Effectiveness and cost-effectiveness of potential responses to future high levels of transmitted HIV drug resistance in antiretroviral drug-naive populations initiating therapy: modelling study and economic analysis

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Abstract

Background: With continued antiretroviral therapy (ART) roll-out in resource limited settings there is evidence of increasing levels of transmission of drug resistant HIV (TDR). This paper compares the effectiveness and cost-effectiveness of the different potential public health responses.

Methods: A model of HIV transmission, progression and the effects of ART, which accounts for resistance generation, transmission and disappearance from majority virus in absence of drug pressure, was used to simulate 5000 ART programmatic scenarios with different levels of detectable resistance in ART initiators without prior antiretroviral drug (ARV) exposure in 2017 (t0). The model was used to predict cost-effectiveness of various potential changes in policy triggered by different NNRTI resistance prevalence levels measured in the population initiating ART.

Findings: At a cost-effectiveness threshold of $500 per QALY, no change in policy was cost-effective, regardless of the level of pre-treatment NNRTI-resistance, due to the increased cost of the policy alternatives. At thresholds of $1000 or above, and at levels of pre-treatment NNRTI-resistance above 10%, it becomes cost-effective to adopt a policy of a single measurement of viral load at 6 months after ART initiation. The policy option of changing the standard first-line to a bPI-based regimen becomes cost-effective at a level of NNRTI resistance above 15% for cost-effectiveness-thresholds above $2000. At current prices, individual level resistance testing prior to ART initiation is not generally a cost-effective option, regardless of cost-effectiveness-threshold.

Interpretation: Results from our model help to inform WHO recommendations on monitoring of HIV drug resistance in people initiating ART and provide a framework to inform change in policy at the country level. . Cost-effectiveness of potential policies to adopt in response to different levels of pre-treatment HIV drug resistance depends upon competing budgetary claims, reflected in the cost-effectiveness-threshold.

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Introduction

Of the approximately 10 million people on antiretroviral therapy (ART) world-wide, most are on first-line non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens[1]. There is the potential that emergence of drug resistance associated with virological failure of such regimens will gradually lead to extensive transmission of drug resistant HIV (TDR), compromising the efficacy of future treatment[2]. The fact that ART is currently delivered in most settings without regular viral load testing to detect virologic failure increases this concern. The World Health Organization (WHO) has developed surveillance strategies for monitoring levels of TDR[3-5] and recent evidence suggests that levels are increasing, albeit slowly[5-7]. For reasons of feasibility and public health relevance, WHO now recommends surveys of drug resistance in populations initiating ART to estimate the prevalence of pre-treatment drug resistance. In the surveys, previous exposure to antiretroviral (ARV) drugs is assessed at time of treatment initiation and resistance prevalence is determined among populations with no previous exposure to antiretroviral (ARV) drugs. As the population assessed in WHO surveys is most probably ARV-naive, observed pre-treatment resistance is likely TDR rather than resistance acquired from drug exposure.

Where substantial levels of NNRTI-resistance are detected in HIV positive populations initiating ART with no prior ARV experience there are a number of potential policy responses. One is to change the recommended national standard first-line regimen to a boosted protease inhibitor (bPI)-based regimen. Another option is to introduce individual-level pre-treatment resistance testing to optimize selection of initial ART regimens on a case by case basis. A third policy option is to introduce routine viral load monitoring of people on ART (e.g. 6 months after ART start and every 12 months thereafter, as recommended by WHO[8]); this approach is not currently widely adopted in most low- and middle-income countries. Measuring viral load allows earlier detection of virologic failure than is the case with CD4 count or clinical monitoring, thus allowing a more prompt switch to second-line ART without unnecessary accumulation of drug resistance. In addition, those found to have a non-suppressed viral load can undergo targeted adherence interventions [9,10]. A fourth new option, which would be cheaper and perhaps more feasible than regular viral load testing, could be to measure viral load at the 6 month time point after ART initiation, with a confirmatory second test at one year after treatment initiation if the 6 month viral load is > 1000 copies/mL, but with CD4 cell count monitoring thereafter. This strategy would allow detection of virological failure which has occurred early after ART initiation, for example that resulting from presence of pre-treatment resistance, allowing prompt switch to second line.

Here we use an individual-based simulation model to compare the effectiveness and cost-effectiveness of the different public health responses described above when triggered by different levels of pre-treatment resistance.

Methods

HIV Synthesis Transmission Model

HIV Synthesis is an individual-based stochastic model of heterosexual transmission, progression and treatment of HIV infection within a southern African context, which has been described previously[11-13]. Resistance is modelled in terms of the presence or absence of specific mutations, with consideration given to the effect of such mutations on virus susceptibility to specific drugs. Distinction is made for each mutation as to whether it is only present in minority virus, so assumed not transmissible, or if it is present in majority virus, and hence assumed transmissible. Additional results and the methodology used for this analysis are described in the Supplementary Methods and Results. A detailed description of the model is available in previously published supplementary material[12]. The model has been employed to contribute to several HIV Modelling Consortium joint modelling projects (e.g. ref 14).

Programmatic scenarios modelled

Each simulation run of our model generates an HIV epidemic with specific programmatic characteristics. In order to use our model to simulate a range of programmatic scenarios with various levels of on-going TDR at t0, (the time point at which the policy decision is being made, arbitrarily designated as the year 2017) each time the model was run we simultaneously varied model parameters (such as the population adherence profile) that determine the level of TDR present in a population By doing this over 5000 times we generated a a range of programmatic scenarios (summarized in Table 1). To ensure that we included scenarios with a high level of TDR, we used a distribution of adherence patterns which includes some with a high proportion of people having poor adherence.

We assume that up to t0 ART had been monitored with use of the CD4 cell count. We also assume that the rate of switching to second-line in patients who have fulfilled the treatment failure definition increases at t0 from 0.03 per 3 months (reflecting that switching to second-line has been slow to occur in many settings) to 0.20 per 3 months so as to ensure that the comparison of strategies is done in the context of them being implemented.

At t0 for each of these programmatic scenarios, we predicted outcomes over 15 years from 2017, for each of the following policy options, according to the current level of NNRTI-resistance in ART initiators without prior ARVs exposure (e.g. women who received ARVs previously for the prevention of mother to child transmission, PMTCT): (i) no change in policy (NNRTI-based first-line ART and routine CD4 cell count monitoring), (ii) change of the standard NNRTI-based regimen to a bPI-based first-line regimen (with use of a different bPI in second-line and replacement of tenofovir with zidovudine or vice versa), (iii) individual-level resistance testing prior to ART initiation to detect key NNRTI mutations to inform whether use of an NNRTI-

based or bPI-based regimen is optimal as first-line treatment, (iv) introduction of routine (at 6 and 12 months after ART initiation and then annual) viral load monitoring, and concomitant cessation of CD4 cell count monitoring, or (v) viral load testing 6 months after ART initiation, with a confirmatory second test at 12 months if viral load is greater than 1000 copies/mL, with CD4 cell count monitoring thereafter. In this last scenario, if the viral load is > 1000 copies/mL on the confirmatory test, patients are switched to second-line.

Economic Analysis

All of the evaluated programmatic intervention alternatives have different implications in terms of health benefits and costs, taking a public health systems perspective. Health benefits were estimated on the basis of quality adjusted life years (QALYs) lived. Costs (in US dollars; $) were estimated based upon resource use in the delivery of the policies and associated unit costs (all unit costs are conceived as being inclusive of supply chain, transport, human resources etc as relevant), with both costs and health benefits discounted to present value using a 3.5% per annum rate. Expected costs and health outcomes (QALYs) associated with each of the policy alternatives are compared to inform which alternative is likely to represent the best value from available resources. The net monetary benefit (NMB) represents a means of summarizing in one measure the benefits and costs of a given policy by putting both on a single scale, that of costs. It is expressed as the QALYs resulting from a policy, multiplied by a cost-effectiveness-threshold (thus converting the QALYs into costs by using the cost effectiveness threshold), less the costs resulting from that policy. The cost-effectiveness-threshold represents the opportunity costs of resources required to fund the intervention, in terms of the health gains those resources could generate if used for alternative purposes[14,15]. To summarize results we indicate the policy option that most often, over the programmatic scenarios for the given t0 level of NNRTI-resistance in ART initiators and for given cost effectiveness threshold, generates the highest NMB, and which is expected to maximize health gains in the population[16,17].

A central concern to inform the efficient allocation of resources to the policy alternatives is what the cost-effectiveness threshold should be in particular countries, with differing levels of resource availability and different claims on their limited budgets. Ultimately this requires assessment of how else resources can generate health gains in the population. Guidance from WHO recommends a threshold equal to a country's gross domestic product (GDP) per capita[18]. However, other analysts have suggested this is too high and risks diverting resources away from greater priorities (e.g. continued expansion of ART coverage)[14,19,20]. The most thorough estimation of a threshold for a particular country comes from the United Kingdom and suggests a level equivalent to 0.52 of GDP per capita[21]. For the more poorly resourced health systems in sub-Saharan Africa a cost-effectiveness-threshold value of $500 or even lower is probably realistic, given that many interventions offering health gains at this amount or less remain unfunded[14,22].

We performed several sensitivity analyses around costing of viral load, resistance testing and of second line bPI regimens.

Role of the Funder

This work was conducted as a collaborative exercise lead by WHO. As such, colleagues at WHO were closely involved in all aspects of the design of the investigation and interpretation of results. WHO themselves received a 7 year grant from the Bill and Melinda Gates Foundation to support a wide range of activities. The work described in the submitted paper is just one of the many deliverables under this grant. This work was not commissioned or influenced by the Foundation but was proposed and initiated by WHO independently. The European Commission had no role in the study itself.

