



PROTOCOL

HVTN 804/HPTN 095

Antiretroviral analytical treatment interruption (ATI) to assess immunologic and virologic responses in participants who received VRC01 or placebo and became HIV-infected during HVTN 704/HPTN 085

DAIDS DOCUMENT ID 38632

Non-IND Protocol

CLINICAL TRIAL SPONSORED BY

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National Institute of Allergy and Infectious Diseases (NIAID)
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Department of Health and Human Services (DHHS)
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1 Protocol summary

Full title:	Antiretroviral analytical treatment interruption (ATI) to assess immunologic and virologic responses in participants who received VRC01 or placebo and became HIV-infected during HVTN 704/HPTN 085
Short title:	HVTN 804/HPTN 095
Sponsor:	NIAID Division of AIDS
Conducted by:	HIV Vaccine Trials Network (HVTN) and HIV Prevention Trials Network (HPTN)
Protocol chairs:	Shelly Karuna, MD, MPH; Katharine Bar, MD
Sample size:	16 – 46
Study population:	HIV-1–infected HVTN 704/HPTN 085 participants who transitioned to Schedule 2 in that trial
Study design:	An exploratory study of HIV-infected participants undergoing an analytical treatment interruption after receiving VRC01 or placebo infusions in HVTN 704/HPTN 085
Study duration:	Study duration is potentially indefinite for a participant maintaining extreme and extended viral control during ATI. Study duration for most participants is expected to be 13-18 months. The maximum anticipated duration for any participant is expected to be approximately 2½ to 3 years.
Study products:	None. Drugs for anti-retroviral therapy (ART) and for pre-exposure prophylaxis (PrEP) will not be provided by the study or paid for using sponsor funds. Procedures for accessing external funding sources for PrEP and ART provision are detailed in the HVTN 804/HPTN 095 Study Specific Procedures (SSP).
Primary objectives:	To evaluate the effect of VRC01 received in the immediate pre-HIV acquisition period and/or during early infection on the time to meeting ART re-initiation criteria in participants undergoing ATI To evaluate the safety of ATI among HVTN 804/HPTN 095 participants

Secondary objectives: To evaluate the effect of VRC01 received in the immediate pre-HIV acquisition period and/or during early infection on the development of anti-HIV immune responses that differ from those of placebo recipients, and whether these immune responses are associated with time to meeting criteria for ART re-initiation in participants undergoing ATI

To evaluate the effect of VRC01 received in the immediate pre-HIV acquisition period and/or during early infection on viral load in participants undergoing ATI

To evaluate the effect of VRC01 received in the immediate pre-HIV acquisition period and/or during early infection on HIV reservoir size before and after ATI, and whether HIV reservoir measurements are associated with time to meeting criteria for ART re-initiation in participants undergoing ATI

1.1 Précis

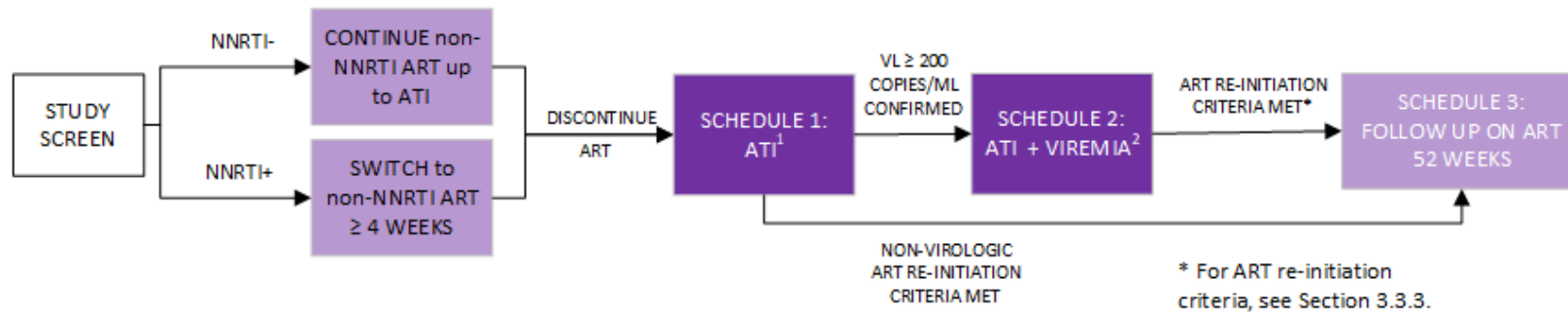
Mounting preclinical (eg, murine, nonhuman primate [NHP]) and clinical evidence suggests that anti-HIV broadly neutralizing antibodies (bnAbs) can mediate sustained virologic control of HIV. While the mechanisms responsible for this control are not known, studies in both animal models and in humans suggest that, in addition to direct viral neutralization, bnAbs can enhance autologous cellular and humoral immune responses to HIV. Hence, by a variety of mechanisms, including formation of immune complexes, modulation of autologous immune responses, dampening HIV replication, exerting a sieve effect at acquisition, and immune pressure during early infection, bnAb concentrations that are insufficient to prevent HIV acquisition may nevertheless facilitate a more effective response to early infection and help set the stage for later durable virologic control. In addition, by these same mechanisms, bnAbs may be capable of limiting the establishment and decreasing the size of the viral reservoir.

The Antibody Mediated Prevention (AMP) studies HVTN 704/HPTN 085 and HVTN 703/HPTN 081, phase 2b studies assessing the ability of the CD4 binding site bnAb VRC01 to prevent HIV-1 infection, provide a unique opportunity to assess these hypothesized bnAb effects as they currently have the only cohort of individuals who have acquired HIV infection in the presence of a bnAb. HIV-1–infected AMP participants were diagnosed soon after acquisition, initiated ART relatively soon after diagnosis, and those in the VRC01 arms had some level of bnAb present at the time of infection. A pause in antiretroviral treatment—that is, an analytical treatment interruption (ATI)—is the only way to determine whether the presence of VRC01 at the time of, or shortly after, acquisition of HIV, results in blunted, delayed, or absent viral rebound following discontinuation of ART, or subsequent immune control of any rebound that may be observed. If such an

impact is observed, ATI is also the best means of assessing mechanisms and predictive biomarkers of that impact through assessment of innate, cellular, and humoral markers along with characterization of the viral reservoir. To avoid misattribution of extended or sustained virologic control, should such control be observed, a comparator group of HIV-1–infected placebo recipients will also be enrolled. Extensive virologic, immunologic, and safety monitoring will be conducted, and the trial has been formulated for consistency with recent consensus guidelines on the design and conduct of ATI studies (1, 2), particularly with respect to risk mitigation measures.

The study schema is shown below.

1.2 Schema



	SCREEN	PRE-DISCONTINUE ART	SCHEDULE 1			SCHEDULE 2			PRE-REINITIATE ART	SCHEDULE 3		
			ATI WEEKS 0-8	ATI WEEKS 10-24	ATI WEEKS 28-52 ¹	ATI + Viremia WEEKS 0-8	ATI + Viremia WEEKS 10-36	ATI + Viremia WEEKS 40-52 ²		FOLLOW UP ON ART WEEKS 0-12	FOLLOW UP ON ART WEEKS 12-28	FOLLOW UP ON ART WEEKS 40-52
Plasma HIV RNA	✓	✓	WEEKLY	Q2 WEEKS	Q4 WEEKS	WEEKLY	Q2 WEEKS ³	Q4 WEEKS	✓	Q2 WEEKS	Q4 WEEKS	Q12 WEEKS
CD4+ & CD8+ T cell counts	✓	✓	Q2 WEEKS	Q4 WEEKS	Q8 WEEKS	Q2 WEEKS	Q4 WEEKS ⁴	Q8 WEEKS	✓	Q4 WEEKS	Q8 WEEKS	Q12 WEEKS
Hematology & Chemistries	✓	✓	Q4 WEEKS		Q8 WEEKS	Q4 WEEKS		Q8 WEEKS	—	Q4 WEEKS	Q12 WEEKS	Q12 WEEKS

¹ QUARTERLY FOLLOW-UP VISITS MAY CONTINUE BEYOND WEEK 52 FOR PARTICIPANTS WHO DO NOT MEET CRITERIA FOR TRANSITION TO SCHEDULE 2.

² QUARTERLY FOLLOW-UP VISITS MAY CONTINUE BEYOND WEEK 52 FOR PARTICIPANTS WHO DO NOT MEET CRITERIA FOR ART RE-INITIATION.

³ OR WEEKLY FOR WEEKS 10-24, IF VL ≥ 200 copies/mL

⁴ OR Q2 WEEKS FOR WEEKS 10-24 IF VL ≥ 200 copies/mL

1.3 Protocol team

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2 Background and rationale

2.1 Antiretroviral therapy

Antiretroviral therapy (ART) can now achieve prolonged suppression of plasma viremia in most HIV-infected individuals. Consequently, ART has dramatically improved the mortality, morbidity, quality of life, and overall clinical course of infected individuals. However, ART alone has been unable to completely eradicate HIV; plasma viremia rapidly rebounds with reactivation of persistent viral reservoirs in almost all chronically HIV-infected individuals upon cessation of therapy (3-6). Persistence of HIV reservoirs, even with successful suppression of plasma viremia by ART, is a major obstacle to HIV eradication.

Furthermore, clinically successful suppression of HIV comes at a cost: long-term toxicity, drug-drug interactions, drug resistance and pill fatigue necessitate a continued search for effective alternatives for achieving durable control of HIV replication in infected individuals. Thus, one of the highest priorities for the HIV field is the search for therapeutic strategies that can eliminate or control HIV replication and reservoirs in the absence of ART. One potential strategy is to provide passive immunization via broadly neutralizing monoclonal antibodies (bnAbs) against HIV.

2.2 Broadly neutralizing antibodies (bnAbs)

Over the past decade, several bnAbs have been discovered and isolated and their HIV-1 target sites and mechanisms of neutralization have been elucidated (7-14). These efforts have informed the development of recombinant HIV vaccine immunogens designed to elicit broadly neutralizing antibodies (11, 15-19) and they have set the stage for an evaluation of these antibodies' potential as tools for HIV-1 prevention (ie, passive immunization or antibody-mediated prevention), treatment, and possibly cure (20-25). Results from early phase clinical trials using different classes of bnAbs such as those targeting the CD4 binding site (VRC01 and 3BNC117) and the V3 loop (10-1074 and PGT121) have been encouraging, demonstrating the potential for—and challenges of—developing anti-HIV-1 bnAbs as preventive and therapeutic agents (26-29).

Several early phase trials in HIV-uninfected and HIV-infected individuals demonstrated the safety, tolerability, antiviral activity, and pharmacokinetics of VRC01 (26, 27, 30-32) and in 2016 VRC01 advanced to the first bnAb prevention efficacy trials in HIV-uninfected individuals, the Antibody-Mediated Prevention (AMP) trials HVTN 704/HPTN 085 and HVTN 703/HPTN 081.

2.3 bnAbs can mediate virologic control

Preclinical (eg, murine, NHP) and clinical (ie, human) evidence is mounting in support of the premise that anti-HIV bnAbs can mediate sustained virologic control of HIV. In a preclinical experiment designed to assess the impact of early immunotherapy postacquisition, VRC01 was administered 10 days after SHIV_{SF162P3} inoculation (immediately prior to projected peak viremia) in six rhesus macaques, while another six macaques received a combination of VRC07-523LS + PGT121, and another six macaques received ART alone from day 10. Though SHIV_{SF162P3} is ~10-fold less sensitive to VRC01 than most isolates and both VRC07-523LS and PGT121 are more potent than VRC01, suppression of viral replication was comparable across all groups prior to the development of anti-mAb antibodies, a known limitation of the NHP model for bnAb administration (see [Figure 2-1](#)) (33).

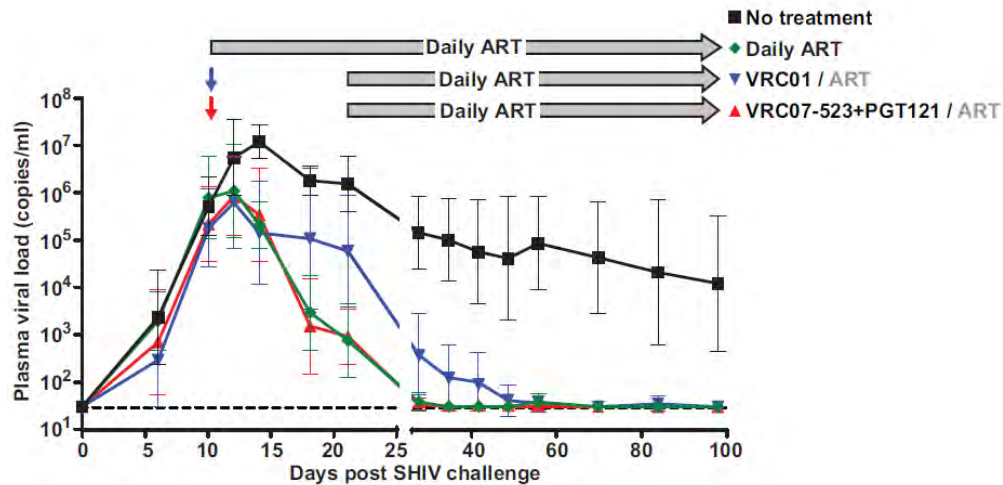


Figure 2-1 Geometric mean plasma SHIV viral loads (pVL) for the untreated group and the 3 treatment groups (n = 6 per group). The error bars represent the 95% confidence intervals at each time point. From (33) Figure 2B.

In another recent study (34), macaques were infected with SHIV_{AD8-EO}. Three days after infection (prior to antibody seroconversion), the animals were randomized to receive either a 2-week course of 10-1074 and 3BNC117 or standard ART. At 15 weeks postinfection, the ART group discontinued ART. Six of the 13 animals treated with 10-1074 and 3BNC117 exhibited prolonged suppression of plasma viremia long after serum levels of infused antibodies became undetectable; in five of these controller macaques, this period of suppression followed an initial rebound of viremia with preservation of CD4⁺ T cells (see [Figure 2-2](#) and [Figure 2-3](#)). Although the 7 noncontroller bnAb-treated macaques did not fully suppress virus, 4 of those 7 maintained CD4⁺ T cell counts and low levels of viremia (10⁵ – 385 copies/mL) without ART for 2-3 years postinfection. Thus, 10 of the 13 bnAb-treated macaques appeared to benefit from early immunotherapy. In contrast, none of the 3 ART-treated animals exhibited sustained suppression of plasma viremia following discontinuation of

ART. No significant differences in HIV-specific CD8+ or CD4+ T-cell responses or anti-gp120 binding antibody levels were observed in controller and noncontroller bnAb-treated macaques, but infusion of a T-cell-depleting anti-CD8 β mAb in the 6 controller animals led to depletion of CD8+ T cells and the rapid reappearance of plasma viremia, suggesting that the prolonged suppression of viremia observed in these animals resulted from potent antiviral CD8+ T-cell immunity induced by the short course bnAb treatment amidst low levels of viral replication (34).

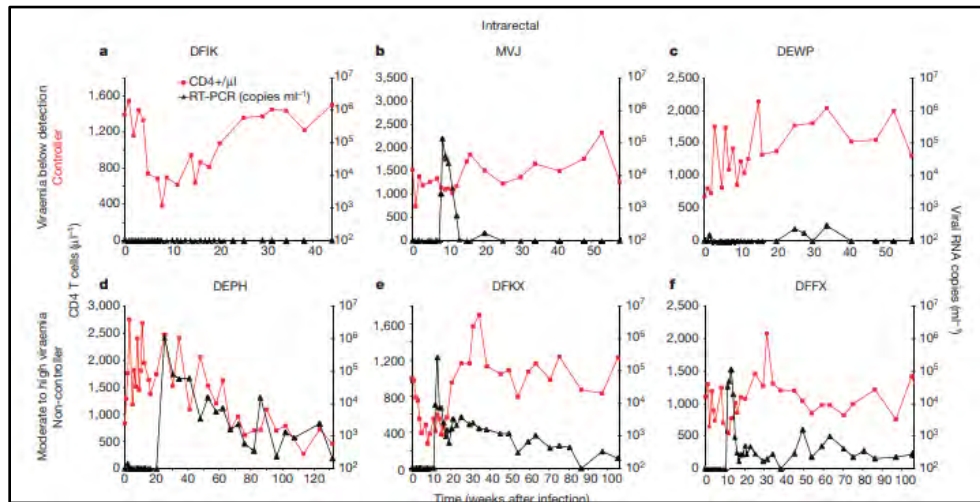


Figure 2-2 Establishment of controller status in bnAb-treated animals inoculated with SHIV_{AD8-EO} by the intrarectal route (a-f). Plasma viral loads (black) and CD4+ T-cell levels (red) are shown in three controller (a-c) and three noncontroller (d-f) macaques. From (34), Figure 2.

