

# MONITORING, SURVEILLANCE AND CONTROL OF HIV DRUG RESISTANCE: THE EXPERIENCE OF A HIGH BURDEN COUNTRY



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In 2012, the South African National HIV drug resistance working group (coordinated by the Department of Health and comprising relevant stakeholders from National Department of Health, public, academic and private health clinicians and laboratories) established a strategy for HIV drug resistance prevention, monitoring and control. The strategy aims to address multiple levels of intervention required to establish activities needed to prevent, detect and monitor the emergence of drug resistance.

Antiretroviral therapy (ART) has provided unprecedented gains and benefits, particularly in countries with heavy HIV burdens. South Africa has the largest number of people living with HIV, recently estimated at 6.4 million, of who >2 million are receiving ART (1). The widespread availability of ART has resulted in significant increases in life expectancy from 52 years in 2005 to 61 years in 2014. AIDS-related deaths are estimated to have decreased from 363,910 in 2005 (51% of all deaths) to 171,733 deaths in 2014 (31% of all deaths), and the infant mortality rate has fallen from 58 deaths per 1,000 live births in 2002 to 34 in 2014 (2). The use of ART to prevent mother-to-child transmission (pMTCT) has significantly reduced infection rates in infants to <3% (3).

The scale up of ART is inevitably accompanied by the emergence of HIV drug resistance (HIVDR), which can compromise the success of ART (4). Resistance is caused by mutations within the viral enzymes that result in a significantly reduced susceptibility to antiretroviral agents. Poor adherence or, in rare situations, factors that lower antiretroviral drug concentrations (e.g. malabsorption, drug interactions) favour the selection of resistant variants. HIVDR can be selected for during regimen failure (acquired or ADR), and transmitted to ART-naïve, newly-infected individuals

(transmitted or TDR). Studies conducted in South Africa have shown a high prevalence of ADR in patients failing first-line ART regimens, similar to that reported from other low- and middle-income countries and evidence of TDR has also been documented (5). Given the large number of people in South Africa on ART and high HIV incidence rates, the ongoing surveillance of HIVDR is therefore critical for the continued efficacy of the ART programme to reduce HIV-related morbidity and mortality in South Africa.

## The South African National Treatment Program

The South African national treatment programme, implemented in 2004, provides ART utilizing a population-based approach with standardized first and second-line regimens as recommended by the World Health Organization (WHO), coupled with regular viral load monitoring. Tenofovir replaced stavudine in 2010 in first line recommendations. In 2013, a fixed dose combination (FDC) of tenofovir, emtricitabine and efavirenz became available for first-line treatment of all adults in the state sector, and is now used in the vast majority of patients. The use of FDCs is encouraged as they are likely to reduce HIVDR selection by avoiding the risks associated with pharmacy stock-outs of one or two drugs in a regimen, and to simplify adherence. Furthermore, viral load

monitoring allows for detection of regimen failure and switch. Protease-inhibitors are used in second-line treatment of adults and in first-line treatment of young children and have been associated with higher levels of viral suppression and lower rates of HIVDR.

Access to third-line ART was implemented in 2013 in the public sector. Empiric switches to third-line ART following virologic failure are not recommended as many of these patients have no PI resistance, and are possibly still failing due to poor adherence. Currently, HIVDR testing is provided for adults and children failing a PI regimen, and access to third-line ART requires demonstration of PI resistance. Selecting individuals who are likely to benefit from third-line ART requires a thorough assessment of adherence and exposure to PIs for a minimum of 12 months. Once PI resistance has been confirmed, a new regimen is constructed based on ritonavir-boosted darunavir together with the most active dual NRTI combination (always including lamivudine/emtricitabine), with the addition of raltegravir and possibly also etravirine for patients with more extensive resistance. The third-line regimen is approved by a small central committee of experts. However, an algorithm based recommendation for selecting third line antiretrovirals has been developed to facilitate regimen selection.

