AIDS, Publish Ahead of Print

DOI: 10.1097/QAD.0000000000002234

Simplifying switch to second line ART: Predicted effect of defining failure of first-line efavirenz-based regimens in sub-Saharan Africa by a single viral load > 1000 copies/ml

Amir Shroufi[1]
Gilles Van Cutsem[1]
Valentina Cambiano[2]
Loveleen Bansi-Matharu[2]
Kristal Duncan[1]
Richard A. Murphy [3]
David Maman[1]
Andrew Phillips[2]

1. Médecins Sans Frontières, South Africa)

2. Institute for Global Health, UCL, London, UK
3. Division of Infectious Diseases, Los Angeles Biomedical Research Institute, Harbor-UCLA Medical Center, Torrance, California, USA

Corresponding author, Amir Shroufi, amir.shroufi@doctors.org.uk

Authors' contributions: Amir Shroufi, Gilles Van Cutsem and Andrew Phillips developed the research question. Andrew Phillips led the analysis. All authors contributed to the development of the manuscript and its writing.

Funding: no specific funding was obtained for the writing of this manuscript

Conflict of interest statements: The authors have declared that no competing interests exist

Ethics committee approval: Given that this work involves modelling only, this was not required

Abstract

Background: Many individuals failing first-line antiretroviral therapy (ART) in sub-Saharan Africa never initiate second-line antiretroviral treatment (ART) or do so after significant delay. For people on ART with a viral load (VL) > 1000 copies/ml, the World Health Organization (WHO) recommends a second VL measurement 3 months after the first VL and enhanced adherence support. Switch to a second-line regimen is contingent upon a persistently elevated VL > 1000 copies/ml. Delayed second-line switch places patients at increased risk for opportunistic infections and mortality.

Methods: To assess the potential benefits of a simplified second-line ART switch strategy, we use an individual-based model of HIV transmission, progression and the effect of ART which incorporates consideration of adherence and drug resistance to compare predicted outcomes of 2 policies, defining 1st-line regimen failure for patients on efavirenz based ART as either (i) two consecutive VL values > 1000 copies/ml, with the second after an enhanced adherence intervention (implemented as per current WHO guidelines) or (ii) a single VL value > 1000 copies/ml. We simulated a range of setting-scenarios reflecting the breadth of the sub-Saharan African HIV epidemic, taking into account potential delays in defining failure and switch to second line ART.

Findings: The use of a single VL > 1000 copies/ml to define ART failure would lead to a higher proportion of persons with NNRTI resistance switched to second-line ART (65% vs 48%; difference 17% [90% range 14% - 20%]), resulting in a median 18% reduction in the rate of AIDS-related death over setting scenarios (90% range 6% - 30%; from a median of 3·1 to 2·5 per 100 person years) over 3 years. The simplified strategy also is predicted to reduce the rate of AIDS conditions by a median of 31% (90% Range 8% - 49%) among people on 1st line ART with a viral load > 1000 copies/ml in the past 6 months. For a country of 10 million adults (and a median of 880,000 people with HIV), we estimate that this approach would lead to a median of 1,322 (90% range 67 to 3,513) AIDS deaths averted per year over three years. For South Africa this would represent around 10,215 deaths averted annually.

Interpretation: As a step towards reducing unnecessary mortality associated with delayed second line ART switch, defining failure of first-line efavirenz-based regimens as a single VL>1000 copies/ml should be considered.

Funding: No specific funding was obtained for the analysis or writing of this manuscript.

Keywords: AIDS, HIV, modelling, second line, ART, antiretroviral, strategy, virological failure, treatment failure, efavirenz, viral load strategy

Introduction

In 2017, almost 22 million of 36·9 million people living with HIV globally have successfully initiated antiretroviral therapy (ART)[1]. For the individual and public health benefits of ART to be realised, antiretroviral programmes, previously focussed on ART initiation, must retain patients in care and achieve high rates of virological suppression. This requires optimizing management of those failing ART.

Viral load (VL)monitoring has been recommended by the WHO for the identification of treatment failure, to prompt enhanced adherence support and to allow for early identification of patients requiring a switch to second line ART.[2] For patients with a VL > 1000 copies/ml, the WHO recommends a confirmatory VL measurement 3 months after the first VL and enhanced adherence support, with switch to second line ART contingent upon a persistently elevated VL. The main justification for this strategy is the preservation of costlier second-line ART for patients who may, after enhanced adherence support, re-suppress virus without switch.

There are important limitations to this approach. Firstly, existing research suggests that between 50 and 90% of patients experiencing virologic failure on first-line ART with a single VL > 1000 copies/ml have non-nucleoside reverse-transcriptase inhibitor (NNRTI) resistance. [3–12] Secondly, despite the increased availability of VL monitoring, many programs fail to switch failing patients promptly– with delays frequently exceeding one year– leading to avoidable morbidity and mortality, as well as elevating the risk for the development of additional drug resistance and transmission of drug-resistant virus.[13–18] Thirdly, the evidence suggesting that enhanced adherence counselling (EAC) leads to re-suppression is limited [19,20]. Re-suppression after a single VL>1000 c/ml has been reported to occur in 20% to 50% of individuals, but with suppression being particularly unlikely if drug resistance is present.[21,22] For those that do re-suppress virus, the duration of re-suppression

is often limited, particularly if preceded by months of high-level viremia, as is commonly the case.[19,23–26] Finally, although the CD4 cell count at ART initiation has slowly increased in African contexts, patients who fail first-line ART continue to have advanced immunodeficiency at failure making rapid viral re-suppression urgent[27]. For example, the median CD4 cell count among a cohort of patients failing first-line ART in Johannesburg (recruited between 2008 and 2012) remained below 150 cells/µl. [28]

The importance of this issue is likely to increase further in coming years. Data from several Low-Middle Income Countries (LMICs) suggest that the ART-experienced patients account for 10 - 30% of patients initiating or re-initiating first-line NNRTI-containing ART, a proportion that is likely to increase substantially following the rapid expansion in HIV treatment coverage.[29,30] Prior exposure to ART – regardless of VL – in people restarting ART is associated with increased risk of virological failure.[31] Because of the higher risk of suboptimal treatment outcomes in this group, WHO's recent guidelines on HIV Drug Resistance indicated that consideration should be given to initiate non-NNRTI based ART in patients re-starting antiretrovirals.[32] In practice to date, however, this is rarely done.

