Lesotho HIV Drug Resistance Survey

Key Findings Report

2018

PEPFAR
U.S. President's Emergency Plan for AIDS Relief

BOPHELO
MINISTRY OF HEALTH

icap Global Health

Acknowledgements

The 2018 Lesotho HIV Drug Resistance (HIVDR) Survey was implemented by ICAP at Columbia University (ICAP) in collaboration the Lesotho Ministry of Health (MOH) with funding from the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) through the U.S. Centers for Disease Control and Prevention (CDC).

ICAP provided overall technical oversight and direction for all aspects of the project, including protocol development, survey design, implementation and monitoring, data analysis, report writing, and communication of survey results. **CDC** provided leadership and oversight in protocol development, implementation and communication of survey results; executing CDC laboratory capacity planning for genotyping for the survey, including oversight role in genotyping activities; and the supervision, coaching, and training of Lesotho National Reference Laboratory (NRL) lab personnel on genotyping and related procedures. **Lesotho MOH** provided leadership and oversight in protocol development, implementation, monitoring, and communication of survey results. They also authorized and coordinated participation of the NRL and district health authorities.

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Its contents are solely the responsibility of ICAP and do not necessarily represent the official views of the U.S. Government.

Introduction

As countries strive to achieve the *Joint United Nations Programme on HIV/AIDS (UNAIDS) 90-90-90 targets* by the year 2020 and 95-95-95 targets for elimination of AIDS as a public health threat by 2030, knowledge of viral load (VL) suppression in patients on antiretroviral therapy (ART); emerging HIV drug resistance (HIVDR) among individuals failing ART; and the prevalence and pattern HIVDR in those initiating ART (pre-treatment HIV drug resistance or PDR), can assist countries to optimize their ART programs. Such population data can help countries to assess ART program performance in maximizing VL suppression and identify the most beneficial first-line treatment regimen for their populations; provide insight on the extent to which patients are switching therapies unnecessarily; and inform selection and management of second-line therapies.

Since 2003, ICAP at Columbia University (ICAP) has delivered transformative solutions to strengthen health systems in over 30 countries. Drawing from its extensive experience building the capacity of ministries of health (MOH) to conducting high-quality public health surveillance, ICAP collaborated with the Government of Lesotho through the MOH to implement the 2018 Lesotho National HIV Drug Resistance Survey in adults living with HIV infection (ALHIV) between August 2018 and January 2019.

Funded by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) with technical assistance from the U.S. Centers for Disease Control and Prevention (CDC), this was the first nationally representative survey on HIV-1 drug resistance in adults that the explored the overall prevalence of drug resistance and VL suppression in Lesotho.

The main objectives of this survey were: (1) to estimate a nationally representative prevalence of HIVDR among adults newly initiating ART (PDR); (2) to estimate a nationally representative prevalence of VL suppression (< 1000 copies/ml) among adults receiving ART; (3) to estimate a nationally representative prevalence of HIVDR among adults receiving ART with virologic failure at 12 months (ADR12) and 48 months (ADR48); and (4) to estimate nationally representative retention rates at 12 months (RET12) among individuals receiving ART.

THE MAIN OBJECTIVES OF THIS SURVEY WERE:

1. to estimate a nationally representative prevalence of HIVDR among adults newly initiating ART (PDR)
2. to estimate a nationally representative prevalence of VL suppression (< 1000 copies/ml) among adults receiving ART
3. to estimate a nationally representative prevalence of HIVDR among adults receiving ART with virologic failure at 12 months (ADR12) and 48 months (ADR48)
4. to estimate nationally representative retention rates at 12 months (RET12) among individuals receiving ART

Evaluation Design and Methods

The 2018 Lesotho HIVDR Survey was a descriptive, cross-sectional survey of HIVDR that used genotypic resistance testing, a type of resistance test that detects drug-resistant mutations in HIV genes. This test measures the prevalence and describes the patterns of PDR in HIV-infected ART-naïve and experienced adults and measures the prevalence and describes the patterns of Acquired Drug Resistance (ADR) in HIV-infected, ART-experienced adults with virologic failure.

To achieve a nationally representative prevalence estimate for the survey, the team used random sampling to select and sample 30 of the 173 clinics eligible for the survey nationwide based on providing ART to more than 200 adult patients.