Much of the success of the national programme has been due to a decentralization approach towards ART provision and scale-up, with widespread Nurse Initiated Management of ART (NIMART) and training of nurses at all health facilities, including primary care clinics. Importantly, one programme monitoring system, the Three Interlinked Electronic Register (Tier.net), is implemented at all facilities. This incorporates data from paper-based or electronic registers and allows for minimum data elements and indicators to be reported monthly at district and provincial levels. However, as yet, Tier.net is unable to track patients between facilities, compromising long-term retention and adherence. Patients have been reported to fall out of facility programmes at rates approaching 40% after two years: reasons include defaulting treatment completely, transferring to other government or private sector programmes, or death. A single patient identifier that will allow for differentiation between those who default and those who simply transfer between facilities is needed since tracking of people on ART is critical to containing the spread of HIVDR, and has been agreed to by the national Department of Health.

### **The South African National Strategy for HIVDR prevention and monitoring**

In 2012, the South African National HIV drug resistance

working group (coordinated by the Department of Health and comprising relevant stakeholders from public, academic as well as private health-care clinicians and laboratories) developed a strategy for HIVDR prevention, monitoring and control. The strategic objectives of this working group are:

- ▶ To prevent HIVDR by identifying associated risk factors and devising new preventive strategies;
- ▶ To monitor HIVDR through ongoing national surveillance of selected populations;
- ▶ To develop sufficient capacity to address the increasing need for HIVDR testing, clinical interpretation and management;
- ▶ To strengthen HIVDR monitoring and evaluation, through central data repositories, regular reporting and epidemiological analysis.

The National HIVDR Working Group has drafted a national strategy for HIVDR prevention and monitoring, and is currently preparing an implementation and budgeting plan. The group meets quarterly, to discuss and provide advice on issues related to HIVDR in the country.

In addition, guidelines on the use of resistance testing have been published by local Southern African experts that encompasses a more patient-focused and research-intensive approach (6). The recommendations include HIVDR testing of all first and second-line failures as well as infants exposed to pMTCT. While these recommendations are being adopted in some centres, at present they are not practical on a national level, given the scale of the ART programme in South Africa and the lack of sufficient laboratory and general infrastructure. In addition, recent major developments, such as the EARNEST study results, have yet to be evaluated and integrated in to more updated guidelines (7). Nevertheless, this is an active group that promotes and supports a role for HIVDR testing and routinely hosts skills building workshops and conferences to promote a better understanding of HIVDR.

### **Early warning indicators for HIVDR**

WHO has recommended a set of five early warning indicators (EWIs) for HIVDR which includes measuring on-time pill pick-up, retention in care, pharmacy stock-outs, appropriate dispensing practices and virological suppression (8). The National Strategy for HIVDR plans to extract EWIs from patient records, ART registers and pharmacy records, in order to provide individual facility-based performance assessments. These indicators are intended to enable targeted interventions aimed at improving daily practices to minimize the risks of HIVDR emergence and optimize HIV care. A plan to phase in EWI reporting through Tier.net is in development,

spanning three phases over a five-year period. The pilot assessment (2014/15) will be carried out in two districts in two provinces and will assess the quality of data in each health facility, the availability of laboratory support to the facility, and the human resources capacity at the facility to implement this analysis. The second and third phases will expand this to at least half of, then all, facilities using Tier.net nationwide. A local collaboration of health and human rights non-governmental organizations, in consultation with the Department of Health, have set up a national monitoring system to assess and address drug stock outs, with a strong focus on ART and TB.

### Surveillance of HIVDR in South Africa

To support programmatic data, South Africa has adopted the WHO-recommended approach for national HIVDR surveillance, including estimation of rates of resistance in adult and paediatric patients at the time of initiating ART (pre-treatment HIVDR or PDR surveys) and those receiving ART (ADR surveys), patients infected with resistant HIV strains (TDR surveys) and infants infected with HIV despite possible exposure to PMTCT (paediatric HIVDR surveys) (8). The WHO study protocols are readily available, standardized, and can easily be adapted to become country-specific. The HIVDR Working group is tasked with prioritizing, implementing, and assessing the outcomes from these surveys.

TDR surveys have been conducted in South Africa since 2002 using samples from primagravid young women participating in the national annual antenatal survey. These assessments have shown that transmitted resistance was low prior to and for the first five years of the national ART programme. However, moderate levels (5–15%) of transmitted resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) drug class have been detected in KwaZulu-Natal, the province with the highest HIV burden and largest ART programme. More recently, TDR has been estimated to be at moderate levels to NNRTIs in additional provinces (9). A pilot study to assess ADR in KwaZulu-Natal was conducted in 2013, and a national ADR survey is currently underway in sentinel sites to estimate levels and patterns of HIVDR in treated individuals. These surveys serve to assess the performance of and identify gaps in the ART programme. Surveys among children <18 months of age are also ongoing making use of specimens collected as part of early infant diagnosis (EID) testing, many of who will have been exposed to antiretroviral drugs through PMTCT programmes.