From a public health perspective, it was hoped that replacing CD4 count with VL for the assessment of treatment failure would increase the proportion of patients failing ART promptly switched to second-line ART. However, these expected gains have generally not yet been achieved and the proportion of patients on second-line ART remains very low at an estimated 1-5% [33–35]. After two years on ART, programmes report failure rates of around 14%, highlighting the magnitude of unmet need for second line [36].

The VL algorithm is one of many factors that may act to hamper appropriate use of second line ART; others include access to medicines, incomplete coverage of VL, inadequate communication of result and failure to appropriately action results received, as well as a lack

of appreciation as to the high prevalence of failure among individuals with elevated viral loads, who may then be more likely to attribute viraemia to adherence problems. However, given the algorithm's importance and modifiability at the policy level, it warrants careful consideration from those seeking to address the large unmet need for second line therapy.

Against this background, it is necessary to explore potentially accelerating switch to second line ART with simplifcation of the switch algorithm. We use an established model of HIV transmission, progression and the effect of ART which incorporates drug resistance to estimate the impact of simplifying the definition of 1st line ART failure from two elevated VLs to a single VL > 1000 copies/ml.

Methods

We used the HIV Synthesis Model, an individual-based simulation model of HIV transmission, progression and the effect of ART, considering specific drugs and resistance mutations, and which has previously been used to address policy questions in relation to HIV and ART programs[37–39]. In brief, the model generates a population of adults who are each tracked over their lives in 3-month time periods for HIV testing, risk of condomless sex and risk of HIV acquisition. Those who acquire HIV are tracked with respect to VL, CD4 count, occurrence of WHO stage 3 and 4 conditions, clinic attendance and drop-out, current use of specific antiretroviral agents, presence of specific resistance mutations, adherence to ART and toxicities associated with ART.

We initially based the demographics and HIV/ART features of the population around those encountered in Malawi, but ran the model 500 times, each time sampling from a set of parameters to reflect the diversity of the epidemic across populations in sub-Saharan Africa, as illustrated in Table 1. Each of the model simulation runs that were executed reflects a different potential programmatic situation which we call a setting scenario.

For each setting scenario, we assume a baseline date of October 2018 (2018·75). We compare predicted outcomes of two strategies, defining 1st line regimen failure for people on efavirenz (EFV)-based ART by either (i) two consecutive values > 1000 copies/ml, at least 3 months apart, with the second after an enhanced adherence intervention (the current WHO recommended strategy) or (ii) a single value > 1000 copies/ml, (with the enhanced adherence intervention initiated at the time of the first VL > 1000 copies/ml under both scenarios). We refer to the latter as the simplified strategy.

We assume that from 2016 VL monitoring, with differentiation of care based on whether a person is virologically suppressed, was introduced (i.e. reduced clinic visits for people with VL < 1000 copies/ml)[37]. We consider that while VL testing is scheduled at 6 and 12 months immediately after ART initiation, and then annually, it is not always the case that a VL measure is successfully carried out (the probability ranges from 0·2 to 0·85 before the baseline date of 1st October 2018). We assume that when a scheduled measure is not done it will be attempted 3 months later, with the same probability of success. Before baseline, the rate of switch to a second line regimen is determined for each setting scenario by randomly choosing a value from 0·05, 0·20, or 0·50 with equal probability. Within the model, we consider rates of interruption of ART with an associated risk of being lost to follow-up and subsequent probability of returning to care, a probability that is highest if a person becomes ill with a WHO stage 4 condition. The assumptions in the model around patterns of adherence and the effect of the enhanced adherence intervention lead to a median of 36% being re-suppressed after the enhanced adherence intervention in the absence of a switch (Table 1).

In order to be able to identify effects of differences in definition of 1st line failure we assumed (in our main analyses) that from the baseline date the rate of switch after detection of failure 1st line failure (whatever the failure definition) is 0·85 per 3 months and the probability of VL

measures being performed is 0·85 for all setting scenarios. We explored lower probabilities in sensitivity analyses.

Results

Table 1 shows the range of characteristics of the setting scenarios in 2018, just before the consideration of the change in strategy for defining 1st line EFV-based ART failure.

Over a three year follow-up period (Table 2), the strategy of using a single VL > 1000 to define failure of EFV-based first-line ART (simplified strategy), instead of two consecutive values (current strategy), is predicted to result in a 18% (90% range 6%-30%) reduction of the AIDS death rate among people with previous or current VL > 1000 while on ART (Figure 1). The simplified strategy also is predicted to reduce the rate of AIDS conditions by a median of 31% (90% Range 8% - 49%) among people on 1st line ART with a VL > 1000 copies/ml in the past 6 months. For a country of 10 million adults with 880,000 people with HIV, this is estimated to lead to a median of 1,322 (90% range 67 to 3,513) AIDS deaths averted per year over three years. For South Africa this would represent 10,215 deaths averted annually (see supplementary table 1 , http://links.lww.com/QAD/B475). For a country of 10 million adults under the current strategy, we estimate 301 (90% range 33-1,338) switches per year among those without resistance being present under the base case scenario, compared to 7,285 (90% range 3,538-14,653) such switches using the single VL strategy (see supplementary table 2, http://links.lww.com/QAD/B475).

The effect of the simplified strategy was slightly less (from 18% to 17%) when we assumed that during the three year follow–up a substantially lower probability of VL measures performed as planned (0·20 per 3 months instead of 0·85), and from 18% to 9% if the probability of switching to a second line regimen after the failure criteria are met was substantially lower (0·20 per 3 months instead of 0·85) (Table 3). Variations in the extent to which people re-suppress VL (increasing to >40%) after the adherence intervention without a

change in regimen has only a small impact on these results, as does the level of HIV incidence (table 3).

