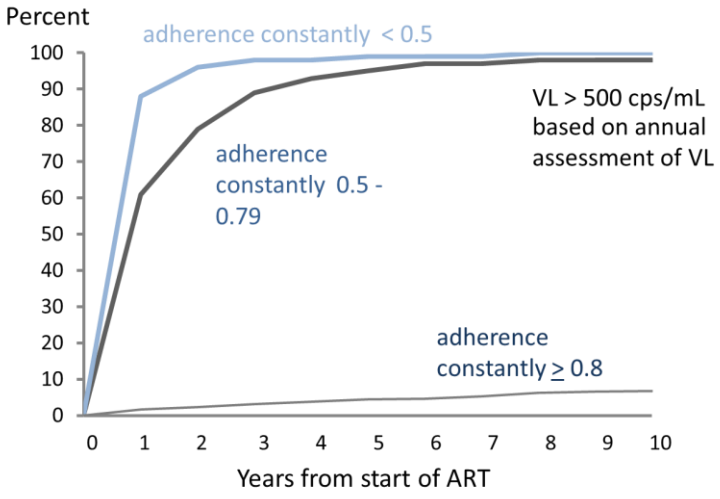


Figure S10: Risk of NNRTI resistance with virologic failure while on ART, according to adherence level



The distribution of adherence over the first year of ART has been compared with data from a large programme in Zambia (see Figure S11; (Chi 2009)). The degree to which outputs on viral load at one year from start of ART is shown in Figure S12. These are reconstructed outcomes for all people who have initiated ART in Zimbabwe (the overall mean CD4 count at initiation is 145 /mm^3). Figures S13 and S14 compare Kaplan Meier estimates of time to virologic failure and resistance, respectively, between the model and observed data, in the latter case from the UK due to the lack of data from sub-Saharan Africa. Figure S15 illustrates the proportion of people with resistance (amongst those on ART with non-suppressed viral load) and corresponds to estimates from the large WHO resistance surveillance.

Figure S11. Distribution of average adherence level over first year of ART (for those on ART at 1 year).

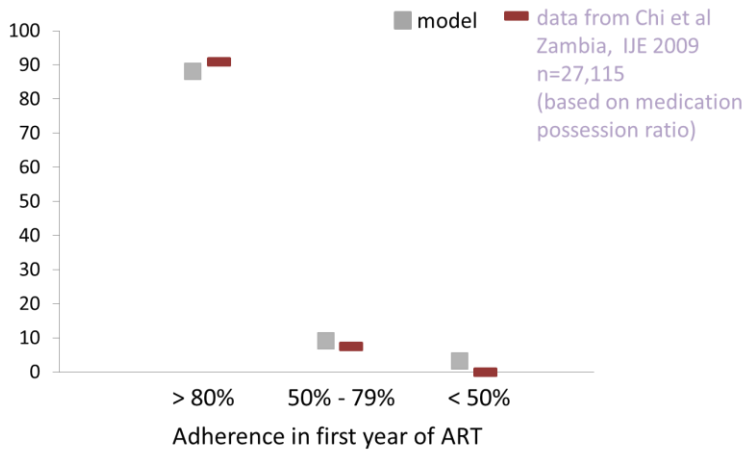
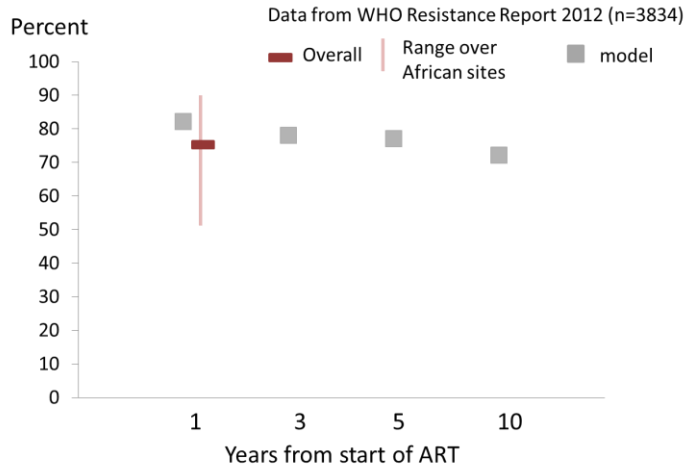


Figure S12. (a) Percent of people alive at given time points from start of ART who have viral load suppression and (b) percent of people alive and on ART at given time points .from start of ART who have viral load suppression (WHO Resistance Surveillance Report 2012(WHO 2012)).

(a)



(b)

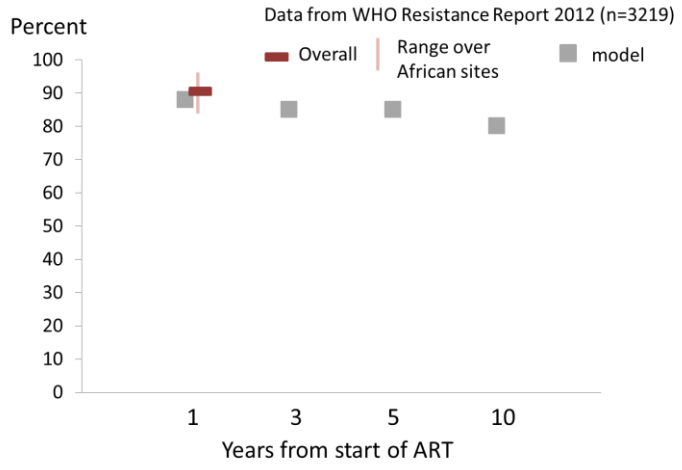


Figure S13. Kaplan Meier estimates of risk of virologic failure while on ART, by time from start of ART.

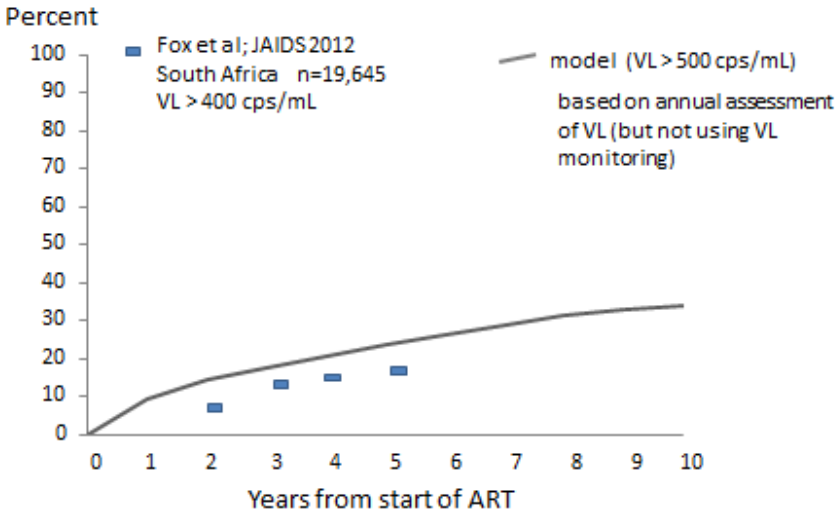


Figure S14. Kaplan Meier estimates of risk of NNRTI resistance with virologic failure while on ART, by time from start of ART (Cozzi-Lepri 2010).

