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BRIEF REPORT

Herpes Simplex Virus Type 2 Acquisition Among HIV-1–Infected Adults Treated With Tenofovir Disoproxyl Fumarate as Part of Combination Antiretroviral Therapy: Results From the ACTG A5175 PEARLS Study

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Objective. Tenofovir disoproxyl fumarate (TDF) disoproxyl fumarate (TDF) has in vitro activity against herpes simplex virus type 2 (HSV-2) and reduced HSV-2 acquisition as preexposure prophylaxis. Whether TDF-containing antiretroviral therapy (ART) reduces HSV-2 acquisition is unknown.

Design. Secondary analysis of AIDS Clinical Trials Group A5175, a randomized, open-label study of 3 ART regimens among 1571 participants.

Methods. HSV-2 serostatus was assessed at baseline, at study exit, and before a change in ART regimen.

Results. Of 365 HSV-2–seronegative persons, 68 acquired HSV-2, with 24 receiving TDF-containing ART and 44 receiving ART without TDF (HSV-2 seroconversion incidence, 6.42 and 6.63 cases/100 person-years, respectively; hazard ratio, 0.89; 95% confidence interval, .55–1.44).

Conclusions. HSV-2 acquisition was not reduced in HIV-infected, HSV-2–uninfected persons during TDF-containing ART.

Keywords. HIV-1; HSV-2; prevention; tenofovir; antiretroviral therapy; Africa.

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Herpes simplex virus type 2 (HSV-2) seroprevalence is high among human immunodeficiency virus type 1 (HIV-1)–infected persons, with prevalence of 60% in the United States among men who have sex with men and 85% in Africa among heterosexuals [1]. HSV-2 infection increases the HIV-1 load [1], the risk of HIV-1 transmission by 2-fold [2], and the rate of HIV-1 disease progression [3]. Because of the high prevalence of HSV-2 and the synergistic interaction between HSV-2 and HIV-1, which increases the susceptibility to infection with and the infectiousness of HIV-1, effective strategies for preventing HSV-2 infection are needed.

Tenofovir disoproxil fumarate (TDF) has anti–HSV-2 activity in vitro, as demonstrated by inhibition of the cytopathicity of laboratory strains of HSV-1 and HSV-2 in human fibroblasts and keratinocytes, with a median effective concentration (EC_{50}) ranging from 103 to 193 μg/mL, which is markedly higher those for acyclovir, adefovir, and cidofovir [4]. Pericoital use of 1% TDF vaginal gel, which achieved high intravaginal concentrations, significantly reduced HSV-2 acquisition by 51% in the CAPRISA 004 study [5]. In a secondary analysis of HSV-2 acquisition among HIV-1–seronegative participants in the Partners Preexposure Prophylaxis Study (Partners PrEP Study) who were initially HSV-2 seronegative, HSV-2 acquisition was reduced by 35% among those randomly assigned to receive oral preexposure prophylaxis daily, either TDF alone or coformulated with emtricitabine (FTC/TDF), compared with findings in the placebo group [6]. In contrast, HSV-2 acquisition was not reduced in the Preexposure Prophylaxis Initiative (iPrEX) trial of oral FTC/TDF PrEP in men who have sex with men [7]. However, adherence was substantially lower in the iPrEX trial, compared with that among HIV-uninfected persons in an HIV-serodiscordant partnership in the Partners PrEP Study (54% vs 82%), as measured by detectable TDF levels in a random sample of preexposure prophylaxis recipients from each study [8, 9].

These results suggest that oral TDF dosing may provide modest protection against HSV-2 acquisition if adherence to daily dosing is high. Given that the HSV-2 prevalence is high in HIV-1–infected persons and increases HIV-1 infectiousness and disease progression, an important question is whether TDF, as part of combination antiretroviral treatment (ART), reduces HSV-2 acquisition among HIV-1–infected persons who are uninfected with HSV-2. Because of its high potency against HIV-1, tolerability, and excellent safety, TDF is the most common antiretroviral among the nucleoside/nucleotide class prescribed as part of ART. If TDF is demonstrated to reduce the risk of HSV-2 acquisition in HIV-1–infected persons, it would provide an additional clinical and

public benefit as part of combination ART, in addition to its potent suppression of HIV-1.