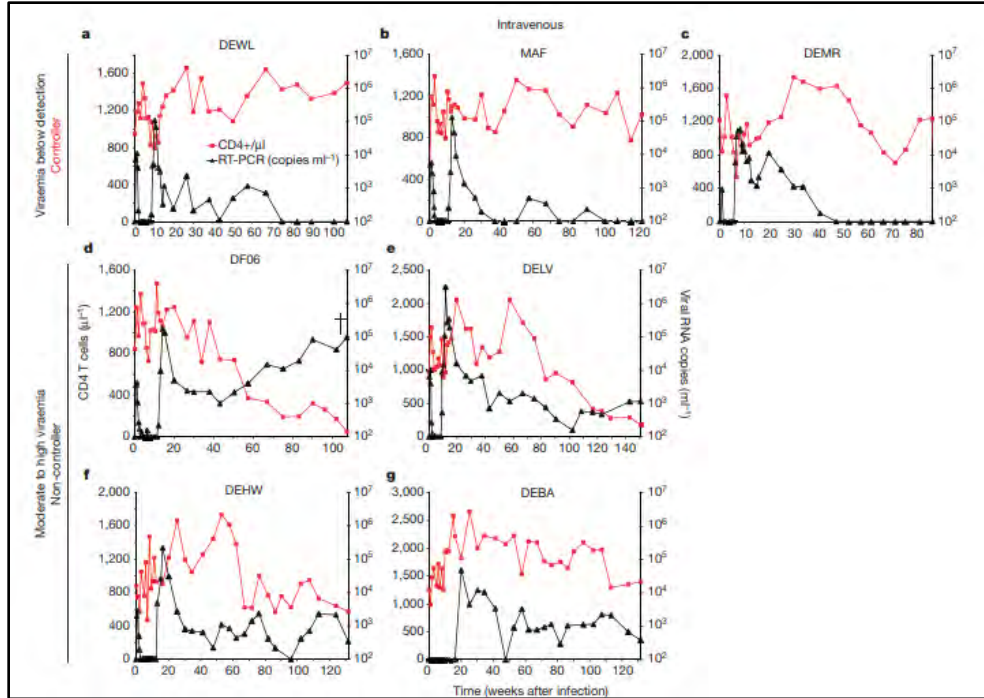


Figure 2-3 Establishment of controller status in bnAb-treated animals inoculated with SHIV_{AD8-EO} by the intravenous route (a-g). Plasma viral loads (black) and CD4⁺ T-cell levels (red) are shown in three controller (a-c) and four noncontroller (d-g) macaques. From (34), Figure 3.

3BNC117 and 10-1074 in combination, and 3BNC117 alone, have also been associated with virologic control in humans. Thirteen individuals with chronic HIV who received 2 or 4 3BNC117 infusions, immediately prior to analytical treatment interruption and then separated by three or two weeks, respectively, had a mean time to virologic rebound of 6.7 weeks (range of 5-9 weeks) after two infusions of the antibody or 9.9 weeks (range of 3-19 weeks) after four infusions of the antibody. Eleven chronically infected individuals who received 3BNC117 and 10-1074 immediately prior to and 3 and 6 weeks after analytical treatment interruption had a median time to virologic rebound of 21 weeks (range 5 to >30 weeks) (35, 36) (see [Figure 2-4](#)).

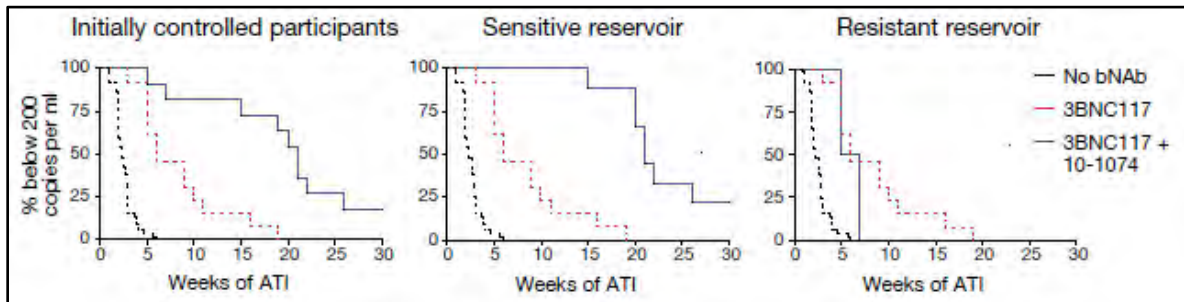


Figure 2-4 Kaplan-Meier plots summarizing time to viral rebound for the participants with HIV-1 RNA < 20 copies per ml two weeks before and at the start of ATI (n = 11, left), for the participants sensitive to both antibodies (n = 9, center), and for the participants that showed pre-existing resistance to one of the antibodies (n = 2, right). The y axis shows the percentage of participants that maintain viral suppression. The x axis shows the time in weeks after start of ATI. Participants receiving the combination of 3BNC117 and 10-1074 are indicated by the blue line. Dotted red lines

indicate a cohort of individuals receiving 3BNC117 alone during ATI (35) (n = 13) and dotted black lines indicate a cohort of participants who underwent ATI without intervention (37) (n = 52). From Mendoza, et al. (36), Figure 1c.

2.4 bnAbs modulate the autologous immune response to acute HIV infection

The mechanisms underlying bnAb-mediated virologic control are unknown, but there are clues in experiments that highlight bnAb-associated enhancement of autologous cellular and humoral responses. Adoptive transfer experiments have demonstrated that 3BNC117 can accelerate clearance of HIV-infected cells (see [Figure 2-5](#)) (38).

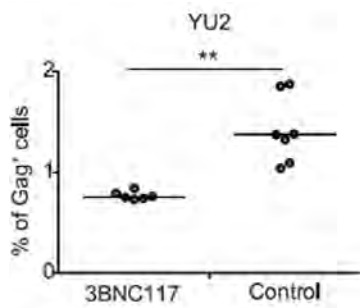


Figure 2-5 Percentage of Gag+ cells among CD3+CD8- cells in mice treated with 3BNC117 (600 mcg) or mice treated with isotype control 5 hours after HIV-1_{YU2}-infected cell transfer. From (38) Figure 2A.

Barouch, et al. demonstrated increased CD8+ T cell-mediated virus inhibition and decreased CD8+ and CD4+ T cell exhaustion in the presence of PGT121 compared to control as well as increased titers of autologous neutralizing antibody in macaques receiving PGT121, 3BNC117, and b12 (see [Figure 2-6](#) and [Figure 2-7](#)) (39).

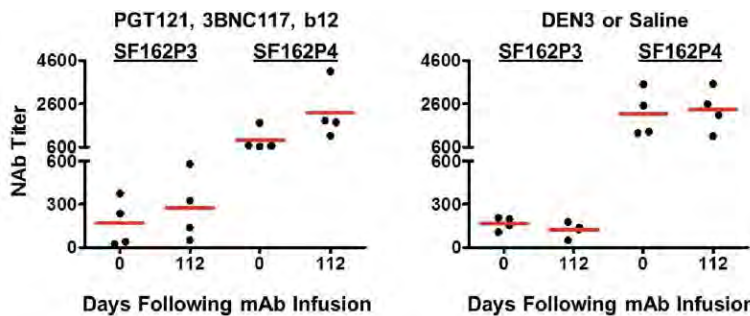


Figure 2-6 SHIV_{SF162P3} and SHIV_{SF162P4} serum neutralizing antibody titers (ID₅₀) in the macaques described in [Figure 2-7](#) after administration of the triple PGT121, 3BNC117, and b12 monoclonal antibody cocktail. From (39) Extended Data Figure 2.

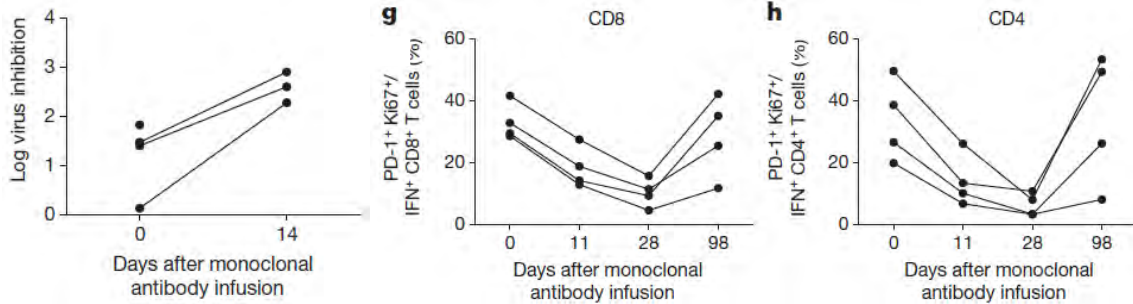


Figure 2-7 Therapeutic efficacy of the triple PGT121, 3BNC117, and b12 monoclonal antibody cocktail. LEFT: Log inhibition of viral replication in CD8+ T-lymphocyte-dependent virus suppression assays after monoclonal antibody infusion. One animal had no recoverable virus at week 2. CENTER and RIGHT: PD-11Ki671 expression on Gag-specific CD8+ (center) and CD4+ (right) T lymphocytes after monoclonal antibody infusion. From (39) Figure 1f, 1g, and 1h.

Enhanced humoral responses—specifically, elevated levels of HIV Env-specific antibodies—were also observed in macaques by Bolton, et al. (33). In this study, antibody titers in animals that received either VRC01 or VRC07-523LS + PGT121 with ART exceeded titers achieved by animals receiving ART alone (see Figure 2-8).

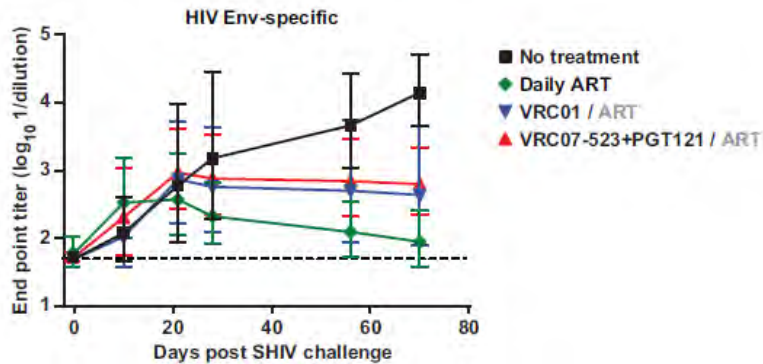


Figure 2-8 Geometric mean endpoint titer values for plasma reactivity to HIV-1 SF162 gp120 (anti-HIV Env) determined by ELISA for each group (n = 6) at the indicated days postinfection. Error bars represent the 95% confidence intervals; the dotted lines indicate the limit of detection for the assay. From (33) Figure 3B.

Haigwood, et al. demonstrated accelerated development of autologous neutralizing antibodies in macaques. Uninfected macaques were assigned to no immunization (n = 4) or passive immunization, 1 and 14 days after challenge, with either normal IgG (n = 6) or SIVIG (n = 6), which is a polyclonal IgG obtained from a healthy SIV-infected nonprogressor with high-titer neutralizing activity. Three of the 6 animals that received SIVIG showed accelerated development of neutralizing antibodies, in contrast to the animals that received normal IgG or no IgG (see Figure 2-9). These SIVIG-associated antibodies contributed to rapid control of post-acute phase viremia, resulting in delayed disease onset (40).

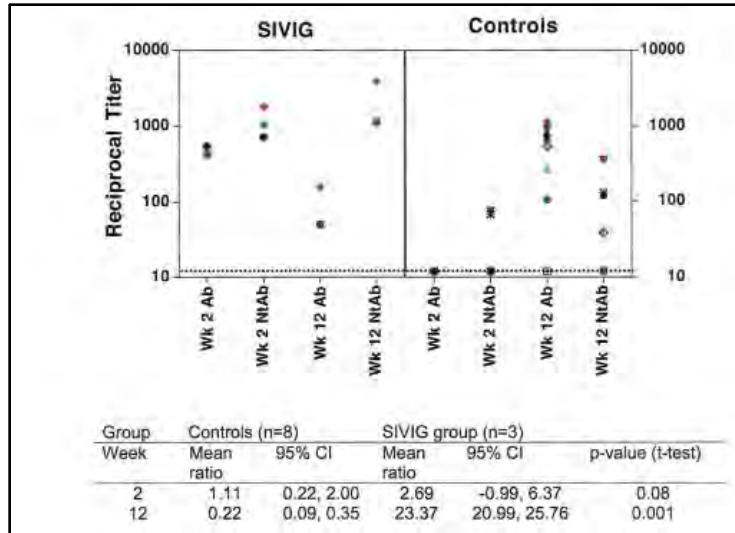


Figure 2-9 Scatter plot of Env-specific binding and SIVsmE660 nAbs at weeks 2 and 12 in macaques that seroconverted. Note that some symbols overlap. Mean ratios are noted for each group at weeks 2 and 12, with 95% confidence intervals. From (40), Figure 5.

Schoofs, et al. also observed significantly increased autologous neutralizing antibody breadth and potency in chronically infected viremic individuals who received 3BNC117 compared to controls (see [Figure 2-10](#)) (41).

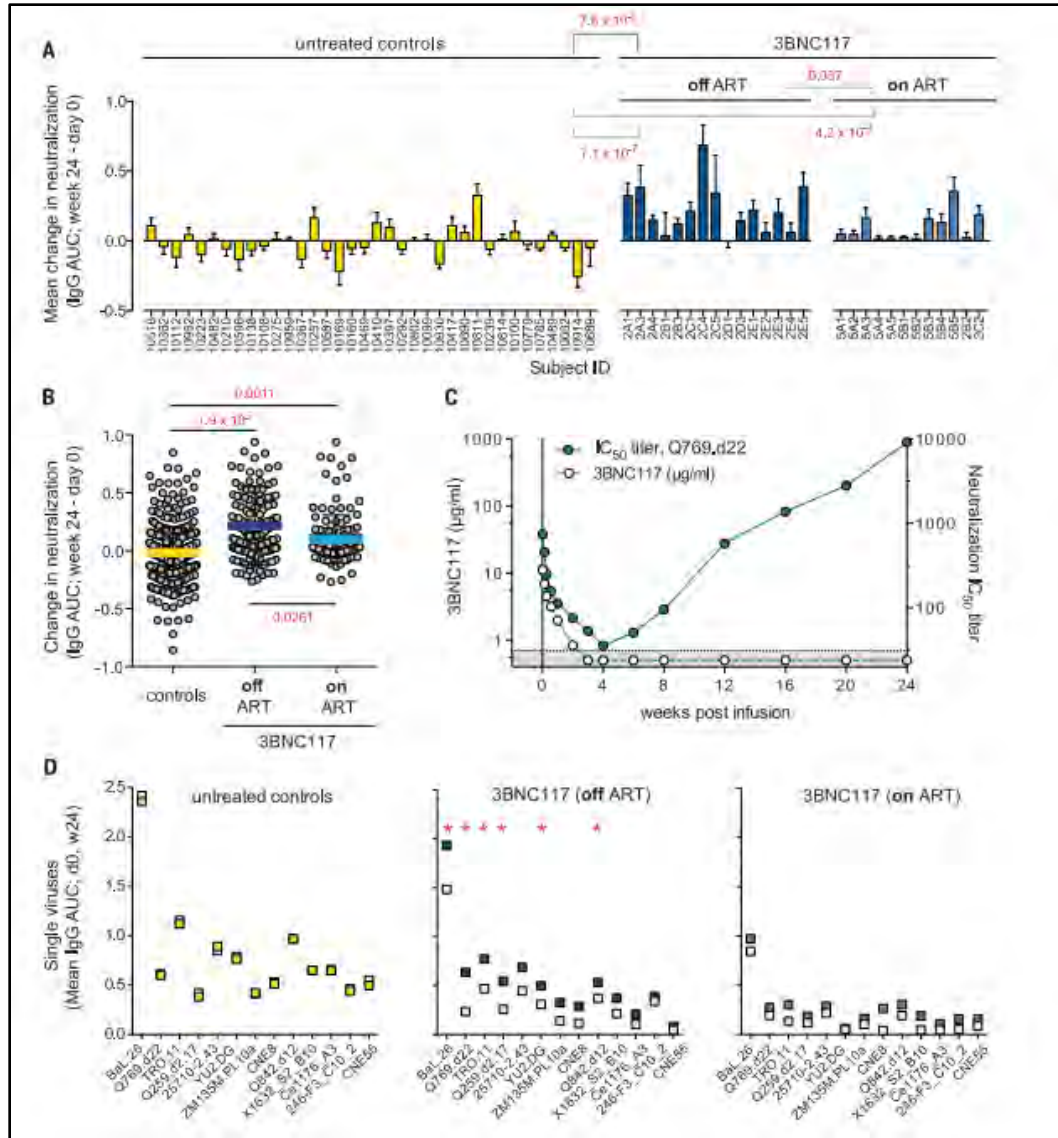


Figure 2-10 Heterologous antibody responses. (A) The difference in overall AUC (mean AUC change) per individual in TZM.bl assays against 13 heterologous viruses for d0 versus week 24 IgG obtained from 36 untreated viremic controls (mean sampling interval 26.8 weeks), 15 viremic individuals infused with 3BNC117 (mean sampling interval 24.1 weeks), and 12 ART-treated individuals receiving 3BNC117 infusion (mean sampling interval 24.0 weeks). (B) The aggregated differences in AUC between d0 and week 24 IgG assayed by TZM.bl for all viruses and all individuals. Each dot represents a single AUC difference for a single virus from one individual displayed in (A). Colored bars represent the mean of all AUCs. (C) 3BNC117 antibody levels (ELISA, white) and TZM.bl neutralization titer against tier 2 strain Q769.d22 (green) in patient 2A3. (D) Mean AUCs of IgGs of all individuals at d0 (gray) and week 24 (color of respective group) for each HIV-1 pseudovirus tested. Changes in neutralization of viremic control individuals without 3BNC117 infusion are shown in yellow (left). Change in neutralization of 3BNC117-treated individuals are shown in dark blue (off ART, middle) and light blue (on ART, right). Red stars indicate significant p-values after Bonferroni correction (threshold $p < 0.0038$). From (41), Figure 2.

Furthermore, bnAbs appear to render otherwise-ineffective autologous antibodies more effective. In a hu-mice model in animals lacking autologous neutralizing antibodies, 10-1074 administered in combination with an autologous tier-1

neutralizing antibody (either 10-188 or 1-79) was associated with significantly greater reduction in viremia than 10-1074 or the autologous bnAbs alone. Additional experiments (data not shown) suggested that bnAbs directed viral evolution to variants more sensitive to autologous tier-1 nAbs, while the autologous nAbs also appeared to limit viral evolution away from the bnAb (see [Figure 2-11](#)) (42).

