HIV Genetic Diversity to Infer PrEP Adherence at the Estimated Time of Infection

Olivia Council[1], Susan Ruone[1], Philip Mock[2], George Khalil[1], Marcel E. Curlin[3], Janet McNicholl[1], Walid Heneine[1], Kachit Choopanya[4], Michael Martin[2], J. Gerardo García-Lerma[1]

[1]Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention, [2]Thailand MOPH-US CDC collaboration, [3]Department of Medicine, Division of Infectious Diseases, Oregon Health and Sciences University, Portland Oregon, [4]Bangkok Tenofovir Study Group

*Contact info:
e-mail: jng5@cdc.gov
Phone: 404-639-4987

ABSTRACT

BACKGROUND: Adherence in pre-exposure prophylaxis (PrEP) trials can be inferred by measuring drug concentrations at the time of HIV diagnosis. However, results do not necessarily reflect pill taking behavior around the time of HIV infection. The Bangkok Tenofovir Study (BTS) evaluated the efficacy of daily oral PrEP with tenofovir (TDF) among persons who inject drugs. We used molecular tools and adherence diaries from BTS participants to define pill taking behavior at the estimated time of infection.

METHODS: HIV genetic diversity was studied in 11 participants who became infected with HIV during periods of daily directly observed therapy (DOT) with TDF and in 13 placebo recipients. HIV *env* (V1-V5) was amplified from plasma collected at the first nucleic acid test positive (NAT+) visit using single genome amplification. The diversity structure of the virus population seen in this sample was used to estimate time since infection (±95% confidence interval) using the Poisson-Fitter tool. The number of TDF doses taken within the confidence interval of infection were then computed from adherence diaries.

RESULTS: The estimated time since infection in the TDF group ranged from 8 (95%CI=1-16) to 75 (49-100) days (median=41) and did not differ from that seen in the placebo group (median=15 days; p=0.433). Analysis of missed TDF doses within the estimated period when HIV infection occurred showed perfect adherence in 5/11 (45%) participants, nearly perfect adherence in two (67/69 and 95/100 possible doses taken), low adherence in one (52 out of 71 possible doses taken) and non-adherence (no TDF taken) in three. The 2-5 missed doses in the two participants with nearly perfect adherence were recorded immediately before (3-4 days) or after (1-2 days) the estimated day of infection. TDF exposure in adherent participants was associated with low plasma virus loads at the first NAT+ visit (13,465 RNA copies/ml vs. 294,000 in placebo infections; p=0.033) and infection with single variants (8/8 vs.8/13 in the placebo group; p=0.063) although the latter was not significant at the 0.05 level.

CONCLUSIONS: We used molecular tools to characterize adherence to PrEP at the estimated time of HIV infection, and demonstrated breakthrough infections under conditions of perfect or near perfect adherence to TDF. These results highlight the utility of molecular tools to improve computation of the biological efficacy of PrEP. Pre-diagnosis drug activity by PrEP reduces acute viremia and may favor the transmission of single variants.

BACKGROUND

- **Adherence in PrEP trials has been generally defined as having measurable drug in plasma or PBMCs**
- **Drug concentrations in plasma measured a single time associated with a scheduled clinical encounter may not necessarily reflect consistent adherence and may be subjected to social desirability bias whereby less adherent subjects may take the study product immediately before their visit so as not to disclose their nonadherence**
- **Defining drug concentration at the time of HIV infection will shed light on true biological efficacy of PrEP**
- **The Bangkok Tenofovir Study (BTS) evaluated the efficacy of daily oral PrEP with TDF among persons who inject drugs**

We used molecular tools to infer the estimated time of infection in seroconverters from the BTS trial, and computed pill taking behavior during this period of time using adherence diaries

OBJECTIVES

To define pill taking behavior at the estimated time of infection in seroconverters from the BTS TDF PrEP trial and infer biological efficacy of PrEP with TDF

METHODS

HIV SEROCONVERTERS FROM THE BANGKOK TENOFOVIR STUDY (BTS) TRIAL

Adherence diaries

11 participants infected with HIV during periods of daily directly observed therapy with oral TDF