To assess whether TDF reduced HSV-2 acquisition in HIV-1–infected persons, we evaluated HSV-2 seroconversion rates among HIV-1–infected persons who were initially uninfected with HSV-2 and were enrolled in an international, multicenter, randomized, open-label trial of TDF and non-TDF combination ART regimens.

METHODS

Study Population

This is a secondary data analysis of AIDS Clinical Trials Group (ACTG) A5175 (the Prospective Evaluation of Antiretrovirals in Resource-Limited Settings [PEARLS] study), which was an open-label, randomized trial of the safety and efficacy of 3 combination ART regimens as the initial ART regimen: a TDF-containing regimen including TDF, emtricitabine, and efavirenz; a non–TDF-containing regimen including zidovudine, lamivudine, and efavirenz; and a non–TDF-containing regimen including didanosine, emtricitabine, and atazanavir [10]. Eligible participants were ≥18 years old; were HIV-1 seropositive; had a $CD4^+$ T-cell count of <300 cells/μL; had received ART for a cumulative duration of ≤7 days; had normal neutrophil counts, renal function, and liver function; were not pregnant; and were using effective contraception. A total of 1571 HIV-infected persons were enrolled from India, Brazil, Malawi, South Africa, the United States, Peru, Zimbabwe, Haiti, and Thailand from 2005 through 2007, with visits every 8 weeks for testing for pregnancy, analysis of renal function, liver function testing, and measurement of HIV-1 RNA loads and $CD4^+$ T-cell counts. Participants were allowed to change ART regimens on the basis of serious abnormal laboratory findings, drug intolerabilities, or virologic failure.

Laboratory Methods

HSV-2 serostatus was determined in archived sera from participants, using a stepwise approach to HSV-2 testing at the University of Washington Virology Laboratory. Baseline sera were tested for HSV-2 by using the Focus HerpeSelect 1/2 enzyme immunoassays (EIA; Cypress, CA). Samples with an index value of ≤0.9 were considered negative for HSV-2 antibodies, and those with Focus EIA values of >3.4 were considered HSV-2 seropositive [11]. Samples with intermediate Focus EIA values (ie, index values of 1.0–3.4) were analyzed using an HSV-2 Western blot [12], performed at the University of Washington Virology Laboratory, to clarify HSV-2 baseline serostatus. For individuals with a negative or indeterminate baseline HSV-2 status, their exit sample was tested for HSV-2 by using the same algorithm. For HSV-2 seroconverters who switched ART regimens during follow-up, the last sample before ART regimen switch was tested for HSV-2.

Statistical Analysis

The primary exposure of interest was TDF as part of combination ART, so the 2 non–TDF-containing ART regimens were compared to the TDF arm (TDF, emtricitabine, and efavirenz). 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. To minimize misclassification of TDF exposure, the as-treated analysis censored follow-up before the first ART regimen switch for those who switched regimen groups during follow-up. We compared groups by using the Turnbull algorithm for interval-censored survival analysis and estimated the hazard ratio (HR) after assuming an exponential survival distribution. Analyses were conducted with SAS 9.4 (Cary, NC).

RESULTS

Of the 1571 participants enrolled into ACTG A5175, 1567 were randomly assigned to receive 1 of 3 ART regimens. Baseline sera were available from 1166 participants, of whom 799 (69%) were HSV-2 positive. The 365 participants who were HSV-2 seronegative at baseline composed the sample for this analysis, among whom 69% were male, and the median age was 33 years (interquartile range [IQR], 27–39 years) (Table 1). Baseline median $CD4^+$ T-cell count was 174 cells/μL (IQR, 105–324 cells/μL) in the TDF-containing arm and 192 cells/μL (IQR, 88–241 cells/μL) in the non–TDF-containing arms. The median duration of follow-up for the 365 participants was 2.61 years (IQR, 0.94–3.49 years).

ART Regimen Switch

During study follow-up, 128 of 365 participants (35%) who were HSV-2 seronegative at baseline switched ART regimens: 27 of 130 (21%) randomly assigned to the TDF-containing regimen switched to a new regimen that did not include TDF, and 101 of 235 (43%) randomly assigned to one of the non–TDF-containing regimens switched to a new regimen that included TDF. The median time to first switch in ART regimen for the non–TDF-containing arms was 1.93 years, compared with 3.07 years for the TDF-containing arm.

