Open Forum Infectious Diseases

BRIEF REPORT

Human Immunodeficiency Virus-1 Drug Resistance Patterns Among Adult Patients Failing Second-Line Protease Inhibitor-Containing Regimens in Namibia, 2010–2015

Souleymane Sawadogo,[1] Andreas Shiningavamwe,[2] Clay Roscoe,[1] Andrew L. Baughman,[1] Taffa Negussie,[1] Gram Mutandi,[1] Chunfu Yang,[3] Ndapewa Hamunime,[4] and Simon Agolory[1]

[1]Division of Global HIV and Tuberculosis, Windhoek, Namibia; [2]Namibia Institute of Pathology, Windhoek; [3]Division of Global HIV and Tuberculosis, Atlanta, Georgia; [4]Ministry of Health and Social Services, Windhoek, Namibia

Three hundred sixty-six adult patients in Namibia with second-line virologic failures were evaluated for human immunodeficiency virus drug-resistant (HIVDR) mutations. Less than half (41.5%) harbored ≥1 HIVDR mutations to standardized second-line antiretroviral therapy (ART) regimen. Optimizing adherence, viral load monitoring, and genotyping are critical to prevent emergence of resistance, as well as unnecessary switching to costly third-line ART regimens.

Keywords: ART; drug resistance; Namibia; second line.

In 2016, globally, 54% of people living with human immunodeficiency virus (HIV) were estimated to be on antiretroviral therapy (ART), and, between 2005 and 2016, acquired immune deficiency syndrome (AIDS)-related deaths decreased by 48% [1]. The 2016 World Health Organization guidelines for ART in low- and middle-income countries recommends implementing routine viral load (VL) testing to detect virologic failure (VF) and to monitor treatment response to ART. However, limited availability of VL monitoring and delayed switching to second-line ART in some settings could contribute to the accumulation of HIV drug resistance (HIVDR) in populations living with HIV/AIDS in sub-Saharan Africa (SSA).

The Namibian National ART guidelines recommends VL testing 6 months after switching to second-line ART. If the VL level is >1000 copies/mL, intensive adherence counseling is performed and VL testing is repeated after 3 months. If the follow-up VL level is >1000 copies/mL, the patient is considered to have second-line VF and is referred to the Central Clinical Committee for HIVDR testing to determine the antiretroviral (ARV) combination needed for a third-line regimen based on observed mutations.

METHODS

A retrospective data review of laboratory genotyping results was conducted for adult patients (>15 years) treated with a second-line ART regimen containing lopinavir/ritonavir (LPV/r) and 3 nucleoside reverse-transcriptase inhibitors (NRTIs) with VF who had HIVDR tests performed between 2010 and 2015. During the study period, Namibia's first-line ART was lamivudine (3TC), tenofovir (TDF), and nevirapine (NVP) until 2014, then changing to emtricitabine (FTC), TDF, and efavirenz (EFV). Second-line ART consisted of zidovudine (ZDV), 3TC, TDF, and LPVr. Third-line ART is determined on a case-by-case basis by the HIVDR Clinical Review Committee using clinical history and genotype results [2]. Between 2010 and 2015, a total of 898 adult and pediatric patients suspected of failing second-line ART had genotyping requested, and this investigation evaluated the prevalence and patterns of HIVDR mutations in adults with suspected second-line VL failure with genotype results.

We identified 366 adult patients with HIVDR results available. The HIVDR mutations causing low-, intermediate-, or high-level of resistance, using the Stanford HIVdb algorithm, were identified. Resistance patterns were analyzed for any association with gender and age.

RESULTS

A total of 366 adult patients with genotype results were included, 51.1% were female, and the median age was 40 (interquartile range, 33–47). Human immunodeficiency virus-1 subtype C represented 90% of cases, followed by recombinants B/C (5%), and 08_BC/C, and CRF02_AG (3% each).

Overall, 58.5% (214 of 366) of the patients demonstrated no HIVDR mutations, and 41.5% harbored 1 or more HIVDR mutations. The prevalence of the most common mutations observed for NRTIs were as follows: any 138 (37.7%); M184V 114 (31.1%); T215Y/F 46 (12.6%); D67N 36 (9.8%); M41L 32 (8.7%); K219Q/E 31 (8.5%); K70R 26 (7.1%); and L210W 15 (4.1%). For protease inhibitors (PIs), the most common mutations observed were as follows: any 37 (10.1%); V82A 25 (6.8%); M46I/L 24 (6.6%); L76V 12 (3.3%); I54V 10 (2.7%); L90M 7 (1.9%); and I84V 6 (1.6%). Of all patients with resistance to PIs (n = 37), 20 (54.1%) also had thymidine analogue mutations

Received 19 October 2017; editorial decision 2 January 2018; accepted 10 January 2018.
Correspondence: S. Sawadogo, MSc, Florence Nightingale Street, Windhoek, Namibia (bya7@cdc.gov).

