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# Drug-resistant HIV-1 in sub-Saharan Africa: clinical and public health studies

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# Chapter 16

# Global threat from drug resistant HIV in sub-Saharan Africa

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## ABSTRACT

Roll-out of antiretroviral treatment for HIV in sub-Saharan Africa has been accompanied by rising rates of drug resistance. Raph Hamers and colleagues call for improved patient management and population based drug resistance surveillance to be integrated into national treatment programmes.

Since its introduction 16 years ago, combination antiretroviral therapy for HIV infection has saved millions of lives. In sub-Saharan Africa, the region with the highest HIV/AIDS burden, high level political commitment and substantial international funding have led to an unparalleled scale-up of access to treatment over the past eight years [1]. More than five million Africans infected with HIV are receiving antiretroviral therapy today—nearly half of those who are in immediate need [1]. However, little attention has been paid to the potential emergence and spread of drug resistant HIV and its public health implications. Drug resistant HIV variants selected for during treatment failure (acquired resistance) have the potential to limit the response to subsequent treatment and constitute a reservoir for onward transmission to newly infected individuals (transmitted resistance). Drug resistant HIV may severely restrict therapeutic options, and treatment costs will greatly increase when more people need second and third line antiretroviral regimens. It is therefore important for national HIV treatment programmes to monitor and manage mounting drug resistant HIV.

## HIV DRUG RESISTANCE

In developed countries, management of combination antiretroviral therapy is based on individualised specialist care that includes frequent monitoring of plasma viral load to detect treatment failure, drug resistance testing to guide regimen choices, and a wide armamentarium of antiretroviral drugs (table 1) [2]. In Europe and North America, HIV sequential mono and dual therapies of nucleoside reverse transcriptase inhibitors (NRTIs), initially led to high levels of acquired and transmitted resistance [3-5] but careful management and use of more potent antiretroviral regimens have seen levels of transmitted resistance stabilising or declining [6-8].

By contrast, for resource limited countries the World Health Organization has developed a public health approach based on a decentralised service delivery, empirical first and second line antiretroviral regimens, and clinical or immunological definitions of treatment failure in the absence of monitoring of plasma viral load (table 1) [9]. Standard first line regimens include a dual NRTI backbone and a non-NRTI [9]. Second line regimens combine a ritonavir boosted protease inhibitor with two unused or recycled NRTIs [9], although availability may still be restricted [1].

Although the roll-out of antiretroviral treatment in sub-Saharan Africa used triple therapy from the onset, national health systems in many African countries have serious deficiencies that may exacerbate the development of drug resistance. These include the widespread use of low cost, substandard regimens (such as stavudine as part of first

**Table 1.** Differences in approaches to providing combination antiretroviral therapy between developing and developed countries

| | Developing countries | Developed countries |
|---|---|---|
| Treatment model | WHO public health approach | Specialist driven, individualised patient management |
| Choice of regimen | WHO recommended empirical first line (2NRTIs+non-NRTI) and second line (bPI+2 unused/recycled NRTIs) therapies; restricted drug options, routine drug resistance testing not available. | Wide armamentarium of antiretroviral drugs<br>Individualised therapies by routine use of drug resistance testing before starting or switching treatment |
| Therapeutic monitoring and diagnosis of treatment failure | WHO definitions of treatment failure using clinical criteria and, if available, CD4 cell counts. HIV viral load testing not generally available.<br>Frequent unnecessary switching and prolonged failure | Close HIV viral load monitoring and timely regimen switching |
| Resources and infrastructure | Shortage of health professionals, limited training, deficient adherence counselling, inconsistent drug supply, weak enforcement of quality standards | Specialist care, intensive adherence counselling, continuous availability of drugs |
| Antiretroviral history | Roll-out since 2004-5 has used triple therapy | Widespread use of sequential mono and dual therapies before 1996 |
| | Widespread use of single dose nevirapine for prevention of vertical HIV transmission | Since 1996, triple therapy, individualised regimens and close viral load monitoring |

NRTI, nucleos(t)ide reverse-transcriptase inhibitor; bPI, ritonavir boosted protease inhibitor.

line treatment [10] and single dose nevirapine for prevention of mother to child HIV transmission); restricted access to monitoring of plasma viral load [11, 12]; treatment interruptions because of drugs supplies running out [13, 14]; suboptimal long term adherence [15]; and frequent drug-drug interactions (such as nevirapine with rifampicin in patients co-infected with tuberculosis) [16].