[Table 3 here]

Under the simplified strategy, a higher proportion of people on 1st line ART are predicted to be classified as having fulfilled first line failure criteria (current strategy: 8% (90% range: 5% - 11%) vs simplified strategy: 19% (90% range 14% - 26%)) and a higher proportion of people with drug resistance to EFV will have been switched to second line ART (current strategy: 48% (90% range 33% - 59%) vs simplified strategy 65% (90% range 51% - 74%)) (Table 2). Among those defined as failing EFV-based first line ART, 99% (90% range 95% - 100%) vs. 82% (90% range 68%-91%) are predicted to have drug resistance to at least one first line drug for the current vs the simplified VL strategy respectively (Table 2).

Compared to the current approach, the simplified strategy is predicted to result in a higher proportion of individuals on ART being virologically suppressed, 92% vs 94% (Table 2), a 2.9% increase in the "3rd 90" of the 90-90-90 goals.

Discussion

We evaluated the predicted impact of dropping the requirement for a second VL value of greater than 1000 copies/ml prior to switching to a 2nd line regimen by simulating the HIV epidemic in a range of setting-scenarios to reflect the diversity of the sub-Saharan epidemic. We found that such a change in strategy would be predicted to significantly reduce the rates of AIDS deaths and AIDS conditions among people with an elevated VL on first-line ART. For a country of 10 million adults in the context of the range of HIV prevalences in our setting scenarios (a median 880,000 people living with HIV), the number of AIDS deaths

averted per year in the three years from 2018 is a median 1,322 (90% uncertainty range 67 to 3,513).

We studied here the impact of the criteria for defining treatment failure in isolation. We have not assumed that the use of a single VL measure definition is associated with any concomitant benefits in terms of propensity for VL measures to be done as scheduled, or in the probability of a switch being made once the criteria are met. However, in order to understand the potential impact of this change, we have considered in our main analysis a relatively high rate of switch (0·85 per 3 months) in people with virological failure (regardless of the switch strategy). This means assuming that there are no other major constraints to prevent people from switching. In sensitivity analyses, we showed how the effect of changing the first-line EFV failure criteria was lower if we assume lower probabilities for VL measurement being done and / or for switching once the failure criteria are met. This indicates that, to be most beneficial, a change in the failure criteria should be accompanied by an increase in the rate of switching once failure criteria are met. The likelihood of an increase in switching is not implausible given that the single switch strategy reduces the number of steps necessary to switch and the observed delays at every step of the current strategy.

Using this model we have previously found that use of a single value to define first-line failure, without a confirmatory value, is likely to be more effective (avert more DALYs) than use of a confirmatory test, but not to be cost effective in the context of low-income settings in sub-Saharan Africa due to the high cost of PIs [37]. Although the price of LPV/r and ATV/r have dropped from $243·00 and $243·00 in 2014 to $202·80 and $159·00 in 2017 respectively (procurement costs only),[40–42] this may not be sufficient to make the simplified switch strategy cost effective. However, as second-line ART becomes more affordable, the cost-effectiveness analysis may also eventually favour the single VL strategy. Given that the

strategy is more effective than the current strategy, were the costs of second line to approach those of EFV based first line (as in the case of dolutegravir (DTG), for example) the single VL switch strategy may be more favourable than the existing strategy also from an economic perspective. For implementers considering the case for a simplified switch to newer regimens it should be noted that the use of DTG, with an optimised NRTI backbone, is now recommended as a second line option by WHO[43]. For patients failing existing EFV based first line in settings where DTG is being rolled out, these results provide support to programmes considering switching to DTG based ART on the basis of one elevated VL.

In keeping with the available literature [19,21,23–26] we capture in our model that very high levels (76%, see table 1) of people with a single VL value > 1000 copies/ml have drug resistance to EFV and thus likely do require a change in regimen; underlining the limited scope for second-line preservation among failing patients.

In considering the role of the current strategy for switching to second-line ART it should be noted that there are many reasons why a patient may not be switched, including suboptimal uptake of VL testing, slow turnaround of VL test results, and failure to make use of VL test results, once obtained, in patient management decisions. Indeed only a small proportion of individuals with a single elevated VL receive the second VL, suggesting that patients with first-line regimen failure continue to be poorly served by existing algorithms[44].

Another problem with existing practices around first-line regimen failure are delays in the delivery of the enhanced adherence intervention. In our simplified scenario the enhanced adherence intervention is still provided, but this occurs at the time of switch, removing the possibility that switch may be delayed by, or contingent upon completion of this intervention. The current use of the enhanced adherence intervention may be exacerbated by a conservative approach favouring the conservation of first-line ART, with some clinics having concerns as to the cost or availability of second line ART[45], or wider concerns as to the

options available for subsequent third-line[46]. However, those with high viral loads are often more vulnerable patients including children, adolescents, and those with more advanced disease,[19] placing these individuals at increased risk of death. Hence, while the barriers to second line switch are multiple, the requirement for a confirmatory VL introduces an additional delay which in most routine settings is much longer than the intended three months, often with associated patient harm.

In terms of achieving sufficient adherence, while there is evidence to support counselling for adherence at the time of ART initiation[47], by the time a person previously suppressed on ART presents with a high VL it is much less certain whether the intervention will be useful and whether any re-suppression achieved will be durable[26,48]. For individuals who admit to having poor adherence it may still be reasonable to provide the opportunity to re-suppress their VL on 1st line ART. In cases however where an individual states that they have adhered well, immediate switch is likely preferable, at which time an enhanced adherence intervention may still be commenced.

