UNIVERSITY of WASHINGTON
DEPARTMENT OF GLOBAL HEALTH

*International Clinical Research Center (ICRC), University of Washington
UW Box 359927, 325 Ninth Ave, Seattle , WA, 98104
Phone: 206 520 3820, Fax: 206 520 3831, Email: ccelum@uw.edu

CROI Abstract 728
Session: Herpes Virus Coinfections
Session Day, Date and Time: Thursday, February 25

HSV-2 acquisition among HIV-1 infected adults with tenofovir-based ART in ACTG A5175

Connie Celum[1], Ting Hong[1], Anne Cent[1], Rhoda Morrow[1], Jared Baeten[1], N. Kumarasamy[2], Beatriz Grinsztejn[3], Mina Hosseinipour[4], Thomas Campbell[5], and the ACTG PEARLS/A5175 team

[1]University of Washington, Seattle, USA; [2] YRG Care, Chennai, India; [3]Fiocruz, Rio de Janeiro, Brazil; [4]University of Chapel Hill, NC; [5]University of Colorado, Denver, CO

Background

- HSV-2 infection is highly prevalent (50-90%) in HIV-infected persons and associated with increased HIV viral load and greater risk of HIV transmission and disease progression.
- Tenofovir disoproxil fumarate (TDF) has *in vitro* efficacy against HSV-2 and reduced HSV-2 acquisition by 30% in HIV-1 uninfected persons on PrEP (Celum, Ann Intern Med 2014).
- Although a majority of HIV-infected persons are on TDF-containing antiretroviral treatment (ART), the efficacy of TDF to reduce HSV-2 acquisition in HIV-infected persons is unknown.

Methods

- ACTG A5175 (PEARLS) was an open label RCT, which enrolled 1571 ARV-naïve HIV-infected persons from India, Brazil, Malawi, South Africa, USA, Peru, Zimbabwe, Haiti, and Thailand from 2005-07, followed through 2010 (Campbell, PLoS Med 2012).
- Participants were randomized to receive: either a TDF-containing regimen (TDF, FTC, & EFZ), *or* a non-TDF regimen (ZDV, 3TC, & EFZ, *or* DDI, FTC, & ATZ).
- We analyzed HSV-2 serostatus of archived sera at baseline and exit visits by Focus HSV-2 EIA with HSV Western blot to confirm indeterminate EIAs (0.9-3.4)
- Efficacy of TDF was assessed using 365 participants who were HSV-2 seronegative at baseline.
- Intent to treat analysis using Cox proportional hazards regression was the primary analysis.
- An as-treated analysis was used to account for the high rate of ART regimen change during follow-up:
  - During ACTG study follow-up, of participants who were HSV-2 seronegative at baseline, 21% in TDF and 43% in the non-TDF regimen group switched ART regimen groups during follow-up.
  - Notably, 31 of 68 (46%) HSV-2 seroconverters switched regimen groups.
  - To minimize misclassification of TDF exposure, the as-treated analysis censored follow-up before first regimen switch for those who switched regimen groups during follow-up.
  - For the 31 HSV-2 seroconverters who switched regimen groups, HSV-2 serostatus was assessed using the last available sample prior to first regimen change.
  - We compared groups using the Turnbull algorithm for interval censored survival analysis, and estimated the hazard ratio assuming an exponential survival distribution.

References
- Campbell TB, Smeaton LM, Kumarasamy N, et al; PEARLS study team of the ACTG. Efficacy and safety of three antiretroviral regimens for initial treatment of HIV-1: a randomized clinical trial in diverse multinational settings. PLoS Med. 2012;9:e1001290.
- Celum C, Morrow R, Donnell D, et al; Partners PrEP Study Team. Daily oral tenofovir and emtricitabine-tenofovir preexposure prophylaxis reduces herpes simplex virus type 2 acquisition among heterosexual HIV-1-uninfected men and women: a subgroup analysis of a randomized trial. Ann Intern Med. 2014; 161:11-9