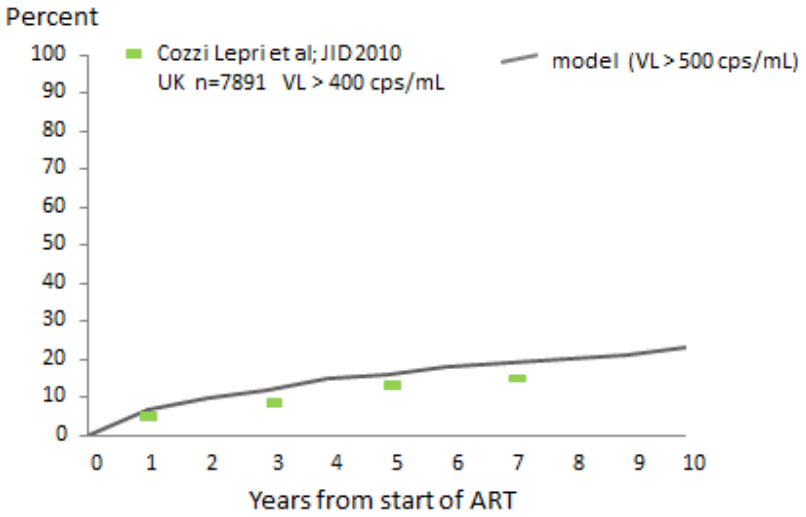
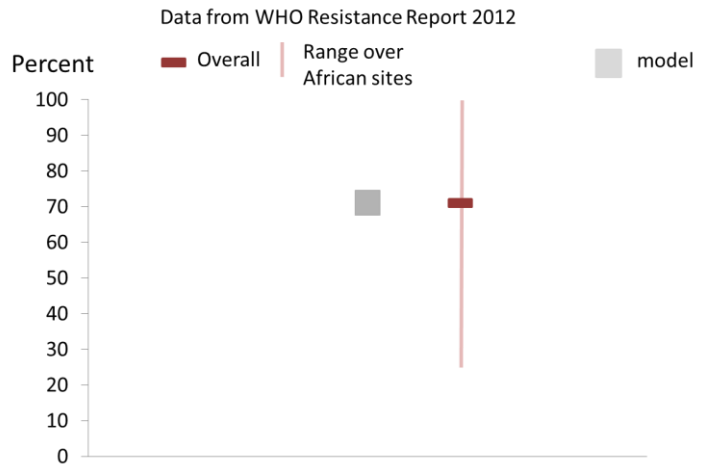


Figure S15. Of people with viral load > 500 at 1 year from start of ART, percent who have NNRTI drug resistance (WHO Resistance Surveillance Report 2012(WHO 2012)).



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 itself, but for those on NNRTI-containing regimens the effective adherence is the adherence + *add_eff_adh_nnrti* (base value 0.1), reflecting the long half life of NNRTI drugs (Cheeseman 1993) which is an advantage as it means such regimens are more forgiving of periods of poor adherence (Bangsberg 2004;Bangsberg 2006a;Bangsberg 2006b;Gardner 2009;Gross 2008;Kobin 2011;Meresse 2014;Parienti 2007). 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 than in those on other 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 (Hill 2013).

Effect of viral load measurement above 1000 cps/mL on adherence

Various factors can influence adherence, including the initial measurement of viral load > 1000 copies/mL which is assumed to lead to an increase in adherence in 70% of people as a result of targeted adherence intervention; this is consistent with data showing that a high proportion of people with measured viral load > 1000 copies/mL who undergo an adherence intervention subsequently achieve viral suppression without a change in ART (Orrell et al 2007, Hoffman et al 2009, Hoffman et al 2013, Rutstein et al 2015) and broadly consistent with a meta-analysis (Bonner et al 2013). Although the appropriate duration to assume for this effect is uncertain (Hoffman et al 2013), the impact of adherence interventions has often been shown to diminish with time (Bärnighausen et al 2011). Based on this overall body of data, we assume that the adherence intervention is effective only the first time it is performed and that for 40% the effect is permanent (i.e. 70% x 40%= 28% of those with a viral load >1000), but that in the remaining 60% (i.e. 70% x 60% = 42% of those with viral load>1000) it lasts only 6 months.

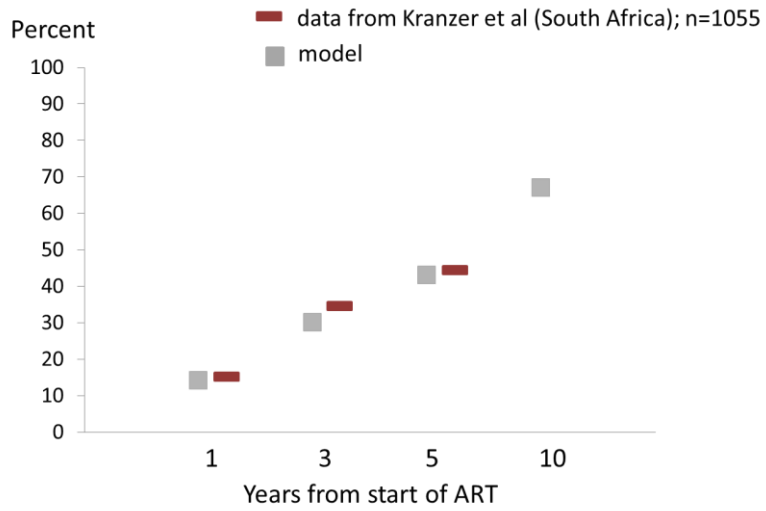
Interruption of ART

People can interrupt ART, and this may be due to not continuing with clinic visits (disengagement, modelled as simultaneous interruption and loss) but ART can be interrupted also in those still attending clinical visits. The basic rate of interruption due to patient choice is *rate_int_choice* (base value: 0.02) - this rate is greater in people with current toxicity (2-fold) (note that in addition to this increased risk of interruption with current toxicity, there is assumed to be some substitution of drugs causing toxicity with available alternatives and a greater rate of interruption in patients with a greater tendency to be non-adherent (1.5-fold if adherence

average *adhav* 50 – 79% and 2-fold if adherence average *adhav* < 50%). In a systematic review, drug toxicity, adverse events and side effects have been found to be the most commonly given reasons for drug discontinuation (Kranzer 2011).

The rate of interruption also reduces with time on ART, decreasing after 2 years. Evidence suggests that rates of discontinuation does decrease over time ((Kranzer 2010;Tassie 2010;Wandeler 2012) although the point at which the risk lowers might be somewhat earlier than 2 years. If adherence average (*adhav*) $\geq$ 80% then there is a 30% chance that interruption coincides with interrupting/stopping visits to the clinic, if 50 <= *adhav* < 80% then 45% chance, if *adhav* < 50% then 60% chance. This is due to an assumption that factors leading to poor adherence are also likely to be associated with interruption. The rate of interruption and disengagement with care is likely to vary by setting. Figure S16 shows a comparison between modelled and observed (from a study by Kranzer et al. (Kranzer 2010)). Kaplan Meier estimates of the percent of people having interrupted or discontinued ART by time from ART initiation.

Figure S16. Percent who have interrupted or discontinued ART by time from initiation.



