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

Supplementary Results 2.

Effects of changes to model considered in sensitivity analyses

The effect of changes to the model were explored in multivariable sensitivity analysis (Tables A and B). The assumptions for which the effect was explored are listed in the first column of both tables. The possible values/options for those assumptions is given in the second column. The probability that each of those options is chosen in any one run of the model is shown in the third column. The uncertainty and sensitivity analyses were done in the following way. First, one of the possible values/options was sampled at random for each assumption. The model was then run using this set of assumptions for all three monitoring scenarios and the outcome – the percent with transmitted resistance in 2020 - was recorded for each of the three monitoring scenarios. This process was repeated 10,000 times. Thus, we obtain 10,000 outcomes for each scenario. The range of differences between monitoring scenarios over these 10,000 runs is summarized in Figure 3 of main paper. This is the uncertainty analysis, which is described in the main paper. The Figure shows that introduction of viral load monitoring in 2010 results in a median 0.3% lower prevalence of transmitted resistance in 2020 (95% plausibility range -2.9% to 4.7%) compared with introduction in 2015, and median 4.2% lower prevalence (95% plausibility range 0.6% to 14.5%) compared with no introduction of viral load monitoring before 2020. This does not overlap 0 and hence indicates that over all 10,000 scenarios over 97.5% result in a situation where there is a higher proportion with transmitted drug resistance if viral load monitoring is not introduced before 2020. .

Table A the considers the scenario in which clinical (WHO 4) monitoring is used and shows the difference in percent with transmitted resistance in 2020 according to variations in each assumption, based on a multiple linear regression model The outcome is the percent with transmitted drug resistance in 2020 based on the clinical monitoring strategy. As indicated in the main paper, the percent with resistance in 2020 is 12.4% if clinical monitoring were used throughout. Consider then, the first row of Table A. This explores the effect of varying the risk behaviour model between the one used in the main analysis (which is shown in bold in the Table to indicate that this is the value/option used in the base model used in the main analysis) and the alternative in which there is symmetry between men and women in risk behaviour and no sex workers. For each run of the model, as indicated in the third column, there is an 80% chance that the base risk behaviour model is used, and a 20% chance that the alternative model is used. The fourth and fifth column shows the results; the

mean difference in percent with transmitted drug resistance in 2020 (using the clinical monitoring strategy). For each possible variation, the option used in the base model is the comparator group. The value of -2.3% indicates that on average there is a 2.3% lower percent with transmitted drug resistance in 2020 if the alternative risk behaviour model is used. So, instead of being 12.4% it would be 10.1%. The fifth column shows the p-value, which is highly significant, which indicates that this difference of 2.3% has not arisen due to chance. The reason why such a modest difference in outcome of 2.3% is associated with such a low p-value is that 10,000 runs were performed so the sample size is very high and even small differences which are likely not of great public health or clinical significance are nevertheless highly statistically significant. Considering the results throughout Table A, it is clear that few of the variations in model assumptions make much difference to the percent with transmitted drug resistance. The largest effects are that there is a lower percent with resistance (by 5.7%) if it is assumed that the diagnosis rate remains low after 2010 (and hence there is a lower proportion of people on ART), and a higher percent with resistance if we assume that transmitted mutations revert at a lower rate than assumed in our base model. Both these make intuitive sense.

Table B is very similar to Table A, but instead of just focussing on the clinical monitoring strategy it shows the additional difference in percent with transmitted resistance in 2020 between viral load and clinical (WHO 4) monitoring strategies according to the same variations in assumptions. This is again from a multiple linear regression model (i.e. the outcome is the difference between the two monitoring strategies in the percent with transmitted drug resistance in 2020). Here the effect of changing the assumptions is even smaller, because we are no longer looking at the effect of changing an assumption on the percent with drug resistance, we are looking at how different the outcome is between two monitoring scenarios each based on the *same* given set of assumptions.

Table A.

