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policy brief

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Drug-resistant HIV in South Africa: Status and response

Summary

As with other antimicrobial agents, widespread use of life saving antiretroviral (ARV) drugs for the management of infection with HIV comes with the risk of the development of antimicrobial resistance. The risk of the development of HIV mutations with resistance to ARVs may be exacerbated by weaknesses in health services and by the loss of patients from the cascade of care. Drug-resistant HIV is associated with a higher risk of mortality, and high levels of drug-resistant HIV will impede progress towards attainment of the 95-95-95 UNAIDS targets and could potentially reverse the remarkable progress that has been made by the antiretroviral treatment (ART) programme to date.

This policy brief presents findings on drug-resistant HIV in South Africa and suggests policy responses to this emerging issue.

Introduction

The 2017 South African HIV prevalence, incidence, behaviour and communication survey (SABSSM V) estimated that there were 7.9 million people living with HIV (PLHIV) in the country.[1] Among them, 4.4 million were on ART, an increase of over 2 million people compared to estimates from the 2012 survey,[2] demonstrating a marked expansion of the ART programme. However, it is notable that an estimated 3.5 million PLHIV were not on treatment in 2017, and the ART programme is therefore still expanding in order to reach the 95-95-95 UNAIDS targets.[3]

As the programme expands, it is critical to monitor the prevalence of drug-resistant HIV to ensure that the treatment regimens remain effective and support attainment and maintenance of viral suppression. HIV drug resistance (HIVDR) surveillance is especially critical in South Africa, which has the largest ART programme globally. Furthermore, South Africa's ART programme has to serve people in diverse settings with heterogeneous challenges to adherence to treatment,[4] factors known to drive HIVDR.

Data from the past 15 years show a marked increase in prevalence of HIVDR worldwide, with rapid increases of pre-treatment drug resistance (PDR) in southern and eastern African countries.[5] In South Africa, studies have also shown varying and increasing levels of drug-resistant HIV. Sentinel surveillance in 2016 found HIVDR in 37.5% of people with prior ART and in 14.2% of those without prior ART.[6]

The 5th South African HIV prevalence, incidence, behaviour and communication survey: What does this survey add to estimates of HIV drug resistance in South Africa?

The 2017 HIV survey included testing for drug-resistant HIV in participants with unsuppressed viral load (viral load ≥1 000 copies/ml), providing a unique opportunity to investigate national level HIVDR in PLHIV.[1] This household-based survey included all sectors of PLHIV, including those who had not yet started treatment, those who had disengaged from care, and those who may have been seeking care in the private sector. These are PLHIV who are very likely to be excluded from HIVDR surveillance methodologies that enrol PLHIV attending public health facilities.

In this survey, more than a quarter (27.4%) of virally unsuppressed respondents had drug-resistant HIV[1] (Figure 1). Resistance was mainly to the non-nucleoside reverse transcriptase inhibitor (NNRTI) drug class used in first-line therapy at the time and was found in 18.9% of the survey participants. One in twelve PLHIV were infected with HIV with dual resistance to both NNRTI and nucleoside reverse transcriptase inhibitor (NRTI) drugs. Fortunately, the prevalence of having resistance to a combination of NNRTI, NRTI and protease inhibitor (PI) drugs was very low (<1.0%). Protease inhibitors are generally used in second-line therapy.

Drug-resistant HIV was more common in males, 29.4% (95% CI 22.5–37.4) compared to females, 25.8% (95% CI 19.8–32.8) for any type of resistance and by drug class (Figure 2).

Drug-resistant HIV was more frequently detected in children, with more than a third of children younger than 14 years old having HIVDR (Figure 3). It was also more frequent in the youth aged 15–24 years than in adults 25 years and older.

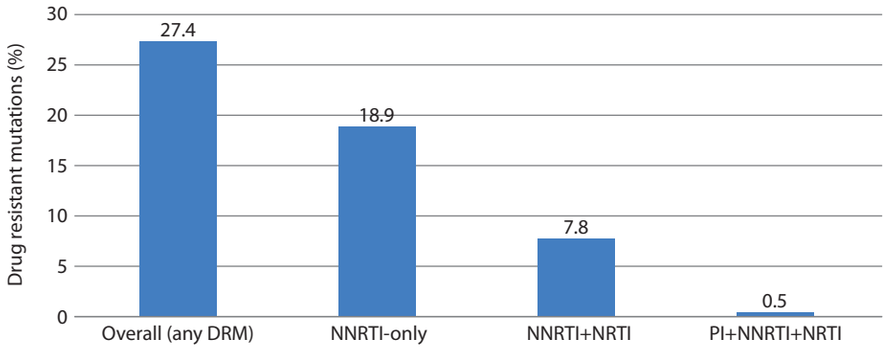

Figure 1: HIV drug resistance

(Source: South African national HIV prevalence, incidence, behaviour and communication survey, 2017)