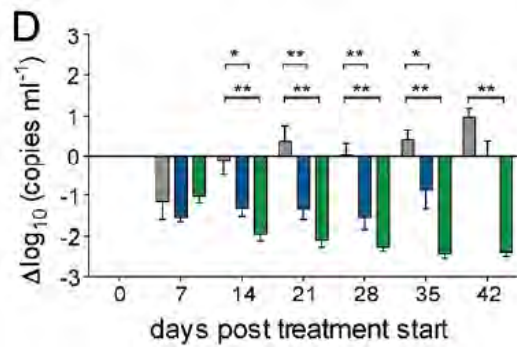


Figure 2-11 Changes of log₁₀ viral load (mean and SEM) of mice treated with 10-1074 (gray), 10-1074 + 10-188 (blue), and 10-1074 + 1-79 (green). Significant differences between treatment groups were determined by using repeated measures ANOVA with a Bonferroni pos-hoc test. *, p < 0.05; **, p < 0.001; ***, p < 0.0001). From (42) Figure 7D.

The concurrent enhancement of both cellular and humoral responses, and the evidence of virologic control in the face of it, calls to mind the immunologic responses to tumor antigens in individuals receiving cancer immunotherapy, and implicates immune complexes formed by bnAbs bound to circulating virus and infected cells (43, 44). Immune complexes act as potent immunogens, as evidenced by work in the HIV vaccine field. A trial of an immune complex vaccine reported that anti-CD4bs complexes with gp120 led to conformational changes in gp120 that stabilized and exposed epitopes in the V3 loop, leading to enhanced antigenicity and immunogenicity compared to gp120 alone (45, 46). This recapitulates the difference in HIV acquisition without bnAbs present (ie, comparable to gp120 alone) compared to acquisition in the presence of bnAbs bound to the gp120, forming immune complexes that stimulate a more effective autologous immune response.

Immune complexes with infected cells and with cell-free virions undergo FcγR-mediated uptake by antigen presenting cells (eg, dendritic cells) and efficient antigen processing via proteasomal and endosomal degradation, that exposes particularly antigenic epitopes for MHCII presentation, stimulating enhanced CD4+ T-cell responses and directing the immunologic response down a Th1 pathway, with enhanced CD4+ co-stimulation, a more efficient cytokine milieu for antiviral control, and enhanced CD8+ T-cell responses. The consequent development of pools of precursor T cells, in particular, sets the stage for durable virologic control, as these cells proliferate in the presence of antigen later, producing large amounts of effector T cells that then clear HIV-infected cells and virions (47-49). In fact, this pathway has been demonstrated in the murine FrCasE retrovirus model that has many similarities to HIV infection. T_{reg} suppression was

also observed in this model after therapeutic bnAb administration and subsequent immune complex-mediated induction of an antiviral host response that preserved immune function and stymied disease development, demonstrating yet another potential contribution to the bnAb-optimized early antiviral responses that may ultimately yield long-term virologic control (50, 51).

Rendering this enhancement of the innate component of the immune response even more effective is bnAbs' binding and neutralization of virus—a direct “debulking” of viral particles and of infected cells, thus limiting the number of virions capable of direct infection and replication and serving to limit viral factors that impair dendritic cell activation and maturation. This “viral debulking” function of bnAbs is analogous to surgical debulking (ie, cytoreductive surgery) performed for some tumors, which is associated with a survival advantage that is attributed in part to improved autologous immune function, with lower levels of tumor factors that impair the host immune response to cancer.

In summary, by forming immune complexes, modulating and enhancing autologous immune responses, dampening HIV replication, and exerting a sieve effect at acquisition and pressure in early infection, even bnAb concentrations that are insufficient to prevent acquisition might nevertheless work in concert with the autologous innate and adaptive immune response to facilitate a more effective response to early infection and to help set the stage for later durable virologic control (52-54).

2.5 bnAbs may limit establishment and decrease the size of the viral reservoir

In addition to, and in part likely due to, their enhancement of innate and adaptive immune responses, bnAbs appear to be capable of limiting the establishment and decreasing the size of the viral reservoir (25, 55). An in-vitro study of cells obtained from chronically infected aviremic humans demonstrated bnAb binding of cell-free virions produced from the latent reservoir, suppression of entry of those virions to activated uninfected CD4+ T cells, and suppression of replication-competent HIV in autologous CD4+ T cells (56). In a humanized mouse model, administration of bnAbs 4 days after infection interfered with the establishment of a reservoir through Fc-mediated mechanisms and, when administered with latency-reversal agents, decreased the size of an established viral reservoir (20). Administration of bnAb with ART to reduce viral load, then of a single bnAb alone after ART termination, was followed by functional virologic control, demonstrating potential synergy between bnAbs and ART for durable viral suppression (57). In macaques, a reduction in cell-associated viral DNA and RNA in peripheral blood mononuclear cells (PBMCs) and tissues was also observed after administration of single and combination bnAb immunotherapy (39, 58).

The mechanisms of these impacts on the viral reservoir are likely myriad and include direct neutralization of virions from reactivated cells and bnAb binding

and Fc-mediated recruitment of cytotoxic immune cells (eg, NK cells) that kill reactivated cells, which may be significantly enhanced by immune complex formation as described above (20, 25, 49). BnAbs accomplish this work of limiting reservoir seeding, and later reducing reservoir size, not only in blood and interstitial fluid but also in some of the principal sites of pre-ART virus production and persistence, lymph nodes and gut-associated lymphoid tissue, in which antiretrovirals have less penetrance (59-61). In one study, a significant reduction of cell-associated SHIV DNA was observed in these tissues after administration of a single bnAb to infected macaques (39) (see [Figure 2-12](#)).

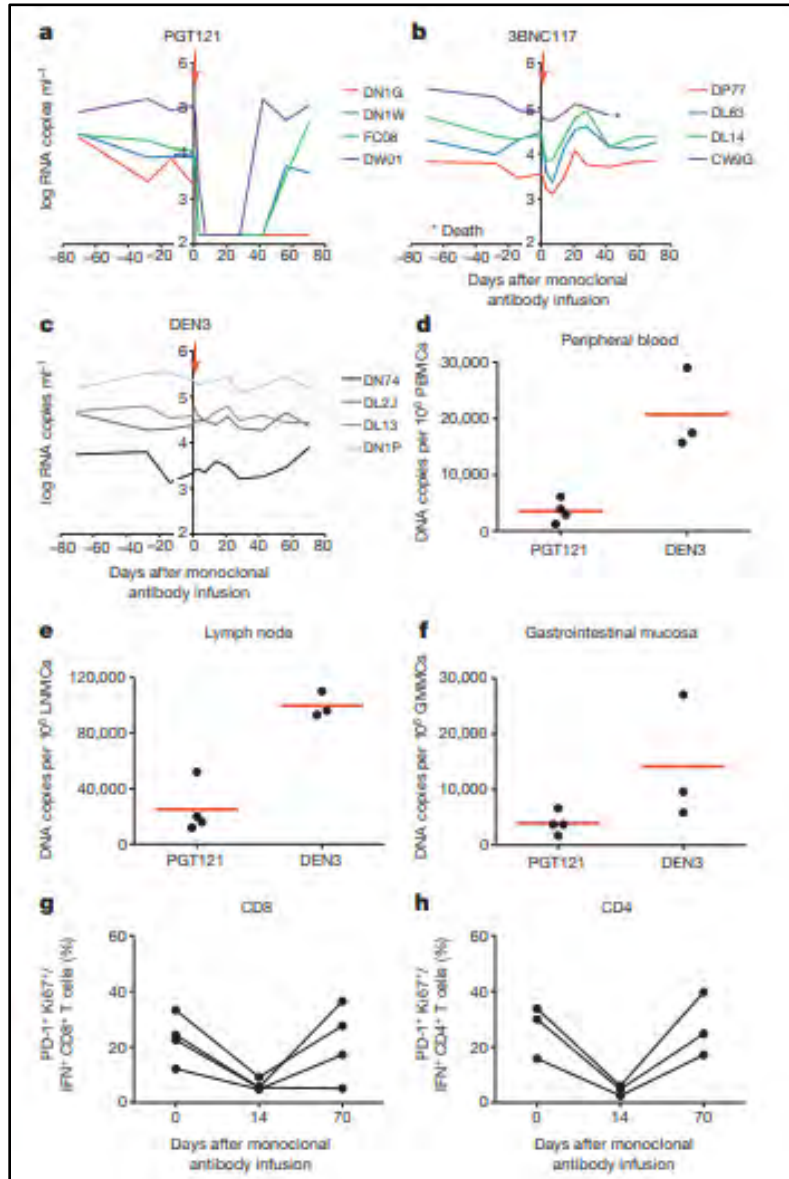


Figure 2-12 Therapeutic efficacy of the single monoclonal antibodies PGT121 and 3BNC117. a-c, Plasma viral RNA (log copies/mL) in rhesus monkeys chronically infected with SHIV-SF162P3 after a single infusion (arrows) of PGT121 (a), 3BNC117 (b), or the control monoclonal antibody DEN3 (c). d-f, Proviral DNA (copies/10⁶ cells) in peripheral blood mononuclear cells (PBMCs) (d), lymph nodes (e) and gastrointestinal mucosa (f) 14 days after the monoclonal antibody infusion in

the animals that received PGT121 or DEN3. Red bars indicate mean values. Assays for one of the DEN3-treated controls failed. g, h, PD-1+ Ki671+ expression on Gag-specific CD8+ (g) and CD4+ (h) T lymphocytes in the monkeys that received PGT121. From (39), Figure 3.

2.6 The HVTN 704/HPTN 085 AMP study

HVTN 704/HPTN 085 opened in early 2016 and enrolled 2701 men who have sex with men (MSM) and transgender (TG) individuals. Participants were randomized 1:1:1 in a double-blind fashion to receive 10 mg/kg VRC01, 30 mg/kg VRC01, or placebo. Participants receive study product via intravenous (IV) infusion every 8 weeks for a total of 10 infusions over 72 weeks and are then followed every four weeks to week 80, and every 8 weeks thereafter to week 104 (62) (see [Table 2-1](#)). In addition to assessing the prevention efficacy of VRC01 and providing further VRC01 safety and PK data, the AMP studies include assessment of functional activity (ie, Fc effector functions), sieve analyses, and correlates analyses. Both AMP studies completed enrollment in October 2018.

Table 2-1 HVTN 704/HPTN 085 AMP schema

	Treatment	N*	Infusion schedule (Weeks)											
			[A = VRC01 infusion; C = Control infusion]											
			W0	W8	W16	W24	W32	W40	W48	W56	W64	W72	W80*	W104†
Group 1	VRC01 10 mg/kg	900	A	A	A	A	A	A	A	A	A	A		
Group 2	VRC01 30 mg/kg	900	A	A	A	A	A	A	A	A	A	A		
Group 3	Control	900	C	C	C	C	C	C	C	C	C	C		

* Due to the randomization scheme, the numbers of VRC01 and control recipients may differ slightly.

♦ Week 80 is the last study visit for the primary endpoint analysis of prevention efficacy.

† Week 104 is the last study visit for the co-primary endpoint analysis of safety and tolerability.

HIV diagnostic testing is conducted every 4 weeks and is accompanied by collection of serum and, at up to four time points, PBMCs for storage. Participants who become HIV-infected discontinue further study infusions and are monitored (on visit Schedule 2) for 24 weeks with viral loads, CD4+ T-cell counts, and VRC01 levels, while providing serum, plasma and PBMCs for storage, functional humoral assays and other assessments. HIV-infected participants are linked to care for ART initiation and additional clinical follow-up.

Most HVTN 704/HPTN 085 participants initiate ART within 4 weeks of confirmation of HIV infection, a mean of 7 weeks after the first RNA-positive HIV diagnostic sample. The vast majority of participants exhibit HIV diagnostic patterns of RNA-positive, EIA-positive, and Bio-Rad Geenius-negative, -indeterminate, or -positive with p31-negative at the time of their confirmatory HIV diagnostic sample, and initiate ART within 4 weeks of this time point.

2.7 Antiretroviral analytical treatment interruption (ATI)

More than 150 studies with ATIs have been conducted since the introduction of combination ART over twenty years ago. Nearly 100 of those were conducted in the first decade of the 21st century, largely seeking to mitigate the risk of ART toxicity, multiresistant virus, and treatment failures (63). Among these was the SMART trial, which evaluated standard continuous ART (n = 2,720) vs. episodic, CD4+ T cell count-guided ART (n = 2,752). In 2006, the SMART team reported a hazard ratio of 2.6 (95% CI 1.9-3.7, p < 0.001) for the combined primary study endpoint of opportunistic disease or death from any cause when comparing episodic ART with standard continuous ART. Of note, the trial enrolled participants with CD4+ counts of > 350 and with any ART history; did not exclude participants with chronic HCV or HBV infection; monitored participants every two months in the first year and then every 4 months thereafter; and re-initiated ART in the episodic arm only when CD4+ T-cell counts dipped below 250 cells/mL. There were no virologic criteria for re-initiating ART, and the median duration of the first ATI in the episodic ART group was 16.8 months (64).

A subset analysis of the SMART data revealed that all SAEs in the trial occurred when CD4+ counts were below 300 cells/mL. This subset analysis was restricted to 16 weeks of treatment interruption, participants with CD4+ T-cell counts > 400 cells/mL, ART re-initiation at CD4+ T-cell count of 350, and participants with no evidence of hepatitis B, hepatitis C, or diabetes at study entry. In participants meeting these criteria, no deaths and no renal or hepatic events were observed; two cardiac events were observed, one in each study group; and there was no difference in AIDS-related events (0.005% in the continuous ART group and 0.002% in the episodic treatment group) (65). These findings of no mortality or treatment-interruption-associated morbidity in this SMART subset are consistent with observations reported for several concurrent and subsequent treatment interruptions (all smaller than SMART; approximately half were randomized clinical trials like SMART) that similarly limited eligibility for and duration of treatment interruption, re-initiated ART at higher CD4+ cell counts, and monitored participants more frequently (66-72).

Treatment interruption designs post-SMART, including the design for HVTN 804/HPTN 095, reflect lessons learned from SMART to mitigate the risks of treatment interruptions. Recent consensus guidelines on the design and conduct of analytical treatment interruptions further codify these risk mitigation measures and the current concept is aligned with these guidelines (see, eg, [Figure 2-13](#) (1, 2))

Panel: Key recommendations

Inclusion criteria

- Stable CD4 counts ≥ 500 cells per μL *
- HIV RNA undetectable on stable ART†
- Otherwise healthy individuals without major comorbidities

Key exclusion criteria

- Active or chronic hepatitis B virus infection, with detectable hepatitis B surface antigen, hepatitis B virus DNA, or both
- Active hepatitis C virus infection, with detectable virus RNA
- Active Mycobacterium tuberculosis infection‡
- History of systemic cancers, such as Kaposi's sarcoma and lymphoma, or other virus-associated malignancies§
- History of HIV-associated dementia or progressive multifocal leukoencephalopathy
- Resistance to two or more classes of antiretroviral drugs¶
- History of cardiovascular event or at high risk of an event (eg, atherosclerotic cardiovascular disease score $> 15\%$)
- History of AIDS-defining illness according to Centers for Disease Control and Prevention criteria
- History of CD4 nadir < 200 cells per μL during chronic stages of infection
- Women who are pregnant or breastfeeding
- Advanced non-alcoholic fatty liver and advanced nonalcoholic steatohepatitis, if evidence for substantial fibrosis (fibrosis score $\geq F2$) or evidence of cirrhosis
- HIV-related kidney disease or moderate-to-severe decrease in estimated glomerular filtration rate ($< 45\text{--}60$ mL/min/1.73 m²)
- Children younger than 2 years of age when the ATI is planned

Monitoring

- HIV RNA monitoring weekly for 12 weeks, then every other week
- CD4 count monitoring every two weeks
- Monitoring of clinical symptoms, in particular in people who started ART during the hyperacute HIV phase
- Monitoring of participants' psychosocial experiences

ART restart criteria

- If requested by the participant or their HIV health-care provider
- If participant becomes pregnant
- If ART is deemed medically necessary for non-HIV related causes
- Symptomatic HIV disease||
- Confirmed absolute CD4 value < 350 cells per μL or CD4% $< 15\%$ **
- HIV RNA ≥ 1000 copies per mL for 4 weeks††
- Absolute HIV RNA $> 100\,000$ copies per mL††

Reducing risk of HIV transmission to sexual partners

- Offer pre-exposure prophylaxis and HIV testing referral information that trial participants can provide to their sexual partners

Additional or more stringent criteria might be required based on known toxicities of the study drug(s) or expected risks of the study intervention(s). Inclusion and exclusion criteria, monitoring, and antiretroviral therapy (ART) restart criteria might differ in children depending on age. ART=antiretroviral therapy. *Baseline CD4 counts of ≥ 350 cells per μL might be considered. †Based on FDA-approved HIV RNA quantification assay. ‡Latent tuberculosis infection discussed in the text. §Other malignancies discussed in the text. ¶Defined as single key mutations or an accumulation of minor mutations that result in resistance to entire respective drug classes. ||Symptoms include, but are not limited to, unintentional weight loss ($> 5\text{--}10\%$ of the pre-ATI bodyweight), otherwise unexplained persistent fever ($> 100.4^{\circ}\text{F}/38^{\circ}\text{C}$), persistent night sweats, persistent diarrhoea, oral candidiasis and generalised lymphadenopathy. **Largely dependent on the CD4 entry criteria; a sufficiently large delta between the entry value versus CD4 measurement for ART resumption should be ensured. ††12–16 weeks of uncontrolled viraemia, with HIV RNA of more than 100,000 copies per mL; it might be acceptable in studies in which a stable viral set point is a primary endpoint.

Figure 2-13 Consensus recommendations of the July 9, 2018 forum held at the Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA. From (2).

Specifically, the eligibility criteria recommended in Julg, et al. (2) and proposed by the HVTN 804/HPTN 095 team, help ensure that the risks of hepatic, renal, and cardiac morbidity and mortality observed in SMART are substantially reduced, as individuals are only eligible for treatment interruption if they have no active or chronic hepatitis B; no active hepatitis C; no evidence of other significant liver disease; no significant or unstable cardiac or cerebrovascular disease; and no evidence of HIV-related renal disease or moderate-to-severe reduction in eGFR.