Assumption	Variations explored (base assumption in bold)	Probability of value being selected	Difference in percent with transmitted resistance resistance in 2020 (using clinical monitoring strategy).	p-value
Risk behaviour model	**As documented**	0.80	0	< 0.0001
	Alternative model in which no person has more than 10 new partners in a 3 month period	0.20	-2.3	
Adherence	**As documented (section 5) (probabilities of 4 adherence levels 5%, 10%, 25%, 60%)**	0.80	0	
	Probabilities of 4 adherence levels 15%, 15%, 50%, 20%	0.20	+0.1	0.24
Clinical monitoring strategy	**New WHO 4 event triggers switch**	0.66	0	
	New WHO 3 or 4 event triggers switch	0.33	-1.3	< 0.0001
Underlying rate of diagnosis after 2010 (this rate is increased in presence of clinical diagnoses – see below)	0.005	0.20	-5.7	< 0.0001
	0.025	0.80	0	
Policy for selection for ART initiation after 2010	**CD4 < 350 or WHO 4**	0.50	0	
	CD4 < 200 or WHO 4	0.50	-2.1	< 0.0001
Fold change in sexual risk behaviour consequent on diagnosis with HIV	0.50	0.33	-0.3	< 0.0001
	0.75	0.33	0	
	1.00 (no change)	0.33	+0.2	
Fold increase in HIV diagnosis rate when WHO 4 event is present	5	0.33	-0.5	< 0.0001
	10	0.33	0	
	20	0.33	0.6	
Fold increase in HIV diagnosis rate when	1	0.33	-0.8	< 0.0001

WHO 3 event is present	**3**	0.33	0	
	5	0.33	+0.6	
Fold increase in HIV diagnosis rate when TB disease is present	2	0.33	0.0	0.38
	5	0.33	0	
	8	0.33	0.1	
Probability (per 3 month period) of interrupting ART for reasons apart from drug stock-out)	0.01	0.33	-0.1	< 0.0001
	0.02	0.33	0	
	0.05	0.33	+0.4	
Probability per 3 month period of interrupting ART due to drug stock-out	0.00	0.33	-0.1	< 0.0001
	0.01	0.33	0	
	0.03	0.33	+0.4	
Probability per 3 month period of being lost to follow-up, for those not on ART	0.01	0.33	-0.2	< 0.0001
	0.03	0.33	0	
	0.10	0.33	+0.1	
Probability per 3 month period of return to follow-up, for those lost	0.05	0.33	+0.1	< 0.0001
	0.10	0.33	0	
	0.50	0.33	+0.3	
For those interrupting ART for reasons apart from drug stock-out, probability of being lost to follow-up at the same time	0.1	0.33	+0.1	< 0.0001
	0.3	0.33	0	
	0.7	0.33	-0.33	
For those who have interrupted ART for reasons apart from drug stock-out and remain under clinic follow-up, probability of restarting ART (this is basic rate, actual rate is higher depending on clinical status)	0.2	0.33	-0.3	< 0.0001
	0.4	0.33	0	
	0.8	0.33	+0.3	
Reduction in adherence in those with TB disease or current WHO 4 events	0.10	0.33	-0.4	< 0.0001
	0.20	0.33	0	
	0.30	0.33	+0.2	
Reduction in adherence in those with current drug toxicity	0.02	0.33	-0.5	< 0.0001
	0.10	0.33	0	
	0.20	0.33	+1.9	
Average reduction in adherence with time	**0**	0.80	0	0.65