DRM – drug-resistant mutation; NNRTI – non-nucleoside reverse transcriptase inhibitors; NRTI – nucleoside reverse transcriptase inhibitors; PI – protease inhibitors

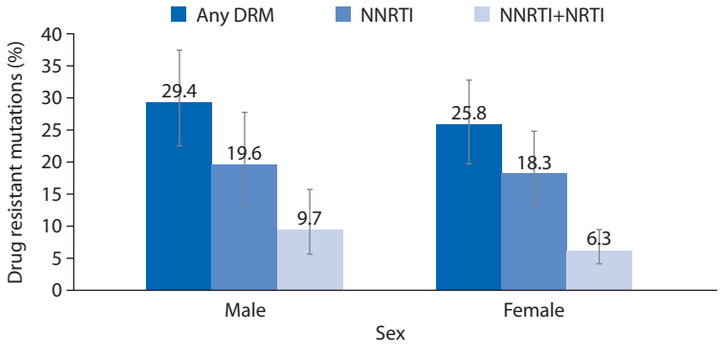

Figure 2: HIV drug resistance by sex

(Source: South African national HIV prevalence, incidence, behaviour and communication survey, 2017)

DRM – drug-resistant mutation; NNRTI – non-nucleoside reverse transcriptase inhibitors; NRTI – nucleoside reverse transcriptase inhibitors

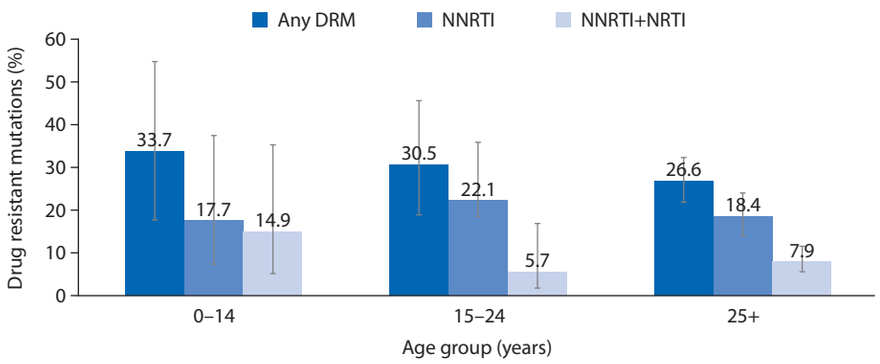

Figure 3: HIV drug resistance by age group

(Source: South African national HIV prevalence, incidence, behaviour and communication survey, 2017)

DRM – drug-resistant mutation; NNRTI – non-nucleoside reverse transcriptase inhibitors; NRTI – nucleoside reverse transcriptase inhibitors

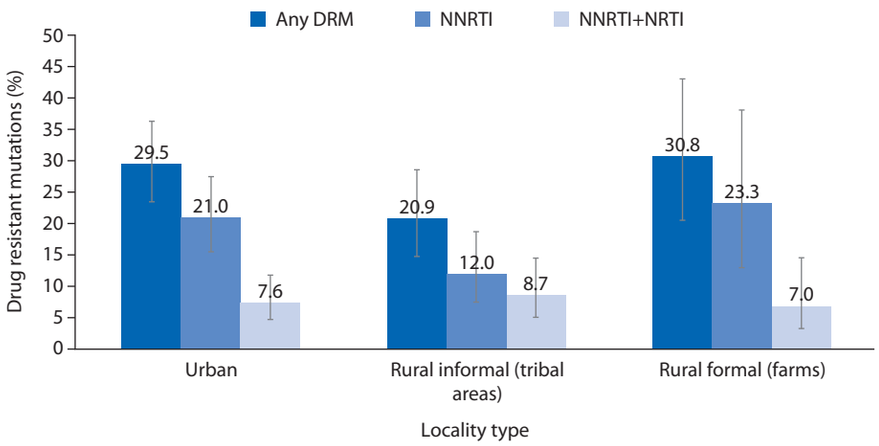

Figure 4: HIV drug resistance by locality type

(Source: South African national HIV prevalence, incidence, behaviour and communication survey, 2017)

DRM – drug-resistant mutation; NNRTI – non-nucleoside reverse transcriptase inhibitors; NRTI – nucleoside reverse transcriptase inhibitors

Table 1: HIV drug resistance by ARV status

(Source: Moyo et al., 2020[8])

ARV status	Any DRM % (95% CI)	NNRTI-only resistance % (95% CI)	Dual NNRTI & NRTI Resistance % (95% CI)
ARV +ve (ARVs detected in blood sample)	55.7 (42.6–67.9)	14.3 (7.5–25.6)	14.3 (7.5–25.6)
ARV –ve (ARVs not detected in blood sample)	22.8 (17.7–28.7)	20.0 (15.4–25.7)	2.1 (0.6–6.8)
ARV defaulters (Reported taking ARVs but ARVs not detected in blood sample)	75.9 (59.2–87.3)	56.4 (34.4–76.2)	14.3 (2.5–52.1)

ARV – antiretroviral; +ve – positive; -ve – negative; DRM – drug-resistant mutation; NNRTI: non-nucleoside reverse transcriptase inhibitors; NRTI: nucleoside reverse transcriptase inhibitors

More than 20% of young people 15–24 years old had resistance to an NNRTI.