Interruption of ART without clinic/clinician being aware

It is known that in some instances people on ART have such poor adherence that they have in fact interrupted or stopped ART entirely but, in the same way that the clinician is not always aware of the true adherence level, they are also not always aware when the person has completely interrupted ART. This means that the clinician (in the absence of a resistance test) may think a patient is virologically failing, because viral load is high, when in fact this is due to interruption rather than resistance. This can be seen from studies on people with virologic failure in which a proportion have no identified resistance mutations (Hamers 2011;Hoffmann 2009;Wallis 2010). Thus, when a person interrupts ART (but remains under care) we introduce a variable that indicates whether the clinician is unaware. *clinic_not_aw_int_frac* (base value 0.6). This value of 0.6 was chosen to produce realistic model outputs for the proportion of people with virological failure who have resistance. If a patient has interrupted ART with the clinician unaware then not only is the patient (wrongly) classified (by the clinician) as virologically failing (if viral load has been measured), but a switch to second line can occur. Figure S15 compares the proportion of people with resistance between our model and WHO survey data.

Re-initiation of ART after interrupting in patients still under clinic 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 *prob_restart* (base value 0.2). 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 since occurrence of clinical disease in a person seen at clinic is likely to prompt ART re-initiation. This will vary by setting but is informed by studies showing that of people who have initiated ART who are still seen at clinic a very high proportion are on ART at 12 months from start of ART (McMahon 2013). Kranzer et al found a rate of restarting ART amongst those that interrupted or discontinued of 21 per 100 person-years but this figure is an overall figure which includes in the denominator those who are not attending the clinic (loss to follow-up and return to care are described below). The equivalent figure, produced as an output from the model is 19 per 100 person-years.

Interruption due to drug stock-outs

The basic rate of interruption due to interruption of the drug supply is *prob_supply_interrupted* per 3 months (base value: 0.01). The rate of resupply (*prob_supply_resumed*) has a base value 0.8 per 3 months. This will vary by setting. There have been reported to be significant issues with drug stock-outs in Zimbabwe in the past (http://www.irinnews.org/report/97224/still-struggling-with-drug-shortages). For patients who have interrupted ART due to interruption of supply the probability of restarting ART per 3 months is *prob_supply_resumed* (base value 0.8).

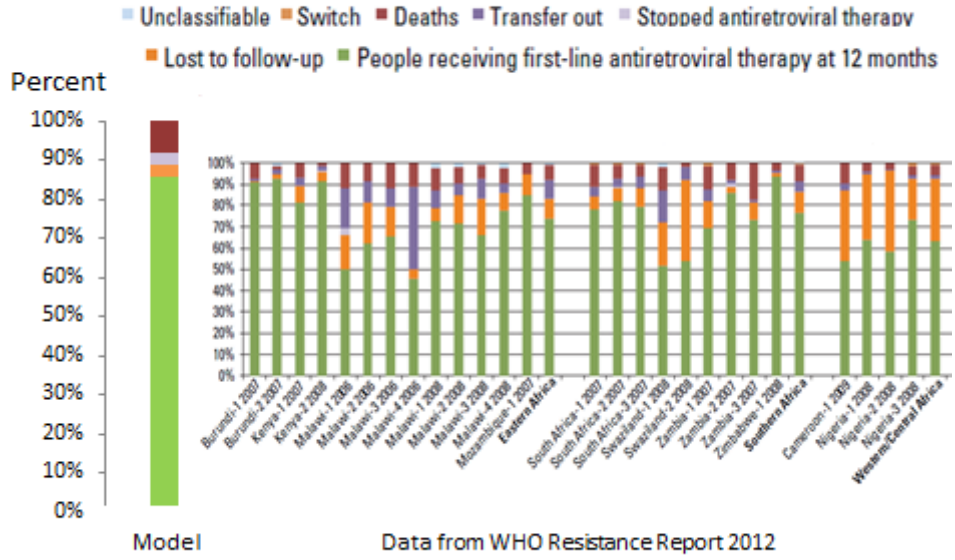
Loss to follow-up while off ART (for reasons apart from drug stock-outs)

The probability per 3 months of interrupting/stopping clinic visits (i.e. being lost to follow-up) is *rate_lost* (base vale 0.05) if adherence average *adhav* $\geq$ 80%. This is increased by 1.5 fold if 50% $\leq$ *adhav* < 80% and by 2-fold if *adhav* < 50%. This high rate is informed by the fact that low numbers of people attending clinics after having been initiated on ART are not still on ART (e.g. WHO 2012 Resistance report). Interruption of ART and loss to follow-up are assumed correlated with the underlying tendency to adhere when on ART because we assume that the same underlying social, practical and economic factors will be an underlying cause of these behaviours.

For people lost to follow-up who are asymptomatic, the probability of returning to clinic per 3 months is *rate_return* (base value 0.05) if adherence average *adhav* $\geq$ 80%. This is decreased by 2-fold if 50% $\leq$ *adhav* < 80% and by 3-fold if *adhav* < 50%. If a person develops a new WHO 3 or 4 event then they are assumed to return to the clinic with probability 1. As mentioned above, this leads to an overall rate of restarting of ART after interruption (including having been loss to follow-up in many cases) consistent with the estimates from South Africa from Kranzer et al, although these will vary by setting (Charurat 2010;Fox 2012;Kranzer 2010).

As output from the model, the retention on ART at 1 year is 94% amongst those still alive. This is difficult to compare with estimates from the literature because few studies are able to know the outcome status of all people initiated on ART, and a high proportion of those lost from a given clinic in fact remain on ART at another clinic or have died. However, taking this into account, this modelled output value of 94% seems consistent with data from the WHO Drug Resistance Surveillance Report (2012) (see Figure S17).

Figure S17. Status at 1 year from start of ART. Data is from WHO Drug Resistance Surveillance Report (2012).



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

This section describes the determination of updated viral load, CD4 count, and acquisition of new resistance mutations in a given time period for people on ART. The updated viral load, CD4 count and risk of new resistance mutations appearing all depend on the effective adherence in the previous and current period, the number of active drugs (*nactive(t-1)*) and the current viral load, as well as the time period from the last time ART was started or restarted. The values of viral load, CD4 count, and resistance mutation risk for any combination of these factors are given in Table S14 below. The rationale behind this approach and how the specific values in the table were chosen is explained below. The choice of values is directly informed by studies in this area and by comparison of model outputs with data. For the new resistance mutation risk, the number in the table is multiplied by the viral load (mean of values at t-1 and t) to give a value for the variable *newmut*, which is used when assessing whether a new mutation or mutations have arisen (see below).

Number of active drugs

We use the concept of the number of drugs that are active, based on presence of resistance mutations to the drugs being used. The level of resistance is determined by the presence of drug resistance mutations, with a given set of mutations being translated into a level of resistance to a given drug on a scale of 0 to 1 in the same way as is done for common resistance interpretation systems. The activity level of a drug is then calculated as 1 minus the level of resistance to the drug. The ability of the number of active drugs, or the genotypic sensitivity score, to predict the viral load outcome is well established (DeGruttola 2000), and the concept of using a genotypic score to define “optimised background therapy” has been common to the design of several trials in treatment experienced patients (e.g. (Grinsztejn 2007)).

