Reduced Inflammation and CD4 Loss in Acute SHIV Infection During Oral Pre-Exposure Prophylaxis

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Background. The impact of pre-exposure prophylaxis (PrEP) with antiretrovirals on breakthrough HIV or SHIV infection is not fully documented. We addressed the hypothesis that SHIV SF162P3 infection despite active PrEP results in altered early immune parameters, compared with untreated infection.

Methods. Eleven rhesus macaques were infected during repeated, rectal, low-dose SHIV SF162P3 exposures while receiving concurrent oral PrEP (Truvada [n = 2] or GS7340 [n = 4]) or as untreated controls (n = 5). We measured SHIV RNA, inflammatory cytokines, CD4 cells, and SHIV-specific and memory T cells until 20 weeks after peak viremia.

Results. SHIV infection during PrEP resulted in 100-fold lower peak viremia and lower IL-15, IL-18, and IL-1Ra levels, compared with controls (P < .05; Wilcoxon rank-sum test). Unlike controls, PrEP-treated macaques showed no significant CD4 cell count reduction during acute infection and developed more SHIV-specific central memory T cells, relative to controls. After in vivo CD8 cell depletion, viral load increased to similar levels, indicating that CD8 cells were critical for viral control in both groups.

Conclusions. PrEP with antiretrovirals has beneficial effects on early SHIV infection even when infection is not prevented. Although long-term immune control could not be examined in this SHIV infection model, our results suggest that PrEP results in improved early disease parameters in breakthrough infections.

Pre-exposure prophylaxis (PrEP) with oral or topical antiretrovirals (ARVs) for the prevention of HIV infection is currently undergoing efficacy evaluation in clinical trials. Four trials have reported efficacy among men who have sex with men and heterosexual couples [1–4]; one trial in women was abandoned because of unlikely efficacy at interim analysis [5], and others are at different stages of completion [6]. Although overall results are encouraging or are pending, it is clear that 100% effectiveness is unlikely to be achievable because of imperfect adherence or efficacy. This raises the question of the consequences of breakthrough infection acquired during PrEP.

To address this, we studied innate immune parameters and adaptive T cell responses during acute infection and PrEP in macaques. Adaptive B cell responses have been addressed elsewhere [7]. Breakthrough SHIV infection during PrEP in macaque models can result in blunted peak and set-point viremia [8–10]. This is most likely because ARV drugs can partially inhibit virus replication even though they did not completely block virus transmission. Because of an expected relationship between viremia and the strength of innate and adaptive immune responses (eg, as in elite controllers) [11], we hypothesized that attenuated PrEP breakthrough infection would be characterized by limited inflammation, limited CD4 cell loss, and alterations in adaptive T cell responses. Such immune parameters during acute HIV infection [12] can further influence infection course and are of interest during preclinical and clinical PrEP evaluation.
We used longitudinal specimens generated during efficacy testing of new intermittent PrEP regimens in macaques [8–10], allowing us to maximize insights from ongoing animal studies. The PrEP efficacy studies were geared toward modeling realistic conditions of sexual HIV transmission during intermittent PrEP. SHIV transmission occurred after repeated, low-dose, rectal virus exposures, allowing establishment of infection and initiation of immune responses under physiologic circumstances. ARVs were given only once per week to model intermittent PrEP use; sporadic nonadherence was not modeled. Drugs were continued with the same regimen after documented infection to study the emergence of drug resistance and to model ARV use intended as PrEP by persons who will not immediately know their HIV status. We used SHIVSF162P3, a R5-tropic virus with mucosal transmissibility. It causes initial viremia similar to acute HIV infection. There is a characteristic, transient, but moderate decrease in blood CD4 T cell count at peak viremia [13, 14]. Unlike HIV infection, however, set-point SHIVSF162P3 viremia near undetectable levels (approximately 50 copies/mL of blood plasma) is reached within 12 weeks, and the infection course is generally nonpathogenic. CD8 cells contribute significantly to SHIVSF162P3 control, as demonstrated by in vivo CD8 cell depletion [15]. Thus, we examined the acute phase, when adaptive immune responses develop to effectively control SHIVSF162P3 [14–16].