There are potential disadvantages of a simplified approach to 2nd line switch. Switching after a single VL > 1000 copies/ml will lead to an increase in the number of individuals without first-line ART resistance being switched unnecessarily. We estimate that this will be the case for around 18% of those switched (see table 2). For South Africa, we estimate that there would be

2,326 individuals without antiretroviral resistance switched per year under the base case scenario, compared to 56,293 individuals without resistance switched were the simplified strategy employed (see supplementary table 2, http://links.lww.com/QAD/B475). The individual and programmatic disadvantages of unnecessary switch warrant consideration. Moving from once daily fixed-dose combination (FDC) first line ART to protease inhibitor (PI) based second line ART can entail an increased pill burden and additional toxicity.

Ritonavir-boosted lopinavir containing regimens are associated with gastrointestinal toxicity and need to be taken twice daily, while atazanavir-based regimens exist in FDC and have a better toxicity profile. From a programmatic perspective, current second line ART is more costly and used on a smaller scale than first line ART, making it more susceptible to stockouts resulting from either forecasting or supply issues[49,50]. We have not assumed first and second line ART to be affected differently by stockouts. Programmes may in the future replace PI-based regimens with (DTG)-based regimens, including possibly FDC, but at this time this remains uncertain.

A limitation of this study is that we do not model cost effectiveness, largely as a result of current uncertainty over what will be the future first and second line regimens in routine use. Affordability can be a leading consideration for national programmes, and this should be determined at the country level, noting that PI based second line regimens costs range from approximately $160 - $200 per person per year[42,51]. To ensure that this health gain can be realised within resource constrained programmes it is imperative that the cost of existing second line regimens decline further and that programmes identify alternative, less costly, more tolerable, second line options. DTG is the backbone of one such regimen and WHO now recommends DTG-based ART as a second line option[43]. It should also be noted that costs have declined since the time the current strategy was developed, at which time second line ART cost up to 17 times more than first line regimens. PI-based ART is now available at less than three times the cost first-line ART and DTG-based second line would be available from the same price (depending upon which NRTI were used) as current EFV based first line regimen[42,52]. These cost improvements make economic arguments against the wider use of second line ART less relevant. Our results apply only to EFV containing first line and not for responding to DTG-based ART failure. Regimen specific failure algorithms may be needed

should the approach modelled here be implemented in a context where both drugs were in use.

WHO guidelines on the public health response to pre-treatment HIV drug resistance published in 2017 recommend that when levels of NNRTI resistance amongst treatment initiators exceed 10% a change from a NNRTI-based first-line regimen to a non-NNRTI-based first-line regimen should be urgently considered[39]. Among people with a single VL measurement documented VL >1000 copies/ml while on treatment, the proportion of people with resistance to EFV/NVP ranges from 50-90% (WHO HIVDR report 2017), thus far exceeding the 10% threshold established for pre-treatment drug resistance. Therefore, a rapid change in regimen after a single elevated VL may be justifiable based on these guidelines.

To summarise, in our model 76% (90% range 55%-89%) of individuals on ART with one elevated VL have NNRTI resistance and do not go on to re-suppress . Currently the majority of these patients are never initiated on second line ART. We identify the current treatment failure algorithm as a contributor to this situation. The unmet need for effective therapy among failing individuals is highly consequential and we estimate that in a country the size of South Africa, the application of a single VL switch strategy – assumed to address some but not all barriers to switch – could prevent an estimated 10,666 deaths per year (see supplementary table 2, http://links.lww.com/QAD/B475). Additionally such a change would improve progress towards the 3rd 90 of the UNAIDS goals by approximately 3%.

As the cost of second line regimens decline, a change of strategy to define failure of EFV-based 1st line ART after a single VL value > 1000 copies/ml should be considered, allowing faster switch to second line, boosting effort to achieve the 3rd 90 and reducing AIDS-related deaths.

Acknowledgements: Legion@UCL for computing the model results.

References

1. UNAIDS. *Fact sheet July 2018 Latest global and regional statistics on the status of the AIDS epidemic.* (2018).

2. World Health Organization & World Health Organization. Department of HIV/AIDS. *Antiretroviral therapy for HIV infection in adults and adolescents : recommendations for a public health approach.* (2010).

3. Steegen, K. *et al.* HIV-1 antiretroviral drug resistance patterns in patients failing NNRTI-based treatment: results from a national survey in South Africa. *J. Antimicrob. Chemother.* **72,** 210–219 (2017).

4. Gupta, R. K. *et al.* Virological monitoring and resistance to first-line highly active antiretroviral therapy in adults infected with HIV-1 treated under WHO guidelines: a systematic review and meta-analysis. *Lancet Infect. Dis.* **9,** 409–417 (2009).

5. World Health Organization, United States Centers for Disease Control and Prevention & The Global Fund to Fight AIDS Tuberculosis and Malaria. *HIV drug resistance report 2017*. (2017).

6. Organization, W. H., Prevention, U. S. C. for D. C. and & Malaria, T. G. F. to F. A. T. and. *HIV Drug resistance report 2012*. (2012).

7. Svärd, J. *et al.* Drug resistance testing through remote genotyping and predicted treatment options in human immunodeficiency virus type 1 infected Tanzanian subjects failing first or second line antiretroviral therapy. *PLoS One* **12,** e0178942 (2017).

8. Sigaloff, K. C. E. *et al.* Short Communication: High Rates of Thymidine Analogue Mutations and Dual-Class Resistance Among HIV-Infected Ugandan Children Failing First-Line Antiretroviral Therapy. *AIDS Res. Hum. Retroviruses* **29,** 925–930 (2013).

9. Tsai, H.-C. *et al.* High rate of HIV-1 drug resistance in treatment failure patients in Taiwan, 2009–2014. *Infect. Drug Resist.* **Volume 10,** 343–352 (2017).

10. Etta, E. M. *et al.* High level of HIV-1 drug resistance mutations in patients with unsuppressed viral loads in rural northern South Africa. *AIDS Res. Ther.* **14,** 36 (2017).

11. TenoRes Study Group. Global epidemiology of drug resistance after failure of WHO recommended first-line regimens for adult HIV-1 infection: a multicentre retrospective cohort study. *Lancet. Infect. Dis.* **16,** 565–575 (2016).

