

# Diagnosis and management of antiretroviral-therapy failure in resource-limited settings in sub-Saharan Africa: challenges and perspectives

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Despite the enormous progress made in scaling up antiretroviral therapy (ART) in sub-Saharan Africa, many challenges remain, not least of which are the identification and management of patients who have failed first-line therapy. Less than 3% of patients are receiving second-line treatment at present, whereas 15–25% of patients have detectable viral loads 12 months or more into treatment, of whom a substantial proportion might have virological failure. We discuss the reasons why virological ART failure is likely to be under-diagnosed in the routine health system, and address the current difficulties with standard recommended second-line ART regimens. The development of new diagnostic tools for ART failure, in particular a point-of-care HIV viral-load test, combined with simple and inexpensive second-line therapy, such as boosted protease-inhibitor monotherapy, could revolutionise the management of ART failure in resource-limited settings.

## Introduction

"This is not the end. It is not even the beginning of the end. But it is perhaps, the end of the beginning."

*Sir Winston Churchill, 1942, speech at the Mansion House, London, referring to the Battle of Egypt*

The scale-up of antiretroviral therapy (ART) in low-income and middle-income countries has been unprecedented, with more than 4 million people in such countries estimated to have access to ART at the end of 2008.<sup>1</sup> Hope and optimism have slowly but steadily begun to replace despair and death in those countries and areas most affected by the HIV/AIDS epidemic. However, challenges remain, particularly in resource-limited settings. Too few people are still receiving treatment, too many patients start treatment late, and the present first-line ART armamentarium is too toxic. One major challenge that is increasingly beginning to confront established HIV care programmes is what to do about ART failure and second-line treatment.

The aim of this Personal View is to review the current difficulties with diagnosing and managing ART failure in resource-limited settings in sub-Saharan Africa, and to expound the rationale and arguments for the development of a point-of-care (POC) viral-load test and second-line treatment based on protease-inhibitor monotherapy. We think that this package is feasible for decentralised care and will facilitate better quality HIV care than is the case at present.

## ART in Africa and low use of second-line regimens

The increased use of ART in sub-Saharan Africa has been a success story for the region. In 2003, about 2% of patients in need of treatment received ART. By the end of 2008, the region had increased this coverage to 44%, with 2.9 million patients estimated to be receiving this life-saving medication.<sup>1</sup> Malawi, a poor, land-locked country in

southern Africa, with an annual gross domestic product of less than US\$200 per person and a population of 13 million,<sup>2</sup> is one of those countries that has done well. In 2003, only a few sites were delivering ART to patients, there were no standardised systems to track cases or outcomes, and patients had to pay for their medication. By the end of December, 2008, over 196 000 new patients had started on ART, which is offered free of charge in the public sector and at a subsidised rate in the private sector (table 1).<sup>3</sup>

In a WHO survey involving national AIDS programmes in countries with a high burden of HIV in 2008, about 98% of patients who had been started on ART were on first-line regimens, the most common being stavudine, lamivudine, and nevirapine.<sup>1</sup> The same survey reported that only 2% of adults and 3% of children were on second-line ART, the usual regimens being based on nucleoside reverse transcriptase inhibitors (NRTIs) and a protease inhibitor, which was invariably ritonavir-boosted lopinavir.<sup>1</sup> However, countries vary in reported use of second-line ART. In South African children, the cumulative probability of switching to second-line ART was 6% at 3 years,<sup>4</sup> whereas in the resource-poor environment of Malawi, which has good national recording and reporting systems, only 518 (0.3%) of the 145 479 patients known to be alive and on ART by December, 2008, had been switched to a second-line regimen.<sup>3</sup>

There are various explanations for low use of second-line ART, but one of the most important is the inability to identify and diagnose patients who have failed first-line therapy. In high-income countries, the diagnosis of ART failure is based on measurements of HIV RNA concentration. For example, in the UK and USA, a plasma HIV RNA concentration of above 50 copies per mL on two consecutive occasions is used to define virological failure.<sup>5,6</sup> In a study of ART in 14 African countries, Akileswaran and colleagues<sup>7</sup> found that 27% of patients who had been on ART for 6 months to 4 years had plasma HIV RNA