We analyzed parameters previously measured in S(H)IV+ rhesus macaques. IFNα, IFNγ, IL-1Ra, MCP-1, IL-15, and IL-18 levels increase during acute SIV infection, in contrast to other inflammatory factors (eg, TNFα and IL-6) [17]. Immune markers HLA-DR and CD38 were not measured, because they fluctuate little during SHIVSF162P3 infection [16]. In contrast, central memory T cells (Tcm) differ in SIV+ macaques with varying immune activation [17]. CD4 cell count measurements can be inconclusive in SHIVSF162P3 infection because of the moderate decrease and rebound within one week [14]. Because plasma IL-15 level and CD4 cell count decreases are inversely correlated in early SIV infection of rhesus macaques [18], we determined IL-15 as a marker related to CD4 cell count, to further substantiate subtle changes in CD4 cell counts during SHIV infection.

## MATERIALS AND METHODS

### Macaques, Virus, PrEP regimens, and Repeat Low Dose (RLD) Virus Challenges

The Animal Care and Use Committee (IACUC) of the Centers for Disease Control and Prevention (CDC) approved all described macaque procedures. These were in accordance with standards established in the Guide for the Care and Use of Laboratory Animals [19]. Eleven male Indian rhesus macaques were housed at the CDC (Atlanta, GA) and underwent efficacy testing of intermittent PrEP (Table 1, and as described [8, 9]). In brief, 2 macaques received oral Truvada [9] (emtricitabine [FTC] [20 mg/kg] and tenofovir disoproxyl fumarate [TDF] [22 mg/kg]), administered 7 days before the first rectal viral challenge and then once weekly 2 hours after each challenge. Four macaques received the novel tenofovir pro-drug GS7340 in 1 weekly dose (13.7 mg/kg) 3 days before SHIV exposure [8]. The genetic identity of 8 MHC alleles with potential impact on SHIV infection course is also shown in Table 1. Mamu-B08 and -B17, associated with superior control of SIVmac239 infection [20, 21], were either not present in the PrEP-group, or were present once in both groups, respectively. Trim5 genotypes were not determined, because SHIVSF162P3 replication is not restricted.
IL-2, CD28high/low, or CCR7+; whereas virus exposures at 10 TCID-50 [8–10] (number of exposures indicated in Table 1]) Viral load was assessed by polymerase chain reaction with a detection limit of 50 copies/mL, as previously described [23].

**Blood Sample Collection, Flow Cytometry, IFNγ Enzyme-Linked Immunospot Assay (ELISPOT), Inflammatory Factors**

We collected blood samples once per week with use of BD Vacutainer CPT tubes (BD Biosciences). PBMCs were counted using an automated Guava cell counter (Millipore). SHIV-specific T cells were determined by IFNγ-ELISPOT, incubating fresh cells with 15-mer peptide pools with 11 amino acid overlaps as described [24].

T cells, gag-specific T cells, intracellular cytokine/chemokine production, and effector and central memory T cell determination (T\(_{EM}\) and T\(_{CM}\)) based on cytokine expression [25], were determined by flow cytometry as described [24]. In brief, freeze-thawed cells were washed, stimulated with gag1/2 peptide pools, and analyzed with antibodies to CD3, CD4, CD8, CD69, CCR7, CD28, IL-2, TNFα, IFNγ, and MIP-1β. Samples were examined on a LSRII flow cytometer (BD Biosciences) and analyzed using FlowJo software, version 7.2.1 (Tree Star). T\(_{CM}\) cells were defined as CD3\(^+\) CD69\(^-\) (IFNγ, TNFα, MIP-1β, and/or IL-2\(^-\)), CD28\(^{high}\), or CCR7\(^-\); whereas T\(_{EM}\) cells were CD3\(^+\) CD69\(^+\) (IFNγ, TNFα, MIP-1β, and/or IL-2\(^+\)), CD28\(^{high}\)/low, or CCR7\(^-\).

After freeze-thawing of plasma, we measured IL-15 using the QuantiKine IL-15 Immunoassay (R&D Systems) and INFγ, IL-18, MCP-1, and IL-1Ra (α = antagonist) with nonhuman primate-specific reagents (Millipore), according to the instructions by the manufacturer, and using a Luminex-100 system (Invitrogen) with Bio-Plex Manager software, version 4.0 (Bio-Rad). INFγ levels in plasma were measured using a human IFNα enzyme-linked immunosorbent assay (ELISA) kit (PBL Interferon Source).