Results

The range of programmatic scenarios at t0 generated is described in Table 1. Supplementary Figure 1 shows the historic trend in HIV prevalence. At t0, the median percentage of people infected with NNRTI-resistant virus is 26% (90% range across programmatic scenarios 11%-46%), while in ART initiators the proportion with NNRTI-resistance in majority virus is lower (11%; 90% range 3% - 24%), both because people starting ART have generally been infected some years before when levels of TDR were lower and because TDR mutations do not persist indefinitely in majority virus. These relatively high average levels of resistance are due to the fact that we are considering a range of potential future scenarios, including those in which levels of TDR have reached very high levels. Figure 1 shows the projected increase in TDR, with a higher level of TDR at infection than is present at the start of ART, but with this difference closing over time.

A range of outcomes after 15 years from t0 of the potential new policies according to the t0 level of NNRTI-resistance in ART initiators is shown in Table 2. Given our assumed rate of switch to a second-line bPI-based regimen after first-line failure of 0.2 per 3 month, the proportion of people on ART who are on a bPI (Table 2a) is projected to rise to 18%, even for programmatic scenarios in which the t0 levels of NNRTI-resistance in ART initiators are below 5% and to much higher levels for situations in which there are higher t0 levels of NNRTI-resistance in ART initiators. As expected, levels of bPI use are higher when a change to a bPI-based standard first- line regimen is recommended than for other policies. The policy which most effectively curbs the increase in NNRTI-resistance (Table 2b) is the policy of changing to a bPI-based standard first- line regimen (although the difference is less marked when considering all resistance, not only NNRTI (Table 2c)) while the impact of the other policies is relatively modest. With respect to viral load suppression (at suppression threshold 500 copies/mL), the proportion of people who are on ART one year from ART initiation who have viral suppression (Table 2d) is projected to decrease over time with the current policy, due to the cumulative effects of increasing TDR. The policies involving introduction of viral load testing have only a small beneficial

effect on this outcome, while the policies of a change to a bPI-based standard first line regimen and the policy of pre-ART resistance testing have a substantial positive effect. Considering the proportion of all people on ART with viral suppression at 15 years after t0 (Table 2e), similar results are achieved by implementing routine viral load monitoring or by changing to a bPI-based standard first-line regimen. Changing to a bPI-based standard first-line regimen leads to the lowest death rate in people on ART (Table 2f), but generally death rates follow a similar pattern as that for the proportion of people on ART with viral suppression. The death rate tends to be higher with increasing t0 levels of NNRTI-resistance in ART initiators, primarily because the underlying adherence pattern is a determinant of both the level of TDR (illustrated in Supplementary Table 2) and of the effectiveness of the treatment, in terms of achieving viral suppression and CD4 cell count increases.

Table 3 shows costs (mean discounted cost per 15-65 year old adult, in US$) according to policy option at t0. The main differences between policy options are associated with choice of ART (higher for the option of a change to a PI-based standard first- line regimen due to the high cost of bPI, which is $219 per year for atazanavir – all unit costs are given in Supplementary Methods and Results), viral load ($45) and resistance tests ($250). Figure 2a shows the most cost-effective policy option for various cost-effectiveness-thresholds and levels of NNRTI-resistance at start of ART at t0 (the increments in costs and QALYs compared with the current in policy are shown in Supplementary Table 1). At a cost-effectiveness-threshold of $500 per QALY, no change in policy is cost-effective, even if the t0 level of NNRTI-resistance in ART initiators is above 25%, due to the increased cost of the alternative policies. At higher cost-effectiveness-thresholds it becomes cost-effective (although requires an increase in overall spend compared with the current policy) to adopt a policy of utilizing a single viral load measurement at 6 months from start of ART if the t0 level of NNRTI-resistance in ART initiators is above 10% for cost-effectiveness-threshold of $1000 and above 5% for a cost-effectiveness-threshold of $1500. For a cost-effectiveness-threshold of $2000 or above, some change to a new policy is indicated regardless of the level of NNRTI-resistance at start of ART. The most effective policy (highest number of QALYs) is the change of the national standard first-line regimen to a bPI-based regimen: for cost-effectiveness-thresholds of $2000, $3000 and $10,000, in our main analysis this was the most cost-effective policy when the t0 level of NNRTI-resistance in ART initiators was above 15%, 15%, and 0%, respectively. In sensitivity analysis in which we varied the cost of bPI (Figure 2b and 2c) such a policy was not cost-effective at cost-effectiveness thresholds up to and including $3000 when the cost of bPI was 1.5 fold the cost assumed in our main analysis, regardless of the t0 level of NNRTI-resistance in ART initiators. On the other hand, if the cost of bPI was halved then the change of the national standard first-line regimen to a bPI-based regimen is the most cost-effective policy in almost all situations. In further sensitivity analyses in which the viral load cost was $15 rather than $45, (Figure 2c and Figure d, in which the cost of resistance test was also lowered, from $250 to $100) the introduction of 6 monthly viral load monitoring is almost universally the most cost-

effective policy, regardless of cost-effectiveness-threshold and level of resistance at t0. If the viral load cost is $15 and bPI cost was halved then the change of the national standard first-line regimen to a bPI-based regimen is the most cost effective approach at high cost effectiveness thresholds and higher t0 level of NNRTI-resistance in ART initiators.

Discussion

We considered effectiveness and cost-effectiveness of various possible policy options for countries to adopt in the face of high levels of NNRTI-resistance detected in people starting ART. For a given level of such resistance, the most cost effective policy is dependent on the cost-effectiveness-threshold for the setting and, in general, when the cost-effectiveness-threshold is around $500 per QALY, no change in policy is cost-effective. At cost-effectiveness-thresholds of $1000, $1500 and $2000 a policy of a single viral load measurement at 6 months after the start of ART becomes cost-effective once the proportion of people with NNRTI-resistance in people starting ART is above 10%, 5% and 0%, respectively. Changing the standard first-line regimen to a bPI-based regimen is generally predicted to be the most effective policy, and can become a cost-effective option at higher cost-effectiveness-thresholds, depending on the level of NNRTI-resistance in people starting ART. If the current cost of bPI were to be reduced by 50%, and if the level of NNRTI-resistance in populations of ART initiators is above 15%, this is predicted to be a cost-effective new policy even if the cost-effectiveness-threshold is as low as $500. On the other hand, if the bPI cost in a country were 50% higher than the value we used, then a change to the standard first-line regimen to a bPI-based regimen is not cost effective, emphasizing the importance of fully understanding the cost implications before making such a change.

In the face of variable and occasionally low adherence, bPI-based regimens are likely to result in better long-term outcomes than NNRTI, regardless of levels of TDR . This is because resistance to bPI is slow to accumulate, even in the face of poor adherence[23-25]. Additionally, HIV virus carrying PI mutations generally replicates poorly[26], CD4 cell count decline is less rapid in the presence of virological failure under a bPI-based regimen than it is under an NNRTI-based regimen[27-29] and there are suggestions that risk of death is higher in those failing with NNRTI-resistance compared to PI resistance[26]. While clinical trials comparing outcomes between NNRTI and bPI regimens as first-line ART have found little differences in viral load outcome[31,32] these studies tend to involve people who are generally more likely to be adherent to ART and our modelling suggests that amongst less adherent people the long term outcomes of bPI regimens will be superior. There is little experience to date on the rate with which PI mutations emerge in people maintained on a bPI regimen in the face of virological failure without options to switch.

As ART coverage increases, it is almost inevitable that prevalence of TDR in people starting ART will rise. It is critical for countries to minimize the rate with which this occurs in order to sustain the huge population benefits of ART. Ensuring high levels of patient adherence to, and retention on ART, as well as maximising HIV transmission prevention are key means by which this can be achieved. Individual-level genotyping is not generally cost effective at this stage. While our results provide broad guidance, as far as is feasible, countries should develop and analyse their own country-specific models to evaluate potential policy changes. This might be particularly helpful, for example, for countries that are transitioning from generalised to concentrated epidemics. Also, further work in understanding what the effective cost-effectiveness threshold is in a given country is clearly needed. With a reduced cost of $15 for viral load measurements, as could well be the case in future given the developments in this area, then use of viral load testing becomes the most cost-effective of the policy changes we considered. Previous modelling (similarly using a viral load cost of $45) suggests that a country should aim to introduce viral load monitoring once it has sustained close to full coverage of ART for those in need[14]. While one benefit of viral load monitoring is that evidence of viraemia on a viral load test can be used to provide targeted adherence counselling to those most in need, which can lead to an increase in adherence[9,10] our analysis does not explicitly include the additional cost of targeted adherence counselling and this will need to be considered if the cost is significant. In addition, our analysis assumes that adherence counselling is offered to all those with a detectable viral load, while this may not be the case in many settings. Further, our modelling assumes an ideal scenario where the implementation of viral load testing is done at the appropriate time and the result are obtained and acted upon, if necessary.

While several models have considered implications of transmission of drug resistant HIV[33-38] only one to our knowledge has previously addressed the question of whether a policy change in the face of a given level of TDR is cost-effective[39]. Walensky et al. investigated whether changing to a bPI-based standard first-line regimen was cost-effective in Cote d'Ivoire and found that such a policy change was not favourable.

An issue we did not consider is that among women receiving ARV drugs for PMTCT it is critical that viral suppression is achieved in order to reduce transmission risk to the child. Changes may be required to regimens used in pregnant women even when levels of resistance in ART initiators are below the level to be cost-effective when considered for the whole adult population on ART. Further modelling is needed to evaluate these issues. For a given cost-effectiveness threshold we have given some indication of the policy alternative likely to be cost-effective for a given level of NNRTI resistance in populations initiating first-line ART. Surveillance of TDR in people ostensibly starting ART for the first time will include some people who have previous undeclared ART use. Thus estimates of levels of pre-ART resistance thought to have arisen due to TDR could be over-estimated by such surveys. Policy-makers should consider this possibility and whether

any policy change proposed would still be indicated if the true level of TDR in people truly initiating ART for the first-time were somewhat lower than that estimated in surveys.