on ART	0.01 per year	0.20	0.0	
Within-person variability in adherence	**as documented** SD + 0.7	0.80 0.20	0 +2.3	< 0.0001
Improvement in adherence with start of second line	0.00 **0.05** 0.20	0.40 0.40 0.20	-0.2 0 +0.0	0.008
Probability (per 3 months) of switch in regimen from 1st to 2nd line after failure criteria met	**0.8** 0.5	0.20 0.80	-0.1 0	0.28
Probability (per 3 months) that ART-naïve women acquire NNRTI resistance as a result of single dose nevirapine for MTCT	**0.005** 0.03	0.80 0.20	0 +2.0	< 0.0001
Fold increase in risk of WHO 3 / TB compared with WHO 4	**1.5** 5	0.5 0.5	0 +0.5	< 0.0001
Rate of transmission per 3 months where unprotected sex partner is in primary infection	0.10 **0.20** 0.40	0.15 0.70 0.15	+1.5 0 -3.3	< 0.0001
Rate of transmission per 3 months where unprotected sex partner has VL < 500	**0.0001** 0.001 0.01	0.33 0.33 0.33	0 -0.1 -0.4	< 0.0001
Factor determining extent to which some transmitted resistance immediately reverts and is effectively lost (1.0 means 0.8 prob reversion for m184v and 0.2 for NNRTI mutations, > 1 means more reversion)	0.5 **1.0** 2.0	0.33 0.33 0.33	+4.0 0 -5.2	< 0.0001
Fold change in natural rate of CD4 count decline for a given current viral load compared with that documented	0.6 **1.0** 1.4	0.10 0.80 0.10	-0.9 0 +0.8	< 0.0001
Fold change in natural rate of viral load rise compared with that documented	0.8 **1.0** 1.25	0.10 0.80 0.10	-0.1 0 +0.6	< 0.0001
Initial mean square root CD4 count at infection	30	0.10	+0.6	< 0.0001

	32	0.80	0	
	34	0.10	-0.4	
Inclusion of super-infection so that infected person can acquire drug resistance by being re-infected by a person carrying drug resistance	**Yes**	0.80	0	< 0.0001
	No	0.20	-2.8	
Reduction in sexual risk behaviour associated with current CD4 count < 100 /mm^3 (risk behaviour is assumed lowered when WHO 4 event present)	**No**	0.66	0	0.70
	Yes	0.33	0	
Increase in risk of mutation development compared with base assumption as documented	0.7	0.33	-1.2	< 0.0001
	1	0.33	0	
	2.0	0.33	+1.9	
Increase in risk of TAM development compared with base assumption as documented	0.7	0.33	-0.3	< 0.0001
	1	0.33	0	
	2.0	0.33	+0.5	
Increase in risk of Q151M multi-nucleoside -associated resistance mutation compared with base documented as documented	**1**	0.33	0.0	< 0.0001
	0.7	0.33	0	
	3.0	0.33	+0.6	
Increase in effective adherence for NNRTIs due to long half life	**0.05**	0.33	+1.3	< 0.0001
	0.00	0.33	0	
	0.10	0.33	-1.0	
Relative potency of lopinavir/r compared with other drugs	**2-fold**	0.66	-0.4	< 0.0001
	1-fold (i.e. equal)	0.33	0	
Adjustment to the CD4 count change when not on PI	**-10 cells/mm^3 per 3 months**	0.33	-1.3	< 0.0001
	-0 cells/mm^3 per 3 months	0.33	0	
	-20 cells/mm^3 per 3 months	0.33	+1.7	
Variability in true underlying CD4 count	SD = **1.2**	0.33	+0.2	< 0.0001
	0.8	0.33	0	
	2.0	0.33	-0.4	
Variability due to measurement error in CD4 count	SD = **2.0**	0.75	0	< 0.0001
	3.0	0.25	+0.4	

Fold change in risk of HIV-related death compared with WHO 4	**0.25** 0.5	0.75 0.25	0 -0.7	< 0.0001
Fold change in rate of WHO 4 disease for given CD4 count, compared with that documented	0.7 **1.0** 1.5	0.33 0.33 0.33	0.0 0 0.0	0.88
Fold increased risk of death when WHO 4 event present	3 **5** 10	0.33 0.33 0.33	0.2 0 -0.4	< 0.0001
Fold increase in risk of death resulting from current TB disease	2 **1.5** 5	0.33 0.33 0.33	0.0 0 0.0	0.38
Patient-fixed fold-change in CD4 count increase when CD4 is increasing	< 0.84 **0.84-1.18** ≥ 1.18	0.33 0.33 0.33	-0.5 0 +0.9	< 0.0001
Additional fold change in CD4 count loss when number of active drugs is low	**No** Yes	0.66 0.33	0 0.0	0.42
Risk of NNRTI resistance associated with stopping NNRTI regimen	**0.05** 0.00 0.30	0.40 0.40 0.20	-0.5 0 +1.8	< 0.0001

Table B.