Recent studies in the region have reported increasing levels of transmitted drug resistance, mostly to non-NRTIs, as treatment has scaled up [17-19]. The rise in resistance to non-NRTIs is of particular concern because this drug class constitutes the foundation of current first line treatment regimens and prevention of mother to child transmission [9, 20]. The PASER-M study in six African countries estimated that the rate of transmitted drug resistance increases at 38% a year after roll-out of antiretroviral therapy [19], and that pre-therapy resistance more than doubles the risk of first line failure and of the further acquisition of drug resistance mutations in the first year of treatment [21]. Notably, we observed alarmingly high (9-12%) levels of transmitted drug resistance in Uganda [19], where antiretroviral treatment was introduced well ahead of nearby countries. With the establishment of the national HIV treatment programme and drug price reductions

in 2000, an estimated 10,000 patients were already receiving antiretroviral drugs by the end of 2002 [22], albeit with frequent interruptions for reasons of cost [14].

## MONITORING VIRAL LOAD

An important challenge for antiretroviral programmes is how to identify patients in whom treatment is failing so that they can be switched promptly to second line therapy. Despite estimates that 10-24% of patients have detectable plasma viral load during first line therapy [21, 23], reported switching rates have been relatively low [1], partly because of the poor sensitivity of clinical and immunological criteria to detect therapy failure [12]. Additionally, the poor specificity of clinical and immunological criteria may lead to up to half of switches being unnecessary, which exhausts drug options and augments costs [12]. Given that the cost of second line drugs is more than double that of first line drugs [24], for every patient that is switched unnecessarily at least one patient will be held back from accessing life-saving antiretroviral treatment.

Although the benefits of routine monitoring plasma viral load in avoiding unnecessary switches [12] and accumulation of drug resistance [11, 12] are increasingly being acknowledged, its cost effectiveness in resource limited settings is still debated. Since any resources used for laboratory monitoring could divert funds away from expanding access to treatment, it is critical to establish optimal cost effective management. We recently established that routine monitoring of either CD4 cell counts or plasma viral load can save 15-30% of the cost of long term antiretroviral treatment in sub-Saharan Africa by averting the high costs of unnecessary switching to second line therapy [25]. Monitoring of plasma viral load has the added advantages of supporting adherence (as lapses are quickly apparent) [26] and identifying patients at risk of developing drug resistance [27] or transmitting HIV [28]. Studies in developed countries have suggested that there is limited benefit from continued measurements of CD4 cell counts in patients who have suppressed viral load [29, 30]. We therefore propose that antiretroviral programmes in sub-Saharan Africa should monitor plasma viral load rather than CD4 cell counts (once CD4 has risen above 200 cells/μL, when prophylaxis for opportunistic infections is no longer indicated). CD4 cell counts should be used only to establish eligibility for starting antiretroviral treatment and to determine the need for prophylaxis for opportunistic infections.

Scaling-up plasma viral load testing in Africa is feasible because recent technological advances have reduced test costs, simplified sample storage and shipment through the use of dried blood spots, and produced simpler and easy to maintain real-time poly-

merase chain reaction machines [31]. As test prices go down, the potential savings from laboratory monitoring will increase further.