concentrations greater than 500 copies per mL. Similarly, in a study of 18 ART clinics, 13 of which were in sub-Saharan Africa, 24% of patients had plasma HIV RNA concentrations greater than 500 copies per mL at 6 months.<sup>8</sup> Single-country studies in Botswana,<sup>9</sup> Malawi,<sup>10</sup> Uganda,<sup>11</sup> South Africa,<sup>12</sup> and Cameroon<sup>13</sup> showed that 15–25% of patients had plasma HIV RNA concentrations greater than 400 copies per mL at 6–36 months after starting first-line ART. Cross-sectional studies often fail to differentiate true virological failure from detectable viral loads due to viral “blips” (occasional increases in viraemia during otherwise successful HIV suppression) or poor adherence. In a cohort study from South Africa, an HIV RNA concentration above 1000 copies per mL was noted in 7% of patients, but after use of targeted adherence interventions by peer counsellors, virological failure (defined as HIV RNA greater than 1000 copies per mL on two consecutive occasions) was only confirmed in 2%.<sup>14</sup>

Important risk factors for the development of drug resistance, particularly in sub-Saharan Africa, include intermittent interruptions of treatment due to drug unavailability (so-called “stock outs”) or side-effects, use of nevirapine-based ART after single-dose nevirapine has been used to prevent perinatal HIV transmission,<sup>15,16</sup> and inadequate nevirapine concentrations resulting from the interaction with rifampicin.<sup>17</sup> A recent systematic review and meta-analysis showed that there might be high levels of genotypic resistance to NRTIs in resource-poor settings, particularly if viral-load monitoring is not available.<sup>18</sup> In Malawi, among patients starting second-line ART in the public programme, 95% had at least one major drug mutation, 93% had dual-class resistance, and 17% of patients had resistance to all available NRTIs.<sup>19</sup>

## Management in routine settings

The main reason for not detecting virological ART failure is lack of resources. Table 2 summarises the differences in gross domestic product, health expenditures, skilled human resources, and HIV burden between the UK and Malawi.<sup>2,3,5,20,21</sup> These disparities explain the way in which ART is managed in the two countries. In brief, the management of patients with HIV in the UK is guided by regular and reliable laboratory monitoring such as CD4-lymphocyte count, plasma HIV RNA concentration, and drug-resistance profiles, with sophisticated technology being used to determine whether certain first, second, or third-line drugs are contraindicated (ie, the presence of HLA-B\*5701 indicates high risk of hypersensitivity to abacavir) or can be used (ie, viral tropism assays for maraviroc).

The management of ART in a resource-poor country such as Malawi could not be more different. Patients are eligible for ART if they are confirmed as being infected with HIV, the patient or guardian understands the implications of ART and life-long therapy, and the patient is assessed as being in WHO clinical stage 3 or 4 or has a CD4-cell count below the threshold for severe immuno-

	Number of ART clinics in the public and private sector	Number of patients registered for ART*
December, 2003	9	3000†
December, 2004	24	13 183
December, 2005	83	38 817
December, 2006	141	85 168
December, 2007	163	146 856
December, 2008	221	223 437

ART=antiretroviral therapy. \*These data are the reported national numbers and include patients who have been transferred between clinics; such transferred patients are thus counted twice (ie, by December, 2008, 27 069 patients had been transferred between clinics, meaning that 196 368 patients had newly started ART). †Estimate. Data obtained from the Department of HIV and AIDS, Malawi Ministry of Health.<sup>3</sup>

**Table 1: Scale-up of antiretroviral therapy in Malawi**

	UK	Malawi
Population	60 000 000	13 000 000
Gross domestic product per head (US\$)	25 000	170
Health expenditure per head (US\$)	3000	15
Physicians (n)	135 000	270
Nurses (n)	700 000	7300
People living with HIV (n)	70 000	950 000
Patients alive on ART (n)	36 000	142 000

Numbers are rounded down. ART=antiretroviral therapy.

**Table 2: Economic and health-care differences between UK and Malawi**

deficiency, which in the case of adults is below  $250 \times 10^6$  cells per L.<sup>22,23</sup> In Malawi, about 75% of the ART clinics have no facility to measure CD4-cell counts, and the emphasis is therefore on WHO clinical staging. If eligible for ART, patients go through a process of group and individual counselling before starting treatment. First-line ART regimen is a standardised generic, fixed-dose combination treatment with stavudine, lamivudine, and nevirapine. All patients starting first-line ART are seen 2 weeks after treatment initiation and then every 4 weeks for the first 6 months. Stable patients are then followed up at 2-monthly intervals for life. Monitoring for treatment response, side-effects, and drug adherence is done clinically, and routine laboratory monitoring is only done at a few central hospitals and externally supported sites. There are two alternative first-line regimens for serious side-effects of ART drugs, and two second-line regimens for ART drug failure in adults and children. Second-line therapy is initiated at central and major district hospitals, based on specialist assessment that can include measurement of plasma HIV RNA. After successful switching, patients might be referred back to their peripheral ART sites with supplies of second-line drugs. This policy theoretically gives all patients access to second-line ART while avoiding inappropriate regimen changes.