Central to ICAP's approach is building system-wide, institutional, and individual capacity to ensure capacity building contextualized to local needs, including the measurable transfer of knowledge, tools, resources, and materials through training. Harnessing expert leadership and innovative approaches to training and capacity building, ICAP designed a training plan, cascading strategies, and supported implementation of five-day trainings for ART clinic staff at the 30 selected clinics on the survey protocol. ICAP also developed standard operating procedures (SOPs) for completion of the survey questionnaires, logbooks, blood specimen collection, and dried blood spot (DBS) specimen preparation and were responsible for screening, obtaining consent, enrolling study subjects in the study, chart abstraction, completing the questionnaire, and collecting DBS specimens from eligible subjects. One laboratory technician attended a six-week training on genotype testing at CDC Atlanta to transfer knowledge and build national lab capacity in DRT.

For the study, all patients newly initiating ART and all patients currently on ART were screened and all eligible patients were consecutively enrolled until each clinic met the required sample size or until a six-month maximum enrollment period passed. A maximum of three patients were enrolled daily in each study arm (PDR, ADR12, ADR48) to minimize disruption of regular services. Data for the consenting study participants were directly extracted from their clinical monitoring chart under normal circumstance. Whenever study-related information was missing from patient records the clinician asked study subjects to update the records. For eligible patients, the ART clinician staff obtained written informed consent; completed

ICAP's Jessica Justman, Senior Technical Director, chairs a session on HIV drug resistance survey implementation in Africa at the 20th International Conference on AIDS and STIs in Africa (ICASA 2019) in Kigali, Rwanda.

the respective PDR and ADR12/48 survey questionnaires; and then obtained a blood sample to prepare DBS. Every week the survey coordinator collected specimens and survey questionnaires from sampled clinics. Once the survey commenced, the study team defined a cohort of patients for retention at 12 months (RET12); identified those who initiated treatment 15 to 27 months back from the start day; and listed chronologically for systematic random sampling of charts all unique identifiers of adults > 18 years. A study team member used the RET12 survey abstraction form to randomly select, retrieve, and abstract charts at each facility.

Leveraging a track record in increasing local ownership of data to ensure high data quality and building country capacity to interpret and use data for decision-making, ICAP analyzed, encrypted, and cleaned the survey data in accordance with recommendations described in the World Health Organization's Surveillance of HIV Drug Resistance in Adults Receiving ART (WHO July 2014) and Surveillance of HIV Drug Resistance in Adults Initiating ART (WHO July 2014) guidance.

Using Stata 15, ICAP HQ generated point estimates and standard error estimates as well as the Stanford HIVdb algorithm to classify HIVDR and calculate prevalence estimates. The survey-generated national estimate of retention was used to estimate adjusted VL suppression for retention. ART clinics were the primary sampling units with stratification by the age of clinics (< 48 months old/ ≥ 48 months old). Data was weighted considering the number of individuals who initiated ART 12 months prior to survey initiation, observed clinic-level survey subject accrual, number of individuals screened, and the number of survey participants with specimens successfully genotyped.