**CD8 Cell Depletion**

Anti-CD8 antibody cM-T807 and control IgG antibodies (IgGv, a polyclonal IgG preparation derived from human plasma) were obtained through the NIH Non-Human Primate Resource and from Centocor. Antibodies were injected subcutaneously at 10 mg/kg at day 0, followed by intravenous injections on days 3, 7, and 10 at a dose of 5 mg/kg. We isolated fresh PBMCs and counted T cells by flow cytometry using antibodies to CD8 (clone DK25, DAKO, Denmark), CD3, and CD4 (clones SP34 and RM4-5, respectively; BD Biosciences). Viral RNA was also monitored at each time point.

**Statistical Methods**

We tested differences between control and PrEP-treated groups for select time points or between time points of a group with Wilcoxon rank-sum tests using GraphPadPrism, version 4.0, or SAS, version 9.2 (SAS Institute). When data from multiple time points per subject were analyzed to compare differences by treatment arm, we used a generalized estimation equations method to estimate robust variances to account for within subject correlation [26]. Temporal decrease in viral load (log-10) in primary infection was examined using mixed effects regression analysis and with left-censoring of undetectable viral load values at <50 copies/mL.

**RESULTS**

**Infection and Viremia**

Immune parameters during acute SHIVSF162P3 infection were compared among 6 PrEP-treated and 5 untreated control macaques after repeated, low-dose, rectal virus exposures. The intermittent PrEP regimens with Truvada or the tenofovir prodrug GS7340 are described elsewhere [8–10]; they were either partially or not effective in preventing infection. Only infected macaques were studied here, whereas immune responses in PrEP-protected macaques were previously examined [24].

Macaques, their treatment and its duration, and the number of virus exposures required for their infection are listed in Table 1.

Figure 1 shows plasma viral load up to 20 weeks after peak viremia. ARV treatment was continued on the same intermittent, once weekly regimen as during PrEP after documented infection for a median of 11.5 weeks after peak viremia, except...
for animal 34912 (Table 1), to monitor for drug resistance development. No resistance mutations developed in this period, as reported elsewhere [8, 9]. Peak viremia was 100-fold lower in PrEP/ARV-treated macaques, relative to control macaques, because treated macaques had a median peak viral load of $10^{5.5}$ RNA copies/mL of plasma, compared with $10^{7.5}$ in untreated macaques ($P = .02$, Wilcoxon rank-sum test). Peak viremia was also low in animal 34912 ($10^{5.3}$ plasma RNA copies/mL, data not shown), the only animal that had ARVs discontinued at the time of infection (Table 1). Temporal decrease in virus load (log-10) after peak viremia differed between the 2 groups (mixed effects regression analysis, $P = .04$); the estimated decrease was 0.14 log$_{10}$ copies/mL per week for controls and 0.24 per week for PrEP/ARV-treated animals.

Inflammatory Immune Factors During Acute Infection

To characterize innate and adaptive immune responses during acute infection, we measured key inflammatory plasma cytokines and chemokines (Figure 2A–2D) [17]. We tested whether IFN$_\gamma$, IL-1Ra, IL-18, INFx, and MCP-1 levels differed at peak viremia during maximal viral replication and inflammation. Median values of IL-1Ra and IL-18 were lower in PrEP-breakthrough–infected macaques, compared with controls (IL-1Ra: 1.9 pg/mL vs. 48.9 pg/mL [$P < .05$]; IL-18: 0.3 pg/mL vs. 58.0 pg/mL [$P < .05$]; Wilcoxon rank-sum tests). Median IFN$_\gamma$ plasma concentrations were 0 and 3.6 pg/mL, and median MCP-1 concentrations were 176 and 257 pg/mL in breakthrough PrEP, compared with control-infected macaques, respectively; these estimated median differences were not statistically significant. IFN$\alpha$ level was not measurable in the samples.

