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Efficacy of Tenofovir-Lamivudine-Dolutegravir for Initial and First-Line Switch ART

Cissy Kityo[1], Caitlyn McCarthy[2], Michael Hughes[2], Catherine Godfrey[3], Carole Wallis[4], Urvi Parikh[5], Sarita Shah[6], Yukari C. Manabe[7], George K. Siberry[8], Isaac Tsikhutsu[9], Elizabeth Woolley[10], John W. Mellors[5], Charles W. Flexner[7], James Hakim[11], for The AIDS Clinical Trials Group A5381/The Hakim Study Team

[1]Joint Clinical Research Centre, Kampala, Uganda, [2]Harvard TH Chan School of Public Health, Boston, MA, United States, [3]Office of the Global AIDS Coordinator, Department of State, Washington, DC, USA, [4]Lancet Labs and BARC SA, Johannesburg, South Africa, [5]University of Pittsburgh, Pittsburgh, PA, United States, [6]Rollins School of Public Health Emory University, Atlanta, USA, [7]The Johns Hopkins University, Baltimore, MD, United States, [8]United States Agency for International Development (USAID), Washington, DC, USA, [9]Kenya Medical Research Institute/Walter Reed Project Clinical Research Center (KEMRI/WRP), Kericho, Kenya, [10]DLH Corporation, Silver Spring, USA, [11]Milton Park CRS, Harare, Zimbabwe

BACKGROUND

- The single-tablet regimen of tenofovir disoproxil fumarate/lamivudine/dolutegravir (TLD) has been rapidly adopted as first- and second-line antiretroviral therapy (ART) in PEPFAR-supported programs.
- There are limited data on the risks and benefits of TLD rollout in programmatic settings where viral load and drug resistance testing are not widely used to guide ART management.
- ACTG A5381 is an observational, longitudinal prospective cohort study to assess efficacy and emergence of HIV drug resistance following initiation of TLD. This report presents results through to 6 months of follow-up for participants switching to TLD from a virally suppressive first-line NNRTI-based regimen (Group 1b) and for those initiating ART with TLD (Group 4).

OBJECTIVES

The primary objectives were to estimate the proportion of participants on TLD with HIV-1 RNA ≤1000 copies/mL at 6 months and the proportion of participants on TLD with new DTG resistance mutations at 6 months within each group.

METHODS

- Adults and adolescents (≥10 years) with HIV were recruited at 13 ACTG sites in 6 countries.
- HIV-1 RNA levels were measured at study entry and at 6 months.
- Standard genotyping was performed for participants with HIV-1 RNA >1000 copies/mL at 6 months of follow-up.
- Proportions were estimated together with the associated two-sided exact 95% confidence intervals based on the binomial distribution.
- Analyses of the primary outcome measures were restricted to participants who were still taking TLD at 6 months.

Among participants on TLD at 6 months of follow-up, 99% who switched to TLD from a virally-suppressive first-line NNRTI-based regimen (Group 1b) and 90% who initiated ART with TLD (Group 4) had suppression of HIV-1 RNA to ≤1000 copies/mL. Of those with HIV-1 RNA >1000 copies/mL, none had clear evidence of emerging INSTI resistance.

RESULTS

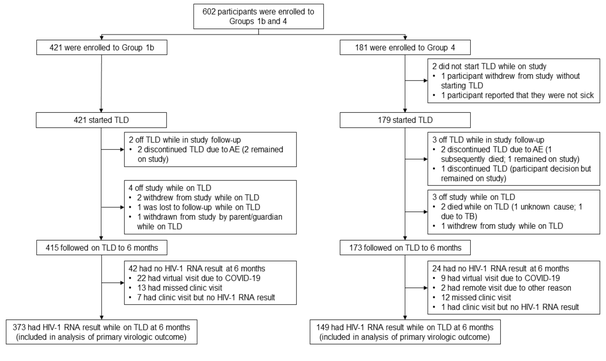
- From October 2019 to October 2020, 600 participants were enrolled and started TLD.
- In Group 1b, median (Q1, Q3) time on ART at start of TLD was 6.6 years (3.3, 10.3).
- Two participants in Group 1b (0.5% of 421) and two participants in Group 4 (1.1% of 179) discontinued TLD due to adverse events before 6 months:
  - In Group 1b, one participant had decreased creatinine renal clearance and acute kidney injury and one had nausea and vomiting.
  - In Group 4, one participant had acute kidney injury and one had increased blood creatinine.