Classification of adherence levels

While we model the adherence level for each individual at each three month time period as a value between 0 and 100%, to determine the viral load, CD4 count and resistance risk, we classify adherence into three levels. This is the simplest approach that allows inclusion of the fact that the relationship between adherence and resistance risk is not linear, since the risk of resistance tends to be lower when the adherence is either low or high, and the risk of resistance is highest when adherence is moderate, allowing enough replication for

mutations to be selected for and enough drug present to allow selection of virus with resistance mutations (Bangsberg 2004;Gardner 2009;Rosenbloom 2012).

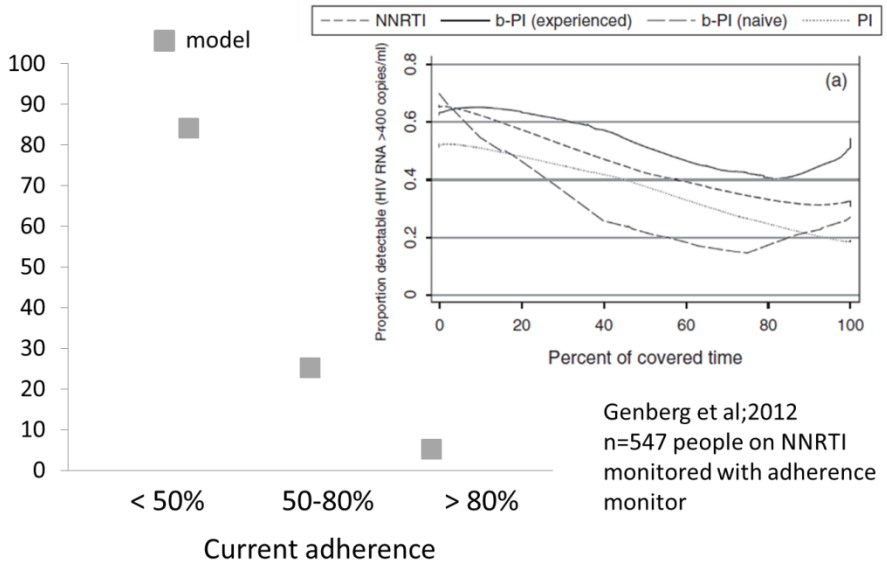
The cut-offs used to define the three adherence levels are 50% and 80%. Adherence-resistance and adherence-viral load relationships differ by regimen type and even specific regimen within a class and any overall breakdown into groups is necessarily a simplification. A cut off of 80% is chosen as the upper level as (unlike for unboosted PI regimens) at adherence levels of at least 80%, NNRTI and boosted PI regimens are likely to have maximal or close to maximal effects on viral load and minimal risk of resistance selection (Parienti 2007). Actual risk of resistance probably depends on the pattern of adherence, not just the average over a three month period, so that a treatment interruption of over 1 week during the three month period, while maintaining an overall average adherence of 80%, could lead to a higher level of risk of resistance emergence than a situation in which the adherence was more uniform over the period (Genberg 2012), although in people who have ongoing viral suppression NNRTI regimens seem to be generally robust to even relatively low levels of adherence (Cambiano 2010b;Gross 2008;Meresse 2014;Parienti 2007). A level below 50% is one that that has been associated with raised risk of detectable viral load (Arnsten 2001;Genberg 2012)

Determination of viral load, CD4 count and risk of resistance in people on ART

Viral load, CD4 count and risk of resistance in the first 3 months after (re-)starting ART

Table S14a shows how the viral load, CD4 count and risk of resistance is determined for people in the first 3 months after starting ART or re-starting ART after an interruption of at least 3 months. Since in this early period on ART, the viral load will depend on the initial value the updated viral load is given as a reduction from the pre-ART maximum viral load. If the number of active drugs is three or more then at a high adherence level (above 0.8) the mean viral load change from the pre-ART maximum is 3 log copies/mL. To reflect the fact that there is variability in the response (Montaner 1998), the value for a given person is sampled from a Normal distribution with standard deviation 0.2. This viral load response diminishes both with decreasing number of active drugs in the regimen being started (which is informed by data from studies relating GSS to virologic outcome, as well as by studies of mono and dual therapy regimens (DeGruttola 2000;Eron 1995;Havlir 1995;Kuritzkes 1996;Larder 1995;Phillips 1997;Wittkop 2011;Wittkop 2013). The viral load response also diminishes with decreasing level of adherence (see Figure S18 and for example Genberg et al). As is well established, the CD4 count response generally mirrors the viral load response, although with very low numbers of active drugs and low adherence there is a mean decrease in CD4 count and still a small decrease in viral load from the maximum.

Figure S18. Model output: of people on ART, percent with current VL >500 according to current adherence. Comparison with data from Genberg at el on electronic monitoring-based adherence measures.



Regarding the risk of new drug resistant mutations arising, Tables S14a-S14c provide a number for "new mutation risk" that is multiplied by the viral load (mean of values at t-1 and t) to give a probability used when assessing whether a new mutation(s) has/have arisen. Values of the new mutations risk have been chosen in conjunction with the translation of presence of mutations into reduced drug activity to provide estimates of resistance accumulation consistent with those observed in clinical practice (Gallant 2004;Harrigan 2005;Johannessen 2009;Ledergerber 1999;Phillips 2001;Phillips 2005;Staszewski 1999a;Staszewski 1999b;van Leth 2004). Risk of new resistance mutations arising increases with decreasing number of active drugs, reflecting the known greater risk of resistance with regimens less able to suppress viral replication, most clearly seen in the fact that mono and dual therapy regimens are highly susceptible to resistance development (Havlir 1995;Kuritzkes 1996;Larder 1995). At low adherence levels, the risk of resistance development is generally low regardless of the number of active drugs, as drug selection pressure is low. However, for those on NNRTI regimens the new resistance mutation risk is assumed to be that for the effective adherence category of 50 – 80% (i.e. maximal) even if the effective adherence is below 50%, reflecting the fact that NNRTI resistance develops easily, even when drug exposure is very low (Bangsberg 2004;Bangsberg 2006b).

Viral load, CD4 count and risk of resistance between 3-6 months from (re-)starting ART

For the period 3-6 months from (re-)start of ART (Table S14b; to reduce the table content we do not provide the matrices of values for the resistance risk or CD4 count, only for the viral load – available in Cambiano et al 2014) we consider the adherence in both the current and previous 3 month period, since the likelihood of reaching viral suppression by 6 months will depend on adherence throughout the whole 6 month period from start of ART, although the adherence in the current period is assumed to be the stronger factor. By 6 months after starting ART, those on 3 or more active drugs with consistently high adherence generally reach a relatively high level of viral suppression, regardless of pre-ART maximal viral load, so a person's viral load is no longer given by the change from baseline but the absolute level of viral load which it is likely they have reached. In these optimal conditions of high adherence and maximal active drugs we assume the viral load has a mean value of 0.5 log, again with variability between individuals. Since most viral load assays have a lower limit of quantification of 40 or 50 copies per mL, it is not actually known what the actual viral load level is, although highly sensitive assays suggest that a proportion of patients reach below 5 copies/mL (0.7 log copies/mL) (Doyle 2012). At lower numbers of active drugs and lower adherence, the viral load is still related to the maximal pre-ART viral load rather than being an absolute value, as the person's viral load has not become so low that the initial value loses relevance. The viral load response decreases with a lower number of active drugs, lower current adherence, and lower adherence in the previous 3 month period. Values for the viral load response between those known from studies (high level of suppression for 3 active drugs and maximal adherence, and only around 0.5 log viral suppression when adherence is < 0.5 even with three active drugs (Gross 2001;Wittkop 2011) are imputed assuming a monotonic relationship. CD4 count responses again mirror the viral load response, as has been extensively studied in patients with ongoing viraemia on ART (Ledergerber 2004). Risk of new resistance mutations again increases with decreasing number of active drugs, if current adherence is in the middle or highest group. The only situation in which risk of new mutations is extremely low is when the number of active drugs is 3 or close to 3 and the current adherence is in the high category.