T cell Immunity

Peripheral blood T cell counts are shown in Figure 3A in samples taken before virus exposures, at peak viremia, and 2, 6, 12, and 20 weeks thereafter. In control animals, there was a temporal drop in overall CD3$^+$ T cell counts at peak viremia ($P = .03$, Wilcoxon rank-sum test) (Figure 3A), which is typical for SHIVSF162P3 infection at peak viremia [14] and is attributable to a decrease in CD4 T cells occurring sharply at this time. This decrease was not seen in PrEP breakthrough infections. At peak viremia, the median number of CD4 T cells was higher in breakthrough PrEP–infected macaques, compared with control macaques ($P = .02$, Wilcoxon rank-sum test) (Figure 3B). Median CD8 T cell counts did not differ between the groups and did not expand significantly, as in previous studies of SHIVSF162P3 infection (data not shown) [14]. During the viral ramp-up phase in SIV infection, IL-15 production precedes the infection of CD4 T cells and their subsequent death [18]. IL-15 concentrations and CD4 cell count decrease have been shown to be inversely correlated [18]. We examined plasma IL-15 level 2 weeks before peak viremia (Figure 3C). Control-infected macaques had higher IL-15 levels, compared with breakthrough-infected macaques ($P < .05$, Wilcoxon
rank-sum test) (Figure 3C). Thus, we observed both higher IL-15 concentrations and lower CD4 cell counts in controls than in breakthrough PrEP-infected animals (Figure 3C).

Antigen (SHIV)-specific T cells were further analyzed by flow cytometry (Figure 4A–4C) and IFNγ-ELISPOT (Figure 4D and 4E). T cells were stimulated with gag-derived peptide pools and identified as antigen specific if this prompted an increase in intracellular IFNγ, IL-2, TNFα, and/or MIP-1β. Infection led to similar increases in the number and percentage of gag-specific T cells in both groups (Figure 4A). Gag-specific central memory T cells (T_{CM}) were analyzed because they can correlate well with restoration of gut-resident CD4 cells [27], an important immunological marker for disease attenuation [28]. More gag-specific T cells had a T_{CM} phenotype in breakthrough PrEP-infected macaques than in controls when combined T cells from peak, and 6, 12, and 20 weeks thereafter were analyzed (P = .04, generalized estimation equations method) (Figure 4B), whereas T_{EM} cells had an inverse distribution in the 2 groups (not shown). We examined the ability of T cells to simultaneously produce multiple cytokines or chemokines (referred to as “factors” in Figure 4C), because this is associated with superb antimicrobial potency [29]. At peak viremia, more gag-specific T cells simultaneously produced 4 factors in breakthrough PrEP-infected monkeys, compared with controls (P = .02, Wilcoxon rank-sum test) (Figure 4C), despite a similar number and percentage of gag-specific T cells (Figure 4A), indicating enhanced potency of gag-specific T cells. Functional differences resolved at later time points (Figure 4C and data not shown).

To study T cell responses to more epitopes, we performed IFNγ ELISPOT analyses using peptide pools with gag, env, pol, vif, vpr, nef, and tat sequences (Figure 4D and 4E). Fresh blood samples were collected on 2 separate occasions 10–12 weeks after peak viremia. When responses to all peptide pools were added, controls showed greater combined T cell responses than did breakthrough PrEP macaques (mean, 2167 SFU/10^6 PBMCs vs. 882 SFU/10^6 PBMCs; P = .001, generalized estimation equations method). Epitope diversity was not significantly different between the 2 groups, however, because a mean of 3.6 peptide pools were recognized with >10% of the response in PrEP-treated macaques, compared with a mean of 2.3 peptide pools in controls (Figure 4E).