Assumption	Variations explored (base assumption in bold)	Probability of value being selected	Additional difference in percent with transmitted resistance in 2020 between viral load and clinical monitoring strategies	p-value
Risk behaviour model	**As documented**	0.80	0	< 0.0001
	Alternative model in which no person has more than 10 new partners in a 3 month period	0.20	-1.1	
Adherence	**As documented (section 5)** (probabilities of 4 adherence levels 5%, 10%, 25%, 60%)	0.80	0	
	Probabilities of 4 adherence levels 15%, 15%, 50%, 20%	0.20	0.1	0.22
Clinical monitoring strategy	**New WHO 4 event triggers switch**	0.66	0	
	New WHO 3 or 4 event triggers switch	0.33	-1.2	< 0.0001
Underlying rate of diagnosis after 2010 (this rate is increased in presence of clinical diagnoses – see below)	0.005	0.20	-3.0	< 0.0001
	0.025	0.80	0	
Policy for selection for ART initiation after 2010	**CD4 < 350 or WHO 4**	0.50	0	
	CD4 < 200 or WHO 4	0.50	-1.3	< 0.0001
Fold change in sexual risk behaviour consequent on diagnosis with HIV	0.50	0.33	-0.2	< 0.0001
	0.75	0.33	0	
	1.00 (no change)	0.33	0.1	

Fold increase in HIV diagnosis rate when WHO 4 event is present	5 **10** 20	0.33 0.33 0.33	-0.3 0 0.4	< 0.0001
Fold increase in HIV diagnosis rate when WHO 3 event is present	1 **3** 5	0.33 0.33 0.33	-0.4 0 +0.3	< 0.0001
Fold increase in HIV diagnosis rate when TB disease is present	2 **5** 8	0.33 0.33 0.33	0.0 0 0.1	0.38
Probability (per 3 month period) of interrupting ART for reasons apart from drug stock-out)	0.01 **0.02** 0.05	0.33 0.33 0.33	+0.2 0 -0.1	< 0.0001
Probability per 3 month period of interrupting ART due to drug stock-out	0.00 **0.01** 0.03	0.33 0.33 0.33	0.0 0 +0.1	0.06
Probability per 3 month period of being lost to follow-up, for those not on ART	0.01 **0.03** 0.10	0.33 0.33 0.33	-0.2 0 0.0	< 0.0001
Probability per 3 month period of return to follow-up, for those lost	0.05 **0.10** 0.50	0.33 0.33 0.33	+0.1 0 +0.2	0.0007
For those interrupting ART for reasons apart from drug stock-out, probability of being lost to follow-up at the same time	0.1 **0.3** 0.7	0.33 0.33 0.33	+0.1 0 +0.3	< 0.0001
For those who have interrupted ART for reasons apart from drug stock-out and remain under clinic follow-up, probability of restarting ART (this is basic rate, actual rate is higher depending on clinical status)	0.2 **0.4** 0.8	0.33 0.33 0.33	-0.2 0 +0.2	< 0.0001
Reduction in adherence in those with TB disease or current WHO 4 events	0.10 **0.20** 0.30	0.33 0.33 0.33	-0.2 0 +0.0	< 0.0001

Reduction in adherence in those with current drug toxicity	0.02 **0.10** 0.20	0.33 0.33 0.33	-0.2 0 +0.7	< 0.0001
Average reduction in adherence with time on ART	**0** 0.01 per year	0.80 0.20	0 0.0	0.88
Within-person variability in adherence	**as documented** SD + 0.7	0.80 0.20	0 2.2	< 0.0001
Improvement in adherence with start of second line	0.00 **0.05** 0.20	0.40 0.40 0.20	-0.1 0 +0.2	< 0.0001
Probability (per 3 months) of switch in regimen from 1st to 2nd line after failure criteria met	**0.8** 0.5	0.20 0.80	+0.2 0	0.0003
Probability (per 3 months) that ART-naïve women acquire NNRTI resistance as a result of single dose nevirapine for MTCT	**0.005** 0.03	0.80 0.20	0 +0.9	< 0.0001
Fold increase in risk of WHO 3 / TB compared with WHO 4	**1.5** 5	0.5 0.5	0 +0.1	0.05
Rate of transmission per 3 months where unprotected sex partner is in primary infection	0.10 **0.20** 0.40	0.15 0.70 0.15	+0.5 0 -1.3	< 0.0001
Rate of transmission per 3 months where unprotected sex partner has VL < 500	**0.0001** 0.001 0.01	0.33 0.33 0.33	0 -0.2 -1.0	< 0.0001
Factor determining extent to which some transmitted resistance immediately reverts and is effectively lost (1.0 means 0.8 prob reversion for m184v and 0.2 for NNRTI mutations, > 1 means more reversion)	0.5 **1.0** 2.0	0.33 0.33 0.33	+1.1 0 -2.2	< 0.0001
Fold change in natural rate of CD4 count decline for a given current viral load compared with that documented	0.6 **1.0** 1.4	0.10 0.80 0.10	-0.3 0 +0.4	< 0.0001