Viral load, CD4 count and risk of resistance after 6 months of (re-)starting ART

Table S14c shows how the viral load, CD4 count and risk of resistance is determined for the situation where a person has been on ART for more than 6 months and the viral load is suppressed or partially suppressed (< 4 log copies/mL). These values are similar to those used for the period 3-6 months from start of ART except that there is assumed to dependence on the adherence in the current 3 month period only.

The situation where the viral load is above 4 log copies /mL, 10,000 copies/mL is treated the same as that in the period 3-6 months from start of ART (described above), with adherence in the current and previous period having some influence.

Comparisons between model outputs and data from the literature in Figures S10-S14 and S16 help to illustrate the extent to which the model captures various aspects of virologic responses to ART. Tables S15 and S16 provide estimates from the model on various other outcomes at time points from start of ART.

Table S14a. 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 ART. 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 lognormal(1,0.5^2) 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 probability is used when assessing whether a new mutation or mutations have arisen.

	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	≥ 80%	-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	≥ 50%, < 80%	-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)	< 50%	-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	≥ 80%	+50	+45	+40	+35	+30	+25	+20	+17	+13	+10	+5	-2	-15
change	≥ 50%, < 80%	+30	+30	+23	+20	+15	+13	+10	+8	+5	+3	+0	-7	-17
(t-1 to t)	< 50%	+5	+4	+3	+2	+1	-1	-3	-6	-10	-11	-12	-13	-18
new mutation	≥ 80%	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	≥ 50%, < 80%	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)	< 50%*	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
	< 50%**	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

* for NNRTI containing regimen, ** for boosted PI containing regimen.

Table S14b. 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
≥ 80%	≥ 80%	0.5	0.8	1.2	1.4	2.0	2.7	-1.7	-1.15	-0.9	-0.75	-0.6	-0.4
≥ 50%, < 80%	≥ 80%	1.2	1.2	1.2	1.4	-2.0	-1.6	-1.2	-1.05	-0.9	-0.7	-0.5	-0.35
< 50%	≥ 80%	1.2	1.2	1.2	1.4	-2.0	-1.6	-1.2	-1.0	-0.9	-0.7	-0.5	-0.2
≥ 80%	≥ 50%, < 80%	1.2	1.6	1.8	2.2	2.4	-2.4	-1.5	-0.9	-0.7	-0.55	-0.4	-0.3
≥ 50%, < 80%	≥ 50%, < 80%	2.5	2.5	2.5	2.5	-1.2	-1.1	-0.8	-0.65	-0.5	-0.35	-0.2	-0.05
< 50%	≥ 50%, < 80%	-2.0	-1.8	-1.5	-1.35	-1.2	-1.1	-0.8	-0.65	-0.5	-0.2	-0.2	-0.05
≥ 80%	< 50%	-0.5	-0.4	-0.3	-0.25	-0.2	-0.15	-0.10	-0.05	+0.0	+0.0	+0.0	+0.0
≥ 50%, < 80%	< 50%	-0.5	-0.4	-0.3	-0.25	-0.2	-0.15	-0.10	-0.05	+0.0	+0.0	+0.0	+0.0
< 50%	< 50%	-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 S14c. 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 lognormal(1,0.5^2) 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 is used when assessing whether a new mutation or mutations have arisen.

	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	≥ 80%	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	≥ 50%, < 80%	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	< 50%	-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	≥ 80%	+30	+28	+25	+23	+21	+19	+3	-5	-9	-10.5	-12	-12
change	≥ 50%, < 80%	+15	+13	+10	+8	-4.5	-7.5	-10	-12	-13	-14	-15	-15
(t-1 to t)	< 50%	-13	-14	-15	-15.5	-16	-16.5	-17	-17	-18	-17	-17	-17
new mutation	≥ 80%	0.002	0.01	0.03	0.08	0.10	0.15	0.2	0.3	0.4	0.45	0.5	0.5
risk	≥ 50%, < 80%	0.15	0.18	0.2	0.25	0.3	0.3	0.3	0.35	0.4	0.45	0.5	0.5
(x log viral load)	< 50%*	0.15	0.18	0.2	0.25	0.3	0.3	0.3	0.35	0.4	0.45	0.5	0.5
	< 50% **	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05

* for NNRTI containing regimen, ** for boosted PI containing regimen.

Table S15. Model outputs of Status of people who started ART, according to time since initiation.

Status	Number of years since start ART 1	3	5	10
On ART VL < 500	76%	65%	56%	39%
On ART VL > 500 no resistance	3%	3%	2%	1%
On ART VL > 500 with 1 or more resistance mutation	7%	8%	6%	5%
Off ART but under care	3%	3%	3%	2%
Off ART not under care	2%	4%	4%	4%
Dead AIDS	5%	10%	16%	27%
Dead non-AIDS	3%	8%	12%	21%

Table S16. Model-derived Kaplan-Meier estimates of proportion experiencing various outcomes by years from initiation of ART.

	Years from start of ART 1	3	5	10
Viral load failure*	9	17	25	38
Resistance mutation (with virologic failure)	8	14	18	25
CD4 count rise of > 100/mm^3	59	84	90	95
CD4 count rise of > 200/mm^3	17	63	77	88
Interruption	14	31	44	68
Loss to follow-up	4	10	15	28
Death	8	17	25	44

* considering viral load annually only, for consistency with countries where virologic failure monitore

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 (S14) 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, ($sd\_patient\_cd4\_rise\_art$)^2)

sd_patient_cd4_rise_art = 0.2

To reflect the fact that the rate of CD4 count increase on ART tends to diminish with time, 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 *poorer_cd4_rise_on_failing_nnrti* (= -6 /mm^3). This applies regardless of viral load level, so PIs are assumed to lead to a more beneficial CD4 count change than NNRTIs (Ledergerber 2004).

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_cd4* = 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. c(t) is the CD4 count at time t, cmin(t) is the CD4 count nadir measured by time t and cc(t-1) is the change in CD4 count from t-1 to t. v

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 (-200,10^2)
if 4.5 <= v(t) < 5	then cc(t-1) = Normal (-160,10^2)
if v(t) < 4.5	then cc(t-1) = Normal (-120,10^2)

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 (-100,10^2)
if 4.5 <= v(t) < 5	then cc(t-1) = Normal (-90,10^2)
if v(t) < 4.5	then cc(t-1) = Normal (-80,10^2)

if time off ART = 9 months:-

if v(t) $\geq$ 5	then cc(t-1) = Normal (-80,10^2)
if 4.5 <= v(t) < 5	then cc(t-1) = Normal (-70,10^2)
if v(t) < 4.5	then cc(t-1) = Normal (-60,10^2)

This is broadly based on evidence from a number of analyses of the effects of ART interruption (e.g. d'Arminio Monforte 2005, Li X 2005, Mocroft 2001, Wit 2005)

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 S17. Risk of development of specific drug toxicities.