This modelling analysis has involved drawing on knowledge acquired within the HIV field on sexual behaviour, HIV transmisison, progression of untreated infection, and effects of therapy [11-13]. While most of these aspects are generally well described, any model is at best an approximation to reality. Though it is important that this limitation is borne in mind, the fact that our model is mechanistic and tries to capture the underlying processes involved in terms of variables that are measured (e.g. CD4 count, viral load, presence of specific resistance mutations), as well as the ultimate endpoint of length of life, means that there is extensive scope to compare the model outputs with observed data, which should enhance the ability to approximate reality.

In conclusion, results from our model help to inform WHO recommendations on monitoring of HIV drug resistance in people initiating ART and provide a framework to inform change in policy at the country level. .

Systematic review

hiv* AND resistance AND cost-effective* on 12 Feb 2014 and again on 13 Sep 2014. We identified only one article directly relevant to the cost effectiveness of different ART approaches in response to levels of transmitted drug resistance[39]

Interpretation

Results from our model help to inform WHO recommendations on monitoring of HIV drug resistance in people initiating ART and provide a framework to inform change in policy at the country level. Cost-effectiveness of potential policies to adopt in response to different levels of pre-treatment HIV drug resistance depends upon competing budgetary claims, reflected in the cost-effectiveness-threshold.

Contributors

All authors contributed to the conception of this modelling cost-effectiveness analysis and had ongoing input into the conduct of the analysis, the underlying assumptions and the interpretation. All authors had critical input into the drafting of the paper. AP, VC and FN programmed and carried out the modelling.

Declaration of Interests

AP has received funding for consultancy work from Gilead Sciences, GSK and Abbvie. AdL has received funding for research, person fees or travel grants from Abbvie, Siemens, Gilead Sciences, Janssen, BMS and

ViiV Healthcare. No other authors have any potential conficts of interest over and above the points mentioned in the *Role of the Funder*.

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Table 1. Characteristics of the simulated modelled HIV programmatic scenarios at t0. (n=5000 programmatic scenarios).

	Median; 90% range (over scenarios)
HIV prevalence (age 15-65 years)	18% (14% - 22%)
Incidence (per 100 person years)	1.1 (0.7 – 1.6)
Of people starting ART, % with NNRTI-resistance*	11% (5% - 22%)
Of people starting ART (no PMTCT), % with NNRTI-resistance*	11% (4% - 22%)
Of people starting ART (no PMTCT), % with resistance*	12% (5% - 24%)
% of new infections with TDR*	29% (12% - 49%)
% of new infections with NNRTI-resistance*	26% (11% - 46%)
Proportion of HIV positive people diagnosed	84% (80% - 86%)
Proportion of HIV positive people started on ART	54% (42% - 62%)
Proportion of HIV positive people currently on ART	46% (34% - 54%)
Proportion of people in need of ART (CD4 cell count 350 criteria) on ART	60% (47% - 68%)
Proportion of people in need of ART (CD4 cell count 350 criteria) ever started ART	73% (61% - 79%)
Proportion of people in need of ART (CD4 cell count 500 criteria) on ART	51% (39% - 60%)
Proportion of people in need of ART (CD4 cell count 500 criteria) ever started ART	63% (50% - 70%)
Of people remaining on ART at 1 year after ART initiation, median % with viral suppression^{++}	69% (42% - 83%)
% of all people on ART with viral suppression^{++}	76% (54% - 85%)
% of people started on ART who are on second-line (bPI) regimen	8% (6% - 11%)
% of all HIV infected people with unsuppressed VL^{+++}	63% (53% - 81%)
Of all people with unsuppressed viral load, % with resistance*,**	23% (13% - 39%)
% with < 3 fully active drugs^{+} at ART initiation	14% (6% - 28%)

* in majority virus; ** whether diagnosed or not; + a drug not fully active if a resistance mutation to that drug present in minority or majority virus. TDR= transmitted HIV drug resistance; NNRTI = non-nucleoside reverse transcriptase inhibitor; ART = antiretroviral therapy; VL= viral load; bPI = ritonavir boosted protease inhibitor. $^{++}$ < 500 copies/mL. $^{+++}$ regardless of whether diagnosed and in care. The number of adults alive in 2017 in the population is a median of 36,500 (90% range 35,500 – 37,500).

Table 2. Outcomes after 15 years from t0 of the five policy options according to the t0 level of NNRTI-resistance among ART initiators. At t0 and 15 years after t0, median (90% range) over programmatic scenarios: **a)** Of all people who have started on ART, % who are on a bPI-based regimen (whether as first- or second-line, **b)** Of people initiating ART, % having NNRTI-resistance (in majority virus), **c)** Of people initiating ART, % having ANY resistance (in majority virus, including NNRTI, NRTI or PI resistance), **d)** Of people remaining on ART 1 year after ART initiation, % with viral suppression, **e)** % of all people on ART with viral suppression, and **f)** Of all people on ART, death rate (per 100 person years) , all according to level of according to level of NNRTI at ART initiation (excluding those with previous ARV use at ART initiation) at t0 and policy option. Results are based on 5000 programmatic scenarios, divided according to t0 level of NNRTI-resistance in ART initiators as follows: < 5% n=451; [5%-10%) n=1800; [10%-15%) n=1518; [15%-20%) n=807; [20%-25%) n=376; ≥25% n=48. Numbers in parentheses are 90% ranges.

Category of NNRTI resistance at ART initiation at t0	**t0 (2017)**	**15 years after t0 (2032)**				
		Current policy	BPI first line regimen[+]	Pre-ART resistance testing[++]	Viral load monitoring [+++]	Viral load test at 6mths [++++]
a) Of all people who have started on ART, % who are on a bPI-based regimen (whether as first- or second-line)						
< 5%	7 (6-8)	18 (16-20)	59 (57-61)	22 (19-25)	17 (14-21)	19 (16-21)
5%-	7 (6-9)	19 (17-23)	61 (58-64)	24 (21-30)	20 (16-26)	21 (18-26)
10%-	8 (7-10)	23 (19-27)	63 (60-66)	30 (25-35)	25 (20-32)	25 (21-31)
15%-	9 (7-11)	26 (21-33)	66 (61-71)	35 (29-43)	31 (24-40)	30 (24-38)
20%-	10 (9-11)	29 (24-34)	69 (63-72)	40 (34-45)	37 (30-42)	35 (29-40)
25%-	10 (9-11)	31 (27-35)	70 (66-73)	43 (39-46)	39 (35-43)	36 (33-41)
b) Of people initiating ART, % having NNRTI-resistance (in majority virus)[*]						
< 5%	4 (2-5)	25 (15-36)	11 (5-19)	22 (13-33)	21 (11-29)	24 (14-35)
5%-	8 (5-10)	32 (20-44)	14 (7-23)	28 (18-40)	27 (16-38)	31 (19-42)
10%-	12 (10-15)	41 (29-51)	17 (9-26)	36 (26-46)	35 (24-45)	39 (27-49)
15%-	17 (15-20)	48 (37-58)	20 (11-31)	44 (33-54)	42 (32-52)	46 (36-56)
10%-	22 (20-24)	54 (44-63)	22 (12-32)	49 (40-57)	47 (36-56)	51 (40-59)
25%-	26 (25-29)	57 (51-65)	24 (14-34)	52 (44-60)	50 (41-55)	53 (44-61)
c) Of people initiating ART, % having ANY resistance (in majority virus, including NNRTI, NRTI or PI resistance) [*]						
< 5%	5 (3-6)	28 (17-41)	20 (10-30)	26 (16-38)	25 (14-36)	28 (16-40)
5%-	8 (6-11)	36 (23-49)	26 (14-38)	33 (22-46)	32 (20-45)	35 (22-48)
10%-	13 (11-16)	45 (33-57)	33 (20-45)	43 (30-54)	41 (29-53)	44 (32-55)
15%-	19 (16-22)	53 (42-64)	40 (27-53)	51 (39-63)	49 (37-61)	52 (41-63)
20%-	24 (22-26)	60 (49-70)	45 (32-58)	58 (47-66)	56 (43-65)	58 (46-68)
25%-	28 (26-32)	64 (56-73)	49 (37-60)	60 (51-72)	59 (51-68)	61 (51-69)
d) Of people remaining on ART 1 year after ART initiation, % with viral suppression						
< 5%	80 (73-86)	69 (60-78)	83 (75-89)	80 (71-87)	71 (62-80)	70 (60-79)
5%-	77 (64-84)	63 (49-74)	81 (69-89)	77 (64-85)	66 (52-76)	65 (51-75)
10%-	67 (46-78)	52 (35-64)	74 (58-84)	68 (49-79)	55 (39-67)	54 (37-66)
15%-	49 (40-70)	36 (26-54)	61 (51-78)	53 (43-73)	40 (30-58)	40 (30-57)
20%-	45 (39-52)	31 (25-39)	58 (51-69)	49 (42-59)	35 (28-46)	34 (28-44)
25%-	44 (38-49)	30 (25-35)	59 (53-64)	50 (44-57)	34 (27-41)	33 (27-38)
e) % of all people on ART with viral suppression						
< 5%	84 (80-86)	83 (79-86)	88 (86-90)	86 (83-88)	87 (83-90)	84 (80-86)
5%-	82 (73-85)	81 (74-85)	87 (82-90)	84 (79-88)	85 (79-89)	82 (75-85)

10%-	74 (56-82)	75 (61-81)	83 (69-88)	80 (66-85)	81 (70-85)	77 (65-82)
15%-	56 (53-76)	62 (56-77)	70 (67-84)	67 (63-82)	71 (66-82)	66 (61-78)
20%-	54 (52-58)	59 (55-64)	68 (67-70)	65 (63-68)	69 (66-74)	64 (60-68)
25%-	54 (52-56)	58 (55-62)	68 (67-69)	65 (63-67)	69 (65-72)	64 (61-67)

f) Of all people on ART, death rate (per 100 person years)

