Drug activity in macaque PrEP breakthrough infections has a transient effect on SHIV DNA reservoirs

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ABSTRACT

Background. Infection of macaques with SHIV during concurrent PrEP with FTC/TDF is associated with reduced acute plasma viremias and limited virus diversity, thus providing a unique model to assess long-term effects of acute antiretroviral treatment. Here, we investigated the effect of PrEP on acute SHIV DNA dynamics in PBMCs, and on the size of the persistent virus reservoir in lymphoid tissues.

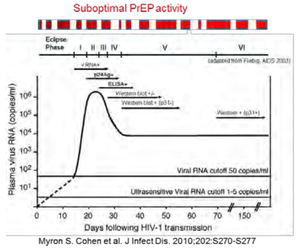
Methods: Cell-associated SHIV DNA levels were measured in PBMCs during acute infection in 8 macaques infected during concurrent PrEP with FTC/TDF combination or single-agent TAF. Macaques continued treatment with 1-2 weekly drug doses to model suboptimal drug exposure during undiagnosed HIV infection in humans. Peak SHIV DNA and AUC values over 5 or 20 weeks, as well as RNA levels, were compared those seen in untreated SHIV infections (n=10). SHIV DNA levels were also measured in lymphoid tissues collected from FTC/TDF or maraviroc PrEP breakthroughs after 1 year of infection.

Results: PrEP breakthrough infections had reduced plasma RNA viremias relative to untreated infections both at peak and during the first 20 weeks of infection ($p<0.005$). SHIV DNA levels in PBMCs were also reduced in PrEP breakthrough infections both at peak and at week 5 ($p = 0.022$ and $p = 0.043$, respectively), but not after 20 weeks of infection. At 1 year, SHIV DNA reservoirs in lymphoid tissues were similar in size among macaques that received PrEP with FTC/TDF (median = 464 SHIV DNA copies/10^6 cells; range, 40-5,346), PrEP with maraviroc (median = 1088 copies/10^6 cells; range, 554-10,090), or placebo (median = 952 copies/10^6 cells; range, undetectable-24,668) ($p>0.05$).

Conclusions: Antiviral drug activity due to PrEP limits acute SHIV replication but has only a transient effect on cell-associated DNA levels in PBMCs and lymphoid tissues. Our model suggests that suboptimal drug exposure in persons that are taking PrEP and become infected with HIV may not be sufficient to reduce the pool of HIV-infected cells, and that treatment intensification may be needed to sustain the virologic benefit from the PrEP regimen.

BACKGROUND

- Early HIV (and SIV) treatment with fully suppressive regimens can substantially reduce cell-associated HIV DNA reservoirs in PBMCs and lymphoid tissue
- Suboptimal adherence to Truvada PrEP and HIV infection creates an opportunity for continued antiretroviral drug activity during undiagnosed infection



Myron S. Cohen et al. J Infect Dis. 2010;202:S270-S277

OBJECTIVES

To investigate the effect of PrEP on acute SHIV DNA dynamics in macaques and on the size of the persistent virus reservoir

METHODS

- SHIV RNA and DNA dynamics defined in macaque placebo and PrEP breakthrough infections **(TABLE 1)**
- SHIV DNA (integrated and unintegrated) measured by a double-stranded primer assay (LOD = 10 DNA copies)
- Plasma RNA measured by a one-step RT-PCR (LOQ = 50 RNA copies/ml)
- Macaques infected rectally with SHIV during concurrent non-daily PrEP regimens with FTC/TDF (n = 6) or single-agent tenofovir alafenamide (TAF; n = 2)
- Antiretroviral treatment with 1-2 weekly pills continued after infection to model suboptimal drug exposure during undiagnosed HIV infection in humans

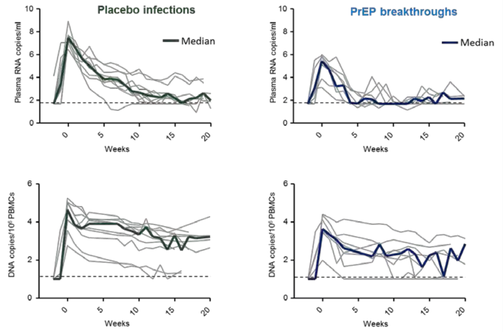
TABLE 1

Group	PrEP/PEP dosing schedule*	Weeks on intermittent treatment after infection**
PrEP infections		
DK40	FTC/TDF (-3d/+2h)	20
33053	FTC/TDF (-24h/+24h)	28
FCW	FTC/TDF (-24h/+24h)	26
35838	FTC/TDF (-24h/+24h)	24
34912	FTC/TDF (-7d/+2h)	10
35032	FTC/TDF (-7d/+2h)	21
DL2L	TAF (-3d)	11
1784	TAF (-3d)	12
		Mean=19
Controls		
62P	-	-
19V	-	-
34F	-	-
AM20	-	-
AO86	-	-
AG94	-	-
AI22	-	-
35720	-	-
33160	-	-
DM46X	-	-

