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PERSPECTIVES

Dolutegravir Resistance in African Programmatic Settings Among Patients With Failure of Dolutegravir-based ART

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Dolutegravir resistance is emerging in routine clinical contexts in southern Africa, primarily in patients with prior treatment experience failing dolutegravir-based antiretroviral therapy (ART). This potential issue was raised by The Nucleosides and Darunavir/Dolutegravir in Africa trial that compared dolutegravir and boosted protease inhibitor–based therapy as second-line ART, in which new dolutegravir resistance was observed at failure. However, recent data suggest that also at risk are patients who were transitioned to dolutegravir from non-nucleoside reverse transcriptase inhibitor–based ART while viremic. Identifying patients experiencing failure of dolutegravir with resistance will be difficult given current gaps in viral load monitoring and limited capacity for genotypic resistance testing. As a result, in the short term, most patients affected will go unrecognized, with particularly important implications for patients affected who have advanced HIV or who are pregnant/breastfeeding. Prospective research is needed to understand the scope of the problem, identify additional risk factors, and determine best management. In the short term, for most patients with dolutegravir resistance and prior non-nucleoside reverse transcriptase inhibitor exposure, the best option will be a timely switch to a regimen anchored by a boosted protease inhibitor, with a high genetic barrier to resistance.

Keywords. antiretroviral drug resistance; dolutegravir; HIV-1; sub-Saharan Africa; virologic failure.

Zindile Ndlovu (identifying details changed), a 37-year-old person with HIV in South Africa, had a worrisome lab finding. Ten years ago, she initiated antiretroviral therapy (ART) with a nevirapine-based regimen but fell out of care. At reengagement, she started second-line therapy consisting of dolutegravir with zidovudine/lamivudine, became briefly suppressed, and was transitioned to dolutegravir, lamivudine, and tenofovir disoproxil fumarate (TLD) with inconsistent follow up. By early 2022, her viral load was 10 500 copies/mL and, despite adherence counseling, she experienced ongoing viremia and progressed to advanced HIV. The clinician received permission from the provincial expert for resistance testing, which revealed nucleoside reverse transcriptase inhibitor, non-nucleoside reverse transcriptase inhibitor (NNRTI), and 3 integrase strand transfer inhibitor mutations (G118R, E138K, and L74M), conferring high-level dolutegravir resistance [1].

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Dolutegravir Resistance in Treatment-experienced Patients With Failure of TLD

Dolutegravir resistance is emerging in routine clinical contexts in southern Africa, primarily in patients with prior treatment experience failing dolutegravir-based ART (Table 1) [2, 3]. It is an important development for which there is little evidence to guide front-line clinicians.

Dolutegravir resistance has not been a major clinical issue in North America and Europe. In clinical trials of treatment-naïve patients, there was not a single case of emergent dolutegravir resistance in more than 2000 participants [4]. However, it can emerge in ART-experienced patients with failure during second-line dolutegravir-based therapy. This was first evident in The Nucleosides and Darunavir/Dolutegravir in Africa (NADIA) study in which participants with prior virological failure of NNRTI-based ART were randomized to a second-line regimen anchored by dolutegravir or darunavir/ritonavir; in NADIA, 9 (38%) of 24 participants subsequently failing in the dolutegravir arm developed integrase resistance. whereas no resistance emerged in the darunavir/ritonavir arm [5]. Nonetheless, in NADIA, the overall efficacy of second-line dolutegravir-based ART was high, and the results helped guide the adaption of dolutegravir after failure of NNRTI-based ART in many countries. However, the implications of the wide

Table 1. Summary of Patients With Emergent Dolutegravir Resistance Mutations at a Single Clinic in KwaZulu-Natal, South Africa