Results

Figure 1. Consort diagram of ACTG 5175 for HSV-2 seroconversion by treatment arm

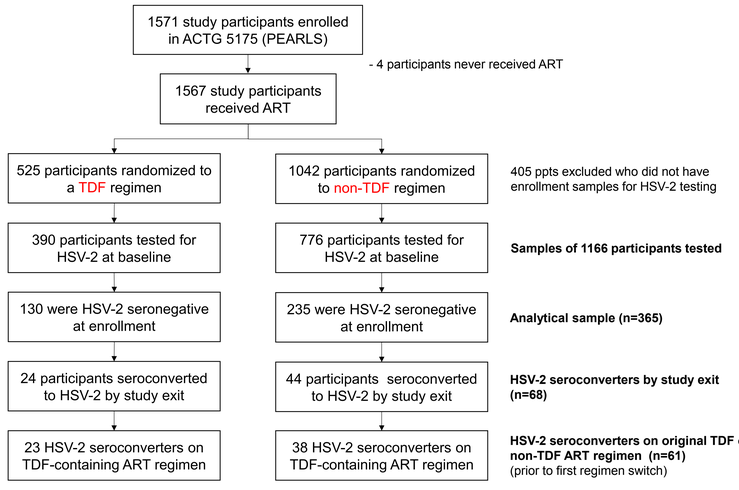


Table 1. Baseline characteristics of HSV-2 seronegative, HIV-1 seropositive participants in ACTG A5175 y by treatment arm

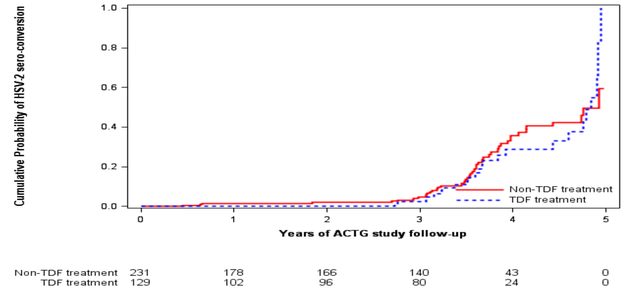
	Median (interquartile range) or N (%)	
	TDF-containing ART arm, N=130	Non-TDF containing ART arm, N=235
Demographic Characteristics		
Male sex	88 (68%)	165 (70%)
Age, years	13 (10%)	35 (14.9%)
18–24	63 (48.5%)	92 (39.1%)
25–34	40 (30.8%)	78 (33.2%)
35-44	14 (10.8%)	30 (12.8%)
≥ 45	13 (10%)	35 (14.9%)
HIV status		
CD4 (media, IQR)	174 (105, 234)	192 (88, 241)
Plasma viral load (log_{10} c/mL median, IQR)	5.1 (4.6, 5.6)	5.1 (4.7, 5.5)
Country		
Brazil	28 (21.5%)	59 (25.1%)
Haiti	9 (6.9%)	14 (6%)
India	21 (16.2%)	40 (17%)
Malawi	5 (3.8%)	10 (4.3%)
Peru	15 (11.5%)	31 (13.2%)
South Africa	11 (8.5%)	11 (4.7%)
Thailand	12 (9.2%)	7 (3%)
United States	29 (22.3%)	63 (26.8%)

Results

Table 2: HSV-2 seroincidence in ACTG A5175 among initially HSV-2 seronegative persons by ART arm

	TDF-containing ART regimen			Non-TDF containing regimen				
	N ppts	# events/ person-yrs	Rate	N ppts	# events/ person-yrs	Rate	Hazard ratio (vs non- TDF ART)	P value
Intent to treat analysis	130	24/274	6.42	235	44/663	6.63	0.89 (95% CI 0.55-1.44)	0.63

Figure 2. ITT analysis cumulative infection curves



- In the as-treated analysis in which we censored follow-up before date of first ART regimen change, no significant difference in HSV-2 seroconversion was observed (HR 0.92, 95%CI 0.45-1.41; p=0.98).

Summary and Discussion

- In this international, multi-site, open label, randomized trial of 3 ARV regimens, annual HSV-2 incidence was high (average of 6.5/100 person years across arms) among HSV-2 seronegative, HIV-infected persons.
- By both intent to treat and as-treated analyses, there was no protective benefit of TDF against HSV-2 acquisition in the randomized comparison.
- Limitations included 1) the high rate of ART regimen switching between TDF and non-TDF groups which led to differential assessment by arm in the as-treated analysis (a higher proportion switched from non-TDF to TDF regimens), and 2) ascertainment of HSV-2 status only at study exit for initially HSV-2 seronegative persons (and prior to ART change for HSV-2 seroconverters who changed regimens) which led to imprecise knowledge of timing of HSV-2 seroconversion. Differences by arm early in follow-up could have been missed.
- Given that TDF is a common backbone of ART in HIV-positive persons and that our findings conflict with reduction in HSV-2 acquisition on TDF and TDF/FTC PrEP in HIV-uninfected persons, further research on whether TDF can prevent HSV-2 acquisition in HIV-infected persons is needed.

Acknowledgements: The authors thank the study volunteers, sites, and the ACTG 5175 team of investigators. We also thank Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb, Gilead Sciences, and GlaxoSmithKline for their support and assistance.