Guidelines for the diagnosis of ART failure in Malawi are shown in the panel.<sup>23</sup> These guidelines differ somewhat

**Panel: Diagnosis of antiretroviral therapy (ART) failure in Malawi—version 3 of the guidelines**

ART failure is defined when conditions A+B+C have been fulfilled:

- (A) On ART for at least 12 months and adhering to therapy.
- (B) Fulfil at least one of the following criteria:
  - (1) the development of a new WHO clinical stage 4 disease or feature,
  - (2) CD4-cell count/percentage that has declined to pretreatment values or less,
  - (3) CD4-cell count/percentage that has declined to below 50% of peak value on ART.
- (C) CD4-cell count below  $200 \times 10^6$  cells per L.

CD4-cell count needs to be repeated after 1 month, and the patient is referred only if the result supports the earlier CD4-cell count. The decision to change to a second-line regimen is made in consultation with a specialist or experienced clinician at one of the dedicated clinics, with access to viral-load tests.<sup>23</sup>

from the WHO recommendations, which also include the development of new WHO clinical stage 3 diseases such as pulmonary tuberculosis and severe bacterial infections.<sup>24</sup> Although these guidelines seem straightforward, their implementation in the field is fraught with difficulty.

### Difficulties in diagnosing therapy failure and initiating second-line ART

Patients on first-line ART, whether healthy or sick, might have difficulty accessing ART clinics because of distance and high costs associated with transport.<sup>25,26</sup> In many rural settings, patients might also choose not to present to medical clinics, frustrated by unavailability of essential medicines and coupled with a strong belief in traditional medicine.<sup>27</sup>

ART clinics are usually busy and understaffed, particularly in district government hospitals, many of which are run by only one or two nurses. In these circumstances, thorough clinical assessment is often impossible and new clinical conditions might be missed. Clinical assessment can also be misleading: WHO clinical stage 4 diseases such as extrapulmonary tuberculosis and Kaposi's sarcoma can develop despite successful ART and a satisfactory CD4-cell count response.<sup>28,29</sup> Clinical indicators also have poor specificity, a problem worsened by symptoms of drug toxicity that can easily be confused with those of opportunistic infections. For example, distinguishing between lactic acidosis (a long-term adverse effect of stavudine) and the development of *Pneumocystis jirovecii* pneumonia can be difficult in the absence of laboratory investigations. Immune reconstitution inflammatory syndromes present early in the course of ART,<sup>30</sup> and should not cause confusion with diseases presenting later as a result of ART failure.

Most patients starting ART in Malawi have no baseline CD4-cell count that would allow detection of a subsequent

decline.<sup>3</sup> CD4-cell count monitoring is only available at a few centres of excellence, and where CD4-cell counts are done, there are sometimes concerns over quality assurance.

Discordant responses of CD4-cell counts and virological load are well known in resource-limited settings.<sup>31</sup> In South Africa, the positive predictive values of WHO clinical and CD4-cell count criteria in diagnosing virological failure were 13% and 38%, respectively, meaning that a large proportion of patients would be incorrectly diagnosed as having treatment failure and switched unnecessarily to second-line therapy.<sup>32</sup> Poor predictive values of CD4-cell count criteria have also been found in Malawi,<sup>29</sup> South Africa,<sup>33</sup> Kenya,<sup>34</sup> and Uganda.<sup>35,36</sup> Whereas some studies have found that the negative predictive value of CD4-cell counts is high,<sup>37</sup> this finding is not consistent: for example, in a relatively well-resourced Médecins Sans Frontières programme in Mozambique, only 33% of patients with plasma HIV RNA concentrations of at least 1000 copies per mL manifested clinical or immunological signs suggestive of virological failure.<sup>38</sup>

In Malawi, the second-line regimen is currently not stocked at peripheral ART clinics for reasons of cost and lack of expertise in its use. Adults on second-line ART take one tablet of zidovudine and lamivudine twice daily, one tablet of tenofovir once daily, and two tablets of ritonavir-boosted lopinavir twice daily. This regimen costs ten times as much as first-line ART and increases the pill burden substantially. The systems of referral for expert assessment and initiation of second-line treatment at central or major district hospitals and back-referral with supplies of second-line drugs are expensive for patients and demanding for health workers. Lack of appropriate guidance to patients for the more complicated regimen might lead to suboptimum adherence on second-line ART. However, in well-resourced clinics, such as those run by Médecins Sans Frontières, a switch to protease-inhibitor-based second-line therapy in situations in which patients have truly failed first-line ART is associated with excellent clinical and immunological outcomes.<sup>39</sup>