< 5%	2.8 (2.2-3.7)	2.5 (2.0-3.1)	2.2 (1.6-2.7)	2.3 (1.8-3.0)	2.4 (1.8-3.0)	2.4 (1.9-3.0)
5%-	3.1 (2.3-4.6)	2.7 (2.0-3.6)	2.2 (1.7-2.9)	2.4 (1.9-3.3)	2.5 (1.9-3.3)	2.6 (2.0-3.5)
10%-	4.1 (2.8-7.4)	3.1 (2.4-4.9)	2.4 (1.9-3.4)	2.8 (2.2-4.4)	2.8 (2.2-4.0)	2.9 (2.3-4.4)
15%-	7.0 (3.6-8.5)	4.5 (2.7-6.1)	3.1 (2.1-4.2)	4.0 (2.4-5.3)	3.6 (2.4-4.9)	3.8 (2.5-5.2)
20%-	7.6 (6.0-8.7)	5.0 (3.7-6.0)	3.4 (2.6-4.1)	4.4 (3.4-5.3)	3.9 (3.2-4.9)	4.3 (3.4-5.2)
25%-	7.7 (6.4-8.5)	5.0 (4.4-5.6)	3.4 (2.9-4.1)	4.4 (3.6-5.2)	3.8 (3.3-4.8)	4.0 (3.6-4.8)

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* including women who have taken antiretroviral drugs for the Prevention of Mother to Child Transmission (PMTCT)

+ change of the standard NNRTI-based regimen to a bPI-based first-line regimen

++ individual-level resistance testing prior to ART initiation to detect key NNRTI mutations to inform whether use of an NNRTI-based or bPI-based regimen is optimal as first-line treatment,

+++ introduction of routine (6m, 12m and then annual) viral load monitoring, replacing 6 monthly CD4 cell count monitoring

++++ a single routine measurement of viral load at 6 months after start of ART, with routine CD4 cell count monitoring. In this last scenario, if the viral load is > 1000 copies/mL, it is repeated 6 months later and if above 1000 copies/mL, a switch to second-line is effected.

Table 3. Distribution of annual per capita discounted costs* over 15 years from t0 (2017-2032; mean discounted cost per 15-65 year old adult in the population per year, in US $) according to policy option at t0. Results based on 5000 programmatic scenarios. See Supplementary Methods and Results for full unit costs.

	Policy option starting from t0				
Resource Item	Current policy	bPI first-line regimen[+]	Pre-ART resistance testing[++]	Viral load monitoring [+++]	Viral load test at 6 months[++++]
ART	9.43	13.60	10.09	9.85	9.71
CD4 cell count	0.83	0.87	0.85	0.12	0.81
Viral load	0	0	0	2.22	0.24
Resistance test	0	0	1.22	0	0
WHO 4 treatment	1.26	1.16	1.21	1.20	1.23
TB treatment	0.41	0.38	0.39	0.38	0.40
WHO 3 treatment	0.47	0.43	0.45	0.44	0.46
Cotrimoxazole	0.15	0.14	0.14	0.16	0.15
HIV testing	3.38	3.37	3.38	3.38	3.38
Clinic visits	5.17	5.24	5.20	5.23	5.21
Total	21.1	25.2	22.9	23.0	21.6

* above facility costs are apportioned to resource inputs

+ change of the standard NNRTI-based regimen to a bPI-based first-line regimen

++ individual-level resistance testing prior to ART initiation to detect key NNRTI mutations to inform whether use of an NNRTI-based or bPI-based regimen is optimal as first-line treatment,

+++ introduction of routine (6m, 12m and then annual) viral load monitoring, replacing 6 monthly CD4 cell count monitoring

++++ a single routine measurement of viral load at 6 months after start of ART, with routine CD4 cell count monitoring. In this last scenario, if the viral load is > 1000 copies/mL, it is repeated 6 months later and if above 1000 copies/mL, a switch to second-line is made

Figure 1. Median (solid lines) and 90% range (dotted lines; showing variability over model simulation runs) prevalence of NNRTI TDR in recently infected people and NNRTI-resistance in ART naïve people at start of ART over 15 years from t0 (2017), with no change in policy, restricted to programmatic scenarios where NNRTI-resistance at start of ART at t0 is < 10%. The t0 level of NNRTI-resistance in ART initiators is calculated as the mean over all four quarters of the year 2016. The plotted values are the median (90% range) over all quarters and all programmatic scenarios for each given year (which is the reason why the 90% range is above 10% at t0 for the t0 level of NNRTI-resistance in ART initiators).

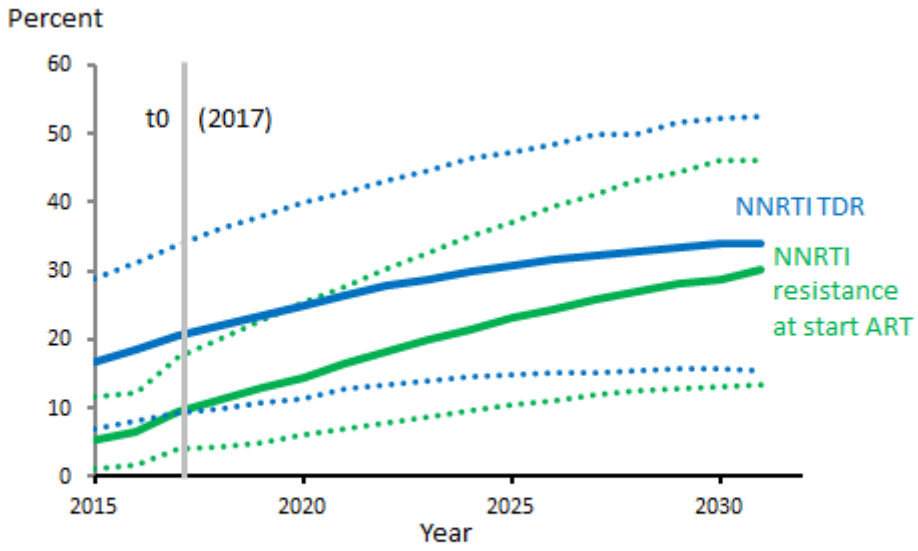
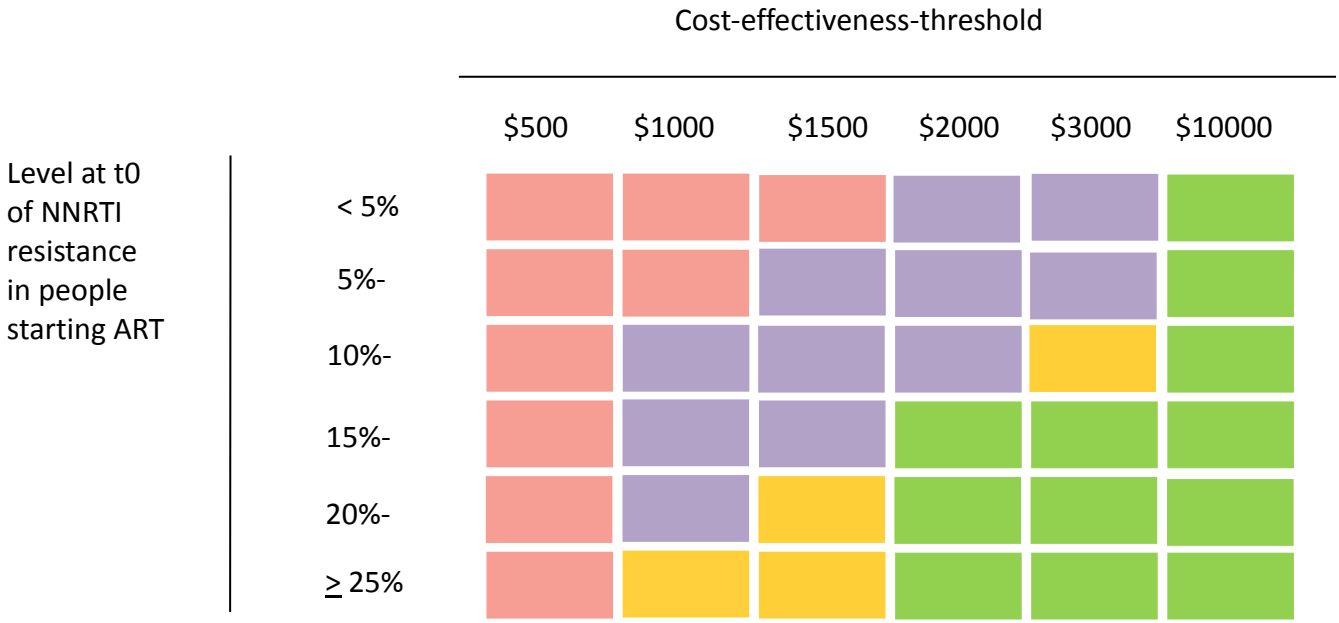
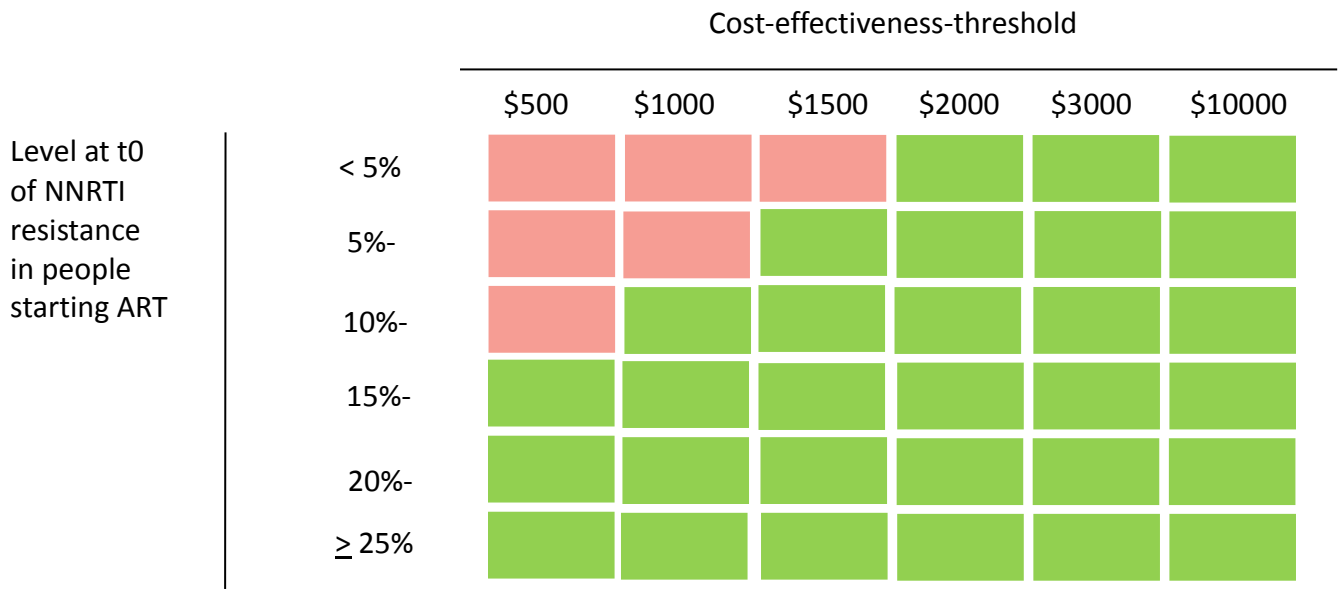