For the as-treated analysis, 31 of 68 HSV-2 seroconverters (46%) at the exit visit had switched their ART regimen during follow-up; 7 of 31 HSV-2 seroconverters were HSV-2 seronegative before their ART regimen switch, and follow-up time after their ART switch was not included in the as-treated analysis.

Efficacy of TDF in HSV-2 Seroconversion and Association With Immunosuppression

In the intent-to-treat analysis, 24 HSV-2 seroconversions were observed in 374 person-years of follow-up in persons randomly assigned to the TDF-containing arm (HSV-2 seroincidence, 6.42 cases/100 person-years), and 44 HSV-2 seroconversions occurred in 663 person-years of follow-up in persons randomly

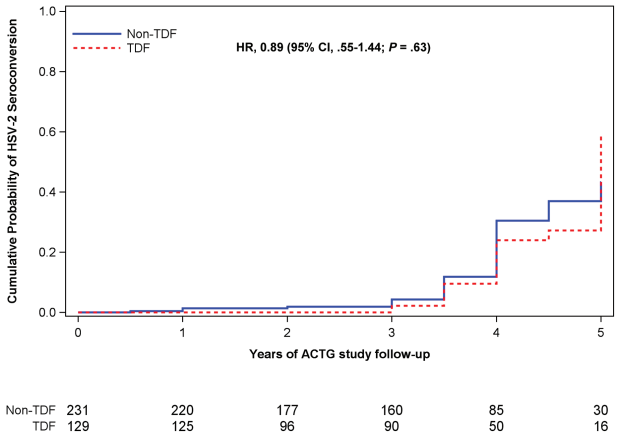

Figure 1. Cumulative herpes simplex virus type 2 (HSV-2) acquisition curves among human immunodeficiency virus type 1 (HIV-1) seropositive, HSV-2 seronegative individuals at baseline, by tenofovir disoproxil fumarate (TDF)-containing versus non-TDF-containing antiretroviral therapy (ART) exposure, in the intention to treat analysis. There was no significant difference in the HSV-2 seroincidence for persons receiving a TDF-containing ART regimen, compared with that for persons receiving non-TDF-containing ART regimens (hazard ratio [HR], 0.89; 95% confidence interval [CI], 0.55–1.44).

assigned to the non–TDF-containing arms (HSV-2 seroincidence, 6.63 cases/100 person-years). There was no difference in the HSV-2 seroincidence between individuals randomly assigned to the TDF-containing arm and those randomly assigned to the non–TDF-containing arms (HR, 0.89; 95% confidence interval [CI], .55–1.44; Figure 1). In the as-treated analysis, in which follow-up was censored before the date of the first ART regimen change, there was also no significant difference in HSV-2 seroconversion by ART regimen (HR, 0.92; 95% CI, .45–1.41; $P = .98$).

The only factor associated with HSV-2 seroconversion was baseline CD4$^+$ T-cell count, for which statistical significance was borderline; there was a 27% increased risk of HSV-2 acquisition for each 100-cell/mL decrease in CD4$^+$ T-cell count, after adjustment for sex and TDF-containing ART regimen (HR, 1.27; 95% CI, .96–1.70). In subgroup analyses stratified by CD4$^+$ T-cell count, the effect of TDF-containing ART regimen varied by baseline CD4$^+$ T-cell count; TDF reduced the HSV-2 seroincidence by 56% (95% CI, 7%–80%) among those with a baseline CD4$^+$ T-cell count of <200 cells/μL but increased it by 94% (95% CI, −10% to 320%) among those with a baseline CD4$^+$ T-cell count of ≥200 cells/μL ($P = .007$ for effect modification).

DISCUSSION

This secondary analysis of the multisite international ACTG A5175/PEARLS study showed no protective effect of TDF against HSV-2 acquisition among the initially HSV-2–seronegative, HIV-1–seropositive persons who were randomly assigned to receive a TDF-containing regimen as their initial

Table 1. Baseline Characteristics of Herpes Simplex Virus Type 2 (HSV-2)–Seronegative, Human Immunodeficiency Virus Type 1 (HIV-1)–Seropositive Participants in AIDS Clinical Trials Group A5175, by Treatment Arm