Given the difficulties in diagnosis and management, what does in fact happen to patients who fail first-line ART in large national programmes? The honest answer is that we do not know, although many patients probably develop HIV-related disease and die. Such cases would be accounted for as "lost to follow-up" or "died" in routine monitoring data. By Dec 31, 2008, 23 699 patients (12%) of the 196 368 new patients who initiated ART in Malawi were known to have died. Although nearly two-thirds of deaths happened within 3 months after starting ART, an increasing proportion of patients are dying later.<sup>3</sup> A further 24 409 patients (12%) were classified as "lost to follow-up", meaning that they have not returned to clinic for 3 months or longer. Operational research has shown that 50% of patients lost to follow-up have died,<sup>40</sup> although more work needs to be done to elucidate when in the course of therapy this takes place. Although much of

current research focuses on establishing the reasons for early ART mortality,<sup>41</sup> better quantitative estimates are needed for late ART deaths and the causes, which are likely to be long-term ART toxic effects, such as lactic acidosis, and development of serious stage 4 disease and ART failure.

## Improving diagnosis and management

### Laboratory monitoring in resource-poor settings

The Development of Antiretroviral Therapy in Africa (DART) trial compared 5-year outcomes in patients in Uganda and Zimbabwe who were randomly assigned to clinical and laboratory monitoring (for side-effects and CD4-cell counts) versus clinical monitoring alone. Differences in mortality and WHO stage 4 event-free survival were small,<sup>42</sup> supporting findings from a previous mathematical model suggesting that the addition of laboratory monitoring for side-effects and CD4-cell counts provides little added benefit compared with clinical monitoring alone.<sup>43</sup> However, these findings do not take into account the poor performance of current clinical monitoring found in routine practice. The DART study also suggested that improved laboratory monitoring has a definite role in guiding the switching of therapy from the second year on ART. A theoretical ART failure model has been described that incorporates treatment and adherence history, clinical events, and basic laboratory results.<sup>44</sup> However, development of a composite diagnostic tool for ART failure that has good test characteristics, yet is simple enough for use in busy, undermanned clinics will be a huge challenge. A different approach is urgently needed.

### A point-of-care viral-load test

The rapid POC HIV test has revolutionised counselling and testing by replacing the cumbersome and slow ELISA method. Development of a rapid POC viral-load test will, we hope, provide a similar revolution in ART management. Field-friendly methods for specimen collection for HIV-1 viral-load measurement in Africa through the use of dried blood spots on filter paper have already been successfully tested in Zambia and rural Tanzania.<sup>45,46</sup> Similarly, substantial progress is being made in the development of a rapid POC test for CD4-cell count, specifically designed for use in resource-poor settings. Such a test is simple to use, relies on finger-prick blood sampling, and is not dependent on instrumentation or electronics. It also has the potential to improve access to ART at an earlier stage than is the case at present in sub-Saharan Africa (unpublished). To be applicable in peripheral clinics and remote health centres in sub-Saharan Africa, a POC viral-load test would need to have the same characteristics as those defined for a POC CD4-cell count test: simple to use and easy to read; independent of instrumentation or electronics; robust and able to withstand increased ambient temperatures without cold-chain shipment or

storage; long shelf-life (longer than 12 months); and inexpensive (no more than \$2 per test to manufacture).

One contentious issue will be the HIV RNA concentration at which virological failure is deemed to occur. We still need to define the viral-load concentrations at which immunological and clinical deterioration happen, and accumulation of important resistance mutations can be expected (ie, those that compromise outcome of standard second-line ART regimens). In Cameroon, 50% of patients with plasma HIV RNA concentrations above 1000 copies per mL harboured drug-resistant strains compared with 70% of patients with above 10000 HIV RNA copies per mL, the latter threshold being the present WHO recommendation for a switch to second-line ART.<sup>13</sup> Waiting until a threshold of 10000 copies per mL has been reached might mean that most patients already have multiple, clinically important, drug-resistant mutations. However, whereas a plasma HIV RNA concentration of 10000 copies per mL might be detectable by traditional immunoassays and technologies such as HIV strip tests, a plasma HIV RNA below 1000 copies per mL might not, which would increase the complexity of the POC test, its cost, and likelihood of successful development.