Eligibility and ART re-initiation criteria and the frequency and type of monitoring also address the HIV-related morbidity and mortality observed in the SMART trial. These safety features include eligibility only after an extended period of virologic suppression on ART; requirement that volunteers on Non-nucleoside reverse transcriptase inhibitors (NNRTI)-based ART regimens switch to short-acting antiretrovirals (Protease Inhibitor [PI]- or Integrase Strand Transfer Inhibitor [INSTI]-based ART regimens) in order to prevent emergence of ART-resistant HIV; that volunteers have neither a history of AIDS-defining illness nor of specified HIV-associated conditions; eligibility only at higher baseline CD4+ T-cell counts (note that Julg, et al. (2) recommends ≥ 500 or ≥ 350 cells/mL, depending on a range of factors); ART re-initiation for any symptomatic HIV disease, CD4+ T-cell counts < 350 cells/mL, or HIV RNA $\geq 1,000$ copies/mL for 4 weeks; and initial monitoring weekly and then biweekly, including CD4+ T-cell counts, viral load, and psychosocial experiences.

The evidence that post-SMART changes in ATI trial design have, in fact, limited the risks of treatment interruption, is growing. For example, Huiting, et al. (73) demonstrated that among 22 participants who initiated ART in early HIV infection and then underwent a 16-week treatment interruption followed by re-initiation of ART, there were no significant differences between pre- and post-ATI CD4+ or CD8+ T-cell counts or percentage and no significant differences in reservoir markers, including HIV DNA, cell-associated RNA, and replication-competent HIV (see [Figure 2-14](#)).

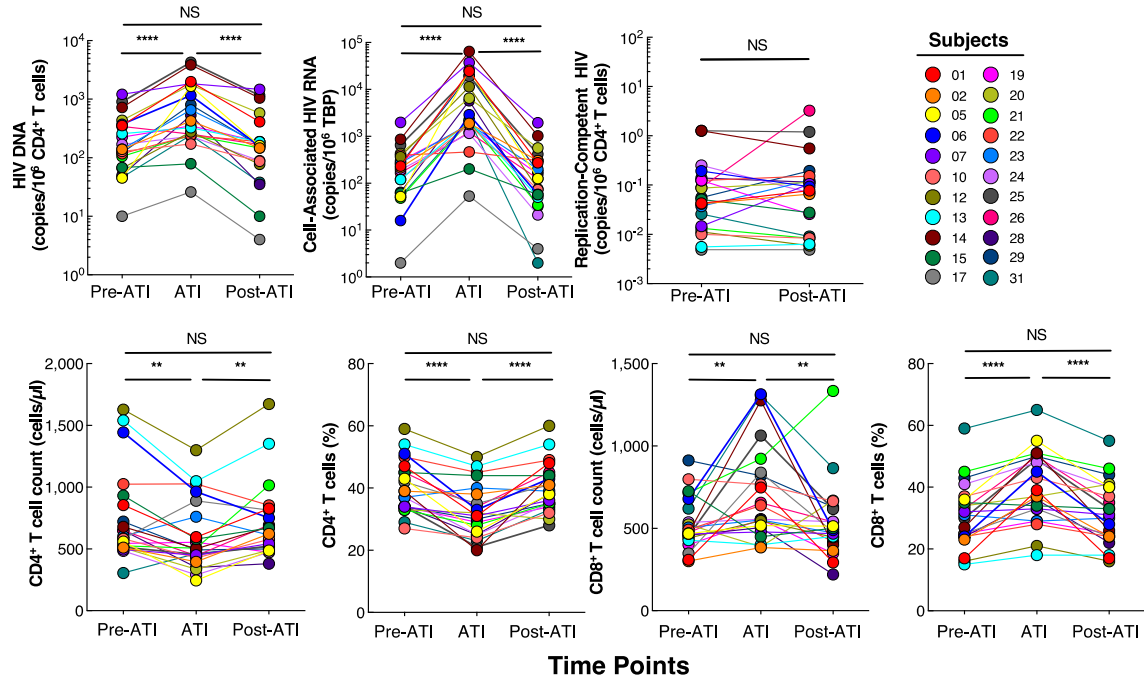


Figure 2-14 Kinetics of HIV reservoirs and immunologic parameters prior to and following ATI and reinitiation of ART. The frequency of CD4+ T cells carrying HIV DNA and cell-associated viral RNA was measured prior to (pre-ATI) and following ATI (ATI) and upon re-initiation of ART (post-ATI). The frequency and cell count of CD4+ and CD8+ T cells are shown at the pre-ATI, ATI, and post-ATI timepoints. Statistical significance was tested with Wilcoxon signed rank test. *p < 0.05, **p < 0.01, ****p < 0.0001, NS, not significant. Adapted from (73) Figure 1.

Bar, et al. (27) reported on 24 participants in two cohorts; in one cohort (A5340), participants had been taking ART for 3.8-6.0 years (median 4.7) and in the other (15-I-0140) participants had been taking ART for 7.7-13.3 years (median 10.0). All participants received VRC01, followed by an ATI, which ended upon confirmation of viral rebound. Median time to viral rebound was 4 weeks in the A5340 trial and 5.6 weeks in the 15-I-0140 trial. VRC01 slightly delayed plasma viral rebound compared with historical controls but did not sustain viral suppression. No safety issues were observed in either cohort.

Clarridge, et al. (74) reported on the ten chronically infected participants in the 15-I-0140 cohort who received VRC01 immediately before and during ATI (median of 8 weeks, range 3-17 weeks). The length of the treatment interruption was governed by the time to meeting ART re-initiation criteria, which included a decrease of > 30% in the baseline CD4+ T-cell count or an absolute CD4+ T-cell count < 350 cells/mL, sustained (≥ 4 weeks) plasma viremia > 1,000 copies/mL, any HIV-related symptoms or pregnancy (27, 74). During treatment interruption, total HIV DNA in CD4+ T cells increased significantly from pre-interruption levels and all participants rebounded, with median peak viremia of 30,950 copies/mL observed (range 340 - 273,221). By 6-12 months post-ATI, reservoir size, including the proportion of near full-length, genome-intact proviral sequences and structurally defective proviral sequences, and immune markers of

exhaustion and activation returned to pre-ATI levels; CD4+, CD8+ (including activated CD8+), B, and NK cell levels also returned to pre-ATI levels; and there was no evidence of emergence of antiretroviral drug resistance mutations in intact proviral DNA sequences.

Similar findings were reported by Salantes, et al., among 14 chronically infected individuals who received VRC01 immediately prior to and during treatment interruption (median of 6 weeks, range 3-14 weeks) in A5340. The length of the treatment interruption was governed by the time to meeting ART re-initiation criteria, which included CD4+ T-cell count < 350 cells/mL or a return of HIV viremia defined as HIV RNA \geq 200 copies/mL followed by HIV RNA \geq 1,000 copies/mL or three consecutive measurements of \geq 200 copies/mL. No significant changes in pre or postinterruption reservoir size or composition were observed by quantitative PCR, cell-associated RNA or quantitative viral outgrowth assay (QVOA). Perhaps most relevant to HVTN 804/HPTN 095, these findings remained true for participants with very small and relatively less heterologous reservoirs pre-ATI (eg, participant 7 in Figure 2-15) (75).

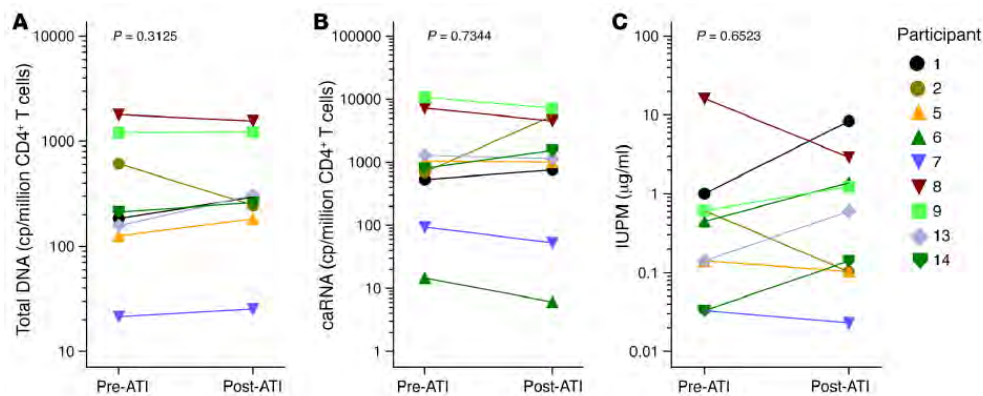


Figure 2-15 Quantitative measures of reservoir change. Pre-ATI and post-ATI values (obtained at study entry and more than 6 months after viral suppression following ART re-initiation, respectively) of total HIV-1 DNA in CD4+ T cells (A), cell-associated HIV-1 RNA (caRNA) in CD4+ T cells (B), and the frequency of resting CD4+ T cells bearing replication-competent virus (IUPM) (C) are shown for each A5340 participant. Total DNA is not shown for participant A06, because the values were below detectable levels at both timepoints. P-values shown in A–C indicate the significance of the within-participant changes and were determined by Wilcoxon signed-rank test. From (75), Figure 2.

Strongin, et al., assessed reservoir measures in 12 early- and chronic-treated participants across four ACTG studies that included ATI. Participants had at least 1 year of suppressive ART prior to treatment interruption that lasted a median of 12 weeks. No change in integrated HIV DNA was observed between baseline, pre-ATI samples and samples six months after ART re-initiation (76). In a shorter-term ATI, with a median duration of approximately 4 weeks, Papasavvas, et al., demonstrated similar findings among 23 chronically-treated, ART-suppressed individuals. As expected, treatment interruption was accompanied by decreases in CD4+ T cells and increases in HIV viral load, markers of T-cell activation (eg, HLA-DR and CD38 co-expression), and levels of cellular HIV

DNA (total DNA and 2-LTR [long terminal repeat] circles in PBMCs) and cellular RNA (by PCR). However, upon re-initiation of ART, viral re-suppression was achieved at a median of 13 weeks and levels of CD4+ T cells, T-cell activation markers, and cellular HIV DNA and RNA returned to baseline, pre-ATI levels (77).

A recent meta-analysis offers further reassurance of the safety of ART treatment interruption with respect to rates of adverse events experienced by participants in trials with treatment interruptions. The meta-analysis included 7,104 participants across 22 studies with varying ATI designs, allowing for comparisons of outcomes across trials with different eligibility criteria, treatment interruption duration, follow-up intervals and ART re-initiation criteria. The overall rate of adverse experiences (AEs) during ATIs longer than 4 weeks' duration was 3% (95% CI 0%-7%) and was lower in studies with monitoring \leq every 2 weeks (0%; 95% CI 0%-1%) than in studies with less frequent follow-up (6%; 95% CI 2%-13%; p-value for interaction = 0.01). Among the studies reporting new viral resistance mutations emerging during ATI, a 3% (95% CI 0%-8%) rate of such mutations was observed, with a higher rate in studies with less frequent monitoring (9%; 95% CI 3%-16%) compared to the rate observed in trials with more frequent (\leq every 2 weeks) monitoring (0%; 95% CI 0%-1%; p = 0.03). Of note, the analysis was unable to discern which ART regimens preceded ATI in all of these trials, thus limiting their ability to account for trials with NNRTI switch periods to reduce the risk of the development of viral drug resistance mutations. Baseline CD4+ T-cell count was also associated with outcomes, with baseline CD4+ T cells > 500 cells/mL associated with the fewest AEs (0%; 95% CI 0%-3%) (78, 79).

The authors conclude that treatment interruption can be conducted safely—with no lasting negative impact on clinical, immunologic, immune activation or virologic parameters—when appropriately designed, including frequent monitoring and appropriate duration, eligibility and re-initiation criteria. The cited authors of the meta-analysis and assessments of ATI impacts described above specifically note that appropriate re-initiation criteria should allow for viral spikes (ie, without re-initiating ART prematurely) that may be necessary to elicit the ART-free, virologic suppression potential of immunomodulatory interventions, like bnAbs (73, 78-82).

The mitigation of risk in treatment interruptions relies on the optimal implementation of eligibility assessment, monitoring, timely ART re-initiation, and other risk mitigation practices. An assessment of site capacity to implement these aspects of the treatment interruption design—for example, capacity for weekly and biweekly clinic visits, including retention and adherence metrics thus far, and access to ART for timely re-initiation, including metrics of initial ART uptake—was completed prior to the determination of participating sites. Ongoing monitoring of the implementation of these risk mitigation measures will be in place throughout the trial's conduct. However, even with these measures, treatment interruptions do still entail risk and promise no anticipated benefit.

These points must be made clear in an informed consent for individuals contemplating any interruption in their antiretroviral therapy.

A pause in antiretroviral therapy—with careful eligibility criteria, frequent clinical and laboratory monitoring, and clear criteria for ART re-initiation—is a safe and acceptable strategy to evaluate the efficacy of VRC01 in this population of antiretroviral-treated HIV-infected adults. Current and prior studies of immune-based therapy, including a subgroup analysis of the SMART study, support the value, safety and acceptability of interruptions in antiretroviral therapy to assess virologic efficacy in this context (27, 35, 65, 73, 80, 83-87). In addition, while there remains uncertainty regarding how best to measure the latent HIV reservoir, several recent studies of participants undergoing similar short-term interruptions in antiretroviral therapy have noted no persistent changes in the size of the latent reservoir of infected CD4+ T cells following re-suppression by ART, based on the measures currently thought to reflect HIV reservoir size (73-80). Specifically, ATI with intensive monitoring evaluating time to viral rebound has been advanced as a careful approach to utilizing a pause in ART to allow observation and insight regarding novel therapeutic approaches to control HIV off ART (61, 88, 89).

2.8 An AMP ATI

To date, most efforts to explore the potential for bnAbs to facilitate durable virologic control have taken place in chronically infected individuals who, in some cases, initiated ART before the advent of guidelines directing ART initiation immediately upon HIV diagnosis. Even when ART initiation and viral suppression are achieved relatively early postacquisition, inflammation and impaired immune responses accrue over time in chronic infection, contributing to morbidity and mortality and likely facilitating viral persistence through several mechanisms, rendering ART-free control or cure more challenging (90-95). Consider, for example, the two cohorts described in Bar, Sneller, et al. in which VRC01 was administered to chronically HIV-infected individuals prior to treatment interruption (27). Only a slight delay in viral rebound compared to historical controls was reported (median of 4 weeks in Bar's A5340 cohort and median of 5.6 weeks in Sneller's NIH 15-I-0140 cohort). The individuals in these cohorts had the heterologous viral populations typically observed in individuals with chronic infection. In 1 of the cohorts (A5340), most participants had virus with preexisting resistance to VRC01; and the prevalence of preexisting resistance predicted viral rebound patterns. Analysis of HIV sensitivity to an array of bnAbs in the second cohort (15-I-0140) suggested similar results. Evidence of VRC01-mediated selective pressure on rebounding virus was observed in most participants; and of only 2 participants who rebounded with HIV expressing VRC01-sensitive envelope glycoproteins, 1 rebounded only after VRC01 concentrations waned (27). Thus, while there was clearly an effect of VRC01 on the virus, it was insufficient to induce meaningful control in the face of

heterologous and VRC01-resistant viral populations in hosts with chronic infection.

In distinct contrast, the AMP team is in the singular position of having an opportunity to explore the potential for VRC01 to facilitate ART-free durable virologic control when present at the time of acquisition—acquisition by an immunologically intact host of a relatively homologous virus in the presence of a bnAb with considerable breadth. The potential of VRC01, and of bnAbs more generally, in this unique immunologic context is explained by the hypothesis detailed above that considers the true complexity and interdependencies of the autologous immune response to HIV—innate, cellular, and humoral responses all modulated by the presence of bnAbs, like VRC01, binding HIV envelope proteins—a hypothesis based in extensive preclinical and clinical evidence of the potential impact of bnAbs on the earliest moments of HIV infection.

AMP participants who acquired HIV are unique: they are diagnosed with HIV soon after acquisition due to monthly HIV diagnostics on-study; they initiate ART soon after diagnosis due to AMP-facilitated linkage to ART; and those randomized to receive VRC01 have circulating bnAb at the time of acquisition due to the q8-week frequency of infusion and VRC01 pharmacokinetics. This sets the stage for formation of immune complexes of VRC01 bound to free virions or HIV-infected cells which, as detailed above, can modulate the immune response and, thus, the course of infection. This cohort offers a singular opportunity to assess the potential impact of very early immunotherapy on the immunologic and virologic trajectory of infection, a contribution that recent preclinical and clinical data suggests could meaningfully enhance our understanding of HIV pathogenesis and illuminate potential host defenses, and means of enhancing them, that previous HIV preventive, therapeutic, or curative interventions have heretofore not identified or successfully engaged.

A pause in antiretroviral treatment is the only way to determine if the presence of VRC01 at the time of, or shortly after, acquisition of HIV results in a blunted, delayed or absent plasma viral rebound off ART, or subsequent control of rebound that may be observed. If such an impact on viral rebound is observed, ATI is also the best means of assessing mechanisms and predictive biomarkers of that impact through a detailed assessment of innate, cellular, and humoral markers along with characterization of the viral reservoir.

Recent research has suggested that viral rebound may be predicted by duration of infection, length of ART suppression, CD4+ T-cell nadir, total HIV DNA and cell-associated HIV RNA, among others; but samples and validation of these potential predictors are limited and there is no consensus biomarker predictive of durable viral suppression (37, 59, 96). Identification of reliably predictive biomarkers could inform future therapeutic and cure trial design and guide allocation of limited resources, advancing promising therapies more efficiently, and limiting exposure of trial participants to ineffective interventions. The AMP trial has pre and postinfection serum and limited PBMC samples on each

participant, including samples obtained ≤ 4 weeks from the time of acquisition and pre-ART. Thus, across currently available and proposed samples, ATI among AMP participants provides a unique opportunity to contribute to the exploration and validation of biomarkers, many observed in the preclinical studies described in Section 2.3 through 2.5 above, that may predict the virologic and immunologic course of infection among bnAb and placebo recipients.