12. World Health Organization. *Global action plan on HIV drug resistance 2017–2021*. (2017).

13. Rohr, J. K. *et al.* Predictors of time to switch to second line art after first line failure in Johannesburg South Africa. in *Top Antivir Med* **22,** 280 (2014).

14. Narainsamy, D. & Mahomed, S. Delays in switching patients onto second-line antiretroviral treatment at a public hospital in eThekwini, KwaZulu-Natal. *South. Afr. J. HIV Med.* **18,** 5 pages (2017).

15. Petersen, M. L. *et al.* Delayed switch of antiretroviral therapy after virologic failure

associated with elevated mortality among HIV-infected adults in Africa. *AIDS* **28,** 2097–107 (2014).

16. Ramadhani, H. O. *et al.* The Effect of Switching to Second-Line Antiretroviral Therapy on the Risk of Opportunistic Infections Among Patients Infected With Human Immunodeficiency Virus in Northern Tanzania. *Open forum Infect. Dis.* **3,** ofw018 (2016).

17. Murphy, R. A., Court, R., Maartens, G. & Sunpath, H. Second-Line Antiretroviral Therapy in Sub-Saharan Africa: It Is Time to Mind the Gaps. *AIDS Res. Hum. Retroviruses* **33,** 1181–1184 (2017).

18. Petersen, M. L. *et al.* Delayed switch of antiretroviral therapy after virologic failure associated with elevated mortality among HIV-infected adults in Africa. *AIDS* **28,** 2097–107 (2014).

19. Jobanputra, K. *et al.* Factors Associated with Virological Failure and Suppression after Enhanced Adherence Counselling, in Children, Adolescents and Adults on Antiretroviral Therapy for HIV in Swaziland. *PLoS One* **10,** e0116144 (2015).

20. McCluskey, S. M. *et al.* Brief Report: Appraising Viral Load Thresholds and Adherence Support Recommendations in the World Health Organization Guidelines for Detection and Management of Virologic Failure. *JAIDS J. Acquir. Immune Defic. Syndr.* **76,** 183–187 (2017).

21. Gupta, R. K. *et al.* High Rate of HIV Resuppression After Viral Failure on First-line Antiretroviral Therapy in the Absence of Switch to Second-line Therapy. *Clin. Infect. Dis.* **58,** 1023–1026 (2014).

22. Hamers, R. L. *et al.* Cohort profile: The PharmAccess African (PASER-M) and the TREAT Asia (TASER-M) monitoring studies to evaluate resistance--HIV drug resistance in sub-Saharan Africa and the Asia-Pacific. *Int. J. Epidemiol.* **41,** 43–54 (2012).

23. Hoffmann, C. J. *et al.* Durable HIV RNA resuppression after virologic failure while remaining on a first-line regimen: a cohort study. *Trop. Med. Int. Heal.* **19,** 236–239 (2014).

24. Sörstedt, E. *et al.* Viral blips during suppressive antiretroviral treatment are associated with high baseline HIV-1 RNA levels. *BMC Infect. Dis.* **16,** 305 (2016).

25. Greub, G. *et al.* Low-Level HIV Viral Rebound and Blips in Patients Receiving Potent Antiretroviral Therapy. in *8th Conference on Retroviruses and Opportunistic Infections* Abstract 522 (2001).

26. Hermans, L. *et al.* High rates of viral resuppression of first-line ART after initial virological failure. in *Conference on Retroviruses and Opportunistic Infections (CROI)* 1118 (2018).

27. Calmy, A., Ford, N. & Meintjes, G. The Persistent Challenge of Advanced HIV Disease and AIDS in the Era of Antiretroviral Therapy. *Clin. Infect. Dis.* **66,** S103-SS105 (2018).

28. Rossouw, T. *et al.* HIV drug resistance levels in adults failing first-line antiretroviral

therapy in an urban and a rural setting in South Africa. *HIV Med.* **18,** 104–114 (2017).

29. Osler, M. *et al.* The Continuing Burden of Advanced HIV Disease Over 10 Years of Increasing Antiretroviral Therapy Coverage in South Africa. *Clin. Infect. Dis.* **66,** S118–S125 (2018).

30. Ousley, J. *et al.* High Proportions of Patients With Advanced HIV Are Antiretroviral Therapy Experienced: Hospitalization Outcomes From 2 Sub-Saharan African Sites. *Clin. Infect. Dis.* **66,** S126–S131 (2018).

31. Gupta, R. K. *et al.* HIV-1 drug resistance before initiation or re-initiation of first-line antiretroviral therapy in low-income and middle-income countries: a systematic review and meta-regression analysis. *Lancet Infect. Dis.* **18,** 346–355 (2018).

32. World Health Organization. *WHO Guidelines on the public health response to pretreatment HIV drug resistance*. *WHO* (World Health Organization, 2018).

33. ART-LINC of IeDEA Study Group *et al.* Switching to second-line antiretroviral therapy in resource-limited settings: comparison of programmes with and without viral load monitoring. *AIDS* **23,** 1867–1874 (2009).

34. Haas, A. D. *et al.* Monitoring and switching of first-line antiretroviral therapy in adult treatment cohorts in sub-Saharan Africa: collaborative analysis. *lancet. HIV* **2,** e271-8 (2015).

35. Madec, Y., Leroy, S., Rey-Cuille, M.-A., Huber, F. & Calmy, A. Persistent difficulties in switching to second-line ART in sub-saharan Africa--a systematic review and meta-analysis. *PLoS One* **8,** e82724 (2013).

36. Boulle, A. *et al.* Seven-year experience of a primary care antiretroviral treatment programme in Khayelitsha, South Africa. *AIDS* **24,** 563–572 (2010).

37. Phillips, A. *et al.* Sustainable HIV treatment in Africa through viral-load-informed differentiated care. *Nature* **528,** S68–S76 (2015).

38. Phillips, A. N. *et al.* Risks and benefits of dolutegravir-based antiretroviral drug regimens in sub-Saharan Africa: a modelling study. *Lancet HIV* **6,** e116–e127 (2019).