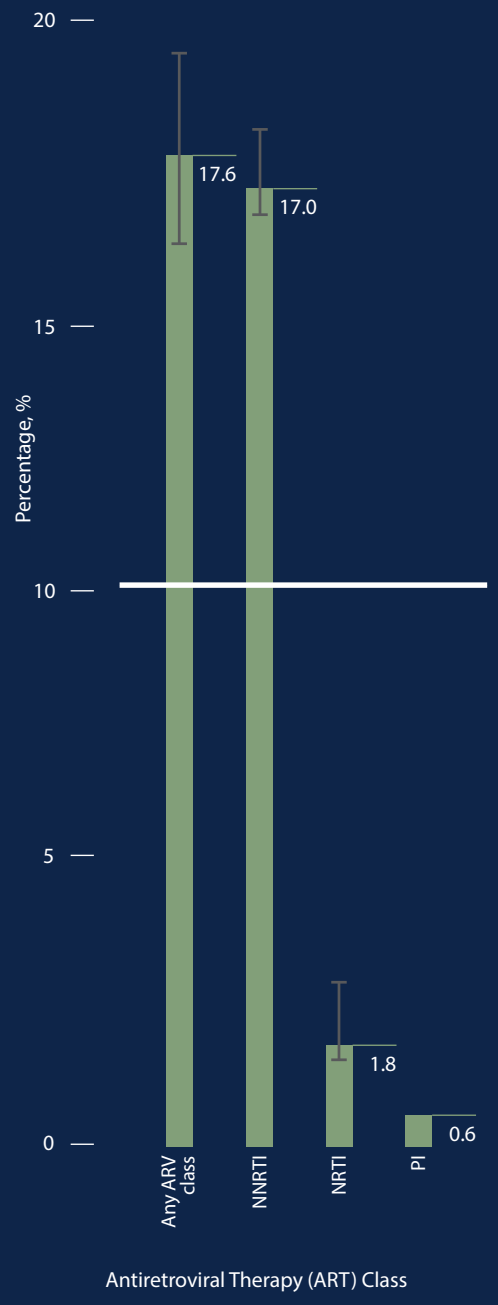
Findings

Pre-treatment Drug Resistance (PDR) Prevalence

Among 418 patients enrolled in the PDR cohort, all initiated a first line ARV regimen; 5.4% had prior ARV exposure; and 390 (93.1%) were successfully genotyped for HIV ARV resistance. The overall prevalence of any ARV drug resistance was 17.6%, which was higher among women (19.0%) than men (14.7%). The youngest group, ages 18-24 years, had the highest drug resistance prevalence (24.1%) and the oldest group (>= 45) had lowest prevalence (14%), although these differences were not statistically significant.

Drug resistance was significantly higher in patients with prior ARV exposure (44.6%) than those without (16.2%). In exploring drug resistance by ARV drug class (Figure 1), NNRTI had the greatest prevalence of drug resistance (17.0%) with less detected in NRTI (1.8%) and PI (0.6%). All the patients who had resistance to NRTI were also resistant to NNRTI. The frequency of any drug resistance mutation (DRM) indicated that NNRTI DRMs occurred at higher frequency: NVP (17.0%), EFV (17.0%) and RPV (10.5%). The most frequently occurring mutations in PDR cohort were K103NS/N/KN (12.9%).

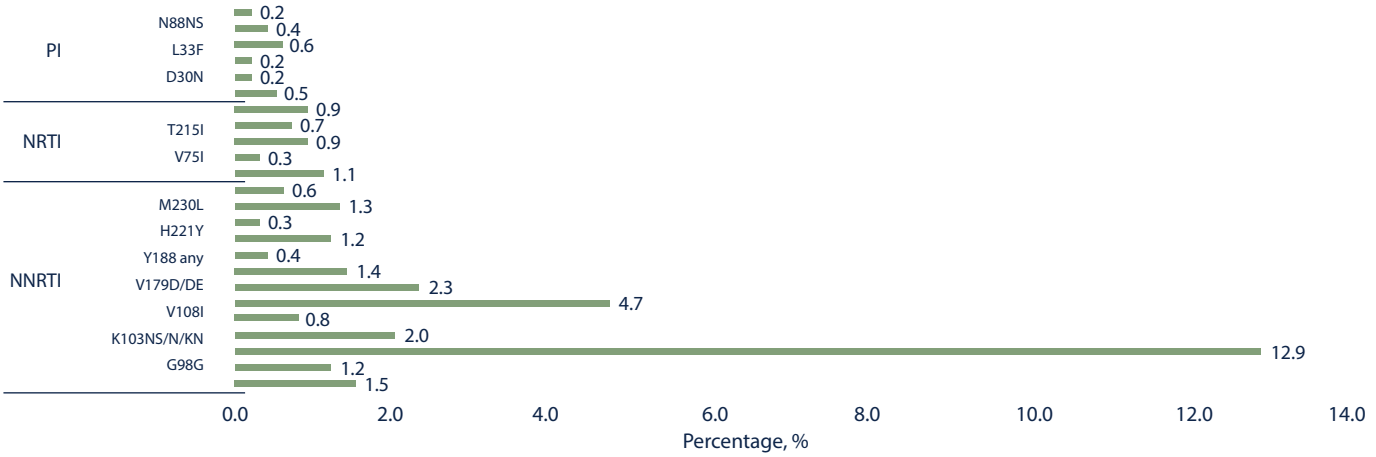
Figure 1
Pre-treatment Drug Resistance (PDR) Prevalence by ART class, %, n=390



Notes: *a. Any drug resistance is defined as low, intermediate or high level resistance according to the Stanford HIVdb to one or more of the following drugs or drug classes: NVP, EFV, any N(t) RTI, DRV/r, LPV/r, or ATV/r. Drug resistance to NNRTI is defined as having low, intermediate or high level resistance to NVP or EFV. Drug resistance to NRTI is defined as having low, intermediate or high-level resistance to any N(t)RTI, including: 3TC, ABC, AZT, D4T, DDI, FTC, TDF. Drug resistance to PI is defined as having low, intermediate, or high-level resistance to DRV/r, ATV/r or LPV/r. This definition is applied to all tables in this document, unless noted otherwise specifically.*