Gender	Nadir CD4, cells/μL[a]	Active Infection	Treatment Experience (and OOC)	VL at DTG-based ART Start, copies/mL	ART[e]	VL at Failure, copies/mL	Time to Emergent Resistance[b]	Resistance Mutations	Predicted Dolutegravir Resistance[c]	Subsequent Regimen/ Outcome
F	124	None		18 500	TLD	10 550	236 wk[d]	M184V M41L T215Y A98G G190A K101E E138K G118R L74M	High	DRV/r + TDF/3TC VL was 202 copies/mL 12 wk after switch
F	409	None	TDF/FTC/EFV – 188 wk OOC – 85 wk TDF/FTC/EFV – 81 wk	160 000	DTG + AZT/ 3TC	3481	121 wk	NI55H S147G T97A L47I S119R L100I/L	Intermediate	ATZ/r + TDF/3TC VL was undetectable 16 wk after switch
F	99	TB after switch to boosted PI-based ART	TDF/FTC/EFV – 55 wk OOC – 276 wk	503 533	DTG + AZT/ 3TC	213 298	69 wk	M184V A98G K101E G190S E138K G118R T66A/T L74I	High	DRV/r + TDF/3TC DRV/r-based ART stopped because of drug-drug interaction between DRV/r and TB therapy and 9 mo after switch VL 18 769 copies/mL
F	131	None	TDF/FTC/EFV – 176 wk LPV/r + AZT/3TC – 17 wk OOC – 92 wk LPV/r + AZT/3TC – 191 wk ATZ/r + TDF/ 3TC – 36 wk	86 188	DTG + AZT/ 3TC	3265	78 wk	M184V V106I G190A R263K	Intermediate	DRV/r + TDF/FTC VL was 589 copies/mL 12 wk after switch

Abbreviations: 3TC, lamivudine; ART, antiretroviral therapy; AZT, zidovudine; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; NVP, nevirapine; OOC, out of care; TB, tuberculosis; TDF, tenofovir; TLD, tenofovir/lamivudine/dolutegravir; VL, viral load.

[a]Nadir in this series refers to lowest CD4 cell count before switch to dolutegravir-based ART (TLD).

[b]This corresponds to the time between initiation of dolutegravir-based ART and when integrase inhibitor resistance documented.

[c]The resistance level is based on the Stanford HIVdb Program accessed 4/28/2024: https://hivdb.stanford.edu/hivdb/by-patterns/.

[d]The delayed genotype was in part related to the patient falling out of care for 12 mo because of cancer diagnosis.

[e]ART refers to ART regimen when dolutegravir resistance was documented.

implementation of dolutegravir as second-line ART in programmatic settings where viral load monitoring is less robust and patients experience treatment failure longer were not known [6].

A key question, therefore, has been if dolutegravir resistance would emerge in routine African settings among patients receiving TLD. Part of the answer comes from a study in Mozambique that prospectively followed patients who had transitioned to TLD from prior NNRTI-based ART [7]. Investigators enrolled patients (n = 716) who, after transition to TLD, experienced an elevated viral load >1000 copies/mL. Among this group, 70% of patients resuppressed after adherence intervention, 30% (n = 216) had persistent virologic failure, and 6% (n = 45) developed dolutegravir resistance. Notably, a higher risk for dolutegravir resistance was observed in patients who were virologically unsuppressed when transitioned from NNRTI-based ART to TLD. These data not only illustrate the potential for dolutegravir resistance in the routine settings, but also highlight an additional patient population at risk: patients not defined as having first-line failure but who were viremic at transition to TLD. For example, in 2018, 750,000 patients in Malawi transitioned to TLD without viral load testing [8]. Despite a higher baseline risk for dolutegravir resistance, this group is considered in most national algorithms to be receiving "first-line ART" and, at failure, would not be prioritized for resistance testing or switch interventions [9].

Distinguishing Treatment-naive Patients at low-risk for Dolutegravir Resistance

An additional nuance is that making the distinction in the clinic between treatment-naïve and treatment-experienced patients is not always straightforward [10]. In a South African cohort, 53% of patients presenting for "initial ART" use in the pre-TLD era had evidence of ART exposure [11]. Undisclosed use of ART may result from movement between ART programs, stigma, postpregnancy loss from care, ART sharing, and care churn [10, 12, 13]. Despite these challenges, at the individual level, accurately assigning a patient with failure of TLD into a category according to whether there was a prior treatment failure will be helpful in prioritizing the use of resistance testing.