2.9 Ethical considerations

In the last two decades of treatment interruption conduct, an ethical framework for the conduct of such studies has evolved. There is general agreement that the risks of treatment interruption must be minimized; the trial must provide valuable data to answer an important question; and there must be no other methods entailing less risk that could answer that question (97, 98).

While ethicists have noted that “in general, the risks of the ATI itself, when closely monitored, are considered to be low,” risk mitigation is an essential part of the design of any treatment interruption. Risk mitigation includes, but is not limited to, adoption of appropriate eligibility criteria; efforts to enhance potential participant benefits; community engagement in the design and implementation of the trial; frequent participant monitoring, balanced with considerations of participant burden; and a sound informed consent process. The informed consent process should acknowledge the risks and the lack of anticipated individual benefits, the fact that treatment interruptions are not recommended in clinical care, and the fact that ART guidelines recommend lifelong treatment (97, 98).

Each of these recommendations has been adopted by the HVTN 804/HPTN 095 Protocol Team. The HVTN 804/HPTN 095 informed consent process and Sample Informed Consent Form (SICF) include all points noted above and include elements demonstrated to improve the quality of informed consent in not only HIV research but also other fields (see Section 12.1). Trial design, including eligibility and ART re-initiation criteria, ATI duration, and monitoring frequency, are modeled on the most recent consensus guidelines for treatment interruption design (see Figure 2-13 above) (1, 2). The HVTN 804/HPTN 095 Protocol Team will implement not only rigorous counseling for participants on reducing HIV transmission risk to their partners but also a program for PrEP provision to participants’ partners while the participant is enrolled; HIV genotyping (not standard of care in many AMP regions, unless first-line ART options have been exhausted); and accelerated, physician-led ART (re-initiation) access for participants in regions where ART stock-outs, public nurse-led care, and a window of several weeks between meeting ART re-initiation criteria and ART initiation could pose challenges for participants.

As all potential participants in HVTN 804/HPTN 095 would come from the parent HVTN 704/HPTN 085 study, early engagement of investigators and community representatives in several communities where HVTN 704/HPTN 085

is being conducted has already been initiated and is ongoing. These consultations with community stakeholders and investigators include an overview of the history and current context of treatment interruption, including potential risks and region-specific considerations. They also provide an opportunity for dialogue about the immunologic hypotheses and design for HVTN 804/HPTN 095 and began laying a foundation of authentic stakeholder engagement in the earliest weeks of development of this study. See Section 2.11 below for further details.

2.10 The necessity of the AMP placebo control group

As noted in the recently published Julg, et al., consensus guidelines for ATI conduct, “if a placebo group is necessary for the findings of the study to be properly interpreted, it could be considered unethical not to include a placebo (ie, when a placebo is a scientific necessity, it is arguably an ethical imperative as well)” (2). Having reviewed available historical and concurrent controls and finding them inadequate to support evaluation of the immune-mediated hypotheses described above, it is clear that enrolling a subset of AMP placebo participants is necessary for the correct interpretation of the results of HVTN 804/HPTN 095. Hence, HVTN 804/HPTN 095 clearly appears to meet this consensus guideline. Considerations contributing to this conclusion are summarized below.

First, post-treatment control (PTC) appears to be associated with early ART initiation, smaller HIV reservoirs, and longer ART duration pre-ATI (see [Figure 2-16](#); note that follow-up of participants in some of these cohorts continues, hence change in duration of virologic control is expected over time). PTCs, who have typically initiated ART in Fiebig stages III-V, exhibit sustained virologic control in the absence of ART (81, 99-101). The VISCONTI series reported a median remission of 9.3 years (range 4.5-12 years) among 20 PTCs (102). PTCs are immunologically distinct from elite controllers in that they generally lack protective HLA alleles and strong HIV-specific immune responses. While data remain limited on this cohort, the PTC phenotype suggests that early ART can durably alter the virus/host relationship, leading to possible long-term ART-free remission (81, 99-102).

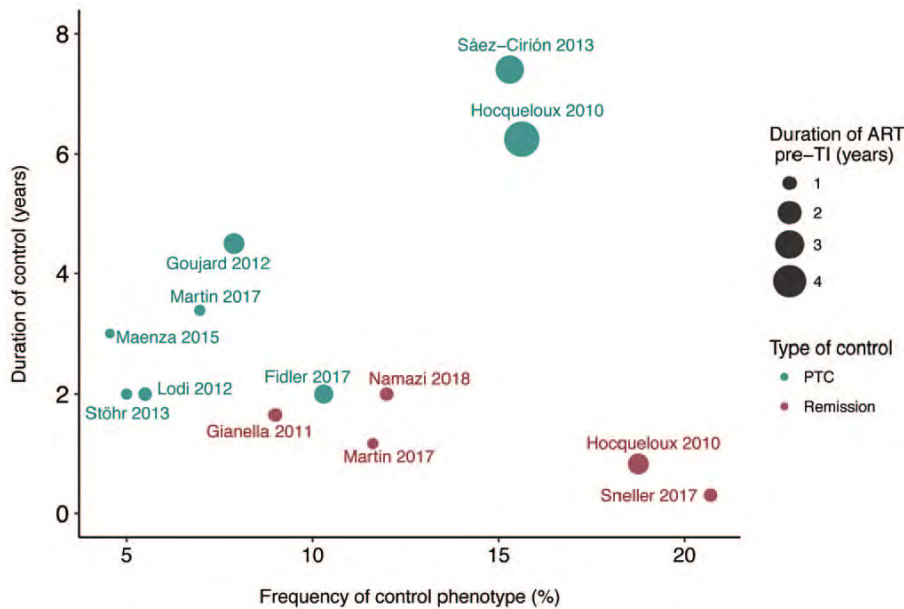


Figure 2-16 Estimates of the frequency of post-treatment control and remission. Each data point represents an individual study, which has measured the frequency of post-treatment control or remission following treatment interruption among individuals who commenced ART during primary HIV infection (PHI). Included are analyses of the following studies: CASCADE (103, 104), ANRS Primo (105), VISCONTI (99, 106), SPARTAC (107, 108), CHAMP (81), ZHPI (109), SeaPIP (110) and NCT01859325 (80). Those which define post-treatment control (here considered to be > 24 months following treatment interruption) are colored green, those defining remission (> 4 months following treatment interruption) are shown in red. In some cases, a study explored both phenotypes; where possible these are disaggregated and listed twice, otherwise these are shown as remission. The duration of control is the time between treatment interruption and viral rebound, or the end of follow-up, and is plotted at the median value amongst controllers. The size of the point corresponds to the median duration of ART prior to treatment interruption amongst controllers. Where a study did not report either of these values, the minimum value for inclusion is used instead. From (111) Figure 1 (references added).

Most AMP participants are estimated to initiate ART in Fiebig stages that may contribute to smaller reservoirs (eg, Fiebig III-V), and many AMP participants will have been on ART for well over a year by the time of the implementation of HVTN 804/HPTN 095. Considerable evidence suggests that these factors are likely to promote virologic control independent of, or potentially synergistically with, the hypothesized contribution of VRC01 (33, 81, 99-102, 111). However, the extent of control due to these non-immunotherapy-based factors cannot be predicted—estimates vary widely across studies of post-treatment control. Hence, some control group is essential in order to distinguish viral control attributable to VRC01 receipt from that caused by early ART initiation. Unfortunately, we have been unable to identify any clinical study cohort outside AMP that is sufficiently comparable to AMP placebo recipients to provide an adequate control comparator (see [Table 2-2](#)). In the absence of a placebo control group, the risk of misattributing observed control to VRC01 and, thus, misdirecting resources to the exploration of that perceived VRC01-mediated control, is high in this cohort.

Table 2-2 Potential historical comparator cohorts for AMP ATI

Cohort Considered	Key Differences/ Limitations	References
Thai RV397	<ul style="list-style-type: none"> • Different study population: Thai with 80% CRF01_AE • Substantially different ART re-initiation criteria: confirmed HIV-1 RNA >1,000 copies/mL; single HIV-1 RNA >10,000 copies/mL; HIV-1 RNA rise $\geq 0.5 \log_{10}$ copies/mL/day; confirmed CD4+ T-cell count <350 cells/mm³; CD4+ T-cell count decline >50% from baseline prior to ATI; CDC Category B or C disease; acute retroviral syndrome (ARS); pregnancy; or participant request 	(112)
Thai RV411	<ul style="list-style-type: none"> • Different study population: Thai with 100% CRF01_AE; ART initiated at Fiebig I • Substantially different ART re-initiation criteria: 2 viral load measurements >1000 copies/mL 1 to 2 days apart 	(113)
CHAMP	<ul style="list-style-type: none"> • Different study population: CHAMP cohort includes participants from 14 studies who initiated ART during early and chronic infection; “early-treated participants” identified in 7 study cohorts but how “early-treated participants” is defined varies greatly among these (see Supplemental Table 1); post-treatment control defined as off ART ≥ 24 weeks with viral loads ≤ 400 copies/mL at $\geq 2/3$ of timepoints 	(81)
pDNA-IL-12 Vaccine	<ul style="list-style-type: none"> • Substantially different ART re-initiation criteria: sustained (≥ 4 weeks) plasma HIV-1 RNA >50,000 copies/mL; confirmed CD4+ T cell decline >30%; absolute CD4+ T cell count <350/mm³; ARS. 	(80)
ACTG historic cohorts	<ul style="list-style-type: none"> • Substantially different “viral rebound” criteria: 2 consecutive HIV-1 RNA >200 copies/mL or one HIV-1 RNA >1000 copies/mL • Time to viral rebound not analyzed for participants for whom ART was initiated during acute or early infection 	(37)
SeaPIP	<ul style="list-style-type: none"> • Different study population: post-treatment controllers (HIV-1 RNA <500/mL for >24 months); ART initiated at Fiebig I-VI • Substantially different “virological failure” criteria: first of two HIV-1 RNA >500 copies/mL or one HIV-1 RNA >500 copies/mL followed by ART resumption 	(110)
VISCONTI	<ul style="list-style-type: none"> • Different study population: post-treatment controllers (HIV-1 RNA <500/mL for >24 months) 	(99)
SPARTAC	<ul style="list-style-type: none"> • Different study population: 40% women • Short course ART, mixed regimens (48 weeks, 12 weeks, no ART) • Substantially different endpoints: CD4+ T cell count <350/mm³ or long-term ART initiation (SPARTAC); HIV-1 RNA ≥ 400 copies/mL (Stöhr, Martin) 	(67, 99, 107, 108)
CASCADE	<ul style="list-style-type: none"> • Substantially different endpoints: loss of “post-treatment controller” status defined as first of 2 consecutive HIV-1 RNA >50 copies/mL; alternative endpoints HIV-1 RNA >400 copies/mL and >1000 copies/mL 	(103, 104)
Primo-SHM	<ul style="list-style-type: none"> • Different study population: ART initiated at Fiebig I-VI; ART duration 24 or 60 weeks • Substantially different endpoints: CD4 cell count <350 cells/mm³ on two separate occasions, severe constitutional symptoms, or AIDS-defining event 	(114)
ANRS PRIMO Cohort	<ul style="list-style-type: none"> • Different study population: 36% women • Substantially different endpoints: first of two HIV RNA values ≥ 50 copies/mL or first of two HIV RNA values >500 copies/mL 	(105)
ZHPI	<ul style="list-style-type: none"> • Substantially different endpoints: time to VL or ART re-initiation not measured 	(109)

Second, HVTN 804/HPTN 095 holds promise for identification of mechanisms and biomarkers of virologic control that can only be realized with the inclusion of a control group for comparison. Early immunotherapy can modulate the host immune response to HIV. However, the nature of immunotherapy-induced differences in early host-viral dynamics and their impact on later control are unknown and preclinical and clinical evidence of bnAb-mediated control suggests that these differences may be subtle and challenging to identify (34-36, 38-41). Coupled with the fact that the underlying mechanisms of post-treatment control are also unknown, a post-AMP treatment interruption without a control group is at risk of misperceiving not only the true “cause” of control itself (ie, early ART vs. VRC01), but also the immunologic mechanisms underlying and the predictive biomarkers of that control. Since the value of understanding and correctly attributing underlying immunologic mechanisms, which might efficiently direct HIV vaccine and other preventative and curative efforts, and the value of reliable identification of biomarker(s) of control, which might ultimately abrogate the need for treatment interruptions, is exceptionally high, this would be an immense opportunity lost (37, 88, 115).

To illustrate the hazards of misattribution based on inadequate controls, consider the example of a therapeutic HIV vaccine trial in 30 HIV-infected participants who, like AMP participants, initiated ART early in infection. Three of fifteen placebo participants exhibited evidence of sustained viremic suppression (ie, VL < 40 copies/mL throughout treatment interruption), with at least two placebo recipients exhibiting control for two or more years. Notably, three placebo participants in this trial had spikes in viremia ranging from nearly 30,000 to nearly 200,000 copies/mL prior to a period of undetectable viral load (see [Figure 2-17](#)) (80). Based on these results, further investment in this vaccine was redirected. In contrast, investigators in a concurrent trial of an HIV therapeutic vaccine with romidepsin (116), also conducted among early-treated individuals but without a placebo group, reported a high rate of virologic control (38% by their definition of control which, if applied to the placebo group in the study by Sneller, et al., would yield a comparable 40% rate of control). The initial high enthusiasm to credit this observation to the vaccine + romidepsin regimen was tempered based on results in the placebo group of the comparable Sneller, et al. cohort. In fact, an editorial accompanying the report by Sneller, et al., noted that “there is substantial variation in viral rebound dynamics in analytic treatment interruption studies, significantly limiting the scientific value of non-placebo-controlled study designs” (82).

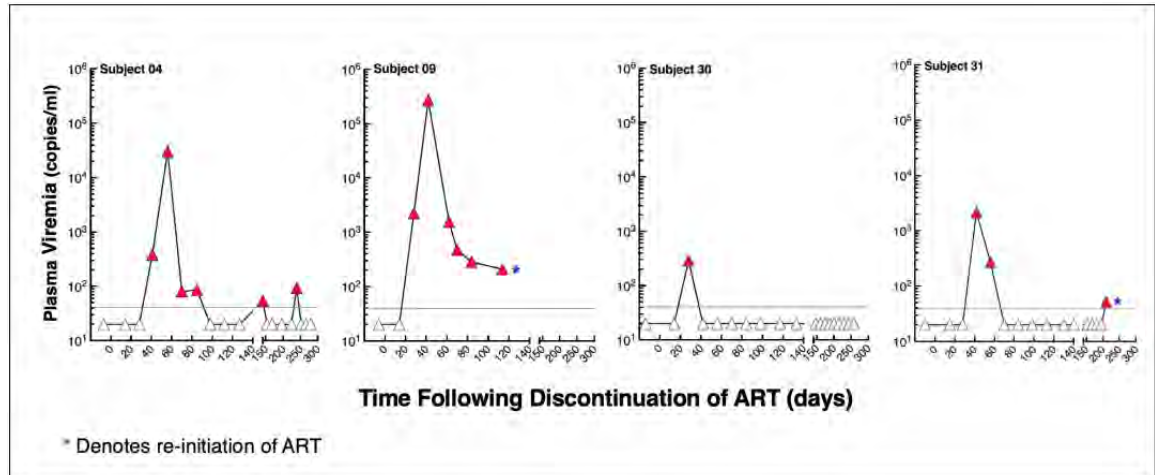


Figure 2-17 Plasma viremia of individual study participants after discontinuation of ART. Participants 04, 30, and 31 received placebo and participant 09 received the studied vaccine. Graphs were extracted from (80).

Control and putative predictors or biomarkers of control have been explored in prior treatment interruptions with and without control groups, largely among individuals chronically infected with HIV or, more recently, among individuals initiating ART in Fiebig I-II (37, 59, 96), including in a cohort initiating ART early and receiving VRC01 (112). Both types of cohort have been considered as potential historical or concurrent controls for HVTN 804/HPTN 095. However, ATIs in these studies used different criteria for re-initiating ART and different virologic and immunologic monitoring frequencies than will be used in HVTN 804/HPTN 095 and the participants in these cohorts differ from the HVTN 804/HPTN 095 cohort in several ways that render them poor comparators for the present study cohort.

In these other published cohorts, ART was restarted once plasma viremia reached a prespecified level (eg, 1,000 copies/ml; (112)) with no additional parameter for duration of plasma viremia above this level. ART re-initiation criteria that do not allow for duration of viremia will miss a significant proportion of post-treatment controllers (eg, Participant 30 and 31 in [Figure 2-17](#) above). Such spikes may be necessary to stimulate precursor T cells “primed” in early infection by antigen-presenting cells whose function may be uniquely enhanced by early immunotherapy (see [Section 2.3](#)). In addition, these historical trials monitored plasma viremia and CD4+ T-cell counts at intervals that differ from those proposed in the current study. It would be misleading to compare the efficacy endpoint for HVTN 804/HPTN 095 with historical controls from prior studies that utilized differing criteria for restarting ART and differing frequencies of virologic/immunologic monitoring.

Furthermore, cohorts of individuals who initiated ART while chronically infected or during early acute infection may be less than optimal for identifying control or its correlates and are particularly insufficient for comparison to the HVTN 804/HPTN 095 cohort. By the time infection has progressed in chronically-

infected individuals, HIV has successfully evolved, outpacing and overwhelming the immune system, hiding any HIV “Achilles heel” and suppressing host responses potentially capable of exploiting HIV’s vulnerabilities. When ART has been initiated and viral replication has been suppressed in acutely infected individuals, as with Fiebig I and II ART initiation in the USMHRP/Thai SEARCH cohorts, the host immune system has seen so comparatively little HIV that its initial (ie, “prime”) or later (“boost”) response may not have been successfully or fully triggered. Indeed, individuals who initiated ART in Fiebig I-II appear to demonstrate much lower rates of post-treatment control than those who initiated ART in somewhat later Fiebig stages, possibly because individuals who initiate ART earlier in infection have been exposed to insufficient antigen to prime an immune response capable of later control (111, 113, 117). Hence, both chronic and early acute (ie, Fiebig I-II) cohorts may not sufficiently express some immunologic factors capable of facilitating virologic control, or may not express them in sufficient quantities, thus limiting the capacity of such cohorts to best contribute as comparators to the HVTN 804/HPTN 095 cohort (49, 113).