Figure 2

Prevalence of Mutations in PDR Cohort, %, n=390

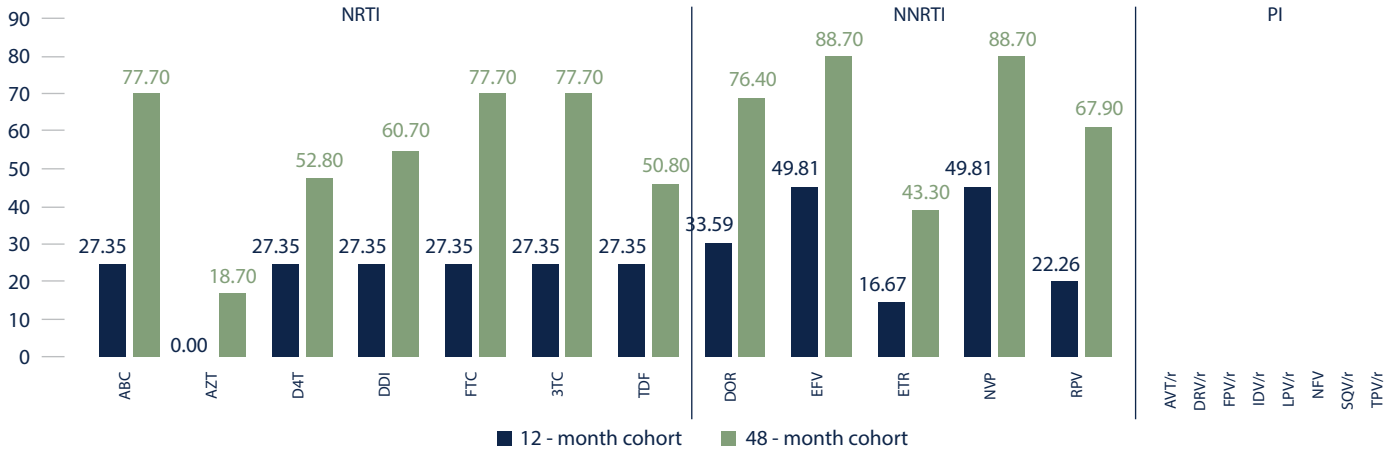


Prevalence of Acquired Drug Resistance (ADR)

The ADR cohorts enrolled 385 patients in the 12-month and 490 patients in the 48-month cohort. The majority of participants in the 12-month cohort (65% women with a mean age of 36 years) were in WHO stage I (83.5%) or WHO stage II (10.4%); only 1.2% of participants had prior ARV/PMTCT exposure before initiating ART this time; and almost all participants were on first line regimens (99.3%). The 48-month cohort (77.5% women with a mean age of 44.7 years) had a higher proportion of patients in WHO stage III (9.7% vs 6.1%) and WHO stage IV (1.4% vs 0.1%). HIV VL tests were conducted for patients in the 12-month and 48-month ADR cohorts and DBS specimens on patients with VL > 1000 copies/ML were genotyped for ARV resistance mutations (22 samples in the 12-month cohort and 40 DBS specimens in the 48-month cohort). Among the patients with VL >1000 copies/ML, HIV drug resistance prevalence was much higher in the 48-month cohort (88.7%) than the 12-month cohort (49.8%). Stratified by drug class, the NNRTI resistance prevalence in 12-month cohort and 48-month cohort was 49.8% and 88.7%, respectively, while the NRTI prevalence was 27.4% and 79.7%, respectively. All the patients had resistance to NRTI also had resistance to NNRTI. None of the patients developed resistance to PI in both cohorts. In factoring in all the patients with VL < 1000 copies as having no drug resistance, the prevalence of any drug resistance was 3.2% in the 12-month cohort and 6.9% in the 48-month cohort. Exploring the frequency of any ADR to individual ARV drugs (Figure 3) indicated higher prevalence of ADR to individual ARV drugs among the 48-month cohort.