Open Forum Infectious Diseases®
Published by Oxford University Press on behalf of Infectious Diseases Society of America 2018.

DOI: 10.1093/ofid/ofy014

(TAMs). Of those with both PI HIVDR and TAMs, 8 (40%) had 2 TAMs and 11 (55%) had ≥3. Of the 20 total cases with PI HIVDR and TAMs, 6 patients (30%) had both type 1 and type 2 TAMs, with the remainder having only type 1 (n = 8, 40%) or only type 2 (n = 6, 30%).

A total of 152 (41.5%) patients had HIVDR mutations to the standardized second-line ARV drugs (SLDs), including 45 (12.3%) with resistance to 1 drug, 30 (8.2%) with resistance to 2 drugs, 61 (16.7%) with resistance to 3 drugs, and 18 (4.9%) with resistance to all 4 SLDs (Figure 1). The number of patients with resistance to NRTIs used in standardized second-line ART was variable: 3TC 126 (34.4%), azidothymidine 89 (24.3%), and TDF 104 (28.4%). The number of patients with resistance to LPV/r was 37 (10.1 %), and the resistance rate to LPVr did not differ per year (8.0%–12.0%, P = .98). No association was observed between HIVDR and age (>25 versus 16–24 years) (relative risk [RR] = 0.87; 95% confidence interval [CI], 0.52–1.43; P = .46) or sex (female versus male) (RR = 1.05; 95% CI, 0.76–1.44; P = .70).

DISCUSSION

This study has several important findings. First, 58.5% of the patients with second-line failure did not harbor any HIVDR to SLDs, suggesting that most VFs were not due to HIVDR. This observations suggests that intensified adherence counseling and management of side effects may be the best first approach to managing a detectable VL after starting second-line ART [3]. As reported in other countries in SSA [4], the high rates of no HIVDR detected in patients suspected of failing second-line ART highlights the importance of routine HIV VL monitoring for early detection of ART nonadherence, followed by genotype testing for patients clearly suspected of failing second-line ART. This approach can help prevent unnecessary switching to costly third-line drugs, which should be preserved for patients with confirmed second-line ART failure [5, 6]. Inappropriate switching to second- and third-line ART drains limited resources, with recent pricing data estimating the cost of first-line ART at US dollars (USD)$106, compared with second-line ART at USD$286 and third-line ART at USD$1859 [7].

Second, any resistance to the NRTI backbone used in second-line ART regimens was observed in 138 (37.7%), of which 32 (23.2%), 31 (22.5%), and 75 (54.3%) patients were resistant to 1, 2 or 3 drugs, respectively. The NRTI resistance observed could partially or completely render the NRTI backbone ineffective in patients being evaluated for third-line ART. However, the low PI resistance rate (10.1%) to LPV/r observed in this study is reassuring, considering that genotypic resistance testing may not accurately predict NRTI activity when prescribing protease inhibitor-based ART to patients failing second-line ART. The PI-based regimens have demonstrated full virologic suppression in this setting, even with no predicted NRTI activity, suggesting a role for NRTI resistance mutations in reducing viral fitness [8].

Third, the 10.1% of patients who had resistance to LPVr were considered to have true second-line VF, and this finding highlights the need for HIVDR testing for second-line ART patients with true VF (not VF secondary to poor adherence) to ensure these patients are prescribed effective third-line ART regimens.

Finally, the prevalence rates for overall, class- and drug-specific HIVDR in this study were comparable to HIVDR prevalence studies that have been performed in other countries in SSA [9–11].

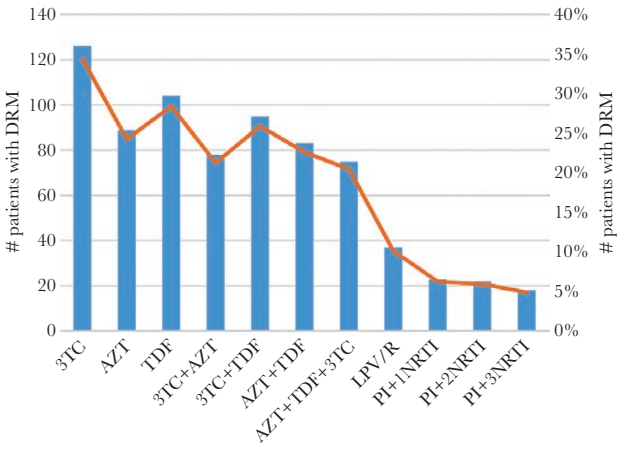

Figure 1. Pattern and prevalence of human immunodeficiency virus (HIV) drug resistance in the 366 patients with confirmed virological failures and treated with the standard Namibia LPV/r-containing second-line antiretroviral regimen from 2010 to 2015. No. of patients with drug-resistant mutations (DRM) (■); percentage of patients with DRM (■).