Variable	TDF-Containing ART Arm (n = 130)	Non–TDF-Containing ART Arm (n = 235)
Demographic characteristic		
Male sex	88 (68)	165 (70)
Age, y		
18–24	13 (10)	35 (14.9)
25–34	63 (48.5)	92 (39.1)
35–44	40 (30.8)	78 (33.2)
≥45	14 (10.8)	30 (12.8)
HIV status		
CD4$^+$ T-cell count, cells/μL	174 (105–234)	192 (88–241)
Plasma viral load, $\log_{10}$ copies/mL	5.1 (4.6–5.6)	5.1 (4.7–5.5)
Sexual activity ≤3 mo before enrollment		
Sex partners, no.		
0	50 (38.5)	100 (42.6)
≥1	78 (60.0)	134 (57.0)
Sex act(s)		
Vaginal only	44 (56.4)	69 (51.5)
Anal only	18 (23.1)	37 (27.6)
Both vaginal and anal	7 (9.0)	9 (6.7)
None	6 (7.7)	13 (9.7)
Country of residence		
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)

Data are no. (%) of individuals or median value (interquartile range).

Abbreviations: ART, antiretroviral therapy; TDF, tenofovir disoproxil fumarate.

ART regimen. This is the first study to evaluate HSV-2 seroconversion in HIV-1–infected persons who are receiving a TDF-containing combination ART regimen. TDF is a common backbone of ART in HIV-1–infected persons and has modest anti–HSV-2 activity in vitro [4], which could be beneficial if it reduced HSV-2 acquisition. The rate of ART change was high (35%), with higher rates of changing to a TDF-containing regimen than to a non–TDF-containing regimen. The as-treated analysis also demonstrated no protective benefit of TDF on HSV-2 seroconversion. However, a lower baseline CD4$^+$ T-cell count was associated with a modestly higher risk of HSV-2 seroconversion during follow-up, and a subgroup analysis demonstrated a 56% reduction in the incidence of HSV-2 seroconversion among HIV-infected persons with a baseline CD4$^+$ T-cell count of <200 cells/μL.

HSV-2 seroincidence was high, with an average of 6.6 cases/100 person-years across the ART arms in this cohort. Given the high HSV-2 seroincidence and the public health

and clinical significance of HSV-2 infection in HIV-1–infected persons, owing to its role in increasing the HIV-1 load [1], the risk of HIV-1 transmission [2], and the risk of HIV-1 disease progression [3], interventions are needed to reduce HSV-2 acquisition in the minority of HIV-1–seropositive persons who are HSV-2 seronegative. Although the EC_{50} of TDF is high for HSV-2 and oral TDF did not reduce HSV-2 shedding rates in HIV-1/HSV-2 dually infected persons [13], a modest effect of oral TDF was observed on HSV shedding and lesion rates and the quantity of HSV shed among HIV-1–seronegative, HSV-2–seropositive persons in the per-protocol analysis [14]. Lower TDF concentrations may be necessary for prevention of HSV-2 acquisition than suppression of HSV-2 reactivation.

Limitations of this study include a 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-containing regimens to TDF-containing regimens), which was accounted for in the statistical analysis. HSV-2 seroconversion was assessed 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 the timing of HSV-2 seroconversion. Thus, differences in HSV-2 seroconversion by ART arm early in follow-up could have been missed. Adherence measurements in ACTG A5175 were based on pill counts and self-report from a provider-administered interview, and although these measurements have limitations, analyses of pill counts indicated highest adherence in the TDF-containing ART arm [15], indicating that low adherence is not likely a major factor in our findings. Approximately one quarter of samples from ACTG 5175 were not available for testing owing to the inability to obtain regulatory approval for international shipping of samples from the local repositories, which reduced our power.

In summary, we did not find evidence of reduced HSV-2 acquisition in HIV-1–seropositive persons who were randomly to receive a TDF-containing initial ART regimen, except among those with a $CD4^+$ T-cell count of <200 cells/μL, who had a higher risk of HSV-2 acquisition, when compared to combination ART without TDF. Our findings do not support the effects of TDF gel, which achieves high vaginal concentrations [5], or oral TDF and TDF/FTC preexposure prophylaxis on reducing HSV-2 acquisition in HIV-uninfected persons [6]. Further research is needed on whether TDF or the TDF prodrug TDF alafenamide prevent HSV-2 acquisition in HIV-infected persons.

Notes

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