Levels of drug-resistant HIV were higher in people who lived on farms (30.8%) than in those in urban areas, and were lowest at 20.9% among those who lived in rural tribal areas (Figure 4).

More than half of participants on ART but with viraemia had drug resistant HIV, a proportion which is lower than anticipated, as clinic-based surveillance of HIVDR in patients failing ART indicate HIVDR prevalence rates of >80%.[7] Not surprisingly, the rates of HIVDR were higher in participants categorised as ART defaulters (75.9%). Of significant concern, HIVDR was reported in 22.8% of persons not receiving ART.

Programmatic implications

These findings indicate concerning levels of HIVDR in the country and are consistent with increasing levels of drug-resistant HIV reported from other countries in the region. There are high levels of HIVDR across all age groups, but more so in children, in those living in farming areas where health services may be limited, and particularly in those who have stopped taking treatment. The findings further emphasise the support for high quality ART services with programmatic actions that respond, prevent, and monitor HIVDR, as recommended in the WHO Global Action plan on HIVDR.[9]

Recommendations: Responding to and preventing HIVDR

1. Support, strengthen and accelerate the roll-out of DTG

South Africa has responded to the increasing levels of HIVDR by recommending alternative treatment regimens and updating the ART guidelines in line with internationally recommended triple drug regimens. First-line ART therapy now includes dolutegravir as the backbone, which is available in a fixed dose combination (FDC) of Tenofovir (TDF) 300 mg + Lamivudine (3TC) 300 mg + Dolutegravir (DTG) 50 mg (TLD) for all eligible adults, adolescents and children over the age of 10 years and weighing 35 kg or more, to replace the efavirenz-based regimen.[10] These regimens are recommended in certain populations by the WHO for countries where NNRTI resistance exceeds 10%.[11] The TLD regimen has been shown to be more advanced because it: i) suppresses VL more rapidly, ii) has a higher drug resistance barrier and is thus more durable, iii) is user friendly with fewer side effects and being a smaller tablet in size, and iv) has fewer drug interactions (in women and girls of childbearing potential the TLD regimen is through informed choice, with the TEE available as an alternative).

2. Support and strengthen entry into treatment and retention in care

While the TLD regimen is more durable, its efficacy should be preserved by coupling with stronger treatment adherence support measures and uninterrupted access to treatment to

reduce defaulting from ARVs and loss from care. Data on the quality of care indicators associated with emergence of HIVDR showed unsatisfactory performance of retention in ART in the 12 months after initiating treatment in South Africa.[7] Therefore, both patient and health system level factors that affect patient retention in care and adherence to treatment must be addressed, including implementation of context specific ART delivery models.

3. Ensure consistent supply of ARVs to all facilities

ARV stockouts result in treatment disruption where people are sent home without treatment or with sub-optimal regimens. ARV stock-outs have previously been reported in South Africa.[12] In the 2017 Stop Stockouts survey, 16% of participating facilities reported an ARV or TB medicine stockout in the preceding three months. Paediatric ARVs were also frequently out of stock. South Africa is also among the countries that have reported ARV disruption due to COVID-19,[13] although there has been a swift response to address the COVID-related disruptions. The proactive response in the context of COVID-19 should also be applied to address the gaps that were present even before COVID-19, including the application of the UNAIDS recommendations[14] to ensure supply and quality of ARVs.

4. Address treatment access disparities in different localities

The 5th South African HIV prevalence, incidence, behaviour and communication survey found higher levels of drug-resistant HIV in farming areas where access to health services may be limited. Efforts to prevent drug-resistant HIV should also focus on disparities in access to ARV services between rural and urban areas. The 2015 Rural health fact sheet reported persisting inequities between urban and rural health care.[4] Special attention should be directed to services in these areas including strengthening partnerships with developmental partners with capacity to reach these areas.

5. Focus on children

While SA has long prioritised prevention of mother to child transmission (PMTCT) and ART for children, there is still need for close monitoring of ART in children to ensure adequate dosing, adherence to treatment, sustained paediatric drug supply, and early reaction to failing regimens as part of addressing HIVDR in children.[15] Although there has been improvement in the availability of paediatric-friendly formulations, several drugs remain difficult for children to take due to unpalatability, side effects and drug-to-drug interactions. Research and innovation are needed in this area.