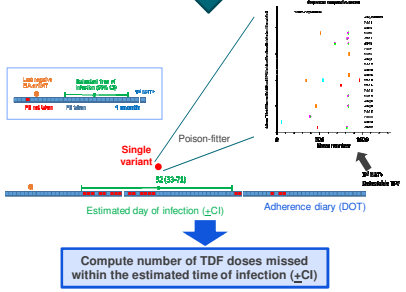
Define pill taking behavior during the months prior to infection

Molecular tools

Diversity structure of the virus population at 1st NAT+ sample by single genome amplification

Single variant infection

Estimate time since infection using the Poisson-Fitter tool*

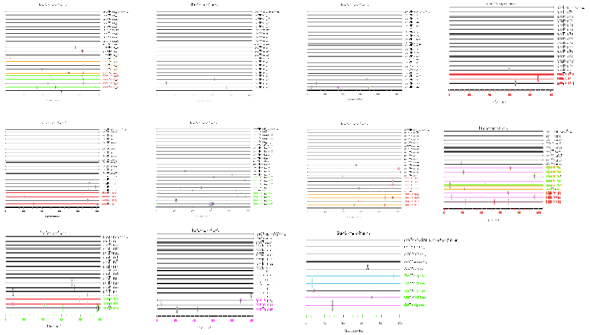


Compute number of TDF doses missed within the estimated time of infection (±CI)

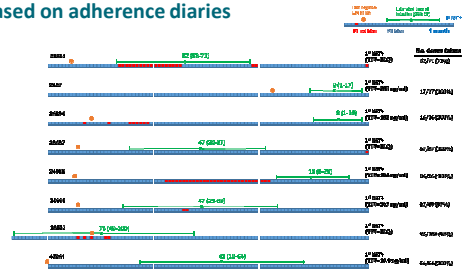
*Postulates; infection initiated by a single genetic strain; mutation rate set to 2.16e-5; viral population grows exponentially during the early phases of infection prior to the onset of the host immune response.
Time since infection estimated based on a model of exponential evolution and random accumulation of mutations

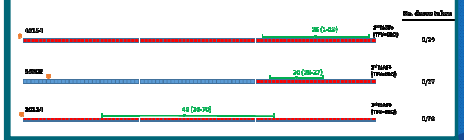
RESULTS

Virus diversity at the first NAT+ specimen using single genome amplification



Estimated time of infection and number of TDF doses taken based on adherence diaries





Characteristics of participants infected with HIV during periods of directly observed therapy

Sample ID	Plasma VL*	Plasma TFV*	Time since infection	N. Pill taken/total possible pills***
21843	434	BLQ	52 (33-71)	53/71 (75%)
2427	675,000	288	9 (1-17)	17/17 (100%)
26204	36,100	182	8 (1-16)	16/16 (100%)
48154	536,799	BLQ	15 (1-29)	0/29 (0%)
28687	61,397	BLQ	47 (28-67)	67/67 (100%)
34022	5,530	104	16 (5-26)	26/26 (100%)
24660	2,340	367	47 (25-69)	67/69 (97%)
18053	21,400	BLQ	75 (49-100)	95/100 (95%)
35802	15,612	BLQ	20 (13-27)	0/27 (0%)
10124	20,914	BLQ	48 (26-70)	0/70 (0%)
45361	1,276	19.9	41 (18-64)	64/64 (100%)
Median	***13,455***		***44 days***	
Placebo (n=13)	294,000 (p=0.03)		15 days (p=0.48)	

*At the first nucleic acid positive (NAT+) specimen; **±95% confidence interval; ***based on adherence diaries under daily directly observed therapy

STUDY SUMMARY

- ✓ We characterized early acute HIV sequences in participants from the BTS PrEP trial that become infected with HIV during periods of daily directly observed therapy
- ✓ The diversity structure of the virus population was used to estimate time since infection; the number of missed TDF doses was computed using adherence diaries
- ✓ Using our model, we demonstrate breakthrough infections under conditions of perfect or near perfect adherence to TDF. These findings highlight the utility of molecular tools to improve computation of the biological efficacy of PrEP.

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Division of HIV/AIDS Prevention

www.cdc.gov | Contact CDC at: 1-800-CDC-INFO or www.cdc.gov/info
The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.