Geography, ethnicity, and HIV clade may also play a role. For example, post-treatment control may be more common among women in sub-Saharan Africa with clade C transmitted/founder viruses than among some other populations. The SPARTAC trial reported an 18.6% rate of post-treatment control overall. A recent SPARTAC sub-study revealed that the African SPARTAC cohort, all females infected with non-B (primarily C) subtypes, was more likely than the non-African SPARTAC cohort to have a VL < 400 copies/mL by study end (HR 3.9, 95% CI 1.75-8.81, $p < 0.001$) (108, 118). And Gossez, et al. reported a 23% rate (5 of 22) of post-treatment control (VL < 400 copies/mL for a median of 188 weeks post-ATI) among Ugandan and South African women who completed 45-50 weeks of ART and demonstrated viral suppression prior to treatment interruption (118). This Gossez, et al. African cohort is comparable to the HVTN 703/HPTN 081 (“sister” AMP study to HVTN 704/HPTN 085) cohort.

Based on the considerations described above, HVTN 804/HPTN 095 meets the criteria under which inclusion of placebo recipients is an ethical imperative (2). Indeed, the same observation was made by Nelson Michael about the Sneller, et al. therapeutic vaccine trial described above in which virologic control and significant variability of viral rebound were observed among placebo recipients following treatment interruption. As Michael noted, “the use of a placebo control was critical to interpreting the results of the study” and was part of “a clinical trial design that affords [research teams] and their volunteers the best chance of reducing volunteer risk for maximal scientific gain” (82). Michael notes another characteristic that strengthened the rigor and scientific contribution of the Sneller vaccine trial and that would apply to the timely conduct of HVTN 804/HPTN 095, as well: reducing observer bias by establishing safeguards such that both the investigators and the participants remain blinded to treatment assignment (82). AMP is projected to be unblinded in Q4 2020.

Hence, the AMP cohort is in a unique position to overcome the challenges that have stymied earlier efforts to identify controllers and potential biomarkers of control. HVTN 804/HPTN 095 could illuminate host-virus interactions that only immunologically-intact hosts (ie, not chronically infected) exposed to moderate viral replication prior to suppression (ie, not treated in Fiebig I-II) and for whom some secondary antigen exposure is allowed (ie, with closely monitored, brief viral load spikes on treatment interruption) may be able to mount. Furthermore, the VRC01-mediated immunomodulation described above could render VRC01-mediated virologic control and its associated correlates or markers more evident—more identifiable by current assays—than control mediated by other factors, either because the immunotherapy-induced mechanisms themselves are more identifiable, or the magnitude of their enhancement by immunotherapy renders them more apparent. No other cohort is in as promising a position to illuminate potentially subtle differences in early, and later, immunologic-virologic dynamics in order to identify host responses critical to viral control, thus highlighting factors we should work to enhance in future strategies for HIV prevention, therapy, and cure. Yet the AMP cohort's ability to do this—to accurately identify correlates mediated by immunotherapy in addition to those mediated by other factors such as early ART initiation common to both VRC01 and placebo participants—requires a control group. That is, identification of immunotherapy-related correlates requires comparison of mechanisms identified in VRC01-recipients to those identified in placebo-recipients.

We note that inclusion of AMP placebo recipients is operationally feasible. In addition to applying the risk mitigation measures described above and throughout this protocol, the HVTN 804/HPTN 095 team, informed by our statistical colleagues, will appropriately limit the numbers of placebo participants—appreciating that prevention efficacy of VRC01 in the ongoing, treatment-blinded AMP trial could lead to an over-representation of placebo participants among the cohort of AMP participants who acquired HIV (see Section 2).

It is important to note that, while post-treatment control appears to be a real phenomenon and, particularly in the AMP cohort, could severely limit interpretation of HVTN 804/HPTN 095 control and immunologic profiles without placebo participants, the true incidence of this phenotype is unknown and AMP participants should not enter ATI with any anticipated benefit of a treatment interruption. Furthermore, any AMP placebo participants would not be expected to experience bnAb-induced, immune-mediated control, ie, control enhanced by early immunotherapy. The HVTN 804/HPTN 095 team is committed to making this clear in the informed consent document (see [Appendix A](#)) and process, developed with our regulatory and community partners.

2.11 Feasibility

The HVTN 804/HPTN 095 team has the significant advantage of data and experience from the AMP Study to inform an assessment of the feasibility of

HVTN 804/HPTN 095, appreciating that while this concept is significantly different from the parent AMP Study, all participants for HVTN 804/HPTN 095 will be from the AMP cohort at sites and in communities now familiar to the AMP and HVTN 804/HPTN 095 teams. AMP accrual and retention rates, early termination rates, data quality and safety have been excellent by any standard, perhaps particularly so considering the demanding nature of the two AMP trials (HVTN 704/HPTN 085 and HVTN 703/HPTN 081) that, together, enrolled 4,625 participants for two years of monthly clinic visits and q8-weekly intravenous infusions (119, 120). In over 35,000 IV infusions administered to date, no procedural complications (eg, local IV site infection,) have been observed; two thirds of participants receive VRC01 and very low rates of infusion reactions have been observed, all of which have been medically managed exceptionally well (119, 121).

While overall performance in AMP has been exceptional, the HVTN 804/HPTN 095 team also considered site-specific performance and other considerations in determining which sites will implement HVTN 804/HPTN 095. Considerations include: site-specific retention performance; timeliness and accuracy of safety data submission; access to potentially eligible participants; site capacity for frequent clinic visits and close clinical monitoring of participants; access to and capacity for close partnership with primary HIV care, including timely ART re-initiation; and site willingness to participate, including receptivity of site investigators, community representatives, and regulatory authorities.

Partnership with regional investigator, regulatory, and community representatives for the development of HVTN 804/HPTN 095 has already begun in earnest and is ongoing.

A consultation with Peruvian investigators, regulatory and public health representatives, and community representatives, including representatives on the local Community Advisory Board (CAB), was held in April 2019 in Lima, Peru. Attendees were engaged and were universally supportive of HVTN 804/HPTN 095 moving forward in Peru in their communities, with some participants stating, “*We need this,*” and “*Continue with the study development as soon as possible.*” A postconsultation survey clearly reflected that attendees understood and supported the HVTN 804/HPTN 095 concept and design, and their understanding and engagement was also evident in attendee questions and dialogue throughout the consultation.

Early in development, the HVTN 804/HPTN 095 team also solicited and received input and support from the Martin Delaney Collaboratory Community Advisory Board (MDC CAB), whose US-based members reviewed the concept and provided positive feedback on the concept’s rationale and design. MDC CAB members also contributed to engagement throughout May 2019 with HVTN and HPTN community representatives, including the AMP Community Working Group (AMP CWG), whose members include community educators, recruiters, and CAB members from each AMP site. Several forums also provided

opportunities for discussion and feedback regarding HVTN 804/HPTN 095 with all AMP Protocol Team and site (eg, investigators, clinic coordinators) representatives and AMP CWG members.

Community engagement and site readiness, as described above, is necessary but not sufficient to support the conduct of HVTN 804/HPTN 095. AMP participant willingness to participate in the ATI is a crucial additional feasibility consideration. Again, interim data from AMP provides some insight here.

A mixed-methods AMP sub-study enrolled 300 participants—50 AMP participants from each of six sites based throughout the US. Upon exiting the AMP Study, each participant took part in a brief survey and a 60-minute interview regarding their demographics, understanding of bnAbs, and any enrollment or retention barriers and facilitators they experienced. In an interim analysis, about a quarter of participants expressed concerns about the AMP Study time commitment or the experimental nature of the VRC01 product and the associated uncertainty regarding its efficacy. All participants expressed a strong sense of appreciation for and positive identification with their clinical research site. For example, one participant noted: *“I’m going to volunteer for clinical research, especially if it’s research that’s going to affect the community that I’m part of”* and another enthused *“I’m such a big fan of [the CRS] that any research study that they pretty much put forward, I’m like interested in, or definitely highly support.”* Several participants cited the additional medical care they received at the clinic as a facilitator of ongoing study participation: *“[staff member name] took on this role of like a secondary primary care physician for me. In addition to the care I was getting at my doctor’s office, I also felt like I was getting another set of eyes on me. I just felt cared for.”* Another observed *“I liked how I got tested so often, and they were there to help me with any concerns I had, whether in regard to the infusion or to getting tested for other STDs or STIs.”*

While the scope of the sub-study is limited to the US, anecdotal evidence from sites around the world, coupled with the exceptional accrual and retention observed in the AMP studies to date (120), suggests that the experience participants have with their HVTN and HPTN AMP sites, globally, is a strongly positive motivator for continued engagement with their site. Furthermore, many sites retain engagement with their participants through various means even post-AMP and have the ability, prespecified in site-specific AMP consent forms approved by their Institutional Review Boards/Ethics Committees (IRBs/ECs), to reach out to participants after they’ve exited the trial to inquire about their interest in possible future research.

Thus, the conduct of HVTN 804/HPTN 095 as described herein is thought to be highly feasible thanks in large part to the selection of sites for AMP and their conduct of the study, including their relationships with site participants and their community and regulatory partners.

2.12 Conclusion

The AMP ATI is uniquely positioned to test for ART-free virologic control among individuals who acquired HIV in the presence of circulating bnAb, and to enhance understanding of the immunologic (ie, host) and virologic mechanisms and biomarkers of control. Here, we have an opportunity to translate the intriguing preclinical observations in SHIV-infected primates (34) to humans. This trial will extend early clinical observations, explore potential mechanisms, validate biomarkers of control, and discern whether AMP participants who became HIV-infected while on trial may become “post-bnAb controllers,” capable of bnAb-induced immunologic responses that change the course of their infection.

3 Study design

3.1 Hypotheses

3.1.1 Primary hypotheses

- VRC01 recipients who became HIV-infected during HVTN 704/HPTN 085 within 8 weeks of their last study product administration will suppress plasma viremia and maintain CD4+ T-cell counts longer during ATI than placebo recipients who became HIV-infected during HVTN 704/HPTN 085.
- ATI will be safe and well-tolerated in individuals who became HIV-infected in HVTN 704/HPTN 085.

3.1.2 Secondary hypotheses

- VRC01 recipients who became HIV-infected during HVTN 704/HPTN 085 within 8 weeks of their last study product administration will have enhanced cellular and humoral responses compared to placebo recipients who became HIV-infected during HVTN 704/HPTN 085.
- VRC01 recipients who became HIV-infected during HVTN 704/HPTN 085 within 8 weeks of their last study product administration will have more limited viral reservoirs, before and after ATI, than placebo recipients who became HIV-infected during HVTN 704/HPTN 085.

3.2 Objectives and endpoints

3.2.1 Primary objectives and endpoints

Primary objective 1

- To evaluate the effect of VRC01 received in the immediate pre-HIV acquisition period and/or during early infection on the time to meeting ART re-initiation criteria in participants undergoing ATI

Primary endpoint 1

- Time to meeting criteria for ART re-initiation
- Frequency of sustained post-treatment HIV control, defined as ≥ 24 weeks off ART without meeting ART re-initiation criteria

Primary objective 2

- To evaluate the safety of ATI among HVTN 804/HPTN 095 participants

Primary endpoint 2

- Laboratory measures of safety, adverse events (AEs), SAEs (serious AEs), and rates of discontinuation

3.2.2 Secondary objectives and endpoints

Secondary objective 1

- To evaluate the effect of VRC01 received in the immediate pre-HIV acquisition period and/or during early infection on the development of anti-HIV immune responses that differ from those of placebo recipients, and whether these immune responses are associated with time to meeting criteria for ART re-initiation in participants undergoing ATI

Secondary endpoints 1

- Response rate, magnitude, and polyfunctionality of HIV-specific CD4+ and CD8+ T-cell responses as measured by flow cytometry
- Magnitude and breadth of neutralizing antibody (nAb) responses against autologous and heterologous HIV isolates, as measured by TZM-bl neutralization assay
- Non-neutralizing, FcγR-mediated antibody effector functions such as ADCC, ADCP, and virion capture
- Frequency of dendritic cell activation and maturation markers, as measured by flow cytometry or other cell phenotyping assays
- Frequency of T- and B-cell activation and exhaustion markers, as measured by flow cytometry or other cell phenotyping assays

Secondary objective 2

- To evaluate the effect of VRC01 received in the immediate pre-HIV acquisition period and/or during early infection on viral load in participants undergoing ATI

Secondary endpoint 2

- Cumulative incidence of participants with viral load ≥ 200 at weeks 8, 16, and 24

Secondary objective 3

- To evaluate the effect of VRC01 received in the immediate pre-HIV acquisition period and/or during early infection on HIV reservoir size before and after ATI, and whether HIV reservoir measurements are associated with time to meeting criteria for ART re-initiation in participants undergoing ATI

Secondary endpoint 3

- Frequency of CD4+ T cells carrying intact and/or total pro-viral HIV DNA, replication competent virus, and/or cell-associated HIV RNA

3.2.3 Exploratory objectives

Exploratory objective 1

- To assess participant and potential participant motivations, perceptions and tolerance for ATIs, for prolonged viremia, and for trial requirements (eg, ART switches, barrier protection for all sexual activity)

Exploratory objective 2

- To assess social benefits (eg, altruism) and negative social impacts, including but not limited to anxiety regarding being off ART and becoming viremic again and fear of inadvertent HIV transmission to partners

Exploratory objective 3

- To assess participant and potential participant decision-making quality, including perception of being informed, clarity and support in decision making and satisfaction with their choice regarding participation

Exploratory objective 4

- To evaluate the effect of VRC01 received in the immediate pre-HIV acquisition period and/or during early infection on viral kinetics in participants undergoing ATI

Exploratory objective 5

- To determine whether characteristics of the transmitted/founder (T/F) viruses, rebound virus(es), and/or baseline viral reservoirs, including relative VRC01 sensitivity or resistance, are associated with virologic control or the development of anti-HIV immunity among individuals who became HIV-infected in HVTN 704/HPTN 085

Exploratory objective 6

- To assess whether host genetics (eg, HLA type, CCR5 heterozygosity) and sex are associated with time to meeting ART re-initiation criteria among VRC01 or placebo recipients who became HIV-infected in HVTN 704/HPTN

3.3 ATI

For all participants, ATI begins with cessation of ART Schedule 1, *Monitoring ATI*. Participants on ATI (Schedule 1 or 2) who do not meet criteria for moving to the next visit schedule (ie, viral rebound or re-initiating ART), or who meet criteria for re-initiating ART but decline to do so, should continue with extended visits on their current ATI visit schedule until such time as they move to the next visit schedule or are terminated from the study. These Schedule 1 and Schedule 2 extended visits occur quarterly and are designated as Visits Type A and Type B, with procedures specified for each visit type, in the laboratory and clinical procedures tables (see [Appendix E](#), [Appendix F](#), [Appendix H](#), [Appendix I](#), and [Appendix K](#)).

3.3.1 Transition from Schedule 1, *Monitoring ATI* to Schedule 2, *ATI monitoring with viremia*

For participants on Schedule 1, *Monitoring ATI*, the following virologic criterion will trigger a transition to Schedule 2, *ATI monitoring with viremia*:

- Confirmed VL ≥ 200 copies/mL (ie, on 2 consecutive samples).

A confirmatory sample should be drawn as soon as possible following the first VL result ≥ 200 copies/mL.

3.3.2 Transition from Schedule 1, *Monitoring ATI* to Schedule 3, *Follow-up on ART*

For participants on Schedule 1, *Monitoring ATI*, any of the following non-virologic criteria will trigger ART re-initiation and transition to Schedule 3, *Follow-up on ART*:

- Confirmed CD4+ T-cell count < 350 cells/mm³ (ie, on 2 consecutive samples)
- Any HIV-related syndrome (eg, acute retroviral syndrome, an opportunistic infection)
- Pregnancy or breastfeeding
- ART re-initiation requested by participant

- ART re-initiation requested by primary HIV care provider or CRS Investigator of Record (eg, if deemed medically necessary)

A confirmatory sample should be drawn as soon as possible following the first CD4+ T-cell count < 350 cells/mm³.

3.3.3 Transition from Schedule 2, *ATI monitoring with viremia*, to Schedule 3, *Follow-up on ART*

For participants on Schedule 2, *Monitoring ATI with viremia*, the following virologic criteria will trigger ART re-initiation and transition to Schedule 3, *Follow-up on ART*.

From the Week 0 visit to the Week 24 visit in Schedule 2:

- Viral load remains ≥ 1,000 copies/mL for ≥ 4 consecutive weeks AND viral load has not dropped 0.5 log from the previous week

This ART re-initiation criterion applies irrespective of missed visits and must take account of VL results ≥ 1,000 copies/mL experienced by a participant while on Schedule 1. Furthermore, assessing whether participants meet this criterion may require additional visits beyond those scheduled from Week 8 (Visit 48) to Week 24 (Visit 56) in Schedule 2. Ideally, these additional visits will be conducted weekly. These additional visits will be treated as interim visits (for more details, see the HVTN 804/HPTN 095 SSP).

After the Week 24 visit, the ART re-initiation criterion is:

- Confirmed viral load ≥ 200 copies/mL (ie, on 2 consecutive samples).

A confirmatory sample should be drawn as soon as possible following the first VL result ≥ 200 copies/mL. The above virologic ART re-initiation criteria are shown schematically in [Figure 3-1](#).



Figure 3-1 Virologic criteria for transition from Schedule 2 to Schedule 3 (ie, ART re-initiation)

In addition, at any time during Schedule 2, any of the following non-virologic criteria will trigger prompt ART re-initiation and transition to Schedule 3, *Follow-up on ART*:

- Confirmed CD4+ T-cell count < 350 cells/mm³ (ie, on 2 consecutive samples)
- Any HIV-related syndrome (eg, acute retroviral syndrome, an opportunistic infection)
- Pregnancy or breastfeeding
- ART re-initiation requested by participant
- ART re-initiation requested by primary HIV care provider or CRS Investigator of Record (eg, if deemed medically necessary).