## ACCESS TO ALTERNATIVE DRUG REGIMENS

No matter how vigorous and successful the efforts to combat HIV drug resistance might be, given that the numbers of patients receiving antiretroviral drugs in sub-Saharan Africa are growing, increasing numbers will experience therapy failure. This necessitates improved access to alternative drugs with different modes of action and without cross resistance to NRTIs and non-NRTIs. Current WHO guidelines recommend ritonavir boosted atazanavir or liponavir as the preferred protease inhibitors for second line therapy [9]. Observational studies in Africa have shown that empirical boosted protease inhibitor based regimens can successfully resuppress HIV even in patients with extensive NRTI resistance [32, 33]. Clinical trials are underway to further assess the use of boosted protease inhibitors and integrase inhibitors in second line therapy and the potential for nucleoside sparing regimens. A recent meta-analysis suggested that failure of second line treatment was usually due to suboptimal adherence rather than development of resistance to protease inhibitors, which have a high genetic barrier to resistance [34]. Optimal long term support for adherence will therefore be critical because therapeutic options beyond second line regimens are prohibitively expensive for most African countries.

## SURVEILLANCE OF DRUG RESISTANCE

To protect the sustained effectiveness of antiretroviral regimens, population based drug resistance assessment should be routinely integrated into the national HIV treatment programmes. Donors and technical agencies need to work with the national public health authorities to establish surveillance networks for tracking drug resistant HIV and sharing information with health professionals, policy makers, and researchers. WHO has initiated the Global HIV Drug Resistance Network (HIVResNet), which has developed a global strategy that aims to assess the emergence and transmission of drug resistance and to inform treatment guidelines [35]. More than 25 African countries have implemented one or more HIV drug resistance surveys [35], and the first WHO HIV drug resistance global report will be published in July. Additional initiatives, including the PharmAccess African Studies to Evaluate Resistance (PASER) network [36] and the Southern African Treatment and Resistance Network (SATuRN), have contributed by collecting resistance data, building laboratory capacity, and providing education. However, progress is being jeopardised by a decline in international donor support for surveillance.

## QUALITY OF CARE AND UNIVERSAL ACCESS

A recent study estimated that spending $14.2bn during 2011-20 to keep HIV/AIDS patients alive is expected to save 18.5 million life years and yield as much as $34bn through increased labour productivity, averted orphan care, and deferred medical treatment for opportunistic infections and end of life care [37]. In addition to the large health gains, the economic benefits of antiretroviral treatment are likely to exceed programme costs within ten years.

Clearly, the strengthening of national HIV treatment programmes to expand access to treatment while minimising the development of resistance is a global priority. It is thus disappointing that the first casualty of the global financial crisis seems to have been the goal of universal access, with international funding agencies losing political will. The expenditure of the US President's Emergency Plan for AIDS Relief (PEPFAR) has levelled off since 2009 and the Global Fund to Fight AIDS, Tuberculosis, and Malaria has recently said it will fund only the continuation of essential prevention, treatment, and care services that are currently financed. This development will not only affect access but increase drug resistance through a rise in treatment interruptions, under-dosing, drug sharing, and the use of counterfeit drugs.

## CONCLUSION

Rising drug resistant HIV in sub-Saharan Africa is a potential threat to the worldwide control of HIV/AIDS. National HIV treatment programmes should continue to expand access to antiretroviral drugs but also ensure quality in order to preserve treatment options for tomorrow. They need to ensure robust supply chains, improved diagnostic laboratory capacity, introduction of low cost viral load technologies, and the implementation of resistance surveillance (Box). Investment in such infrastructure now will be critical in the medium to long term.

**Box.** Steps to counter rising HIV drug resistance in sub-Saharan Africa
- Robust supply chains.
- Routine monitoring of viral load to ensure appropriate and timely switching.
- Access to second and third line drug regimens.
- Solid framework for surveillance of drug resistance.
- Continued international funding support to reach the goal of universal and sustainable access.

With declining international funding, the most efficient use of available resources will be critical. Mathematic modelling and economic analyses are needed to provide strategic

information to establish the optimal use of diagnostics and drugs and to determine funding priorities. There is no room for complacency. Without cumulative resistance surveillance data and commitment on the part of WHO, international funding agencies, and national governments to address programmatic challenges, emerging drug resistance has the potential to curb, and even reverse, further progress on breaking the HIV epidemic.

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### Contributors

RLH wrote and revised the report. All authors contributed to intellectual content, helped to revise the report, and approved the final version. RLH is the guarantor.

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