Tenofovir concentrations and prophylactic effect in a macaque model of rectal SHIV transmission

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Abstract

Background: Non-human primate (NHP) models are essential in the development and evaluation of pre-exposure prophylaxis (PrEP) strategies, but few studies have compared concentration-effect results from the NHP model with that from human PrEP trials. The objective of this study was to evaluate the impact of dosing strategy on TFV-DP concentrations, accumulation, and half-lives in an NHP model, and to compare the TFV-DP EC90, previously identified in the iPrEx study, to that identified in the NHP model.

Methods: Viable ex vivo PBMC from previously conducted studies that evaluated TDF-FTC for prevention of rectal SHIV transmission were used to assess the impact of dosing schedules on TFV-DP accumulation and half-lives. PBMC were infected with SHIV 2.1 and treated with TDF-FTC at doses of 4 mg/kg FTC, 22 mg/kg TDF for 5 weeks. PBMC were treated with TDF-FTC at doses of 4 mg/kg FTC, 22 mg/kg TDF for 5 weeks. PBMC were treated with TDF-FTC at doses of 4 mg/kg FTC, 22 mg/kg TDF for 5 weeks. PBMC were treated with TDF-FTC at doses of 4 mg/kg FTC, 22 mg/kg TDF for 5 weeks.

Results: The concentration-effect data were analyzed using a Cox proportional hazards model with the effect of TFV-DP concentration on the rate ( Hazard) of HIV infection for the hiPSC-kHSL cells. The results of the concentration-effect data are shown in Figure 4. The relationship between SHIV risk reduction and TFV-DP concentration is depicted in Figure 4.

Conclusions: The concentration-effect data showed an approximate hazard ratio of 0.02 per log10 unit decrease in TFV-DP concentration with a 40% reduction in risk of SHIV acquisition (17% to 56%), p = 0.002. The relationship between SHIV risk reduction and TFV-DP concentration is depicted in Figure 4.

Background

Non-human primate and humanized mouse models are especially important in the development and evaluation of PrEP therapies because these models enable investigators to control the virus challenge and drug dosing, thereby providing a cost-effective and efficacious way to advance the most promising PrEP regimens toward Phase 3 clinical trials.

The aim of the present study was to estimate the concentration-effect relationship between intracellular TFV-DP and reduced risk of virus acquisition in the macaque rectal challenge model.

Methods

This was an evaluation of drug concentrations from stained viable PBMC from previously conducted studies that evaluated TDF-FTC for prevention of rectal SHIV transmission. Briefly, anesthetized adult rhesus macaques were inoculated once weekly, for up to 14 weeks, with SHIV/SF162P3, a chimeric virus with a genetic rearrangement of HIV-1SF162 on the background of SIVmac239.

Two different TDF-FTC oral dosing strategies were evaluated. One group (hiPSC-kHSL) were given one TDF-FTC dose 3 days prior to each weekly virus challenge (-3 days). A second group (hiPSC-kHSL) were given two TDF-FTC doses; one day prior to each weekly virus exposure and another dose 2 hours after each weekly virus exposure (-3 day/2h). All doses consisted of 20 mg/kg of FTC and 22 mg/kg of TDF. A control group (hiPSC-kHSL) underwent the once-weekly viral inoculation procedures, but did not receive drug.

The time of infection was defined as the week before the first evidence of SHIV RNA positivity in plasma; animals were considered uninfected if they remained seronegative and negative for SHIV plasma RNA and SHIV DNA in PBMCs during the study and during 30 days after challenge.

Results

Viably cryopreserved PBMC were processed from the blood that was collected from all treated macaques at the time of each weekly virus challenge (time 0). TFV-DP and FTC-T were measured in the viably cryopreserved PBMC samples using methods and procedures described previously. The quantification lower range for TFV-DP was 2.5 to 2000 femtomole (fmol) per sample and for FTC was 0.1 to 200 picomole (pmol) per sample. Approximately 4 million total cells were extracted, constituting the sample size, and results were reported as femtomolar or picomolar per million viable cells. The timing of dosing, sampling and viral exposures are shown in Figure 1.

Conclusions

An estimated EC90 of 22.6 (95% CI, 13.8 to 60.8) fmol/10⁶ cells was identified in this animal model. This value compares well to the EC90 value estimated in participants in the iPrEx study of 16 (3 to 28) fmol/10⁶ cells. The cell samples and TFV-DP concentrations from both iPrEx and this study were processed and analyzed in the same laboratory with the same procedures, assays, and instruments.

Figure 4. Kaplan Meier analysis of the proportion infected with SHIV (y-axis) by number of inoculations (x-axis) in the three groups of macaques. The green line is the control group, blue line is 1 dose per week group (-3 day), orange line is 2 doses per week group (-3day/2h).

Figure 3. TFV-DP (left panel) and FTC-T (right panel) concentrations according to study day (x-axis) in the –3day+2h group (open circles) and –3day group (open squares). Data represent mean values and bars SD with the number of macaques contributing to the data represented by the bars.

Figure 2. Kaplan Meier analysis of the proportion infected with SHIV (y-axis) by number of inoculations (x-axis) in the three groups of macaques. The green line is the control group, blue line is 1 dose per week group (-3 day), orange line is 2 doses per week group (-3day/2h).

Acknowledgments

All procedures were reviewed and approved by the CDC Institutional Animal Care and Use Committee. PLA receives study drug from GlaxoSmithKline for research protocols, CDC received FTC and TDF from GlaxoSmithKline for the SHIV-2.1mac challenge study. ADO received a financial support from NIH U01AI84735, CDC intramural funds, and Interagency Agreement Y1-Al-0681-02 between CDC and NIH. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention or NIH.