Fold change in natural rate of viral load rise compared with that documented	0.8 **1.0** 1.25	0.10 0.80 0.10		-0.1 0 +0.4		< 0.0001
Initial mean square root CD4 count at infection	30 **32** 34	0.10 0.80 0.10		+0.3 0 -0.1		< 0.0001
Inclusion of super-infection so that infected person can acquire drug resistance by being re-infected by a person carrying drug resistance	**Yes** No	0.80 0.20		0 -1.3		< 0.0001
Reduction in sexual risk behaviour associated with current CD4 count < 100 /mm^3 (risk behaviour is assumed lowered when WHO 4 event present)	**No** Yes	0.66 0.33		0 0		0.49
Increase in risk of mutation development compared with base assumption as documented	0.7 **1** 2.0	0.33 0.33 0.33		-0.6 0 +0.6		< 0.0001
Increase in risk of TAM development compared with base assumption as documented	0.7 **1** 2.0	0.33 0.33 0.33		-0.1 0 +0.0		0.22
Increase in risk of Q151M multi-nucleoside -associated resistance mutation compared with base documented as documented	1 **0.7** 3.0	0.33 0.33 0.33		0.0 0 +0.2		0.001
Increase in effective adherence for NNRTIs due to long half life	**0.05** 0.00 0.10	0.33 0.33 0.33		+0.8 0 -0.6		< 0.0001
Relative potency of lopinavir/r compared with other drugs	**2-fold** 1-fold (i.e. equal)	0.66	0.33	+0.4	0	< 0.0001
Adjustment to the CD4 count change when not on PI	**-10 cells/mm^3 per 3 months** -0 cells/mm^3 per 3 months -20 cells/mm^3 per 3 months	0.33 0.33 0.33		-1.0 0 +1.4		< 0.0001

Variability in true underlying CD4 count	**SD = 1.2**	0.33	+0.1	< 0.0001
	0.8	0.33	0	
	2.0	0.33	-0.3	
Variability due to measurement error in CD4 count	**SD = 2.0**	0.75	0	< 0.0001
	3.0	0.25	+0.3	
Fold change in risk of HIV-related death compared with WHO 4	**0.25**	0.75	0	< 0.0001
	0.5	0.25	-0.4	
Fold change in rate of WHO 4 disease for given CD4 count, compared with that documented	0.7	0.33	-0.1	0.04
	1.0	0.33	0	
	1.5	0.33	-0.1	
Fold increased risk of death when WHO 4 event present	3	0.33	0.0	< 0.0001
	5	0.33	0	
	10	0.33	-0.2	
Fold increase in risk of death resulting from current TB disease	2	0.33	0.0	0.94
	1.5	0.33	0	
	5	0.33	0.0	
Patient-fixed fold-change in CD4 count increase when CD4 is increasing	< 0.84	0.33	-0.4	< 0.0001
	0.84-1.18	0.33	0	
	$\geq$ 1.18	0.33	+0.7	
Additional fold change in CD4 count loss when number of active drugs is low	**No**	0.66	0	0.49
	Yes	0.33	0.0	
Risk of NNRTI resistance associated with stopping NNRTI regimen	**0.05**	0.40	-0.2	< 0.0001
	0.00	0.40	0	
	0.30	0.20	+0.5	