Toxicity	Drug	Risk of development per 3 months	Probability of continuation if pre-existing
Nausea	atazanavir	1% (5-fold higher in 1st year)	50%
	Zidovudine, ddI, lopinavir	3% (5-fold higher in 1st year)	50%
	ddI	5% (2.5-fold higher in 1st year)	50%
	lopinavir	2% (2.5-fold higher in 1st year)	50%
	atazanavir	1% (2.5-fold higher in 1st year)	50%
Rash	efavirenz	3% (in first 6 months on efavirenz)	
	nevirapine	10% (in first 6 months on nevirapine)	
CNS toxicity	efavirenz	10% (if been on efavirenz <1 year)	80% if been on efavirenz <1 year. 90% if been on efavirenz ≥1 year
Lipodystrophy	d4T	5%	100%
	Zidovudine	1.5%	100%
Peripheral neuropathy	d4T	2% (1.5-fold higher in 1st year)	100% (if remain on d4T)
	ddI	1% (1.5-fold higher in 1st year)	100% (if remain on ddI)
Acute hepatitis	nevirapine	2% (one off risk in 1st and 2nd 3 month periods)	
Anaemia	zidovudine	3% (1.5-fold higher in 1st year)	20%

Headache	ZDV	10% (1.5-fold higher in 1st year)	40%
Pancreatitis	D4T, DDI	0.5% (1.5-fold higher in 1st year)	100%
Lactic acidosis	d4T, ddI	1%	
	Zidovudine, tenofovir	0.01%	
Renal dysfunction	tenofovir	0.35%	

Switching of drugs due to toxicity

If toxicity is present then individual drugs may be switched due to toxicity (nevirapine for efavirenz, zidovdine for tenofovir). ddI is only used if neither zidovudine and tenofovir are available due to toxicity.

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

Accumulation of resistance mutations
newmut (see Table S14 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 S18. Risk of acquiring new resistance mutations.

Resistance mutation	Probability of arising	Conditions
M184	50%	if (on 3TC)
# TAMS increases by 1	20%	if (on ZDV or d4T) and (not on 3TC nor FTC)
	12%	if (on ZDV or d4T) and (on 3TC or FTC)
# TAMS increases by 2	1%	if (on ZDV or d4T) and (not on 3TC nor FTC)
	1%	if (on ZDV or d4T) and (on 3TC or FTC)
K65	2%	if (on tenofovir or ddI) and (on zidovudine or d4T)
	10%	If (on tenofovir or ddI) and (not on zidovudine nor d4T)
L74	1%	if (on ddI)

Q151	2%	if (on ddI or d4T or zidovudine)
K103	20%	If on nevirapine
	60%	If on efavirenz
Y181	40%	If on nevirapine
	10%	If on efavirenz
G190	20%	If on nevirapine
	10%	If on efavirenz
V32	4%	if on lopinavir
I47	4%	If on lopinavir
I50L	3%	If on atazanavir
L76	4%	If on lopinavir
I84	3%	If on atazanavir
N88	3%	If on atazanavir

These values are chosen, in conjunction with values of *newmut{t}*, to provide estimates of accumulation of specific classes of mutation consistent with those observed in clinical practice (UK Drug Resistance Database 2005, Harrigan 2005, Sigaloff 2012). 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 probability (= 0.05) of an NNRTI resistance mutation arising (see, for example, Fox et al, 2008).

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 (Devereux 1999, Devereux 2001, Deeks 2003, Birk 2001, Walter 2002, Hance 2001, Tarwater PM 2003)

Table S19. Probability of loss of acquired mutations from majority virus per 3 months after stopping drugs selecting for mutation.

M184V	0.8
L74V	0.6
Q151M	0.6
K65R	0.6
TAMS (lose all)	0.4
NNRTI mutations	0.2
Protease mutations	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 S20 shows the level of resistance to each drug according to presence of specific resistance mutations.

Table S20. Level of resistance to each drug according to presence of specific resistance mutations.

Resistance mutation	**Drug**	**Level of resistance (1=full resistance)**	**Condition**
M184	3TC or FTC	0.75	
1-2 TAMS	zidovudine or d4T	0.5	No 3TC or FTC in regimen
	zidovudine or d4T	0.25	3TC or FTC in regimen and ever had M184V
	zidovudine or d4T	0.5	3TC or FTC in regimen and never had M184V
2-3 TAMS	tenofovir	0.5	No 3TC or FTC in regimen
	tenofovir	0.25	3TC or FTC in regimen and ever had M184V
	tenofovir	0.5	3TC or FTC in regimen and never had M184V
3-4 TAMS	zidovudine or d4T	0.75	No 3TC or FTC in regimen
	zidovudine or d4T	0.5	3TC or FTC in regimen and ever had M184V
	zidovudine or d4T	0.75	3TC or FTC in regimen and never had M184V

3 or more TAMS	ddI	0.5	
4 or more TAMS	tenofovir	0.75	No 3TC or FTC in regimen
	tenofovir	0.5	3TC or FTC in regimen and ever had M184V
	tenofovir	0.75	3TC or FTC in regimen and never had M184V
5 or more TAMS	zidovudine or d4T	1.0	No 3TC or FTC in regimen
	zidovudine or d4T	0.75	3TC or FTC in regimen and ever had M184V
	zidovudine or d4T	0.75	3TC or FTC in regimen and never had M184V
Q151	zidovudine or d4T ddI	0.75	
K65	d4T	0.5	
	tenofovir or ddI	0.75	
	ddI	0.75	
K103	nevirapine or efavirenz	1.0	
Y181	nevirapine	1.0	
	efavirenz	0.75	
G190	nevirapine	1.0	
	efavirenz	0.75	
I47	lopinavir	0.75	
I50L	atazanavir	1.0	
	atazanavir	1.0	
N88	atazanavir	1.0	
1 of (G48, I84)	atazanavir	0.5	
1 of (G48, I84)	atazanavir	1.0	Ever had at least 2 of (V32, M46, I54, V82, L90)
Both of (G48, I84)	atazanavir	1.0	
1 or 2 or 3 of (V32, M46, I54, V82, L90)	atazanavir	0.5	

At least 4 of (V32, M46, I54, V82, L90)	atazanavir	1.0	
1 of (V32, L76, V82)	lopinavir	0.25	Never had I47
2 of (V32, L76, V82)	lopinavir	0.5	Never had I47
3 of (V32, L76, V82)	lopinavir	0.75	Never had I47
All of (V32, I47, L76, V82)	lopinavir	1.0	
4 of (M46, V82, I84, L90)	Lopinavir	Max(level of resistance as above in this table, 0.5)	
2 or 3 of (M46, V82, I84, L90)	lopinavir	Max(level of resistance as above in this table, 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; http://www.rega.kuleuven.be, http://hivdb.stanford.edu, http://www.hivfrenchresistance.org/

Calculation of activity level of each drug

This is given by 1-level of resistance. For ritonavir boosted PIs it is given by 2 – (2 x level of resistance); i.e. assumed higher potency due to ability to induce sustained viral suppression alone. 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

The rate of WHO 4 diseases according to CD4 count per 3 months is given below.