A confirmatory sample should be drawn as soon as possible following the first CD4+ T-cell count < 350 cells/mm³.

3.3.4 Participants who decline to re-initiate ART

When ART re-initiation criteria are met, CRS staff will strongly recommend that the participant restart ART. Participants who decline to do so should be urged to continue clinic visits per Schedule 2 until such time as the participant re-initiates ART, at which time they should transition to Schedule 3. For additional details, see the HVTN 804/HPTN 095 Study Specific Procedures (SSP).

4 Statistical considerations

4.1 Accrual and sample size calculations

Recruitment will target participants who received VRC01 or placebo and became HIV-infected during participation in HVTN 704/HPTN 085.

We calculate the expected trial sized under different scenarios for the percentage of enrolled participants out of the total number of endpoint infected cases from HVTN 704/HPTN 085; scenarios include 25%, 50%, and 75%. Eligible placebo recipients will be capped such that the overall placebo to VRC01 recipient ratio of enrolled participants is at most approximately 1:1. Given that the parent HVTN 704/HPTN 085 study was randomized at a 1:2 placebo to VRC01 ratio, we would only expect to cap the number of eligible placebo recipients if prevention efficacy (PE) exceeds 50%. Given this constraint, along with an assumption of a common prevention efficacy at each dose (PE10 and PE30), the expected trial size will depend on different levels of PE. Under the null hypothesis (PE10 = PE30 = 0%), the total expected number of endpoint infections among placebo recipients is 26 and VRC01 recipients is 55 (Table 4-3 in the parent protocol HVTN 704/HPTN 085); therefore, we assume a trial size of 7, 13 or 20 placebo recipients and 14, 28, or 41 VRC01 recipients depending on the enrollment ratio. Under the alternative hypothesis (PE10 = PE30 = 60%), the total expected number of endpoint infections among placebo recipients is 37 and VRC01 recipients is 30 (Table 4-3 in the parent protocol); therefore, under the different enrollment ratio scenarios, we assume a trial size of 8, 15, or 23 placebo recipients and an equal number of VRC01 recipients so as not to exceed a 1:1 ratio. These six sample size scenarios represent estimated upper and lower bounds for sample size given the expected number of endpoint infections under the null and alternative hypotheses respectively, as well as various scenarios for the percentage of eligible participants who will ultimately enroll in HVTN 804/HPTN 095.

4.1.1 Sample size considerations for time to ART re-initiation criteria

Using data from the placebo arm of a therapeutic vaccine study which enrolled early treated patients (80), we modeled the time T (in weeks) to meet re-initiation criteria as a Weibull distribution with survival function $P(T > t) = \exp[-(\lambda t)^p]$, where $\lambda = \exp(-2.932) = 0.053$ and $p = 2.014$. From these parameters, we estimated the median time to meet re-initiation criteria as 15.6 weeks in the AMP placebo recipients. We can express the treatment effect in terms of either the hazard ratio θ or the factor β by which treatment increases the median time to meet re-initiation criteria; β and θ are related by $\beta = \theta^{-1/p}$.

We model censoring of time to re-initiation criteria using an exponential model and a maximum follow-up time of 72 weeks, where follow-up is censored at a rate of 20% per year due to either study termination or re-initiation of ART before reaching the re-initiation criteria. Simulating 10,000 trials based on these models

of time to re-initiation criteria and censoring, we computed power using a log rank test with alpha equal to 0.05. Power for a 40%, 50%, 60%, and 70% reduction in hazard under different enrollment rate and prevention efficacy scenarios are shown in [Table 4-1](#). These hazard reductions correspond to 29%, 41%, 58%, and 82% increases in the median time to meet re-initiation criteria. Therefore, if VRC01 increases the median time to re-initiation criteria 58% and the enrollment rate is 50%, then under the parent study null hypothesis power to detect a difference in time to re-initiation criteria is 72% while under the alternative hypothesis power is 62%.

Table 4-1 Power under different prevention efficacy results, different enrollment rates and different treatment effects, expressed as either reduction in hazard or percent increase in median time to meet re-initiation criteria

Enrollment Rate		Null hypothesis			Alternative hypothesis		
		25%	50%	75%	25%	50%	75%
Expected number of placebos		7	13	20	8	15	23
Expected number of VRC01		14	28	41	8	15	23
Reduction in hazard	% Increase in median time to meet re-initiation criteria						
		40%	29%	20%	32%	44%	16%
50%	41%	31%	50%	67%	24%	42%	58%
60%	58%	46%	72%	89%	36%	62%	81%
70%	82%	65%	91%	98%	54%	83%	96%

4.1.2 Sample size considerations for safety

The goal of the safety evaluation for this study is to identify safety concerns associated with ATI. The ability of the study to detect serious adverse events (SAEs) (see [Section 4.2.4.1](#)) can be expressed by the true event rate above which at least 1 SAE would likely be observed and the true event rate below which no events would likely be observed. Under the enrollment rate and PE scenarios described in [Section 4.1](#), [Table 4-2](#) shows the true event rate such that there is a 90% chance of observing at least 1 event (or no events) among three groups; 1) the placebo recipients only, 2) the VRC01 recipients only, or 3) all enrolled participants.

Table 4-2 True event rates above which at least 1 SAE (or below which no events) would likely be observed in a group of size *n* participants. Event rates are computed separately for various values of *n* given by the range and midpoint for the estimated number of participants among 3 groups; 1) the placebo recipients only, 2) the VRC01 recipients only, or 3) all enrolled participant based on the enrollment scenarios described in [Section 4.1](#).

<i>n</i>	Placebo recipients			VRC01 recipients			All enrolled		
	7	15	23	8	25	49	16	38	61
At least 1 event	28.0%	14.2%	9.5%	25.0%	8.8%	4.6%	13.4%	5.9%	3.7%
No events	1.5%	0.7%	0.5%	1.3%	0.4%	0.2%	0.7%	0.3%	0.2%

4.2 Statistical analyses

Analyses for primary endpoints will be performed using SAS and R. All other descriptive and inferential statistical analyses will be performed using SAS, StatXact, or R statistical software.

No formal multiple comparison adjustments will be employed for multiple safety endpoints or secondary endpoints. However, multiplicity adjustments will be made for certain laboratory assays, as discussed below, when the assay endpoint is viewed as a collection of hypotheses (eg, testing multiple peptide pools to determine a positive response).

4.2.1 Analysis variables

The analysis variables consist of baseline participant characteristics, safety, and laboratory outcomes for primary- and secondary-objective analyses.

4.2.2 Baseline comparability

Groups defined by the parent protocol treatment arms will be compared for baseline participant characteristics using descriptive statistics.

4.2.3 Primary virologic analysis

In this study we condition on HIV-infection with the intention of comparing virologic outcomes by randomized treatment assignment from HVTN 704/HPTN 085. Since we are conditioning on a postrandomization event, HIV-infection, a two-sample test for a difference in outcome is subject to postrandomization selection bias. A direct comparison of virologic outcomes between treatment groups, which measures the “net treatment effect,” does not have a causal interpretation (122). As an example of the type of bias that can occur, suppose VRC01 protects against mild viruses but is not effective against virulent viruses. If this were true, we might see longer time to re-initiation criteria in VRC01 recipients than placebo recipients whereas, if we restricted only to those participants infected with a virulent HIV strain, we might see shorter time to re-initiation criteria in the VRC01 group. Therefore, a two-sample test comparing time to re-initiation criteria between treatment groups could give a misleading impression that VRC01 shortens viral suppression time during ATI while the causal interpretation of this hypothetical example would be that for virulent viruses, VRC01 increases viral suppression time during ATI compared to placebo.

Approaches will be taken to ensure robust and unbiased results. Implementation of targeted minimum loss-based estimation (TMLE) methods, used to address the objectives in the following sections, will be fully prespecified in the statistical analysis plan (SAP) to ensure objective and reproducible inference.

Each analysis will be done pooling the VRC01 recipients versus placebo recipients with supplemental analyses done separately for each dose group versus the placebo recipients.

4.2.3.1 Time to ART re-initiation criteria

The primary outcome is the time from the start of treatment interruption until the participant meets criteria to re-initiate ART.

A Cox proportional hazards model with the indicator of assignment to a mAb group versus the control group will be used to estimate the cumulative incidence in each of the infected VRC01 and infected placebo groups, as well as the hazard ratio, all with 95% confidence intervals and associated 2-sided p-values, where the model controls for baseline covariates thought to potentially predict both HIV-1 infection and the instantaneous hazard of meeting the ART re-initiation criteria. This is needed for controlling for potential postrandomization selection bias given that analyzed treatment groups are selected postrandomization. Plots of the estimated cumulative incidence will be shown by treatment group.

As a supportive analysis of this hypothesis, targeted minimum loss-based estimation (TMLE) may be used to estimate cumulative incidences of the primary efficacy endpoint over time for the pooled mAb arm and the control arm. Iterative mean-based TMLE is used for this analysis as described by Benkeser et al (123). The Super Learner (124) is used to generate initial estimates of the conditional censoring distribution and the iterated conditional means. This analysis will use TMLE as implemented in the R package `survtmle` available on CRAN (125).

4.2.3.2 Frequency of sustained post-treatment HIV control

The same covariate adjusted model used to estimate cumulative incidence of meeting the re-initiation criteria for ART over time, described in the previous section, will be used to compare the rates of failure to maintain HIV control at 24 weeks between the two treatment groups.

4.2.3.3 Time to viral load ≥ 200

Secondary endpoint 2 is time until the participant has a viral load ≥ 200 . The same methodology used to assess time to ART re-initiation criteria will be used for this endpoint. In this analysis we will compare cumulative incidence at week 8 in each of the infected VRC01 and infected placebo groups supplemented by a sensitivity analysis based on cumulative incidence at weeks 8, 16, and 24.

4.2.4 Primary safety analysis

4.2.4.1 AEs and SAEs

AEs will be summarized using MedDRA System Organ Class and preferred terms. Tables will show by treatment arm the number and percentage of

participants experiencing an AE within a System Organ Class or within preferred term category by severity or by relationship to treatment interruption. For the calculations in these tables, a participant with multiple AEs within a category will be counted once under the maximum severity or the strongest recorded causal relationship to treatment interruption. Formal statistical testing comparing arms is not planned since interpretation of differences must rely heavily upon clinical judgment.

4.2.4.2 Local laboratory values

Box plots of local laboratory values will be generated for baseline values and for values measured during the course of the study by treatment arm and visit. Each box plot will show the first quartile, the median, and the third quartile. Outliers (values outside the box plot) will also be plotted. If appropriate, horizontal lines representing boundaries for abnormal values will be plotted.

For each local laboratory measure, summary statistics will be presented by treatment arm and timepoint, as well as changes from baseline for postenrollment values. In addition, the number (percentage) of participants with local laboratory values recorded as meeting Grade 2 AE criteria or above as specified in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events will be tabulated by treatment arm for each timepoint after initiation of treatment interruption. Reportable clinical laboratory abnormalities without an associated clinical diagnosis will also be included in the tabulation of AEs described above.

4.2.4.3 Reasons for discontinuation of ATI and early study termination

The number and percentage of participants who discontinue ATI and who terminate the study early will be tabulated by reason and treatment arm.

4.2.5 **Secondary analyses of immune responses and reservoir measurements**

Analyses of immune responses and reservoir measurements will be descriptive using appropriate plotting techniques for describing measurements at a fixed time point (eg, boxplots and barplots) or longitudinally (eg, spaghetti plots) separately by treatment group. In addition, if enough samples are assayed we plan to do inferential and descriptive analyses as described in the following sections.

4.2.5.1 Evaluate the difference in anti-HIV immune responses or reservoir size between VRC01 and placebo recipients

TMLE will be used to estimate mean endpoints in each of the infected VRC01 and infected placebo groups, as well as the mean difference, all with 95% confidence intervals and associated 2-sided p-values, where the TMLE controls for all baseline covariates thought to potentially predict both HIV-1 infection and one of the secondary endpoints under study. This is needed for controlling for

potential postrandomization selection bias given that analyzed treatment groups are selected postrandomization.

4.2.5.2 Assess whether anti-HIV immune responses or reservoir size are associated with time to meeting ART re-initiation criteria

Cox regression will be used to estimate cumulative incidence over time for groups defined by levels of immune response or reservoir size for each treatment group.

5 Study population

Participants for this trial will be recruited from among former HVTN 704/HPTN 085 (NCT02716675) study participants who transitioned to Schedule 2 in that study and who meet the following inclusion/exclusion criteria.

5.1 Inclusion criteria

1. **Estimated date of HIV-1 acquisition** within 8 weeks of participant's last HVTN 704/HPTN 085 infusion (see HVTN 804/HPTN 095 SSP).
2. **Initiated ART within 28 weeks** of HVTN 704/HPTN 085 HIV-1 date of diagnosis.
3. **Receiving continuous ART for at least 1 year**
 - ART interruptions of up to 7 days and ≥ 90 days prior to enrollment are acceptable.
 - Within- and between-class changes in ART within the previous year are acceptable.
4. If on an NNRTI, **willingness and ability to switch** to a PI- or INSTI-containing regimen for at least 4 weeks prior to ART interruption.
5. **Willingness to interrupt ART** for up to 24 weeks or up to the time of meeting ART re-initiation criteria (Section 3.3).
6. **Willingness to re-initiate ART** upon meeting study ART re-initiation criteria.
7. **Willingness to use barrier protection** (ie, male or female condoms) for all sexual activity until after confirmation of viral suppression following ART re-initiation
8. **Willingness for CRS staff to contact primary HIV care provider** to exchange information regarding HVTN 804/HPTN 095 and participant medical history.
9. Site investigator anticipates that a **fully active alternative ART regimen** could be constructed and would be available in the event of virologic failure on the participant's current ART regimen.
10. **Access to a participating CRS** and willingness to adhere to study visit schedule and to be followed for the planned duration of the study.
11. Ability and willingness to provide **informed consent**

12. **Assessment of understanding:** volunteer demonstrates understanding of this study; completes a questionnaire prior to enrollment with verbal demonstration of understanding of all questionnaire items answered incorrectly.
13. **Agrees not to enroll in another study** of an investigational research agent for the duration of the participant's trial participation.

Laboratory Inclusion Values

Immunology/Virology

14. **HIV-1 infection**, with reactive HIV-1 antibody and any Multispot or Geenius HIV-1/HIV-2 results, documented by the HVTN 704/HPTN 085 HIV diagnostic algorithm.
15. **Plasma HIV-1 RNA $\geq 1,000$ copies/mL** by any assay, prior to initiating ART.
16. **CD4+ cell count ≥ 450 cells/mm³** obtained within 90 days prior to enrollment.
17. One **plasma HIV-1 RNA below the lower limit of quantitation (LLOQ)** of an VQA-certified or DAIDS-approved assay and collected:
 - at screening, within 90 days prior to enrollment; and
 - greater than 9 months prior to the screening HIV-1 RNA.

Hematology

18. **Hemoglobin (Hgb) ≥ 10.0 g/dL** for volunteers who were assigned female sex at birth, ≥ 11.0 g/dL for volunteers who were assigned male sex at birth.
19. **Absolute neutrophil count (ANC) ≥ 750 cells/mm³**
20. **Platelets $\geq 100,000$ cells/mm³**

Chemistry

21. **ALT < 2.5 times the institutional upper limit of normal and direct bilirubin** within the institutional range of normal.
22. **Estimated glomerular filtration rate (eGFR) > 60 mL/min/1.73m²**

Reproductive Status

23. **Volunteers capable of becoming pregnant:** negative serum or urine beta human chorionic gonadotropin (β -HCG) pregnancy test performed at the screening visit and prior to enrollment. Persons who are NOT capable of becoming pregnant due

to having reached menopause (no menses for 1 year) or having undergone total hysterectomy or bilateral oophorectomy or tubal ligation (verified by medical records) are not required to undergo pregnancy testing.

24. **Reproductive status:** A volunteer who is capable of becoming pregnant must agree to consistently use effective contraception (see [Appendix B](#) and HVTN 804/HPTN 095 SSP) for sexual activity that could lead to pregnancy from at least 21 days prior to enrollment through confirmation of viral suppression following ART re-initiation.
25. **Volunteers capable of becoming pregnant must also agree not to seek pregnancy through alternative methods**, such as artificial insemination or in vitro fertilization, until after confirmation of viral suppression following ART re-initiation.

5.2 Exclusion criteria

1. Any **plasma HIV-1 RNA \geq LLOQ** of VQA-certified or DAIDS-approved assay (LLOQ: 75, 50, 40, or 20 copies/mL) within 12 months prior to enrollment.
 - NOTE: Two “blips” (ie, plasma HIV-1 RNA $>$ LLOQ) $<$ 400 copies/mL are allowed if preceded and followed by values $<$ LLOQ and if the blips occur more than 6 months prior to enrollment.
2. **History of AIDS-defining illnesses** or US Centers for Disease Control (CDC) **Category C events** per the current list on the CDC website (see HVTN 804/HPTN 095 SSP).
3. **Autoimmune disease**, including Type I diabetes mellitus (Not excluded from participation: Volunteer with mild, stable and uncomplicated autoimmune disease that does not require consistent immunosuppressive medication and that, in the judgment of the site investigator, is likely not subject to exacerbation and likely not to complicate AE assessments).
4. **Immunosuppressive medications** received within 6 months before enrollment (Not exclusionary: [1] corticosteroid nasal spray; [2] inhaled corticosteroids; [3] topical corticosteroids for mild, uncomplicated dermatologic condition; or [4] a single course of oral/parenteral prednisone or equivalent at doses \leq 60 mg/day and length of therapy $<$ 11 days with completion at least 30 days prior to enrollment).
5. **Blood products** received within 120 days before planned ART interruption.
6. **Investigational research agents**, other than experimental vaccine(s) (See Exclusion Criterion #7), received within 30 days before planned ART interruption.