Virological testing has also been shown to be a useful operational support tool for improving adherence and patient support.<sup>14,47</sup> Thus, widespread availability of a viral-load test might help to conserve first-line regimens and might have a preventive dimension in ART failure. In the development of a POC viral-load test, clear guidance will be needed on the viral-load threshold around which action is taken, the frequency of testing, when to repeat the test if the viral load is high, and when to switch therapies.

### A simpler second-line ART regimen

Rolling out ART to primary health-care level will inevitably require task shifting to cope with the ever growing numbers of patients being initiated and maintained on life-long treatment.<sup>48</sup> Therefore, second-line ART must be made as simple as possible. Given the high genetic barrier to resistance, the use of ritonavir-boosted lopinavir, atazanavir, or darunavir is being considered as monotherapy.<sup>49–52</sup> The AIDS Clinical Trials Group (sponsored by the US National Institutes of Health) is currently doing a clinical trial on ritonavir-boosted lopinavir in patients on failing non-NRTI regimens (ClinicalTrials.gov reference NCT00357552). The UK Medical Research Council is planning the EARNEST (Eastern and Southern African Network for Evaluation of Second-Line Therapy) clinical trial, which will randomise patients to receive a boosted protease inhibitor and two NRTIs (as per current WHO guidelines), boosted protease-inhibitor monotherapy, or boosted protease inhibitor plus the integrase inhibitor raltegravir.

Boosted protease-inhibitor monotherapy for second-line ART is attractive for the following reasons: it is



independent of resistance to first-line agents; the non-overlapping resistance profile with first-line drugs makes resistance testing redundant; toxic effects due to NRTIs are eliminated; drug costs are minimised; and in busy clinics, there is less room for error by both health-care provider and patient. In most patients who fail first-line therapy in Africa, NRTIs in second-line treatment might be expected to have very little activity due to the presence of extensive NRTI resistance. Currently ritonavir-boosted lopinavir is the protease inhibitor of choice in resource-limited settings because of its heat-stable formulation and substantial experience with its use. Ritonavir-boosted atazanavir is attractive because of once daily dosing and safety: it has a more favourable lipid profile and causes less lipodystrophy, although it is commonly associated with hyperbilirubinaemia.<sup>53</sup> However, although atazanavir is available in heat-stable tablet form, it must be boosted with low-dose ritonavir, which is still only available in soft gel capsules that are sensitive to heat.

For patients in whom tuberculosis heralds the failure of first-line ART, there will be a need to find solutions to the use of protease inhibitors with antituberculosis treatment. The ideal option would be for rifabutin to replace rifampicin, but the former drug is still expensive and rarely available in resource-limited settings. The other, less desirable and complex, option is to continue with rifampicin but increase protease-inhibitor boosting, which could compromise safety.<sup>24</sup>

## Conclusions

ART scale-up in sub-Saharan Africa is a relatively new phenomenon, but one that is already changing the landscape of health-care provision. Life-long chronic care is required for the effective and safe administration of therapy to the millions of African patients who will eventually need it. Complicated ART delivery models will not work,<sup>54</sup> and simple, robust systems are needed to protect health services from being overwhelmed.

First-line ART must be protected for as long as possible by paying due attention to issues of adherence, consideration of less-toxic yet simple-to-take regimens, and an earlier start of therapy, the latter having a potential survival advantage and associated with a lower risk of drug-resistance mutations.<sup>55–57</sup> The current clinical and immunological criteria to diagnose ART failure in Africa are unreliable, with many patients who fail not being detected and others being prematurely switched, at great cost to individuals and to programmes.<sup>58</sup> We believe that a POC viral-load test has the potential to dramatically improve the management of patients, although operational research will be needed to determine the thresholds required and the frequency of testing. If more patients are identified with ART failure, an easy-to-use and relatively inexpensive second-line therapy has to be available. Boosted protease-inhibitor monotherapy is an attractive option,<sup>59</sup> and needs to be assessed for both feasibility and efficacy in the field.

## Contributors

ADH and RZ wrote the first draft of the paper. All co-authors contributed to the subsequent draft and the revised paper as a result of reviewers' comments and suggestions. All authors have read and approved the final paper.

## Conflicts of interest

We declare that we have no conflicts of interest.

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The views expressed in this Personal View are those of the authors and might not necessarily reflect those of the institutions for which they work.

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