Table S20. Rate of WHO stage 4 disease according to CD4 count and viral load.

If cd4 > 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

This is informed by Phillips AIDS 2004.

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.

If CD4 count is meausured and current value < 350 /mm3 then patient assumed to have 80% chance of starting PJP prophylaxis after 1996

If patient has current WHO stage 3 or 4 condition they are assumed to have an 80% chance of starting PJP prophylaxis

If CD4 count is measured then PJP prophylaxis assumed to stop if current value > 350/mm3.

If the patient has been continuously on ART for 2 years with no WHO 3 or 4 condition in previous 6 months then it is assumed that PJP prophylaxis is stopped.

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 0.6, to reflect that being on ART 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 fold_incr_who3 (= 5) higher.

Risk of HIV-related death

As for WHO 4 except risk *fold_decr_hivdeath* - fold lower (= 0.25).

CD4-, viral load- age-specific death rate raised *incr_death_rate_tb*-fold (= 10) if current TB and *incr_death_rate_adc*-fold (= 10) if current WHO 4 disease. We assume 15% of HIV-related deaths (ie not including deaths that arise due to background mortality rates) are classified as non-HIV-related.

9. Details relating to modelling the monitoring strategies

A key consideration in modelling use of viral load measured using dried blood spots (DBS) from whole blood is to take account the reduced accuracy of detection of viral load > 1000 copies/mL, compared to measurement on a plasma sample obtained by phlebotomy, which relates to low sample volume and presence of ribonucleic acid (RNA) in cells which may be inadvertently amplified along with RNA in plasma. As part of modelling the underlying natural history of HIV and the effect of ART we model the true underlying viral load, and then consider the viral load as measured in a plasma sample by sampling it from a Normal distribution with mean the true underlying viral load and a standard deviation of 0.22 log copies/mL (Brambilla et al 1999, Raboud et al 1996). Viral load as measured in DBS has been compared with viral load measured in plasma with varying results, but the standard deviation of the difference between the measurement in plasma and on DBS has been found to be in the region of 0.4-0.6 log copies/mL, with greater variability at lower viral load levels (Andreotti et al 2010, Marconi et al 2009, Arredondo et al 2011, Pirillo MF-Pinson et al 2011, Fajardo et al 2014, Smit et al 2014, Ondoa 2014, Mavedzenge 2015), with sensitivity for the 1000 cut-off generally varying between 81-95% and specificity generally varying between 88% and 97% (World Health Organisation Technical Report), with variation by assay, so selection of assay for DBS is important.

It is unclear whether the variation in viral load results from use of DBS samples compared with plasma samples is all additional variability on top of the variation seen in plasma measurement compared with actual known virus input (which we have taken as a standard deviation of 0.22). In our base analysis this is determined as follows:

Viral load measured on whole blood = 0.5 x true viral load + 0.5 x viral load measured on plasma + offset + Normal (0, $(0.50 + 0.05 \times (4 - \text{true viral load}))^2$) where offset = 0 in the base case.

This corresponds to an average standard deviation of the difference between VL on whole blood (e.g. DBS, or POC which uses whole blood) and plasma of 0.64 log copies/mL. The sensitivity and specificity of detection of a viral load level > 1000 copies/mL varies according to the distribution of underlying viral load of those tested, as the variability is higher at low VL level. On average over the 20 year period this corresponds to sensitivity and specificity of 86% and 92% of DBS (vs plasma), respectively, for the 1000 threshold. In sensitivity analyses we consider modifications as follows; (a) offset = + 0.5, resulting in sensitivity 96% and specificity 79%, (b) offset = -0.5 (resulting in sensitivity 71% and specificity 97%, (c) $(0.50 + 0.05 \times (4 - \text{true viral load}))^2$ replaced by $(0.40 + 0.05 \times (4 - \text{true viral load}))^2$, resulting in sensitivity 88% and specificity 93%, (d) $(0.50 + 0.05 \times (4 - \text{true viral load}))^2$ replaced by) $(0.50 + 0.20 \times (4 - \text{true viral load}))^2$, resulting in sensitivity 85% and specificity 79%.

As well as eliminating the time delay involved with sending samples to a central lab for testing, use of POC assays may also reduce loss of samples and results which occurs with transporting to labs and communicating results (Rutstein et al 2015), although this must be balanced against the possibility of POC instruments occasionally being in need of repair, which occurs also with CD4 count POC machines. In our base case scenario we assume that there is a 0.85 chance of a given viral load or CD4 count being done as scheduled with a result successfully received. In some cases the cost of the test will be incurred even when the test result is not received and in the absence of data to inform this probability we assume that this occurs with probability 0.25 across all viral load and CD4 tests.

For our main comparison of the seven monitoring strategies in Table 1 of the main paper, several sensitivity analyses were performed in addition to the changes in sensitivity and specificity (a)-(d) above. These are to consider (e) a population adherence profile so there is a greater likelihood of poorer adherence, (f) future increases in condomless sexual behaviour in the population, (g) a permanent increase in adherence as a result of viral load measurement alert in none rather than 40%, (h) a permanent increase in adherence as a result of viral load measurement alert in 100% rather than 40%, (i) a policy of initiation ofART at diagnosis, (j) a reduced frequency of clinic visits if the CD4 count has been measured to be > 350 /mm^3 in the past year, (k) a switch rate of 0 (so the only benefit of monitoring is to inform who should be seen less frequently), (l) a lower prevalence of HIV in 2014 (1.5% instead of 15% in base case), (m) a higher prevalence of HIV in 2015 (33% instead of 15% in base case), (n) a lower proportion on ART in 2015 (33% instead of 56% in base case), (o) a higher proportion of people with HIV on ART in 2015 (70% instead of 56% in base case), (p) a 5% discount rate instead of 3%, (q) a 10 year time horizon instead of 20 years, (r) 2 times higher rate of ART interruption if visit frequency has been reduced due to viral load being < 1000 copies/mL, and (s) 2 times lower rate of ART interruption if visit frequency has been reduced due to viral load being < 1000 copies/mL.

We also carried out the following one way sensitivity analyses around our comparison between viral load using DBS and using plasma-based POC test, considering possible further advantages of POC tests in addition to the greater accuracy and lack of time delay considered in our main analysis. We considered what this ICER would be if (i) a POC test would have a greater penetration and allow reach to a greater proportion of the population (i.e. that 20% of the population would not have access to viral load testing unless a POC test was available), (ii) the rate of loss from care for people on ART is 20% lower due to POC viral load tests being available, (iii) a POC viral load allows an increase in the probability of switch once failure occurs from 0.5 per 3 months to 0.8 per 3 months, and (iv) that the error in DBS is all additional error to the plasma level (i.e. rather than being based on 0.5 x true viral load + 0.5 x viral load measured on plasma, being based only on 1.0 x viral load measured on plasma).

To control Monte Carlo error, 500 repeat runs were done for each strategy and means taken. To assess the stochastic error that remains as a result of this procedure, we repeated the calculation of the ICER for viral load-informed differentiated care ($326) 20 times (i.e. 500 runs for no monitoring and 500 runs for viral load-informed differentiated care repeated 20 times). The standard deviation for the variability was $5.