Table 1. Baseline Characteristics

		Group 1b (N=421)	Group 4 (N=179)
Sex	Female	336 (80%)	76 (42%)
Gender identity	Cisgender	421 (100%)	177 (99%)
Age (years)	Mean (s.d.)	40 (11)	36 (10)
	Median (Q1, Q3)	41 (33, 47)	35 (28, 42)
	Min, Max	10, 74	18, 61
	# missing	0	0
Country	Haiti	7 (2%)	47 (26%)
	Kenya	123 (29%)	29 (16%)
	Malawi	40 (10%)	71 (40%)
	South Africa	139 (33%)	4 (2%)
	Uganda	54 (13%)	25 (14%)
	Zimbabwe	58 (14%)	3 (2%)
HIV-1 RNA (log_{10} copies/mL)	Mean (s.d.)	1.6 (0.2)	4.1 (1.3)
	Median (Q1, Q3)	1.6 (1.6, 1.6)	4.4 (3.5, 5.1)
	Min, Max	1.3, 3.0	1.6, 6.2
	# missing	0	0
	<50 copies/mL	402 (95%)	25 (14%)
	50-200 copies/mL	12 (3%)	1 (1%)
	201-1,000 copies/mL	7 (2%)	10 (6%)
	1,001-10,000 copies/mL	0 (0%)	30 (17%)
	10,001-100,000 copies/mL	0 (0%)	65 (36%)
	>100,000 copies/mL	0 (0%)	48 (27%)
CD4 count (cells/mm³)	Mean (s.d.)	711 (317)	362 (283)
	Median (Q1, Q3)	679 (471, 893)	302 (165, 517)
	Min, Max	56, 2277	1, 1574
	# missing	11	10

HIV-1 RNA results below the assay lower limit of quantification (LLQ) are imputed to be the LLQ minus one.

Figure 1. STROBE Diagram



RESULTS

Table 2. Proportion of Participants on TLD at 6 Months with HIV-1 RNA Suppressed to Three Thresholds: ≤1000, ≤200, and <50 copies/mL

	Group 1b (N=421)		Group 4 (N=179)	
	N/total on TLD with measurement	% (exact 95% CI)	N/total on TLD with measurement	% (exact 95% CI)
Primary virologic outcome:				
HIV-1 RNA ≤1000 copies/mL	369/373	98.9 (97.3, 99.7)	134/149	89.9 (83.9, 94.3)
Exploratory virologic outcomes:				
HIV-1 RNA ≤200 copies/mL	367/373	98.4 (96.5, 99.4)	130/149	87.2 (80.8, 92.1)
HIV-1 RNA <50 copies/mL	358/373	96.0 (93.5, 97.7)	126/149	84.6 (77.7, 90.0)

The total on TLD with measurement was noticeably impacted by the number of participants with missed clinic visits and with virtual visits due to the COVID-19 pandemic at 6 months (see Figure 1).

- A new mutation possibly selected by dolutegravir (DTG) was observed in one participant in Group 1b at 6 months (T97A/T). No Group 4 participants showed DTG resistance at 6 months.

CONCLUSIONS

- TLD was well tolerated and achieved high rates of viral suppression in ART-naïve participants and in participants who switched from virally-suppressive first-line ART.
- An emerging INSTI mutation of uncertain significance was seen in only one participant.
- Early results of ACTG A5381 support transition to TLD.

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