### Scaling up resistance testing for individual patient management

Incorporating HIV drug resistance testing into routine clinical

management in ART-naïve patients and in patients failing first-line ART is currently unrealistic in low-middle income countries such as South Africa, due to the large numbers of people initiating and failing ART and the technological sophistication and costs of current HIVDR tests. Viral failure rates of 10–20% have previously been reported among first-line ART failures which equates roughly to >200,000 HIVDR tests if routine testing were implemented. Although NRTI resistance mutations are commonly present in patients failing first-line ART (5), a number of observational studies have shown that the presence of resistance to the dual NRTIs used in second-line PI regimens does not increase the risk of virologic failure, which illustrates that ritonavir-boosted PIs have high genetic barriers to resistance and are potent (7, 10). There is residual activity of NRTI regimens even with “high level resistance”, notably with resistance mutations to lamivudine (11)/emtricitabine, which is sufficient to achieve virologic suppression when combined with ritonavir-boosted PIs.

### Clinical and laboratory support for HIVDR testing

HIVDR testing occurs in specialized centralized provincial facilities that mostly use in-house genotyping assays. The ongoing expansion of the ART programme and the anticipated increased numbers of patients failing PI-based ART is being supported by expansion of clinical and laboratory capacity. The National Health Laboratory Service is currently capacitating additional facilities to provide five specialized antiretroviral resistance testing centres nationally. These, in conjunction with the surveillance testing laboratory at the National Institute for Communicable Diseases, aim to provide capacity for over 15,000 tests per annum for the public sector. To accommodate further increases in capacity and additional testing recommendations, current research focuses on using next-generation sequencing technologies to allow for pooled testing strategies with higher through-put and exploring simpler and cheaper point-of-care testing options. The number of HIV specialists that can facilitate resistance testing interpretation and deal with complex cases will also need to be increased, who will initially operate at a provincial level with gradual decentralization to district level.

### Data management

Comprehensive, robust and accurate analysis of HIVDR data is essential. A key component of the HIVDR strategy is to develop a central database that can curate, store, analyze and distribute resistance data, collected through routine testing and surveillance activities. In order to accommodate data from a range of systems currently in use, both from private

and public sectors, a minimum set of standardized information has been devised, to be reported to the national database at quarterly intervals. From this, the HIVDR working group will produce written reports and electronic summaries to the National Department of Health. The South African mirror of the Stanford HIV Drug Resistance database is hosted by the Southern African Treatment and Resistance Network (SATuRN <http://www.bioafrica.net/saturn>) and provides a platform from which to develop a centralized database system.

## Conclusion

Significant progress has been made in improving the quality of care for HIV-positive people in resource-limited settings. However, resistance to ART must be monitored quickly and effectively in order to maintain the efficacy of ART regimens. Continued surveillance of HIVDR levels in persons living with HIV and those receiving ART is needed to prevent the widespread emergence of resistance that may have a public health impact. Whilst these efforts are needed to preserve current regimens, this information should further inform new ART options for high burden countries. Such new regimens should prioritize once daily FDC for easier adherence, with higher resistance barriers, and be affordable. Of note, the integrase inhibitor dolutegravir is considered a viable option to replace efavirenz in first-line regimen, due to superior viral suppression (12), fewer side-effects, low dosage and potential low cost, and should be considered in regions with high levels of NNRTI TDR. To support these efforts, continued research is imperative to provide improved regimens, patient monitoring practices and scientific evidence for alternative approaches. ●

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*Professor Francois Venter is the Deputy Executive Director of the Wits Reproductive Health and HIV Institute at the University of the Witwatersrand. He leads multiple antiretroviral treatment optimization studies, and has an active interest in public sector access to HIV services. He is currently working on new first- and second-line antiretroviral options, patient linkage to care interventions, and self-testing projects. Previously, he lead large PEPFAR-funded HIV programmes in South Africa, including one that focused on truckers and sex workers. He has been represented on South African and regional guidelines for over a decade, having done almost all his training within South Africa.*

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