Figure 2. Most cost-effective policy according to level of NNRTI-resistance at ART initiation at t0 and cost-effectiveness-threshold (a); (b) as in a) except with cost of bPI ($195 per year for atazanavir rather than $268 per year in base analysis) reduced by 50%; (c) as in (a) but with cost of bPI increased by 1.5-fold; (d) as (a) but with viral load cost of $15 rather than $45; (e) as in (a) but with unit cost of resistance test $100 instead of $250, and VL cost $15 instead of $45; (f) as in a) but with cost of bPI reduced by 50% ($195 per year for atazanavir and $268 per year for lopinavir/r in base case scenario) and VL cost $15 instead of $45. 5000 programmatic scenarios, divided according to NNRTI-resistance at t0 as follows: < 5% n=451; 5%- n=1800; 10%- n=1518; 15%- n=807; 20%- n=376; ≥25% n=48. Current policy Change in standard first-line regimen to bPI-based regimen Pre-ART drug resistance testing Viral load monitoring Viral load measurement at 6 months from start of ART. For each of the programmatic scenarios, the policy with the highest net monetary benefit is ascertained and the policy that is most frequently has the highest value is indicated as the most cost effective policy.

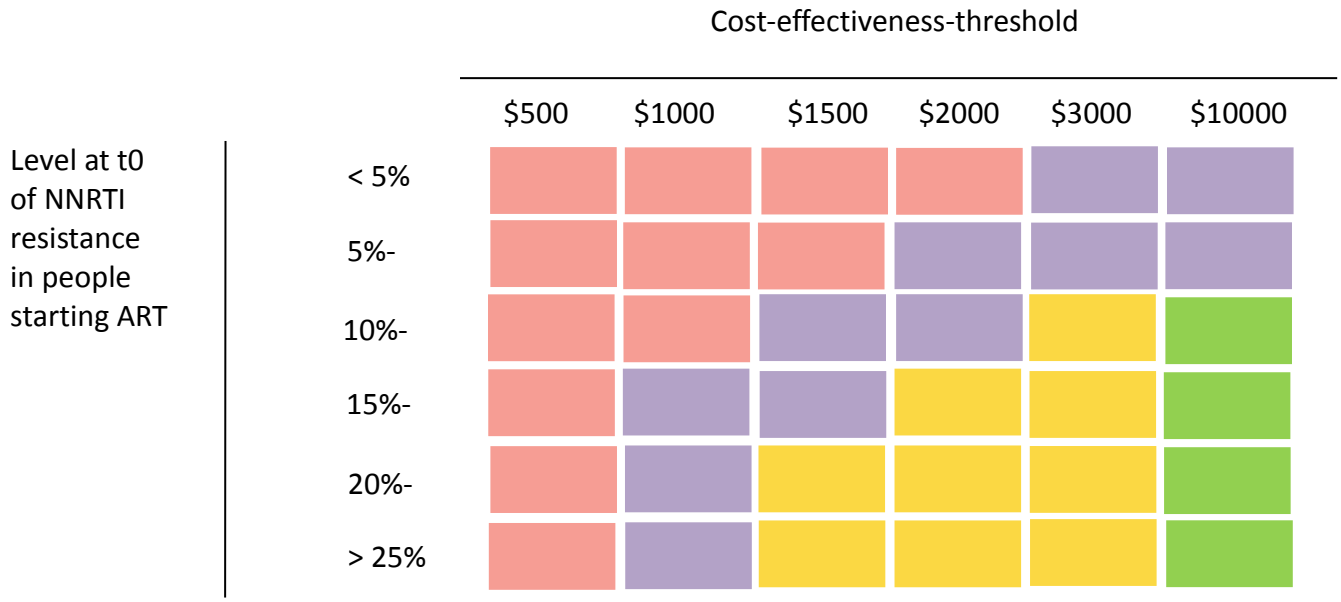
a) most cost-effective policy according to level of NNRTI-resistance at ART initiation at t0 and cost-effectiveness-threshold



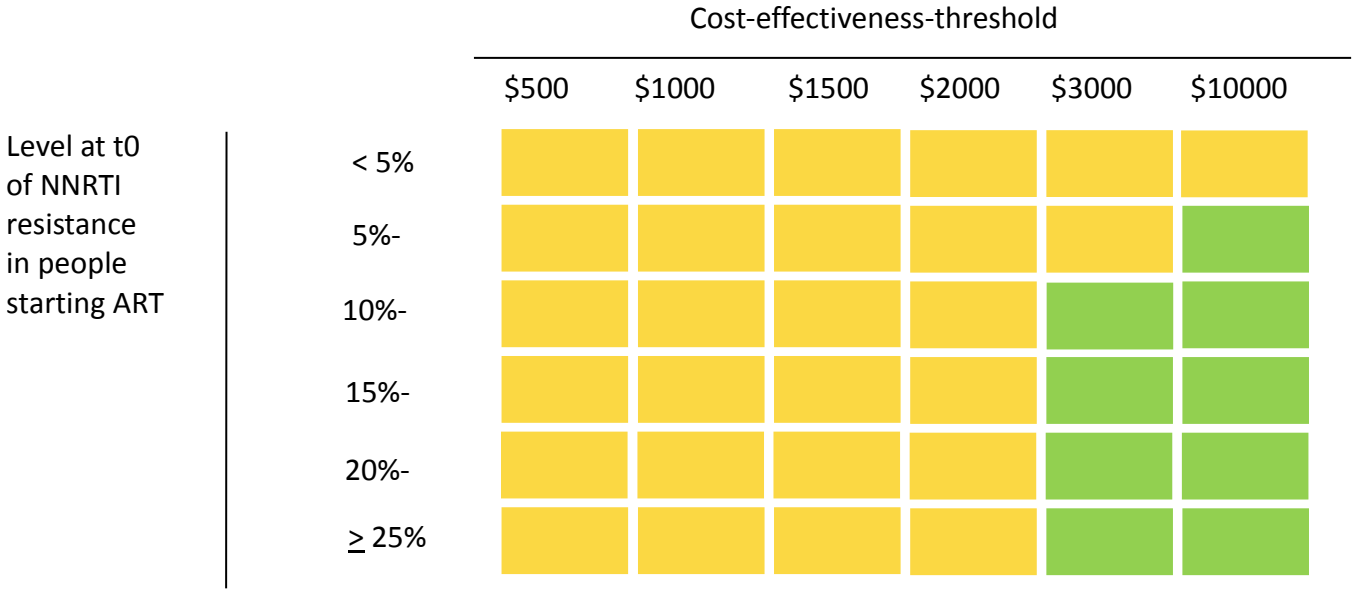
b) as in a) except with cost of bPI reduced by 50% ($219 per year for atazanavir and $268 per year for lopinavir/r in base case scenario).



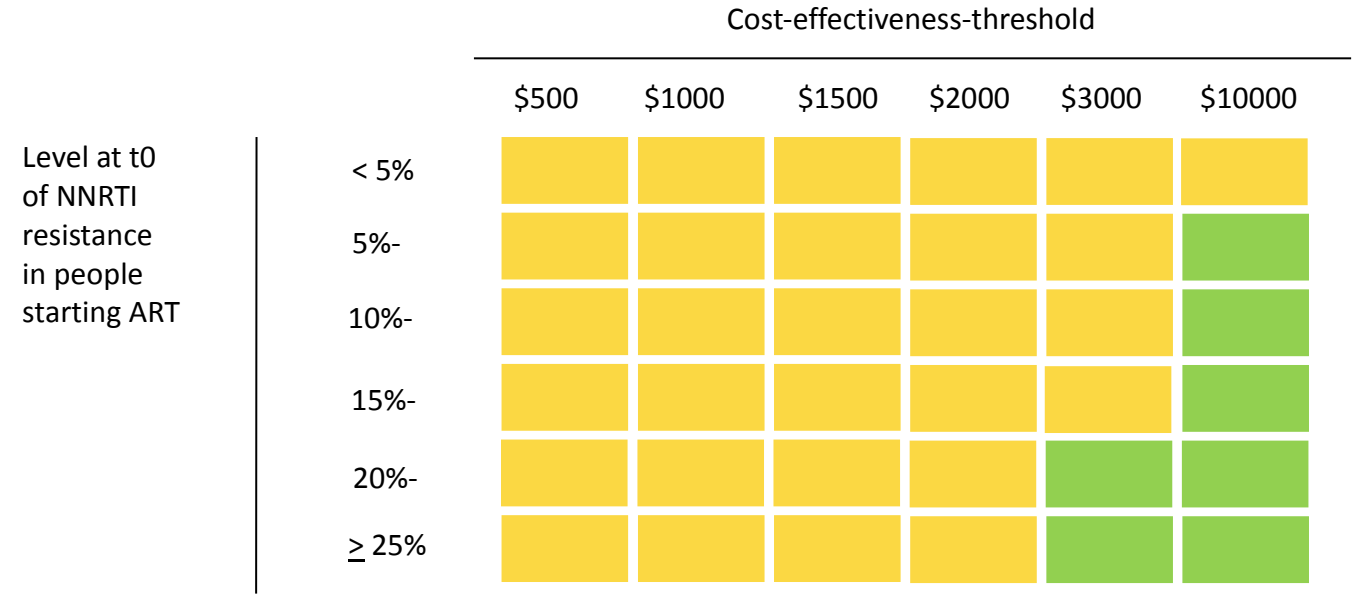
(c) as in a) except with cost of bPI increased 1.5 fold ($219 per year for atazanavir and $268 per year for lopinavir/r in base case scenario).