6. The COVID-19 pandemic

A key factor in 2020, 2021 and the foreseeable future is the COVID-19 pandemic, which has affected access and dispensing of chronic medications including ARVs. The lockdown resulted in some people not accessing their treatment.[16] The government's recovery plan should be ramped up and closely monitored, and the use of the Central Chronic Medicine Dispensing and Distribution (CCMDD) and Pick-Up Points (PuPs) system expanded across all areas of the country.

7. Ongoing monitoring and surveillance

Monitoring of the HIVDR should continue as part of the broader antimicrobial resistance (AMR) monitoring. This is even more critical as ART expands to reach those not yet on treatment. While routine VL measurement is now undertaken,[10] efforts to increase access to routine HIVDR testing should also be increased. This will enable a more rapid response to emerging resistance patterns.

References

1. Simbayi LC, Zuma K, Zungu N, Moyo S, Marinda E, et al. (2018) *South African national HIV prevalence, incidence, behaviour and communication survey, 2017*. Cape Town: HSRC Press
2. Shisana O, Rehle T, Simbayi LC, Zuma K, Jooste S, et al. (2014) *South African national HIV prevalence, incidence and behaviour survey, 2012*. Cape Town, HSRC Press
3. UNAIDS (2014) *Fast-track: Ending the epidemic by 2030*. Accessed 21 February 2021, https://www.unaids.org/sites/default/files/media_asset/JC2686_WAD2014report_en.pdf
4. Rural Health Advocacy Project (n.d.) *Rural health fact sheet 2015*. Accessed 16 February 2021, http://rhap.org.za/wp-content/uploads/2015/09/RHAP-Rural-Health-Fact-Sheet-2015-web.pdf
5. World Health Organization (2017) *HIV drug resistance report 2017*. Licence: CC BY-NC-SA 3.0 IGO
6. Puren A (2016) Prospective sentinel surveillance of human immunodeficiency virus related drug resistance. *NICD Communicable Diseases Communiqué* 15(3) 10–11
7. World Health Organization (2019) *HIV Drug Resistance Report 2019* (WHO/CDS/HIV/19.21). Licence: CC BY-NC-SA 3.0 IGO
8. Moyo S, Hunt G, Zuma K, Zungu M, Marinda E, et al. (2020) *HIV drug resistance profile in South Africa: Findings and implications from the 2017 national HIV household survey*. PLoS ONE 15(11): e0241071. https://doi. org/10.1371/journal.pone.0241071
9. World Health Organization (2017) *Global action plan on HIV drug resistance 2017–2021*. Licence: CC BY-NC-SA 3.0 IGO

10. Republic of South Africa, National Department of Health (2019) *ART clinical guidelines for the management of HIV in adults, pregnancy, adolescents, children, infants and neonates*. Accessed 17 February 2021, https://www.knowledgehub.org.za/system/files/elibdownloads/2020-05/2019%20ART%20Guideline%2028042020%20pdf.pdf
11. World Health Organization (2017) *Guidelines on the public health response to pre-treatment HIV drug resistance*. Licence: CC BY-NC-SA 3.0 IGO
12. Stop Stockouts (2017) *Stop Stockouts 4th national survey report (2017): The fragile system*. Accessed 17 February 2021, https://stockouts.org/Download/Stop%20Stockouts%20National%20Report%20Oct%202018%20High%20res.pdf
13. World Health Organization (2020) *Disruption in HIV, Hepatitis and STI services due to COVID-19*. Accessed 17 February 2021, https://www.who.int/docs/default-source/hiv-hq/disruption-hiv-hepatitis-sti-services-due-to-covid19.pdf?sfvrsn=5f78b742_8
14. UNAIDS (2020) *The impact of the COVID-19 response on the supply chain, availability and cost of generic antiretroviral medicines for HIV in low- and middle-income countries*. Accessed 17 February 2021, https://www.unaids.org/sites/default/files/media_asset/covid19-supply-chain-availability-cost-generic-arv_en.pdf
15. Mo Archary Paediatric Infectious Diseases Unit, King Edward VIII Hospital, UKZN (2018) *HIV Drug Resistance*. Paper presented at XXVII International workshop on HIV Drug resistance and treatment strategies, Johannesburg (22–23 October). Accessed 17 February 2021, https://sahivsoc.org/FileUpload/20181022%20at%2016h20%20Archary.pdf
16. Human Sciences Research Council (2020) *HSRC responds to the COVID-19 Outbreak*. Accessed 17 February 2021, http://www.hsrc.ac.za/uploads/pageContent/11529/COVID-19%20MASTER%20SLIDES%2026%20APRIL%202020%20FOR%20MEDIA%20BRIEFING%20FINAL.pdf

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