39. Phillips, A. N. *et al.* Cost-effectiveness of public-health policy options in the presence of pretreatment NNRTI drug resistance in sub-Saharan Africa: a modelling study. *Lancet HIV* **5,** e146–e154 (2018).

40. Médecins Sans Frontières Access Campaign. *Untangling the web of antiretroviral price reductions (18th edition)*. (2016).

41. Médecins Sans Frontières Access Campaign. *HIV & Opportunistic infection treatment: Spotlight on access gaps*. (2016).

42. The Global Fund. Pooled Procurement Mechanism Reference Pricing: ARVs Q3 2018. (2018). Available at: https://www.theglobalfund.org/media/5813/ppm_arvreferencepricing_table_en.pdf. (Accessed: 4th September 2018)

43. World Health Organization. *Update on antiretroviral regimens for treating and*

preventing HIV infection and update on early infant diagnosis of HIV. (2018).

44. Gibb, J. *et al.* Supporting Quality Data Systems: Lessons Learned from Early Implementation of Routine Viral Load Monitoring at a Large Clinic in Lilongwe, Malawi. *J. Clin. Res. HIV AIDS Prev.* **3,** (2017).

45. Mgosha, P. C. Barriers to Switching Patients to Second-Line Antiretroviral Treatment Among Clinicians in Tanzania. (Walden University, 2017).

46. Srasuebkul, P. *et al.* Impact of drug classes and treatment availability on the rate of antiretroviral treatment change in the TREAT Asia HIV Observational Database (TAHOD). *AIDS Res. Ther.* **4,** 18 (2007).

47. Chaiyachati, K. H. *et al.* Interventions to improve adherence to antiretroviral therapy: a rapid systematic review. *Aids* **28,** S187–S204 (2014).

48. Bärnighausen, T. *et al.* Interventions to increase antiretroviral adherence in sub-Saharan Africa: a systematic review of evaluation studies. *Lancet. Infect. Dis.* **11,** 942–51 (2011).

49. Stop Stock Outs Consortium. *Stop Stock Outs Survey 2015*. (2015).

50. Gils, T. *et al.* Stockouts of HIV commodities in public health facilities in Kinshasa: Barriers to end HIV. *PLoS One* **13,** e0191294 (2018).

51. The Global Fund. Global Fund Procurement Database. (2018). Available at: https://bip2-ext.theglobalfund.org/analytics/saw.dll?Dashboard. (Accessed: 14th May 2018)

52. UNAIDS. *Price reduction of the Dolutegravir-based antiretroviral therapy regimen*. (2017).

53. Zimbabwe National Statistics Zimbabwe & Agency. *Demographic and Health Survey HIV Fact Sheet. Zimbabwe*. (2015).

54. Demographic and Health Survey Program. *Tanzania HIV/AIDS and Malaria Indicator Survey*. (2011).

55. Demographic and Health Survey Program. *Uganda AIDS Indicator Survey*. (2011).

56. The Demographic and Health Survey Program. *2014 Lesotho Demographic and Health Survey HIV Factsheet*. (2014).

57. PHIA Project. *MALAWI POPULATION-BASED HIV IMPACT ASSESSMENT MPHIA 2015–2016*. (2016).

58. PHIA Project. *ZAMBIA POPULATION-BASED HIV IMPACT ASSESSMENT ZAMPHIA 2015–2016*. (2016).

59. PHIA Project. *ZIMBABWE POPULATION-BASED HIV IMPACT ASSESSMENT ZIMPHIA 2015–2016*. (2016).

60. Justman, J. *et al.* Real progress in the HIV epidemic: PHIA findings from Zimbabwe, Malawi and Zambia. in *CROI* Abstract Number: 114LB (2017).

61. Huerga, H. *Mbongolwane and Eshowe HIV Impact in Population Survey | Epicentre*. (2014).

62. Maman, D. *et al.* Closer to 90-90-90. The cascade of care after 10 years of ART scale-up in rural Malawi: a population study. *J. Int. AIDS Soc.* **19,** 20673 (2016).

63. Kim, A. A. *et al.* Undisclosed HIV infection and antiretroviral therapy use in the Kenya AIDS indicator survey 2012. *AIDS* **30,** 2685–2695 (2016).

64. UNAIDS. *Ending AIDS: progress towards the 90–90–90 targets*. (2017).

65. Johnston, V. *et al.* Second-Line Antiretroviral Therapy in a Workplace and Community-Based Treatment Programme in South Africa: Determinants of Virological Outcome. *PLoS One* **7,** e36997 (2012).

66. Johnston, V. *et al.* Outcomes following virological failure and predictors of switching to second-line antiretroviral therapy in a South African treatment program. *J. Acquir. Immune Defic. Syndr.* **61,** 370–80 (2012).

67. Fox, M. P. *et al.* Rates and Predictors of Failure of First-line Antiretroviral Therapy and Switch to Second-line ART in South Africa. *JAIDS J. Acquir. Immune Defic. Syndr.* **60,** 428–437 (2012).

68. Sigaloff, K. C. E. *et al.* Second-Line Antiretroviral Treatment Successfully Resuppresses Drug-Resistant HIV-1 After First-Line Failure: Prospective Cohort in Sub-Saharan Africa. *J. Infect. Dis.* **205,** 1739–1744 (2012).

69. Boender, T. S. *et al.* Accumulation of HIV-1 drug resistance after continued virological failure on first-line ART in adults and children in sub-Saharan Africa. *J. Antimicrob. Chemother.* **71,** 2918–2927 (2016).

70. Wallis, C. L., Mellors, J. W., Venter, W. D. F., Sanne, I. & Stevens, W. Varied Patterns of HIV-1 Drug Resistance on Failing First-Line Antiretroviral Therapy in South Africa. *JAIDS J. Acquir. Immune Defic. Syndr.* **53,** 480–484 (2010).