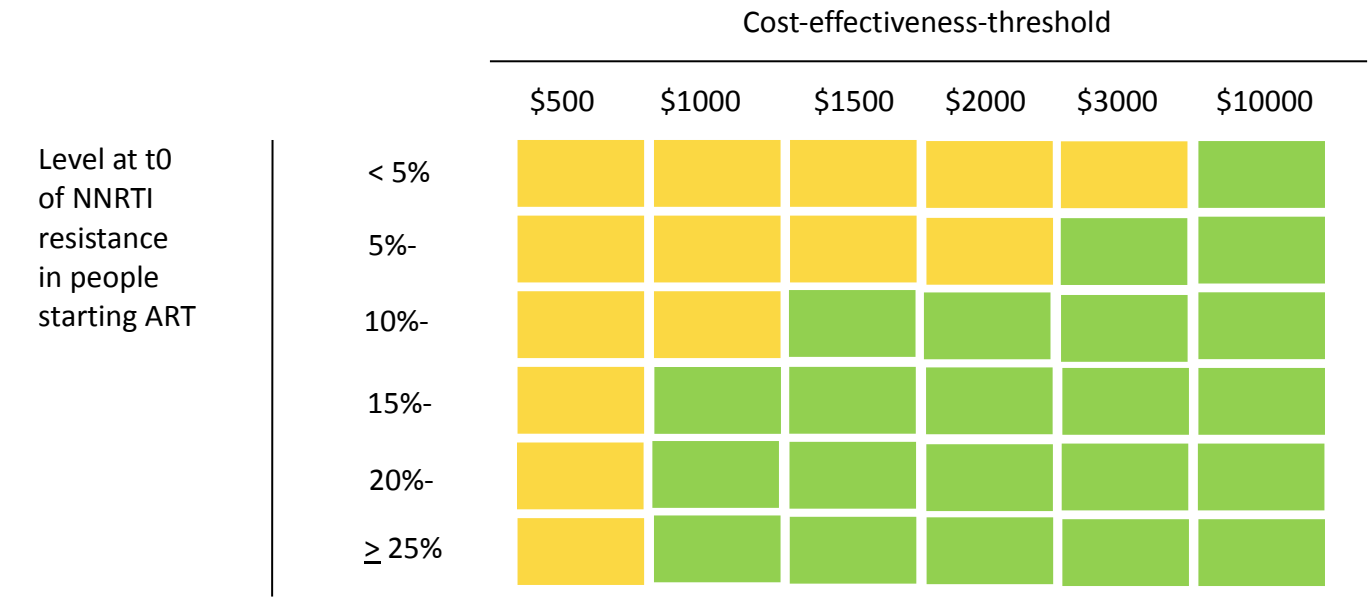
(d) as in a) but with unit cost of viral load tests $15 instead of $45



(e) as in a) but with unit cost of resistance test $100 instead of $250, and VL cost $15 instead of $45



(f) as in a) but with cost of bPI reduced by 50% ($219 per year for atazanavir and $268 per year for lopinavir/r in base case scenario) and VL cost $15 instead of $45



Supplementary Methods and Results

1. Description of methods
2. Supplementary tables and figures
3. Parameter values and distributions

1. Description of methods

HIV Synthesis Transmission Model

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 (1-3). Full updated model details are in the supplementary material for ref 3, but a brief description follows. All variables are updated in 3 month periods in the model, which includes an age- and gender- structure. Sexual risk behaviour is modelled as the number of condomless-sex short term partners and presence of a condomless-sex long-term partner in each period. In any given period, the probability of an uninfected person having a condomless-sex partner who is infected with HIV depends on their number of partners and on the prevalence of HIV amongst partnerships formed by those of the opposite gender, accounting for patterns of age mixing. Given exposure to an infected partner, the probability of transmission depends on the viral load level of the partner (obtained by sampling from the distribution of viral load levels in partnerships formed by HIV infected people, accounting for gender and age), on the estimated risk of transmission at that viral load, presence of a concurrent sexually transmitted infection and on gender. Emergence of resistance on ART is dependent on adherence and the current number of active drugs. Adherence is assumed to have several components, with a distribution across individuals of a life long tendency, and also in the extent of period to period variation. In addition, 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 (with new adherence level sampled from a Normal distribution with mean 90% and standard deviation 5%, and a 10 fold increase in the rate of restarting ART in those who have interrupted) 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 subsequently achieve viral suppression without a change in ART (4-6). The appropriate duration to assume for this effect is uncertain and the impact of adherence interventions has often been shown to diminish with time (7). We assume that the adherence intervention is potentially effective only the first time it is performed and that for 40% the effect is permanent (28% of those with a viral load >1000 copies/mL), but that in the remaining 60% (42% of those with viral load>1000 copies/mL) it lasts only 6 months (except we assume the effect on restarting ART is permanent). We also model the possibility that in some individuals at certain times the adherence is so low that the individual has in fact interrupted ART, although this is undeclared to the clinic so the person is still considered by the clinic in any records kept as being on ART. Such a lack of adherence is thought to explain why some people have no resistance mutations present at virologic failure (8-10), and we mimic this in our model. Regarding resistance and transmission, 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). For people who have become infected with HIV the variables modelled include viral load, CD4 cell count, presence of resistance mutations,

risk of AIDS and death. Resistance is modelled in terms of the presence or not of specific mutations (e.g. number of thymidine analogue mutations (TAMS); presence of M184V (yes or no; y/n), K65R (y/n); L74V (y/n); Q151M (y/n), presence of a key NNRTI mutation (y/n); major PI mutations (y/n). 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 assumed not transmissible, or if it is present in majority virus, and hence assumed transmissible. For a newly infected person, the probability of being infected by a person with resistant virus as their majority virus population is determined by the probability, for the given viral load level of the person from whom the virus has been acquired, that drug resistance mutations are present in the concurrent infected population, again taking into account gender, age and number of partnerships formed. It is not assumed that all resistance mutations present in majority virus of the source partner are established as a mutation in virus in the newly infected person. This is dependent on the specific mutation. If a mutation is transmitted and established in the new host it is assumed to persist in majority virus but with a certain probability of loss of persistence in majority over time (11), but thereafter it remains in minority virus and is selected back as majority virus if relevant ART is initiated. We also consider the possibility of a person who is already infected become super-infected, including with drug resistant HIV (12). NNRTI-resistance acquired through use of nevirapine as PMTCT is assumed to eventually disappear even from minority virus.

The model structure used aims to capture the essence of the underlying biological mechanisms by which resistance and virologic failure arise, and is the result of careful consideration in discussion with virologists, clinicians and other modellers. The use of this structure means that few of the parameter values come directly from specific published values as estimates of the parameters relevant to our model structure are mostly not available. We have generated in the supplementary material to ref 3 a range of model outputs for comparison with published estimates to assess model calibration.

Programmatic scenarios modelled

In order to generate programmatic scenario scenarios with various levels of on-going TDR at t0 – the time point at which the policy decision is being made (which was arbitrarily chosen as the year 2017) we varied many of the parameters that most strongly determine the level of TDR present in a population in 5000 model runs. These were: the adherence profile, the extent to which resistance mutations are transmitted (res_trans_factor; see model details), the rate with which transmitted mutations disappear from majority virus and become present only in minority virus (rate_loss_persistence), the underlying rate of interruption of ART (the actual rate at any point depends also on the average adherence (adhav) and presence of toxicity as well as this underlying rate; see model details), the probability of the drug supply being interrupted, and the rate of generation of new NNRTI drug resistance mutations as a result of interruption (due to the long tail in drug level). Distributions assumed for these are shown below under Parameters and Distributions. In order

to generate programmatic scenarios with a high level of TDR we used a distribution of adherence patterns which includes a relatively high number of programmatic scenarios for which a high proportion of people have poor adherence. In such programmatic scenarios the proportion of people on ART with VL suppressed is low and the death rate of those on ART high. Although there are relatively few data, the proportion of programmatic scenarios in sub Saharan Africa with these characteristics is probably lower than it is in our programmatic scenarios, but we wished to include a high proportion of programmatic scenarios in which levels of NNRTI TDR are high in order to study the effects of potential new policies in this context. For all programmatic scenarios, we assume that ART (first line regimen consisting of stavudine, 3TC and nevirapine before mid-2010 and tenofovir, 3TC and nevirapine after mid-2010) is provided with use of CD4 cell count monitoring to decide on when to start ART (CD4 cell count 200 /mm^3 from 2003; CD4 cell count 350 /mm^3 from 2010, 500 cells /mm^3 from 2017). We assume that up to t0 the CD4 cell count is used to monitor people on first line to determine eligibility for switch to second line (CD4 cell count < 100 cells/mm3, as in the DART trial (13)). In both cases we assume only a 3% chance of switch in each 3 month period after the criteria is fulfilled, to reflect the very low rates of switching seen in practice. Then at t0 for each of these programmatic scenarios we considered what would be the predicted outcomes over the following 15 years (i.e. to 2032) of potential policy options, according to the current level of NNRTI-resistance in people about to start ART, excluding women with previous antiretroviral therapy for PMTCT. The potential policies are as follows (i) current policy, (ii) change of the standard NNRTI-based regimen to a bPI-based first line regimen (with a second line involving continued use of a bPI (bPI) and replacement of the tenofovir with zidovudine), (iii) individual-level resistance testing prior to ART initiation to detect key NNRTI mutations to inform whether to use an NNRTI-based or PI-based regimen as first line, (iv) introduction of routine (6m, 12m and then annual) viral load monitoring, replacing CD4 cell count monitoring (so unlike in the first three policies, in which the above-described CD4 count monitoring is assumed to continue, the first failure criteria is two consecutive viral load values > 1000 copies/mL) , or (v) measurement of viral load at 6 months after start of ART, with a repeat test at 1 year if the value is > 1000 copies/mL , and with first line failure being called if the level at one year is above 1000 cps/mL, but otherwise not replacing CD4 cell count monitoring. We assume that the rate of switching after failure criteria have been fulfilled is increased to 0.2 per 3 months after t0. These potential policies were formulated at a WHO working group meeting in 2012. We undertook 5000 model runs as a balance between having sufficient stability of estimates and feasibility of running very large numbers of simulations. In order to most clearly understand their impact we assume that policies are fully implemented immediately. The model was programmed in SAS 9.3.