The Scope of the Problem of Dolutegravir Resistance at TLD Failure is Uncertain

Short-term outcomes and clinical trial results provide some optimism that the scope of dolutegravir resistance in African settings may be confined to a subset. After transition to TLD from NNRTI-based ART, 12-month viral load >1000 copies/mL was seen in only 5%, 2%, and 6% of patients in South Africa (n = 6370) [14], Malawi (n = 1892) [8], and Tanzania (n = 600) [15] respectively. Additionally, among patients with dolutegravir failure, only 2 (14%) of 14 in Malawi and 3 (10%) of 30 patients in Tanzania had high-level dolutegravir resistance [8]. Additionally, the phase out of zidovudine from national HIV programs may help avoid development of dolutegravir resistance. There was numerically less dolutegravir resistance emerging in patients receiving tenofovir-based backbone regimens compared to zidovudine in the NADIA study. However, even a subset of individuals experiencing dolutegravir resistance is concerning in the context of broad adoption of TLD after prior virologic failure (whether documented or not) in settings with scarce resources for detecting INSTI resistance.

RECOMMENDATIONS

In the short term, it is likely that most patients with TLD failure with dolutegravir resistance in routine African settings will go unrecognized. Even in countries with the capacity to perform resistance testing, guidelines limit access; in South Africa, genotype testing is limited to patients experiencing second-line TLD failure for at least 2 years [9]. Broadening this access would align with newer data and on-the-ground clinician experience.

Prospective studies in patients experiencing TLD failure will be important to define the prevalence of dolutegravir resistance, including cohorts enriched with known and potential higher risk characteristics including prior treatment failure, evidence of inadequate adherence, drug-drug interactions (for example, concomitant rifampicin, which reduces dolutegravir concentration) [16], non-B subtype [17], and the presence of advanced HIV disease [18, 19]. Randomized clinical trials for treatment-experienced patients experiencing failure of TLD should evaluate strategies involving algorithms using adherence interventions, point-of-care drug concentrations, and/or early switch to boosted protease inhibitor (PI)-based ART [20].

Practical challenges include the issue that currently, at the point of care, a clinician must both have the technical expertise to recognize the potential for dolutegravir resistance and—if available—advocate for resistance testing. Moreover, TLD treatment failure will play out in a context in which viral load monitoring is underused or unavailable and delayed recognition of ART failure is already common [6]. As clinicians await further study outcomes, patients with TLD failure living with advanced HIV or pregnant/breastfeeding should be prioritized for early genotypic resistance testing (or if resistance testing is not accessible, early switch to a PI-based regimen) to avoid poor outcomes.

CONCLUSIONS

In summary, dolutegravir resistance is affecting patients in programmatic settings in Africa, and established risk factors consist of prior treatment failure on an NNRTI-based regimen or a history of transition to TLD when viremic, with additional risk factors to be defined. The best management strategy in the context of prior NNRTI exposure is likely to be a switch to a regimen anchored by a boosted PI [8]. Our patient, Zindile, transitioned to a darunavir/ritonavir-based regimen. At 6 months, her viral load was <400 copies/mL. Despite this, Zindile's experience may not be typical. She benefitted from an assertive clinical team within a well-staffed hospital-based HIV clinic that advocated for resistance testing and timely regimen change. The team also had prior experience with other patients with emergent dolutegravir resistance (Table 1). Overall, it is likely that this issue will have greater clinical implications where there are fewer experienced clinicians, more limited access to genotype testing and greater barriers to rapid deployment of boosted PI-based ART options.

Notes

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Patient consent statement. All identifying details in the patient anecdote were modified and informed consent was not obtained.

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