CONCLUSIONS

This study demonstrated extensive NRTI resistance mutations and emerging PI resistance in patients failing second-line ART in Namibia, supporting the importance of optimizing ART adherence, routine VL monitoring to detect early emergence of VF, and genotypic analysis before initiating third-line ART [4]. These findings also underscore the need for increased access to salvage ARVs (eg, durable PIs and integrase strand transfer inhibitors) to ensure that patients failing second-line ART are able to switch to efficacious, third-line ART regimens to prevent the further accumulation of HIVDR.

There are 2 limitations to this study. First, there was no access to individual patient ART regimen history, duration on ART, adherence data, or other clinical information that would have been useful for further interpreting findings. Second, the sample size was relatively small, limiting the power to detect associations and assess confounding factors. The findings of this study provides important information that can be used programmatically for the management of patients with VF on second-line PI-containing regimens in Namibia.

Acknowledgments

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the funding agencies.

Financial support. This project has been funded in part by the President's Emergency Plan for AIDS Relief through the Centers for Disease Control and Prevention under cooperative agreement number U2GPS002058.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. UNAIDS. Fact sheet - Latest statistics on the status of the AIDS epidemic. **2016**. Available at: http://www.unaids.org/en/resources/fact-sheet. Accessed 15 May 2017.
2. National Guidelines for Antiretroviral Therapy, Third Edition, July 2010. Available at: http://www.who.int/hiv/pub/guidelines/namibia_art.pdf. Accessed 15 May 2017.
3. Boyd MA, Moore CL, Molina JM, et al. Baseline HIV-1 resistance, virological outcomes, and emergent resistance in the SECOND-LINE trial: an exploratory analysis. Lancet HIV **2015**; 2:e42–51.
4. Johnston V, Cohen K, Wiesner L, et al. Viral suppression following switch to second-line antiretroviral therapy: associations with nucleoside reverse transcriptase inhibitor resistance and subtherapeutic drug concentrations prior to switch. J Infect Dis **2014**; 209:711–20.
5. Collier D, Iwuji C, Derache A, et al. Virological outcomes of second-line protease inhibitor-based treatment for human immunodeficiency virus type 1 in a high-prevalence rural South African setting: a competing-risks prospective cohort analysis. Clin Infect Dis **2017**; 64:1006–16.
6. Boyd MA, Kumarasamy N, Moore CI, et al. Ritonavir-boosted lopinavir plus nucleoside or nucleotide reverse transcriptase inhibitors versus ritonavir-boosted lopinavir plus raltegravir for treatment of HIV-1 infection in adults with virological failure of a standard first-line ART regimen (SECOND-LINE): a randomised, open-label, non-inferiority study. Lancet **2013**; 381:2091–99.
7. Médecins Sans Frontières. **2016**. Untangling the Web of Antiretroviralprice Reductions, 18th Edition—July 2016. Available at: https://www.msfaccess.org/sites/default/files/ HIV_report_Untangling-the-web-18thed_ENG_2016.pdf. Accessed 18 December 2017.
8. Paton NI, Kityo C, Thompson J, et al. Nucleoside reverse-transcriptase inhibitor cross-resistance and outcomes from second-line antiretroviral therapy in the public health approach: an observational analysis within the randomised, open-label, EARNEST trial. Lancet HIV **2017**; 4:e341–8.
9. Namakoola I, Kasama I, Mayanja BJ, et al. From antiretroviral therapy access to provision of third line regimens: evidence of HIV drug resistance mutations to first and second line regimens among Uganda adults. BMC Res Notes **2016**; 9:515–25.
10. Meintjes G, Dunn L, Coetsee M, et al. Third-line antiretroviral therapy in Africa: effectiveness in a Southern African retrospective cohort study. AIDS Res Ther **2015**; 12:39.
11. Rawizza HE, Chaplin B, Meloni ST, et al. Accumulation of protease mutations among patients failing second-line antiretroviral therapy and response to salvage therapy in Nigeria. PLoS One **2013**; 8:e73582.