Economic Analysis

All of the evaluated alternatives have different cost implications and the ability of health care systems to fund interventions differs widely. The health benefits associated with the alternative policies were estimated on

the basis on quality adjusted life years (QALYs) lived. Costs were estimated based upon resource use in the delivery of the policies (e.g. number of viral load tests provided, first line drug regimen used) and associated unit costs (see below). The time horizon for the analyses is 2017-32, and both costs and health benefits are discounted to present value using a 3.5% per annum discount rate.

The expected costs and health outcomes (QALYs) associated with each of the policy alternatives can be compared to inform which is likely to represent best value from available resources. The results are presented in the form of a ranking of the net monetary benefit across all policy options . The net monetary benefit (NMB) is expressed as the QALYs associated with a policy, multiplied by a cost-effectiveness-threshold, less the costs of that policy. The cost-effectiveness-threshold represents the opportunity costs of resources required to fund the intervention, in terms of the health gains those resources could generate if used for alternative purposes (14). Based on current evidence, the policy that generates the highest NMB should be adopted and can be expected to maximize health gains in the population (15,16). We provide results for a range of cost-effectiveness-thresholds. For the more poorly resourced health systems in sub Saharan a value of $500 or even lower is probably realistic given that many interventions offering health gains at this amount or less remain unfunded.

We assume the objective is to maximize health. Policies are made subject to uncertainty and on the basis of best current evidence. In reality, policy-makers may have the option to undertake more research to guide policy (for instance to better understand the effectiveness of the interventions, or to obtain better estimates of TDR in the population). Furthermore, we assume that there are no costs incurred with the change in strategy beyond those included as depreciation costs in the unit cost estimates. If there are other irrecoverable costs to adopting new policies we assume that the interventions will be used for their full effective lifetimes. This could be important because the introduction of laboratory-based viral load monitoring and resistance testing, in particular, would require significant capital investment that may not be necessary if point of care alternatives become available in the near future.

We performed sensitivity analyses in which we changed the cost of viral load from the $45 in the base scenario to $15, in which we also changed the cost of resistance testing from $250 to $100 and in which we reduced the cost of the bPI by 50%. Also we considered a smaller effect of viral load measurement on adherence.

2. Supplementary tables and figures

Supplementary Table 1. Difference in discounted costs and QALYs over 15 years compared with no change in policy according to t0 level of NNRTI-resistance in ART initiators and new policy option. Mean over 5000 programmatic scenarios.

	New policy option starting from t0			
Level of NNRTI resistance at start of ART at t0	bPI first line regimen[+]	Pre-ART resistance testing[++]	Viral load monitoring [+++]	Viral load test at 6 months after ART initiation [++++]
Difference in discounted cost in 2013 $ (over 15 years; mean over programmatic scenarios) compared with current policy				
Difference in discounted QALYs (mean over programmatic scenarios) compared with current policy				
< 5%	2,456,000 491	826,000 233	1,086,000 327	187,000 128
5%-10%	2,576,000 729	977,000 331	1,161,000 454	224,000 175
10%-15%	2,534,000 1171	1137,000 490	1,192,000 740	306,000 366
15%-20%	2,443,000 1752	1,280,000 728	1,221,000 1174	441,000 674
20%-25%	2,521,000 2192	1,458,000 861	1,297,000 1505	555,000 867
25%-	2,691,000 2505	1,626,000 1070	1,390,000 1746	596,000 893

NNRTI = non-nucleoside reverse transcriptase; bPI = boosted protease inhibitor

+ change of the standard NNRTI-based regimen to a bPI-based first-line regimen

++ individual-level resistance testing prior to ART initiation to detect key NNRTI mutations to inform whether use of an NNRTI-based or bPI-based regimen is optimal as first-line treatment,

+++ introduction of routine (6m, 12m and then annual) viral load monitoring, replacing 6 monthly CD4 cell count monitoring

++++ a single routine measurement of viral load at 6 months after start of ART, with routine CD4 cell count monitoring. In this last scenario, if the viral load is > 1000 copies/mL, it is repeated 6 months later and if above 1000 copies/mL, a switch to second-line is effected.

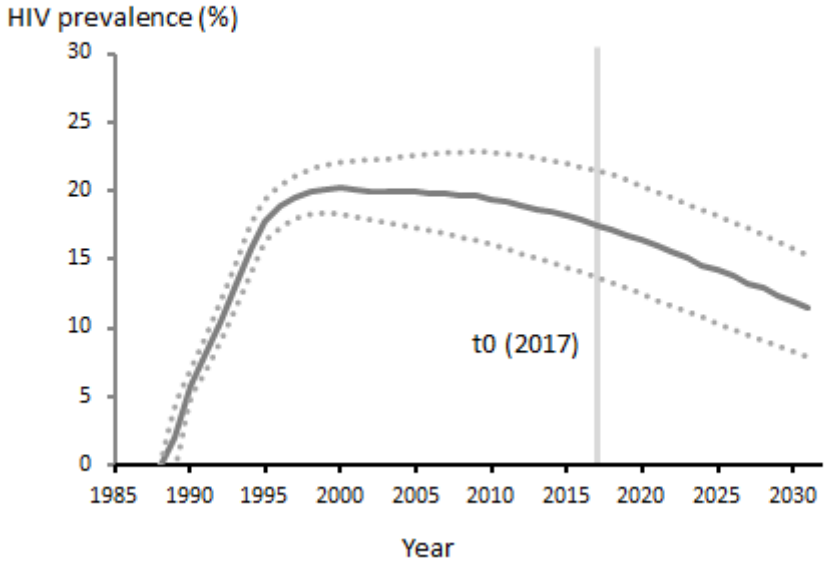
It should be noted that these are mean across all programmatic scenarios in each stratum of t0 level of NNRTI resistance at start of ART. Calculation of the net monetary benefit based on these means is a different approach to that used in Figure 2 of the main manuscript, where the policy with the highest net monetary benefit was calculated for each programmatic scenario and then the one that was most frequently the highest was declared to be the most cost-effective.

Supplementary Table 2. Median (90% range) % with adherence > 80% according to level of NNRTI-resistance at start of ART in 2017 (t0).

Level of NNRTI-resistance at start of ART in 2017

<5%	5%-	10%-	15%-	20%-	25%-
87% (78%-91%)	84% (72% - 90%)	77% (55% - 86%)	60% (42% - 81%)	54% (39% - 67%)	54% (38% - 65%)

Supplementary Figure 1. Median (90% range) prevalence over all 5000 programmatic scenarios, considering no change in policy after t0 (2017).



3. Parameter values and distributions

Details of variables are explained in Model details in Supplement to Ref 3.

Sexual behaviour

Sexual behaviour model structure: base structure (*rbm*=4)

Change in propensity to have a long term condomless sex partner after HIV diagnosis (ch_risk_diag): 9/13

Change in propensity to have short term ("new") condomless sex partners after HIV diagnosis (ch_risk_diag_newp): 5/6

Date at which population level change in condomless sex behaviour occurs (date_ch_risk_beh): 1995

Change in propensity to have condomless sex ("risk behaviour") with short term partners after threshold for population level change in condomless sex behaviour reached (ch_risk_beh_newp): Beta(50,70)

Change in propensity to have a long term condomless sex ("risk behaviour") with short term partners after threshold for population level change in condomless sex behaviour reached (ch_risk_beh_ep): Beta(60,60)

Rate of starting new long term condomless sex partnership in 15-25 year age group (eprate): 0.1

Poisson mean for moderately high short term partner group (see model details) (highsa): 4.5

Poisson mean for highest short term partner group (see model details) (swn):7

Factor to change overall average level of condomless sex with short term partners (newp_factor): 5.5

Proportion of the population who have a lifetime reduced number of condomless sex partners (see model details) (p_rred_p): 0.20

Probability per 3 months of pregnency at age 35-45 (prob_pregnancy_base): 0.037
Fold difference in pregnancy rate at age: 1525: 1.04; 25-35: 1.03; 45-55: 0.975

Transmission

Fold difference in transmission rate for a given viral load (see Model details for base assumption on transmission rate by viral load[2]): 1.0

Rate of transmission in primary HIV infection (lasting 3 months) (tr_rate_primary): 0.25

Transmission rate when plasma viral load is < 500 cps/mL (tr_rate_undetec_vl): 0.001

Fold higher rate of transmission from women to men, compared with men to wormen (fold_change_w): 1.5

Fold higher rate of transmission in young women compared with older women (fold_change_yw): 2.0

Fold higher rate of transmission if current STI present (fold_change_sti): 3.0

Fold lower transmission rate for short term partners compared with long term (reflecting average lower number of sex acts) (fold_tr_newp): 5/14

Super-infection: for people with HIV super-infected with a resistant virus, we assume a low (20%) probability that these mutations are established as resistance mutations.