Figure 3

Prevalence of ADR to Individual ARV Drugs among 12-month and 48-month Cohorts

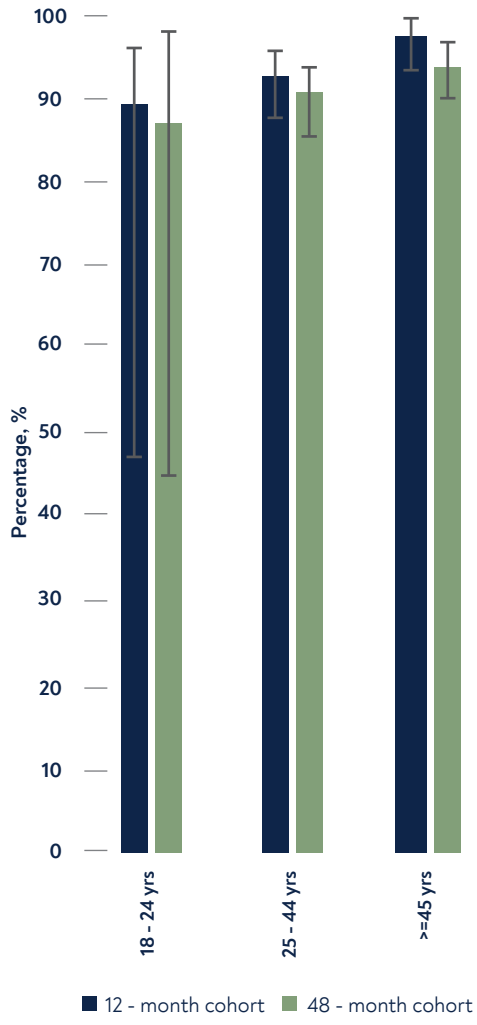


Viral Load Suppression (VLS) in 12-month Cohort

The VL suppression rates among patients in both the 12-month and 48-month cohorts were high at 93.4% and 92.1%, respectively. While there with no observed gender differences in VLS, age differences were apparent with older age groups seeming to have slightly higher VLS in both cohorts (Figure 4). In the 12-month cohort, VLS was much higher among patients without prior ARV exposure than those who had exposure (93.9% vs 63.9%). The 12-month retention rate was 75%, and after adjusted for retention rate, the overall viral suppression rate was reduced to just about 70%.

Figure 4

Viral suppression (< 1000 copies) % by age groups among ADR Cohorts



Note: Two patients in the 12-month cohort did not have VL tests; VLS rates are not adjusted for retention rate.

Conclusion

The 2018 Lesotho National Survey in ALHIV was the first national survey on HIV-1 drug resistance among adults exploring the overall prevalence of ADR and VL suppression in Lesotho. The survey found the levels of pre-treatment NNRTI resistance that exceed WHO's 10% threshold for changing first-line ART. This underscores the need to review national policies on first-line ART regimen composition. The high VL suppression rates (defined as VL < 1000 copies/ml) of 93.4% and 92.1% among participants in the ADR12 and ADR48 cohorts respectively indicate that Lesotho is on track to achieve both the UNAIDS 90-90-90 and 95-95-95 targets for elimination of AIDS as a public health threat by 2030. Yet, this survey also identified low rates of retention (75%) on ART, which resulted in a low retention adjusted VLS estimate of 70% in Lesotho. Although high levels of ADR were observed in this survey, there was no resistance to PI among people failing therapy, which supports the recommendation to treat all individuals failing first-line ART with PI-based regimens.

Using the results of this survey data, the MOH developed a National Strategy for HIV Drug Resistance Prevention, Monitoring and Response 2020-2025. The plan includes five pillars to prevent HIVDR:

- **Prevention and response:** Implement high-impact interventions to prevent and respond to HIVDR
- **Monitoring and surveillance:** Obtain quality data on HIVDR from periodic surveys; expand the coverage and quality of routine VL and HIVDR testing; and monitor quality of service delivery
- **Research and innovation:** Encourage relevant and innovative research for interventions that will have the greatest public health impact on minimizing HIVDR; fill current knowledge gaps on the risk of HIVDR for newer ARV medicines and the impact of service delivery interventions to increase VL suppression and contain HIVDR
- **Laboratory capacity:** Strengthen laboratory capacity and quality to support and expand the use of VL monitoring and build capacity to monitor HIVDR in low- and middle-income countries
- **Governance and enabling environment:** Ensure supportive governance and an enabling environment to address HIVDR, including advocacy, country ownership, coordination

ICAP's achievements during survey implementation included providing:

1. Technical assistance for survey protocol development and facilitation to obtain local and international IRB approvals for the protocol in a timely manner

2. Support for the development all survey related document including survey case report forms, standard operating procedures, and job aids

3. Identification, recruitment, and training/orientation qualified survey staff for survey implementation

4. Support for developing specification, quantification, and procurement for all planned laboratories commodities for the survey including specimen collection and transport commodities (i.e. required DBS collection kits) purchased and supplied in time

5. A one-day workshop with health facility staff where survey staff had to cascade the training under supervision of ICAP Principal Investigators, followed by site activation where the study nurse spent two days at a site to monitor enrolment and blood draw before moving to another site

6. Support through field supervisory visits, remote monitoring of survey implementation, and troubleshooting issues as necessary

7. Development of database and technical assistance for data analysis and dissemination of survey findings

8. Technical assistance for a training held for regional ART Committees on VL focused on best practices in monitoring and managing individuals on ART, including the basics around HIVDR

For more information, visit
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