71. Gregson, J. *et al.* Occult HIV-1 drug resistance to thymidine analogues following failure of first-line tenofovir combined with a cytosine analogue and nevirapine or efavirenz in sub Saharan Africa: a retrospective multi-centre cohort study. *Lancet. Infect. Dis.* **17,** 296–304 (2017).

72. Hamers, R. L. *et al.* HIV-1 drug resistance in antiretroviral-naive individuals in sub-Saharan Africa after rollout of antiretroviral therapy: a multicentre observational study. *Lancet Infect. Dis.* **11,** 750–759 (2011).

73. Médecins Sans Frontières. *Making Viral Load Routine (Part 1: Programmatic Strategies)*. (2017).

Table 1. Characteristics of setting scenarios in 2018, before consideration of a change in 1st line failure definition

Characteristic	Median (90% range) across setting scenarios	Examples of observed data from settings in sub Saharan Africa
HIV prevalence (age 15-49)	8.8% (5.3% - 17.1%)	Lesotho (2014)25% , Tanzania (2011) 5%, Uganda (2011) 9%, Zimbabwe (2015) 14% (2016) 14% [53–56]
HIV incidence (per 100 person years; age 15-49)	0.69 (0.31 – 1.40)	Malawi MPHIA 2016 (0·37%)[57], Zambia ZAMPHIA 2016 (0·66%)[58], Zimbabwe ZIMPHIA 2016 (0·45%)[59], (2·4%)[60], South Africa (0·39%)[61]
Among HIV-infected, % diagnosed	84% (73% - 92%)	Malawi MPHIA (73%)[57], Zambia ZAMPHIA (67%)[58], Zimbabwe ZIMPHIA (74%)[59], South Africa (75%)[61], Malawi [62](77%) (see also [63], which suggests undisclosed diagnosed HIV)
Among those diagnosed with HIV, % on ART	87% (67% - 95%)	[64]
Among those on ART, % with an NNRTI resistance mutation (including minority variants)	18% (12% - 31%)	No direct measures available to our knowledge
Among all people on ART, % with VL < 1000 cps/ml	88% (78% - 93%)	South Africa (60%-88% over districts), ZAMPHIA (89%)[58], MPHIA (91%)[57], ZIMPHIA (87%)[59], (91%)[62], (90%) [61]
Among those initiating ART, % with NNRTI resistance	9% (1% -28%)	Angola (14%), Botswana (8%), South Africa (14%) [12-14] Zimbabwe 11%,
Proportion of ART initiators with CD4 count < 350 at initiation of ART	40% (30% - 52%)	
Among ART-experienced persons, percent who have started second-line	4·8% (1·4% - 12·2%)	Malawi 1·5% (quarterly reports), 2·4% [35]
Overall rate of switch to second-line ART (/ 100 p-yrs)	1·9 (0·7 – 5·0)	2·7 [35]
Among those receiving second-line ART, proportion with VL < 1000 cps/ml	77% (65% - 83%)	48%, 72% [65] South Africa[66] 77%[67], 86% [68], 85% [69]
Among those receiving second-line ART, proportion with a PI mutation	3% (1% - 8%)	6·5% [69], 7% [70]
Among those on ART, proportion with CD4 count > 500 cells /mm^3	49% (38% - 55%)	
Death rate in persons on ART (/ 100 person years)	2·2 (1·6 – 3·5)	

Death rate in persons on 1st line ART (per 100 p-yrs)	2·2 (1·5 – 3·5)	
Death rate in persons on 2nd line ART (/ 100 p-yrs)	3·3 (1·1 – 7·0)	
Death rate in persons who have stopped/interrupted ART (/ 100 person yrs)	14·0 (6·2 – 23·1)	
AIDS death rate in persons with previous or current VL > 1000 while on ART (/ 100 p-yrs)	5·1 (2·2 – 9·6)	
Among persons on 1st line ART with initial measured VL> 1000 cps/ml in past year, % with NNRTI resistance mutation	76% (55% - 89%)	84% (74% - 100%) [71]; 70% [72]
Of people defined as failing efavirenz-based first line ART, % with NNRTI drug resistance·	98% (88% - 100%)	
Of people on 1st line ART with initial vl > 1000 6 months ago, proportion with VL < 1000	30% (8% – 63%)	22% – 50% [73]
Of people on ART who have first experienced VL > 1000 cps/mL 2 years ago, proportion on ART (1st or 2nd line) with VL < 1000 cps/mL.	23% (4% - 57%)	
Of people on 1st line ART with initial vl > 1000 in past year rate of AIDS (per 100 person yrs)	6·1 (1·5 – 12·9)	
Of people on 1st line ART with current vl > 1000, % with CD4 count < 200 / mm^3	36% (27% - 45%)	
Of people on 1st line ART with current vl > 1000, % classified as having fulfilled 1st-line failure criteria	21% (6% - 43%)	
Of people who have been identified as having failed 1st line ART in the past year, % who have been switched to 2nd line	25% (4% - 61%)	[34,35]
Of people switched to 2nd line, proportion with drug resistance to at least 1 first line drug	100% (92% - 100%)	
Proportion of persons with drug resistance to efavirenz who have been switched to 2nd line ART	21% (6% - 46%)	
Of persons on 1st line ART with previous VL > 1000 (at least 6 months after start of ART), percent with VL < 1000 c/ml	36% (22% - 54%)	
Number of AIDS deaths per year (in context of country of 10 million adults with median HIV prevalence 10%)	21,500 (9,000 – 44,000)	
Number of persons on second-line ART (assuming country of 10 million adults with a median HIV prevalence of 10%)	31,000 (8,000 – 105,000)	

Table 2. Comparison of effects of strategy of defining 1st line failure of efavirenz-based regimens by a single VL > 1000 with strategy of two consecutive VL > 1000[+]