Effect of In Vivo CD8 Cell Depletion on Viremia
To further address whether CD8 cells play a critical role in controlling SHIVSF162P3 after breakthrough PrEP and control infections, we depleted CD8 cells in vivo by administering anti-CD8 antibodies to 3 controls and 3 PrEP-breakthrough infected macaques [30] approximately 28 weeks after peak viremia and after PrEP discontinuation. One macaque received control IgG antibodies. Figure 5A shows that the antibody regimen led to a temporal disappearance of blood CD8 cells, except in the control IgG-treated macaque. Simultaneously, plasma viral load increased to similar levels in both control and PrEP-infected macaques (Figure 5B). It peaked at a median 10^5.6 RNA copies/mL in control infected and 10^5.5 in untreated macaques, indicating no statistically significant difference between the groups (P = .7, Wilcoxon rank-sum test). The rate of viral load decrease was also similar between the 2 groups. This indicates that CD8 cells similarly suppress viremia in this phase of breakthrough and control infection. In controls, median viral load after CD8 cell depletion was lower than during primary viremia (P = .04, Wilcoxon rank-sum test). This could be because non-CD8 cell-mediated adaptive immunity (eg, antibodies) developed at this time point of SHIVSF162P3 infection [7]. There were no statistically significant differences between CD4 cell counts in the control and breakthrough-infected groups after CD8 cell depletion (data not shown). In summary, CD8 cell depletion affected the 2 groups similarly, indicating that CD8 cells efficiently control viremia in both groups.
Figure 4. Enumeration and characterization of SHIV-specific T cells (gag-specific [A–C], or specific for gag, env, pol, tat, vif, vpr, and nef products [D and E]).

A. Induction of gag-specific T cells. We identified gag-specific T cells by flow cytometry, after in-vitro incubation of freeze-thawed cells with gag1/gag2 peptide pools, then enumeration of CD3+ cells with intracellular production of IFNγ, IL-2, MIP-1β, and/or TNFα. The left panel shows numbers, the right panel shows percentages of gag-specific PBMCs. 

B. Gag-specific T cells were further analyzed for central memory TCM (shown) or effector memory TEM (not shown) phenotype. TCM cells were defined as CD3+ CD69+ (IFNγ, TNFα, MIP-1β, and/or IL-2)+, CD28high, CCR7+. The asterisk indicates statistical significance ($P = .04$, generalized estimation equations method) between control and PrEP-infected groups when analyzing T cells from peak, and 6, 12, and 20 weeks thereafter, combined. 

C. Gag-specific T cells producing multiple factors (IFNγ, IL-2, TNFα, MIP-1β)

D. IFNγ-ELISPOTs results

E. Epitope diversity

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DISCUSSION

Our studies show that PrEP and continued ARV therapy during breakthrough infection can noticeably and beneficially impact early disease parameters in an animal model with relevance for human PrEP. Early systemic inflammatory parameters were lowered during acute infection acquired on active but nonprotective PrEP, compared with untreated infection, and CD4 T cells were spared from the temporal decrease seen in untreated SHIVSF162P3 infection. These data can inform follow-up studies of ongoing or recently completed PrEP clinical studies. If attenuated acute HIV infection is indeed found after human PrEP, this could result in an overall attenuated HIV disease course. Clinical outcomes warrant further study and could include delayed clinical end points, reduced need for ARV therapy, and lowered transmission rates. These parameters could have a beneficial impact on the HIV/AIDS epidemic.

This study focused on evaluation of immunity during acute infection. At later time points and after PrEP was discontinued, there were subtle effects on T cell maturation, such as central memory development. A more comprehensive evaluation of later immunological parameters was not possible in our experimental system of nonpathogenic SHIV infection. Using more pathogenic SIVmac251 or 239 would permit immune analyses during chronic infection that more closely mimics HIV infection. For example, CD4 cell counts, a major predictor of human HIV disease course, could be differentially followed during their steady decrease, allowing a better understanding of long-term immunological control of the infection. This would also permit further analysis of drug resistance development in the context of ongoing vigorous viral replication. Although no resistance was seen in the PrEP breakthroughs in this study, it remains a major concern for PrEP breakthrough HIV infections, particularly if ARVs are continued in a PrEP regimen after infection. Therefore, any potential benefit in long-term immune control may be offset by increased drug resistance development.

The present study was conducted with small animal groups. Powering future studies with larger group sizes will allow a more in-depth analysis of immunological parameters. Further studies should also discontinue PrEP earlier, simultaneously, and at controlled time points and should enumerate CD4 cells in mucosal tissues (eg, gut). The latter could provide a clearer

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**Figure 5.** In vivo depletion of CD8+ cells. Approximately 28 weeks after peak viremia, CD8+ cells were deleted by anti-CD8 antibody injection (indicated by arrows) in 3 control and 3 breakthrough-infected macaques; 1 macaque received mock IgG antibodies. (A): The disappearance of CD8+ cells from blood was analyzed by flow cytometry on various time points after first antibody administration. Monkey IDs were controls (open symbols): AG94, AI22, 35720; PrEP-treated (filled symbols): 35032, 1784, 4292, and DK43 (IgG control, dotted line). B: Plasma viral loads increased to similar levels in both controls and PrEP-treated macaques after CD8+ cell depletion.
picture of whether gut CD4 counts are spared from destruction, a parameter that has great influence on disease progression [28].