*relative to the time of SHIV exposure
**Treatment with 1-2 weekly drug doses

RESULTS

SHIV plasma RNA and cell-associated DNA in PrEP and placebo infections



	PrEP breakthrough infections (n=8)	Placebo infections (n=10)	
SHIV plasma RNA			
Peak	5.3 (4.2-5.9)	7.5 (7.1-7.7)	$p<0.0001$
AUC_{0-5wks}	23.4 (20.3-28.9)	35.6 (33.5-37.5)	$p=0.0002$
$AUC_{0-20wks}$	48.8 (41.6-61.3)	73.5 (65-81)	$p<0.002$
SHIV DNA in PBMCs			
Peak	3.6 (3.5-4.3)	4.6 (4.0-5.0)	$p=0.043$
AUC_{0-5wks}	20.8 (12.7-26.0)	31.7 (24.3-34.2)	$p=0.043$
$AUC_{0-20wks}$	47.1 (34.7-61)	75.3 (54.9-79.9)	$p=0.065$

Median (interquartile range); two-tailed Wilcoxon rank-sum test

✓ ***PrEP breakthrough infections had reduced plasma RNA viremias relative to untreated infections both at peak and during the first 20 weeks of infection.***

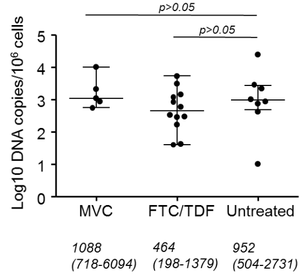
✓ ***SHIV DNA levels in PBMCs were also reduced although the effect was transient and lost after 20 weeks***

Effect of PrEP on SHIV DNA reservoirs in lymphoid tissues

- Cell-associated SHIV DNA levels were measured after PrEP discontinuation in lymph node mononuclear cells (mesenteric, axillary, inguinal) and compared to those seen in placebo infections **(TABLE 2)**
- Tissues collected ~1 year (range = 6-19) after infection

TABLE 2

	PrEP dosing schedule*	Months of infection prior to necropsy
Maraviroc PrEP		
A4E021	-24h/+2h	11
J17	-24h/+2h	12
01D431	-24h/+2h	11
A3021	-24h/+2h	10
32408	-24h/+2h	6
FTC/TDF PrEP		
4270	+2h/+24h	12
DK40	-3d/+2h	11
2E128	+2h/+24h	7
4269	+2h/+24h	10
1800	-2h/+22h	15
DM91	-2h/+22h	16
DL6V	-22h/+2h	16
34912	-7d/+2h	12
DL2T	-3d	8
35489	-3d	8
DK2R	-3d	6
FCW	-24h/+24h	19
UNTREATED		
G47	-	6
A2E027	-	6
A4E037	-	6
79R	-	17
19V	-	9
AG85	-	17
34F	-	18
RKZ7	-	9



✓ ***SHIV DNA reservoirs in lymph node mononuclear cells are similar in size in placebo and PrEP breakthrough infections***

STUDY SUMMARY

- We investigated if transient drug activity in PrEP breakthrough infections has the potential to alter the pool of SHIV-infected cells. This scenario mimics persons receiving PrEP that acquire HIV due to inconsistent adherence and who continue on the PrEP regimens until diagnoses

- The effect of PrEP on the cell-associated DNA reservoir was only transient and was lost during the first year of infection

Findings suggest that ARV drug activity when PrEP fails may not provide adequate drug selective pressure to effectively reduce the pool of HIV-1-infected cells and result in post-treatment virus control (as opposed to fully suppressive HAART regimens)

STUDY LIMITATIONS

-Analysis only quantitative; reduced replication/evolution due to PrEP might result in more genetically homogeneous reservoirs or favor seeding of sequences with replication advantages in the presence of FTC/TFV

-Study measured total cell-associated DNA and did not assess reservoir distribution in cell subsets

-SHIV162p3 infection generally follows a non-pathogenic course; more pathogenic SIVs may be best suited to define long-term effects of PrEP after treatment discontinuation

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Division of HIV/AIDS Prevention

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