	Strategy for defining 1st line failure of efavirenz-based regimen		
	Two consecutive VL > 1000 cps/ml (median 90% range over setting scenarios)	**Single VL > 1000 cps/ml (median 90% range over setting scenarios)**	**Difference ((^ or percent reduction) between policies (mean 95% CI; median 90% range) over setting scenarios))**
Among ART-experienced persons, percent who have started second-line	10.4% (5.6% - 19.1%)	15.2% (9.5% - 26.5%)	+ 5.1% (+5.0%, +5.2%) +4.8% (+3.4% - +7.8%)
Of people on ART who have first experienced VL > 1000 cps/mL 2 years ago, proportion on ART (1st or 2nd line) with VL < 1000 cps/mL.	51% (33% - 68%)	59% (36% - 80%)	+8% (+7% - +8%) +8% (-3% - +19%)
Of people on 1st line ART with initial VL > 1000 in past year rate of AIDS (per 100 person years)	4.7 (2.4 – 8.4)	3.2 (1.6 – 5.8)	30% (28% , 32%) ^ 31% (+8% , +49%) ^
AIDS death rate in people with previous or current VL > 1000 while on ART* ¥	3.1 (1.7 – 6.8)	2.5 (1.3 – 6.0)	18% (18% , 18%) ^ 18% (6% , 30%) ^
% of people with drug resistance to efavirenz who have been switched to second line ART	48% (33% - 59%)	65% (51% - 74%)	17% (17% , 17%) 17% (14% , 20%)
Among those on ART (1st or 2nd line), % with VL < 1000 cps/ml	92% (85% - 95%	94% (89% - 96%)	+2.9% (+2.8% , +3.0%) +2.6% (+1.5% , +4.8%)
Of people switched to 2nd line, proportion with drug resistance to at least 1 first line drug.	99% (95% - 100%)	82% (68% - 91%)	-17% (-18% , -16%) -17% (-28% , -8%)
Of people defined as failing efavirenz-based first line ART, % with NNRTI drug resistance.	97% (75% - 100%)	72% (50% - 86%)	-23% (-24% , -22%) -23% (-36% , -12%)
Of persons on 1st line ART with previous VL > 1000 (at least 6 months after start of ART), percent with VL < 1000 c/ml	55% (41% - 65%)	64% (50% - 72%)	9% (9% , 9%) 9% (6% , 12%)

[+] (mean over 2018·75 – 2021·75 for each setting scenario, then summarized as mean and median over setting scenarios)·

* > 6 months after (re-)starting, and excluding people already started 2nd line before baseline in 2018·75.

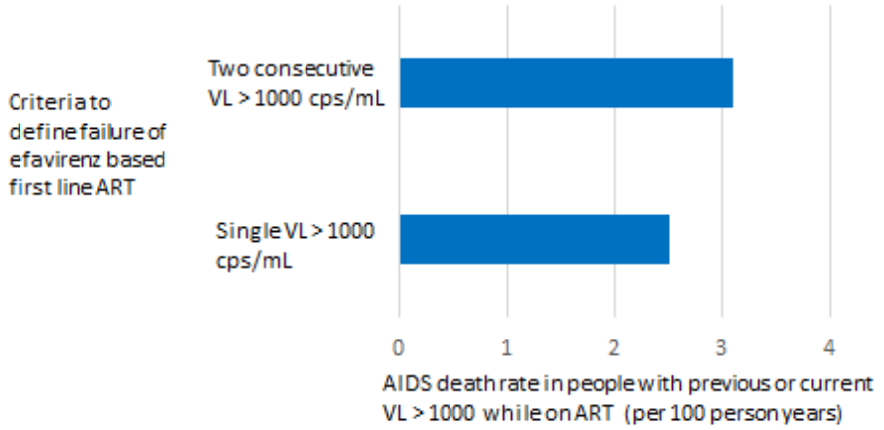
¥ As shown in figure 1

Table 3. AIDS death rate (2018·75 – 2021·75) in people with previous or current VL > 1000 while on ART according to strategy for defining 1st line failure of efavirenz-based regimen: one way sensitivity analysis

	Strategy for defining 1st line failure of efavirenz-based regimen		
	Two consecutive VL > 1000 cps/ml	Single VL > 1000 cps/ml	Percent reduction between policies (mean [95% CI]; median [90% range] over setting scenarios
Base case +	3·1 (1·7 – 6·8)	2·5 (1·3 – 6·0)	18% (18% , 18%) ¥ 18% (6% , 30%) ¥
Restricting to setting scenarios where: Of people on 1st line ART with initial VL > 1000 6 months ago, % with VL < 1000 is > 40% in 2018	3·2 (1·7 – 7·4)	2·7 (1·3 – 6·3)	17% (15% , 19%) 17% (5% , 29%)
Restricting to setting scenarios where: HIV incidence in 2017 < 0·5 / 100 person years	3·2 (1·7 – 6·3)	2·5 (1·3 – 5.2)	19% (17% , 21%) 19% (5% , 32%)
Probability of each scheduled viral load measure being done = 0.20 (0.85 in base case)	3·9 (1·9 – 7·5)	3·1 (1·5 – 6·7)	17% (15% , 19%) 16% (3% , 31%)
Probability of switch to second line (per 3 months) after first line failure criteria fulfilled = 0·20 (0·85 in base case)	4·0 (1·9 – 7·6)	3·7 (1·5 – 7·0)	9% (8% , 10%) 9% (-1% , 18%)

+ 25% of those identified as having failed 1st line ART in the past year switched to 2nd line· Overall rate of switch to second-line ART 1·9 / 100 p-yrs (0·7 – 5·0)·
¥ 6 months after (re-)starting, and excluding people who already started 2nd line before baseline in 2018·75.

Figure 1. AIDS death rate (over 3 years; 2018.75 - 2021.75) in people with previous or current VL > 1000 while on ART according to criteria to define failure of efavirenz based first line ART. (excluding people who had already switched to 2nd line ART before baseline in 2018).



Percent reduction in rate for single VL > 1000 vs two consecutive VL > 1000 cps/mL:
Mean 18% (95% CI 18% - 18%) Median 18% (90% range 6% - 30%)