Our observation of altered immune parameters after PrEP is perhaps not surprising, because ARV therapy initiation very early after transmission has similar effects in macaques and humans [27, 31–39]. Our study design included ARV therapy before and after infection and is therefore highly similar, but not identical, to giving ARV therapy very soon after infection. ARV therapy was discontinued in one macaque, 34,912, immediately after the last infecting virus exposure. This macaque was indistinguishable from the other PrEP-breakthrough macaques in terms of viremia and immunological parameters (data not shown), suggesting that continued ARV therapy was not necessary for the altered infection course. We suspect that the main mechanism of action is the effect of ARVs on reducing viral replication immediately after infection, which in turn reduces priming of the immune system. Continued ARV therapy can also limit virus diversification and suppress emergence of immunological escape mutations, thus enhancing immune control [40]. In addition, it is possible that ARVs modulate specific immune-regulatory factors in PBMCs or monocytes independent of virus, as has been reported for tenofovir and its impact on IL-8, IL-10, and IL-12 production [41]. Lastly, chemo-vaccination before the transmission event [24, 42] may impact the subsequent infection through priming of specific arms of the adaptive immune system before infection.

Because it has previously been reported that there is only a transient (limited to one week) and partial decrease in blood CD4 cell count in SHIV <sub>SP162P3</sub> infection at peak viremia [14], it was expected that differences in CD4 cell counts are only present at this time point. Differences in SHIV-specific T cell counts were not clearly measurable. Similar numbers of gag-specific T cells were found by flow cytometry, but SHIV-specific T cell numbers differed when examined by IFNy-ELISPOT using wider epitope representation. The latter could be explained by greater antigenic stimulation in control infections with higher viremia. It is unclear whether these findings represent real differences or are attributable to individual animals in small study groups. To address the functional role of CD8 cell immunity more definitively, we performed an in vivo depletion of such cells. The ensuing similar viremia levels clearly showed that CD8<sup>+</sup> cells controlled viremia efficiently in both contexts. Thus, the early ARV treatment had not induced a CD8-independent mechanism to suppress viremia. This experiment could not address whether CD8<sup>+</sup> CD3<sup>+</sup> (presumably SHIV-specific T cells) or CD3<sup>+</sup> cells (presumably mostly NK cells) are responsible for the effect. Of note, viral load did not increase to the level seen in acute control infection, possibly because of antibody-mediated immunity at this time point in both control and PrEP breakthrough–infected macaques [7]. Additional studies might shed more definitive light on long-lasting effects of PrEP on T cell maturation (eg, by analyzing the degree of viral divergence in known T cell epitopes from founder virus stocks in control and PrEP breakthroughs) [43].

A recently presented analysis of breakthrough infections from the CAPRISA 004 tenofovir-gel study reports preservation of virus-specific CD4 T cells in intercurrent infections [44], suggesting an attenuated disease course in HIV-infected persons after PrEP. This was not seen in the small number and limited follow-up of breakthrough infections in the iPrEX trial [2], possibly because of low drug adherence in the study. Of note, one patient receiving a prophylactic ARV regimen experienced an attenuated clinical HIV infection characterized by high CD4 cell counts, as reported by a case study [45]. A comprehensive evaluation of HIV disease attenuation after oral and topical PrEP and after vaginal, rectal, and penile infection will be of interest and could even uncover selective benefits of systemic versus topical PrEP use.

In conclusion, our study provides a first characterization of inflammatory markers, T cell memory and epitope specificity, and CD4 cell counts in acute PrEP breakthrough infections of macaques that are acquired during active but only partially effective oral PrEP. These results indicate a potentially beneficial effect of PrEP. Further study is needed to determine whether PrEP during virus acquisition has longer-term effects on immune preservation and control of HIV infection.

Notes

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