Virologic Outcomes with Tenofovir-Lamivudine-Dolutegravir for PI-Based Second-Line ART Failure

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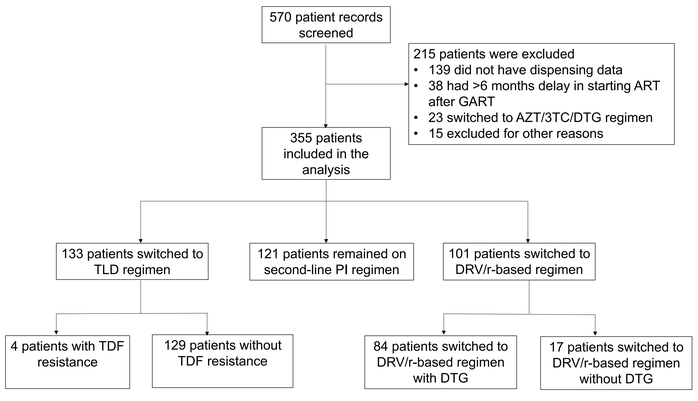
BACKGROUND

In South African antiretroviral guidelines, selected patients failing second-line protease inhibitor (PI) regimens qualify for genotypic antiretroviral resistance testing (GART) – those with PI resistance receive darunavir-based regimens; those without PI resistance continue current regimen with adherence support. The Western Cape Province from September 2020 implemented a strategy of tenofovir-lamivudine-dolutegravir (TLD) for patients, provided there was no tenofovir resistance, irrespective of PI resistance.

METHODS

- An observational cohort study comparing outcomes in patients switched to TLD with those continuing the same PI or switched to darunavir-based regimens.
- We included consecutive patients with virologic failure (two HIV-1 RNA ≥1000 copies/mL despite adherence optimisation) who had been on a ritonavir-boosted lopinavir or atazanavir second-line regimen for at least two years, and in whom a GART was performed.
- The primary outcome was time to virologic suppression (HIV-1 RNA <400 copies/mL). Firstly, comparing those switched to TLD with those continuing the same PI (when no PI resistance detected) and, secondly, comparing those switched to TLD with those switched to a darunavir-based regimen (when PI resistance detected). Follow up was until the primary outcome, or censoring at death, loss to follow-up, or July 2023.

Figure 1: Patient flow diagram



Amongst patients with virologic failure on second-line PI regimens without PI resistance, switching to TLD was associated with improved virologic outcomes compared to those not switching. Virologic outcomes were similar in patients with PI resistance switched to darunavir-based regimens or TLD.

RESULTS

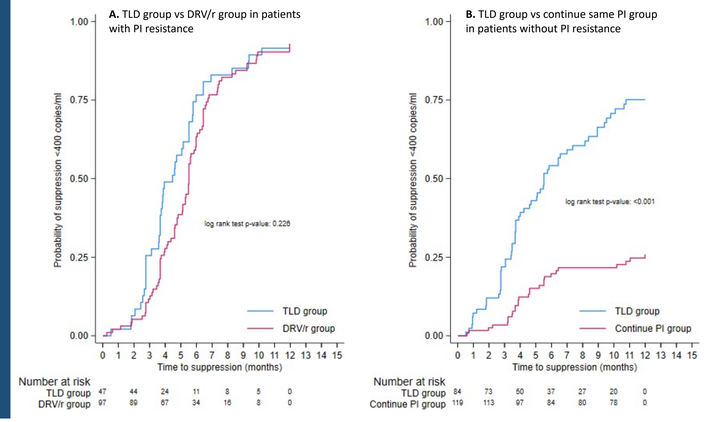
- Data from 355 patients with virologic failure on a second-line PI regimen were analysed; these included 148 patients with PI resistance and 207 patients without PI resistance (**Figure 1**).
- Demographics and clinical characteristics at the time of GART are summarized in **Table 1**.
- Time to HIV-1 RNA <400 copies/mL by study arm is shown in **Figure 2**.
- By 12 months, among patients with PI resistance, 42/47 (89%) in the TLD group had HIV-1 RNA <400 copies/mL compared to 91/99 (92%) in the darunavir group (hazard ratio, 1.11; 95% CI, 0.77–1.60).
- In patients without PI resistance, 66/86 (77%) in the TLD group had HIV-1 RNA <400 copies/mL compared to 42/120 (35%) in those continuing the same PI (hazard ratio, 4.03; 95% CI, 2.71–5.98) - this effect persisted after adjustment for HIV-1 RNA and CD4+ cell count at the time of second-line failure in a multivariate Cox proportional hazard model (adjusted HR, 3.96; 95% CI, 2.25–6.98).
- Two (2%) patients in the TLD group were known to have developed virologic failure with dolutegravir resistance at 1-3 years after switching to TLD.

Table 1: Baseline characteristics at the time of genotypic resistance testing

	PI resistance			No PI resistance		
Variable	**TLD group (n = 47)**	**DRV/r group (n = 99)**	**P-value**	**TLD group (n = 86)**	**Continue PI group (n = 120)**	**P-value**
Age, years	42 (36-48)	40 (36-47)	0.521	40 (34-46)	40 (33-46)	0.636
Female sex, n (%)	31 (66.0)	63 (63.6)	0.784	60 (69.8)	90 (75)	0.405
CD4+ cell count, cells/μL	189 (84-297)	170 (53-322)	0.971	137 (96-230)	135 (71-227)	0.568
HIV-1 RNA, $\log_{10}$ copies/mL	4.4 (3.6-5.0)	4.7 (4.1-4.9)	0.122	4.8 (4.1-5.4)	4.7 (4.3-5.2)	0.977
Receiving TDF at first-line failure, n (%)	36 (81.8)	54 (55.7)	0.003	55 (68.8)	77 (65.8)	0.667
Lopinavir resistance, n (%)	45 (95.7)	93 (93.9)	0.712	0 (0.0)	0 (0.0)	1.000
Atazanavir resistance, n (%)	47 (100.0)	99 (100.0)	1.000	0 (0.0)	0 (0.0)	1.000
Darunavir resistance, n (%)	23 (48.9)	45 (45.5)	0.831	0 (0.0)	0 (0.0)	1.000

Resistance was classified with the Stanford algorithm, with a score of ≥10 indicating at least potential low-level resistance.

Figure 2: Kaplan-Meier for time to virological suppression



CONCLUSIONS

- Amongst patients who had virologic failure on second-line PI regimens, a high proportion of those with PI resistance switched to TLD or darunavir-based regimens achieved virologic suppression.
- The improved virologic outcomes with switching from a failing PI regimen to TLD when there was no PI resistance was likely driven by improved adherence with a better tolerated single tablet regimen.
- Our results provide evidence to support switching to TLD after PI regimen failure with the caveat that only patients without tenofovir resistance were switched to TLD in this study.
- Our findings highlight the need for awareness of the higher risk of dolutegravir resistance in patients with prior regimen failure compared to those never having failed a regimen (i.e. have fully active NRTIs).

ADDITIONAL KEY INFORMATION

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