Adjustment to factor determining extent to which some transmitted resistance is effectively immediately lost (even from minority virus) (res_trans_factor): lognormal(ln 0.8 ,0.20)

Probability per 3 months of loss of persistence of transmitetd mutations from majority virus to minority virus (same for each mutation) (rate_loss_persistence): lognormal(ln 0.02,0.30)

Probability per 3 months of loss of NNRTI mutations, acquired due to PMTCT, from majority virus to become only in minority virus (rate_loss_nnres_pmtct_maj): 0.25

Probability per 3 months of loss of virus with NNRTI mutations acquired due to PMTCT, from minority virus to effectively be extinct altogether (rate_loss_nnres_pmtct_min): 0.25

Prevalence of male circumcision: 0.1

Date of introduction of VMMC: 2008

Rate of increase in probability of VM male circumcision per 3 months: (circ_inc_rate): lognormal(ln 0.003, 0.5)

HIV testing

Date start of testing (date_start_testing): 1996

Initial test probability for those with WHO condition (this increases by 0.008 per 3 mths after testing is introduced, up to 2015) (test_rate_who4): 0.2

Initial test probability for those with TB (this increases by 0.005 per 3 mths after testing is introduced, up to 2015) (test_rate_tb): 0.1

Initial test probability for those with current WHO 3 condition (this increases by 0.0012 per 3 mths after testing is introduced, up to 2015) (test_rate_who3): 0.03

Reduction in rate of testing if never had condomless sex (red_test_neversex): 0.33

Annual linear increase in testing (an_lin_incr_test): 0.000625 x 0.0025
Date start testing ANC (date_start_testanc): 1994

Rate test ANC (rate_testanc_inc): =0.0025

Fold difference in ANC testing rate by age:
fold_probanc_1519=0.73, fold_probanc_2024=1x1.36,,fold_probanc_2529=0.9x1.14, fold_probanc_3039=0.8x1.00, fold_probanc_4049=0.70, fold_probanc_ov50=0.56

Natural progression

Probability of being lost (unlinked to care) at diagnosis (prob_loss_at_diag): 0.6

Initial CD4 count at infection (square root scale) (mean_sqrtcd4_inf): 27.5

Factor adjusting basic rate of natural cd4 decline (see model details) (fx): 1.0

Factor adjusting basic rate of natural viral load change (see model details) (gx): 1.0

Fold increase in risk of WHO 3 condition, compared with risk of WHO 4 condition, for given level of CD4 count, viral load and age (fold_incr_who3): 5

Fold decrease in risk of HIV-related death, compared with risk of WHO 4 condition, for given level of CD4 count, viral load and age (fold_decr_hivdeath): 0.25

Fold difference in risk of WHO 4 condition, for given level of CD4 count, viral load and age, compared with base assumption (see model details) (fold_change_in_risk_base_rate): 1.0

Increase in death rate in 3 months period in which a WHO 4 condition is present (incr_death_rate_adc): 5

Increase in death rate in 3 months period in which TB is present incr_death_rate_tb): 2

Fold difference in non HIV related mortality, compared with base assumption (fold_change_ac_death_rate): 1

HIV monitoring, loss, return, interruption of art and restarting

Risk of loss to follow-up per 3 mths among those not on ART (rate_lost): 0.05

Probability of simultaneously being lost to follow-up amongst those stopping ART (prob_lost_art): 3/11

Probability (per 3 mths) of return to care for person lost (if no WHO 4 condition present – value is 1 if present) (rate_return): 0.05

Basic probability of restart of ART in those remaining under care who have stopped/interrupted ART (this is also influenced by presence of WHO 3 or 4 conditions) (rate_restart): 0.2

Probability of ART initiation per 3 months after eligibility fulfilled, if visting clinic: 0.5

ART

ART introduction date: 2003

Probability of switching to second line treatment, given first line failure (by whatever definition is being used) (pr_switch_line): 0.03 (changes to 0.2 after t0, 2017)

Pattern of adherence*: 1 20%, 2 20%, 3 20%, 4 20%, 5 20%.

Reduction in adherence resulting from presence of TB or a WHO 4 condition (red_adh_tb_adc): 0.1

Average reduction in adherence resuting from current toxicity (the actual reduction varies by inidvidual person) (red_adh_tox_pop): 0.05

Additional "effective" adherence for people on NNRTI regimens due to longer half life (add_eff_adh_nnrti): 0.1

Average change in adherence on second line (degree of change varies by indvidual – note this can be a positive or negative change) (altered_adh_sec_line_pop) = 0.05

Proportion of people for whom a measured viral load > 1000 leads to an improvement in adherence (for the first time such a measurement is made only) (adh_effect_of_meas_alert): 0.7

Extent to which the CD4 change is more favourable on a virologically failing BPI-regimen compared with an NNRTI-regimen (poorer_cd4_rise_on_failing_nnrti): -6

Standard deviation for intra-subject variation in CD4 count (sd_cd4): 1.2

Standard deviation for the measurement error in CD4 count (sd_measured_cd4): 1.7

Base probability of interrupting ART per 3 mths (actual probability also depends on time on continuous ART, presence of current toxicity and average adherence – see model details) (rate_int_choice): lognormal(ln0.03, 0.30)

Probability of drug stock out, and hence ART initerrupted (prob_supply_interrupted): lognormal(ln0.02, 0.30)

Probability that drug supply resumed during stock-out (prob_supply_resumed): 0.8

Probability of NNRTI-resistance emerging in women taking SD nevirapine for PMTCT: 0.35

Probability of NNRTI-resistance emerging in women taking nevirapine plus at least one other antiretroviral for PMTCT: 0.045

Fold difference in risk of mutations arising, for given number of active drugs, viral load and current adherence level, compared with base risk (see model details) (fold_change_mut_risk): 1

Similarly, specifically for thymidine analogue mutations: (fold_change_tams_risk): 1

Similarly, specifically for Q151M cross nucleoside resistance mutation: (fold_change_151_risk): 1

Standard deviation representing inter-patient variation in rate of CD4 rise - when CD4 is rising (sd_patient_cd4_rise_art): 0.2

Risk of NNRTI-resistance emergence due to stopping an NNRTI regimen (due to the tail in presence of drug meaning effective monotherapy): 0.03

Fraction of people who stop ART (and are still visiting the clinic) for whom the clinic is not aware of the interruption and is hence treating the patient as if they were on ART (and hence may switch to the next line having wrongly classified them as virologically failing): (clinic_not_aw_int_frac): 0.6

***** There are various adherence pattern distributions (numbered 1-5) considered. adhav is an individual's average level of adherence and adhvar describes their period to period variability

Adherence pattern 1 (3% probability *adhav* = 0.50 *adhvar* = 0.2, 3% probability *adhav* = 0.80 *adhvar* = 0.2, 14% probability *adhav* = 0.90 *adhvar* = 0.06 , 80% probability *adhav* = 0.95 *adhvar* = 0.05).
Adherence pattern 2 (5% probability *adhav* = 0.50 *adhvar* = 0.2, 10% probability *adhav* = 0.80 *adhvar* = 0.2, 27% probability *adhav* = 0.90 *adhvar* = 0.06, 38% probability *adhav* = 0.90 *adhvar* = 0.05, 20% probability *adhav* = 0.95 *adhvar* = 0.05)
Adherence pattern 3 (15% probability *adhav* = 0.50 *adhvar* = 0.2, 15% probability *adhav* = 0.70 *adhvar* = 0.2, 50% probability *adhav* = 0.90 *adhvar* = 0.06, 20% probability *adhav* = 0.95 *adhvar* = 0.05)
Adherence pattern 4 (30% probability *adhav* = 0.50 *adhvar* = 0.2, 30% probability *adhav* = 0.70 *adhvar* = 0.2, 10% probability *adhav* = 0.90 *adhvar* = 0.06, 30% probability *adhav* = 0.95 *adhvar* = 0.05)
Adherence pattern 5 (30% probability *adhav* = 0.50 *adhvar* = 0.2, 30% probability *adhav* = 0.60 *adhvar* = 0.2, 10% probability *adhav* = 0.70 *adhvar* = 0.06, 30% probability *adhav* = 0.90 *adhvar* = 0.05)

Costs

All costs are in $1000 per 3 month period in 2013.

Drug costs* below increased by 20%** for supply chain etc (as in b) – costs are annual unless stated

zidovudine: 0.070
tenofovir: 0.048
ddI: 0.100
lamivudine: 0.021
stavudine: 0.024
nevirapine: 0.028
efavirenz: 0.039
lopinavir/r: 0.268
atazanavir/r: 0.219

Mean cost of treatment of a WHO 4 condition over 3 months (cost is incurred for 3 months): 0.200[+]
Mean cost of treatment of a WHO 3 condition over 3 months (cost is incurred for 3 months): 0.020[+]
Mean cost of treatment of TB per 3 months (cost is incurred for 6 months): 0.050[+]

Cotrimoxazole annual cost: 0.005 [+]
CD4 count measurement: 0.010 *** [+]
Viral load measurement: 0.045 *** [+]
Clinic visit cost: 0.020 [+]
Resistance test cost: 0.250 [+++]
HIV test (including personnel costs): 0.010 **

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* Untangling the web of antiretroviral price reductions. 16th Edition – July 2013. www.msfaccess.org. (17)
** Eaton J et al. How should HIV programmes respond to evidence for the benefits of earlier treatment initiation ? A combined analysis of 12 mathematical models. Lancet Global Health 2013. (18)
***Keebler D, Revill P, et al. How Should HIV Programmes Monitor Adults on ART? A Combined Analysis of Three Mathematical Models. Lancet Global Health 2013. (19)
+ 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 (18.)
[+++] estimate of potential lowest feasible cost with centralised testing.

Utilities*

Values are 1 except for the following:
Any drug toxicity in current 3 month period: 0.95
Any WHO 3 condition (except TB) in current 3 month period: 0.78
Current TB in current 3 month period: 0.60
Any WHO 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. (20)

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