10. Economic Analysis Methods

To determine cost-effectiveness, the monitoring alternatives ealuated in the study are first ranked on the basis of their effectiveness (i.e. from those leading to fewest DALYs incurred in the population to the highest DALYs incurred). Any strategies that are less effective and more costly than one (or a linear combination) of other alternatives are then removed. All remaining strategies are compared on the basis of the cost-per-DALY-averted (also known as the incremental cost-effectiveness ratio – ICER) compared to the next less effective, less costly alternative. This can be compared to the costs-per-DALY-averted (ICERs) associated with other claims on healthcare resources to determine which of the alternative monitoring policies represent value-for-money.

Policymakers should choose the monitoring policy that is expected to lead to greatest health gains (i.e. is most effective) as long as the ICER is less than ICERs associated with other HIV and healthcare interventions that can no longer be delivered as a result of resources being committed to the monitoring approach. This requires comparison to a cost-effectiveness threshold (CET); which represents the ICER(s) of such forgone interventions. In this way, the monitoring policy would be expected to not just improve the health of patients in receipt of monitoring but also maximise health across the whole population; and can justifiably be deemed "cost-effective".

$$ICER = \frac{Incremental\ cost}{Number\ of\ DALYs\ averted} \leq CET$$

The set of strategies which could feasibly be cost-effective depending on the choice of CET can be shown on the cost-effectiveness plane. In Supplementary Figure 1, those strategies which are cost-effective at different thresholds are shown linked by a solid line. This set of strategies is referred to as the cost-effectiveness frontier. As we move along the line past each strategy, the ICER rises and this would only be cost-effective at a higher CET than the previous strategy (as the incremental cost per DALY averted is higher than that associated with the previous strategy compared to its less effective, less costly comparator).

As an alternative, but equivalent to the ICER vs. CET decision rule we construct a measure termed the net monetary burden of DALYs (NMBn(DALYs)). This is analagous to the measure of net monetary benefit that is frequently used in applied cost-effectiveness analysis using quality-adjusted life years (QALYs) (Stinnett et al 1998; Drummond et al 2005). It presents the results on a monetary scale, where a treatment is worse given higher costs and greater DALYs, which are converted on to the monetary scale using the CET:

$$NMBn(DALYs) = Costs + (DALYs * CET)$$

To be meaningful to inform investment decisions, the NMBn(DALYs) associated with an intervention needs to be compared to other alternatives. When there is only one comparator, results can be expressed *incrementally* and if the intervention has a negative Inc NMBn(DALYs) it would be deemed cost-effective:

$$Inc\ NMBn(DALYs) = Inc\ Costs + (Inc\ DALYs * CET)$$

Where there are more than two alternatives, these can be compared on the basis of their NMBn(DALYs) with that alternative associated with the lowest value being deemed cost-effective. Results are shown using these measures in Table 3 of the main paper.

When the inc. NMBn represents the comparison between two different extents to which an intervention is implemented, it can be viewed as the maximum amount the healthcare system should be willing to spend on implementing the intervention (in addition to the costs of the intervention itself) with it still being regarded as cost-effective. This can be used to guide the level of extra resources that should be committed to improve the implementation and uptake of that intervention if it is currently under-provided and/or under-utilized.

The appropriate CET for any given decision however depends upon the availability of resources in a healthcare system and other calls on the available budget. Robust empirical estimates of CETs for low- and middle-income countries are lacking so this is highly uncertain. In this study, we choose to compare ICERs to a range of cost-effectiveness thresholds. However, as a basis of recommendations and when exploring the sensitivity of some assumptions, we choose to use a CET of $500. We believe this is a reasonable estimate for low resource countries in southern Africa, based on research and current knowledge that reflects other calls on HIV programme resources (Woods et al 2015). In some cases an appropriate threshold is likely to be higher than this; in other cases a lower threshold would be appropriate.

11. Unit Costs and disability weights for DALYs

Table S21. Unit Costs

Item	Unit Cost	Source / explanation
Drug costs per year (including supply chain): First-line: tenofovir/3TC/efavirenz Second-line: zidovudine/3TC/atazanavir	 $144 $312	Untangling the web of antiretroviral price reductions. 17th Edition – July 2014. www.msfaccess.org.
Cost of treatment of a WHO stage 4 condition over 3 months (cost is incurred for 3 months) Cost of treatment of a WHO stage 3 condition over 3 months (cost is incurred for 3 months) Cost of treatment of TB per 3 months (cost is incurred for 6 months) Cotrimoxazole annual cost	$200 $20 $50 $5	Specific data not available on average unit costs of treating WHO stage 3 and 4 conditions and per clinic visit costs - costs used are informed by evidence synthesis from studies that cost according to current CD4 count of those in pre-ART care, cost of ART initiation, which also include costs of CD4 tests (Eaton J et al.)
CD4 count measurement	$10	Hyle, E. P., Jani, I. V, Lehe, J., Su, A. E., Wood, R., Quevedo, J., … Walensky, R. P. (2014). The Clinical and Economic Impact of Point-of-Care CD4 Testing in Mozambique and Other Resource-Limited Settings: A Cost-Effectiveness Analysis. PLoS Med, 11(9), e1001725. doi:10.1371/journal.pmed.1001725. Keebler D, Revill P, et al. How Should HIV Programmes Monitor Adults on ART? A Combined Analysis of Three Mathematical Models. Lancet Global Health 2014. E35-E43.
Viral load measurement:	$22	Human resource costs $3, sample collection consumables $2, relaying of results $2 (this costing information was provided by Medecin Sans Frontiers (MSF) (K Bonner), with the most recent information update February 2014), running the test (including equipment and other costs such as consumables, maintenance and shipping) $15 (http://www.theglobalfund.org/en/mediacenter/newsreleases/2015-06-10_New_Approach_on_HIV_Viral_Load_Testing/ http://www.theglobalfund.org/en/procurement/viral-load-early-infant-diagnostics/)
Non-ART programme costs per year, $40 per year if on tiered care due to viral load < 1000	$80	Bill and Melinda Gates Foundation tiered care meeting report (the per client cost of running the Khayelitsha adherence clubs was $58 per client per year compared to standard clinic care of $108 per client per year. At the Infectious Disease Institute in Kampala, the annual costs per client for physician, nurse, and pharmacy only visits were $60, $45, and $19, respectively).
Cost of the targeted adherence counselling intervention triggered by a viral load > 1000 copies/mL	$10	Assumption
HIV test (including personnel costs)	$10	Eaton J et al. Health benefits, costs, and cost-effectiveness of earlier eligibility for adult antiretroviral therapy and expanded treatment coverage: a combined analysis of 12 mathematical models. Lancet Global Health 2014: E23-E34

Disability weights

(informed from Salomon et al*)

Values are 1 except for the following:

Condition in current 3 month period	**Disability weight for current 3 month period**
Any drug toxicity in current 3-month period	0.95
Any WHO stage 3 condition (except TB) in current 3-month period	0.78
TB in current 3-month period	0.60
Any WHO stage 4 condition in current 3-month period	0.46

* Salomon JA, Vos T, Hogan DR, et al. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. Lancet 2012; 380: 2129–43.

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