7. **HIV or non-HIV experimental vaccine(s) received within the last 1 year.**
Exceptions may be made by the HVTN 804/HPTN 095 PSRT for vaccines that have subsequently undergone licensure by the FDA or by the national regulatory authority where the volunteer is enrolling. For volunteers who have received control/placebo in an experimental vaccine trial, the HVTN 804/HPTN 095 PSRT will determine eligibility on a case-by-case basis. For volunteers who have received an experimental vaccine(s) greater than 1 year ago, eligibility for enrollment will be determined by the HVTN 804/HPTN 095 PSRT on a case-by-case basis.
8. **Licensed live attenuated vaccines** received within 30 days before planned ART interruption (eg, measles, mumps, and rubella [MMR]; oral polio vaccine [OPV]; varicella; yellow fever; live attenuated influenza vaccine).
9. **Licensed vaccines that are not live attenuated vaccines** received within 14 days before planned ART interruption (eg, tetanus, pneumococcal, hepatitis A or B).
10. **Significant or unstable cardiac or cerebrovascular disease** (eg, angina, congestive heart failure [CHF], recent cerebrovascular accident [CVA], or myocardial infarction [MI]).
11. **Hepatitis B surface antigen (HBsAg) or positive HCV RNA** (Not exclusionary: positive HCV Ab with negative HCV RNA).
12. **Pregnant or breastfeeding**
13. **Clinically significant medical condition**, physical examination findings, clinically significant abnormal laboratory results, or past medical history with clinically significant implications for current health. A clinically significant condition or process includes but is not limited to:
 - A process that would affect the immune response;
 - A process that would require medication that affects the immune response;
 - Any contraindication to repeated blood draws, including inability to establish venous access;
 - A condition that requires active medical intervention or monitoring to avert grave danger to the volunteer's health or well-being during the study period;
or
 - Any condition specifically mentioned among the exclusion criteria.
14. **Any medical, psychiatric, occupational, or other condition** that, in the judgment of the investigator, would interfere with, or serve as a contraindication to, protocol adherence, assessment of safety, or a volunteer's ability to give informed consent.

15. **Any medical, psychiatric, occupational, or other condition** that, in the judgment of the investigator, could be exacerbated by events associated with protocol participation, which include: ATI, low-level viremia, subsequent viral rebound, and ART re-initiation.
16. **HIV dementia or other neurologic disease** that, in the judgment of the investigator, would be a contraindication to study participation.
17. **Psychiatric condition that precludes compliance with the protocol.**
Specifically excluded are persons with psychoses within the past 3 years, ongoing risk for suicide, or history of suicide attempt or gesture within the past 3 years.
18. **Malignancy** (Not excluded from participation: Volunteer who has had malignancy excised surgically and who, in the investigator's judgment, has a reasonable assurance of sustained cure, or who is unlikely to experience recurrence of malignancy during the period of the study).
19. **Current untreated or incompletely treated active tuberculosis disease or current latent tuberculosis infection** (Not excluded from participation: Volunteer who has latent tuberculosis infection and is undergoing treatment, with at least one month of treatment completed)
20. **Untreated or incompletely treated syphilis, gonorrhea, or chlamydia infection**

5.3 Criteria for participant early termination

- Pregnancy or breastfeeding (see Section [6.7.1](#))
- Declared intention to become pregnant or begin breastfeeding
- Request by the participant to withdraw
- Request of the primary HIV care provider
- Participant starts ART switch but is not virally suppressed after approximately 12 weeks (see Section [6.1.3](#))
- Participant judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol so as to cause to harm to self or seriously interfere with the validity of the study results
- Participant relocates and remote follow-up or transfer to another CRS is not possible (Note: Remote follow-up is allowable only after confirmation of viral suppression after ART re-initiation; see HVTN 804/HPTN 095 SSP for further detail.)

- CRS determines that the participant is lost to follow-up
- Investigator decides, in consultation with Protocol Team leadership, to terminate participation (eg, if participant exhibits inappropriate behavior toward clinic staff)
- Any condition where termination from the study is required by applicable regulations

5.4 Study termination

This study may be terminated early by the determination of the HVTN 804/HPTN 095 PSRT, a pertinent national regulatory authority, NIH, or the Office for Human Research Protections (OHRP). In addition, the conduct of this study at an individual Network CRS may be terminated by the determination of the IRB/EC and any applicable RE.

6 Study procedures

For all study visits, unless otherwise specified, participants will come to their assigned Clinical Research Site (CRS).

6.1 Schedule 1: Monitoring ATI

6.1.1 Screening

Screening may occur over the course of several contacts/visits. All inclusion and exclusion criteria must be assessed within 8 weeks (56 days) prior to enrollment, unless otherwise specified in the eligibility criteria (Section 5).

After signing informed consent, volunteers will undergo the following procedures, as shown in [Appendix E](#) and [Appendix H](#):

- Assessment of Understanding
- Medical history, including:
 - current psychiatric status and history
 - assessment of routine clinically-indicated vaccinations (note: must be completed prior to ATI initiation (see Section 5.2))
- Complete physical examination
- Assessment of concomitant medications
- HIV transmission risk behavior assessment and counseling
- Contraception status assessment (for volunteers assigned female sex at birth and who are sexually active in a way that could lead to pregnancy; see Section 6.5 and [Appendix B](#))
- Decision aid
- Blood collection for:
 - HIV PCR viral load
 - CD4+ and CD8+ T-cell counts
 - HBsAg and hepatitis C serology
 - QuantiFERON TB test

- Hgb, ANC, platelets
- ALT, direct bilirubin, eGFR
- Syphilis testing
- Urine pregnancy test (for volunteers assigned female sex at birth; persons not of reproductive potential due to having reached menopause (no menses for 1 year), or having undergone hysterectomy or bilateral oophorectomy or tubal ligation [verified by medical records], are not required to undergo pregnancy testing)
- Gonorrhea/chlamydia testing by urine, rectal swabs, and oropharyngeal swabs
- Tuberculin skin test (TST; only if QuantiFERON TB test not available)
- Confirm volunteer eligibility to enroll

6.1.2 Enrollment

- Participants undergoing an “ART switch” will be considered enrolled on the first day of the new ART medication.
- Participants who do not undergo an “ART switch” will be considered enrolled at the initiation of ATI (Day 0).

6.1.3 ART Switch

ART switch

Participants taking NNRTI-based ART regimens are required to switch to a PI- or INSTI-based regimen at least 4 weeks before beginning ATI and must demonstrate viral suppression (ie, < LLOQ) on the new regimen before beginning ATI.

At the clinic visit initiating the ART switch, the participant will undergo the following procedures (see [Appendix E](#) and [Appendix H](#)):

- Targeted (ie, symptom directed) physical examination, including weight and vital signs
- Assessment of concomitant medications
- Intercurrent illness/adverse experiences (AEs)
- HIV transmission risk behavior assessment and counseling

- Contraception status assessment (for participants assigned female sex at birth and who are sexually active in a way that could lead to pregnancy; see Section 6.5 and Appendix B)
- Decision-making assessment
- Psychosocial assessment
- Blood collection for:
 - HIV PCR viral load
 - CD4+ and CD8+ T-cell counts
 - Hgb, ANC, platelets
 - ALT, direct bilirubin, eGFR
- Urine pregnancy test (for volunteers assigned female sex at birth; persons not of reproductive potential due to having reached menopause (no menses for 1 year), or having undergone hysterectomy or bilateral oophorectomy or tubal ligation [verified by medical records], are not required to undergo pregnancy testing)

Post-ART switch contact

The site will make arrangements to contact the participant approximately 2 weeks after initiation of the new ART regimen to assess tolerability of the ART switch and willingness to continue. This contact may be conducted over the phone or in person; see HVTN 804/HPTN 095 SSP for details.

ATI qualification visit

Four weeks or more after initiation of the new ART regimen, participants undergoing an ART switch will return for a clinic visit during which they will undergo the following procedures (see Appendix E and Appendix H):

- Targeted (ie, symptom directed) physical examination, including weight and vital signs
- Assessment of concomitant medications
- Intercurrent illness/adverse experiences (AEs)
- HIV transmission risk behavior assessment and counseling

- Contraception status assessment (for participants assigned female sex at birth and who are sexually active in a way that could lead to pregnancy; see [Appendix B](#))
- Blood collection for:
 - HIV PCR viral load
 - CD4+ and CD8+ T-cell counts
 - Hgb, ANC, platelets
 - ALT, direct bilirubin, eGFR
- Urine pregnancy test (for volunteers assigned female sex at birth; persons not of reproductive potential due to having reached menopause (no menses for 1 year), or having undergone hysterectomy or bilateral oophorectomy or tubal ligation [verified by medical records], are not required to undergo pregnancy testing)

Any participant who is not virally suppressed at the ATI qualification visit will be retested on a weekly basis until virally suppressed. If not virally suppressed by approximately 12 weeks after the start of the ART switch, the participant should be referred to re-initiate their previous NNRTI-containing regimen, will not proceed to the ATI, and will be terminated from the study.

ATI should be initiated no more than 2 weeks after the ATI qualification visit at which samples are collected that demonstrate viral suppression on the new ART regimen.

6.1.4 ATI

For all participants, initiation of ATI is defined as Day 0.

While on Schedule 1, participants will undergo the following procedures, as specified in [Appendix E](#) and [Appendix H](#):

- Complete physical examination OR Targeted (ie, symptom directed) physical examination, including weight and vital signs
- Assessment of concomitant medications
- Intercurrent illness/adverse experiences (AEs)
- ART re-initiation assessment
- HIV transmission risk behavior assessment and counseling

- Contraception status assessment (for participants assigned female sex at birth and who are sexually active in a way that could lead to pregnancy; see Section 6.5 and [Appendix B](#))
- Decision-making assessment
- Psychosocial assessment
- Social impact assessment
- Social impact assessment questionnaire
- Blood collection per [Appendix E](#) for:
 - HIV PCR viral load
 - CD4+ and CD8+ T-cell counts
 - Hgb, ANC, platelets
 - ALT, direct bilirubin, eGFR
 - Syphilis testing
 - ARV detection
 - Intracellular cytokine staining (ICS)
 - Immune cell phenotyping
 - Neutralizing antibodies (nAb)
 - FcR-mediated effector functions
 - HIV reservoir assessment
 - Serum, plasma, and PBMC storage
- Urine pregnancy test (for volunteers assigned female sex at birth; persons not of reproductive potential due to having reached menopause (no menses for 1 year), or having undergone hysterectomy or bilateral oophorectomy or tubal ligation [verified by medical records], are not required to undergo pregnancy testing)
- Gonorrhea/chlamydia testing by urine, rectal swabs, and oropharyngeal swabs

6.2 Schedule 2: Monitoring ATI with viremia

As soon as participants demonstrate viral load ≥ 200 copies/mL, they will transition to Schedule 2, during which they will continue ATI while viremia is monitored. At Schedule 2 timepoints specified in [Appendix F](#) and [Appendix I](#), participants will undergo the following procedures:

- Complete physical examination OR targeted (ie, symptom directed) physical examination, including weight and vital signs
- Assessment of concomitant medications
- Intercurrent illness/adverse experiences (AEs)
- ART re-initiation assessment
- HIV transmission risk behavior assessment and counseling
- Contraception status assessment (for participants who were assigned female sex at birth and who are sexually active in a way that could lead to pregnancy; see Section [6.4](#) and [Appendix B](#)).
- Decision-making assessment
- Psychosocial assessment
- Social impact assessment
- Social impact assessment questionnaire
- Blood collection for:
 - HIV PCR viral load
 - CD4+ and CD8+ T-cell counts
 - Hgb, ANC, platelets
 - ALT, direct bilirubin, eGFR
 - Syphilis testing
 - ARV detection
 - Intracellular cytokine staining (ICS)
 - Immune cell phenotyping

- Neutralizing antibodies (nAb)
- FcR-mediated effector functions
- Serum, plasma, and PBMC storage
- Urine pregnancy test (persons assigned female sex at birth; persons not of reproductive potential due to having undergone hysterectomy or bilateral oophorectomy [verified by medical records], are not required to undergo pregnancy testing).
- Gonorrhea/chlamydia testing by urine, rectal swabs, and oropharyngeal swabs

6.3 Schedule 3: Follow-up on ART

After ART re-initiation criteria are met (see Sections 3.3.2 and 3.3.3), participants will transition to Schedule 3 (see [Appendix G](#) and [Appendix J](#)). In Schedule 3, if virologic resuppression has not been achieved by Week 12, participants may continue with biweekly visits until viral resuppression is achieved. These additional visits will be treated as interim visits (see HVTN 804/HPTN 095 SSP).

At Schedule 3 timepoints specified in [Appendix G](#) and [Appendix J](#), participants will undergo the following procedures:

- Complete physical examination OR targeted (ie, symptom directed) physical examination, including weight and vital signs
- Assessment of concomitant medications
- Intercurrent illness/adverse experiences (AEs)
- HIV transmission risk behavior assessment and counseling
- Contraception status assessment (for participants who were assigned female sex at birth and who are sexually active in a way that could lead to pregnancy; see Section 6.5 and [Appendix B](#)).
- Decision-making assessment
- Psychosocial assessment
- Social impact assessment
- Social impact assessment questionnaire
- Blood collection for:

- HIV PCR viral load
- CD4+ and CD8+ T-cell counts
- Hgb, ANC, platelets
- ALT, direct bilirubin, eGFR
- Syphilis testing
- HIV genotypic antiretroviral resistance
- Viral isolation and sequencing
- Intracellular cytokine staining (ICS)
- Immune cell phenotyping
- Neutralizing antibodies (nAb)
- FcR-mediated effector functions
- HIV reservoir assessment
- Serum, plasma, and PBMC storage
- Urine pregnancy test (persons assigned female sex at birth; persons not of reproductive potential due to having undergone hysterectomy or bilateral oophorectomy [verified by medical records], are not required to undergo pregnancy testing).
- Gonorrhea/chlamydia testing by urine, rectal swabs, and oropharyngeal swabs

6.4 Interim visits

Confirmatory VL samples and confirmatory CD4+ T cell samples may be drawn at interim visits (see Sections 3.3.1, 3.3.2, and 3.3.3). At interim visits for this purpose, the following clinical procedures will be performed:

- Targeted physical exam
- Assessment of concomitant medications
- Intercurrent illness/adverse experiences (AEs)
- ART re-initiation assessment

- HIV transmission risk behavior assessment and counseling
- Social impact assessment

Additional procedures may be performed at the discretion of the clinician.

For additional information on interim visits, including interim visits for other reasons, see the HVTN 804/HPTN 095 SSP.

6.5 Early termination visit

At an early termination visit for a participant on Schedule 1 or 2, CRS staff should consider performing procedures specified for Extended Visit Type A (see [Appendix E](#), [Appendix F](#), [Appendix H](#), and [Appendix I](#)). Such participants will be urged to re-initiate ART under the care of their primary HIV care provider (see HVTN 804/HPTN 095 SSP for additional details).

At an early termination visit for a participant on Schedule 3, CRS staff should consider performing procedures specified for Week 40 (Visit 91) (see [Appendix G](#) and [Appendix J](#); see HVTN 804/HPTN 095 SSP for additional details).

6.6 Contraception status

Contraception status is assessed and documented at every scheduled clinic visit from screening through confirmation of viral resuppression following ART re-initiation for a participant who was assigned female sex at birth and who is sexually active in a way that could cause that participant to become pregnant. Prior to enrollment and until viral resuppression is confirmed following ART re-initiation, staff will ask participants to verbally confirm their use of adequate contraceptive methods (see [Appendix B](#)). A participant who was assigned female sex at birth and is sexually active in a way that could cause that participant to become pregnant should be reminded at all scheduled clinic visits of the importance of using contraception and should be referred to specific counseling, information, and advice as needed. This reminder should be documented in the participant's study record.

Self-reported infertility—including having reached menopause (no menses for 1 year) or having undergone hysterectomy, bilateral oophorectomy, or tubal ligation—must be documented in the participant's study record.

6.7 Specific clinical management considerations

6.7.1 Pregnancy or breastfeeding

Volunteers who are pregnant or breastfeeding are not eligible to participate in this study. Participants who become pregnant or are breastfeeding during the ART switch will not be allowed to interrupt ART and will be terminated from the study immediately. Participants who become pregnant or are breastfeeding during the ATI phase will re-initiate ART as soon as possible. Post-ATI follow-up will continue per Schedule 3 for up to 24 weeks after viral re-suppression is confirmed following ART re-initiation.

Participants who become pregnant or begin breastfeeding while on Schedule 3 (ie, after ART re-initiation) will continue per Schedule 3 for up to 24 weeks after viral re-suppression is confirmed.

If a participant completes the study or chooses to discontinue from the study before the pregnancy ends, then CRS staff should request permission to contact the participant regarding pregnancy outcomes at the end of the pregnancy. If obtained, pregnancy outcomes will be recorded on a CRF at the end of the pregnancy. All pregnancies must be reported to the Antiretroviral Pregnancy Registry.

6.7.2 Acute retroviral syndrome

Acute retroviral syndrome (ARS) is a rare diagnosis to be made by a CRS clinical IoR or designee or a primary HIV care provider. The HVTN 804/HPTN 095 PSRT is available for consultation on possible ARS, as needed. Participants with this diagnosis will re-initiate ART as soon as possible.

Signs and symptoms that may support a diagnosis of ARS include, but are not limited to, unintentional weight loss > 5% of pre-ATI body weight, otherwise unexplained persistent fever [$> 38^{\circ}\text{C}$], persistent night sweats, persistent diarrhea, oral candidiasis, and generalized lymphadenopathy.

7 Study products

There are no study products. Drugs for ART and PrEP will not be provided by the study or paid for using sponsor funds. Procedures for accessing external funding sources for PrEP and ART provision are detailed in the HVTN 804/HPTN 095 (SSP).

8 Laboratory

8.1 CRS laboratory procedures

The HVTN 804/HPTN 095 Site Lab Instructions and HVTN 804/HPTN 095 SSP provide further guidelines for operational issues concerning the clinical and processing laboratories. These documents include guidelines for general specimen collection, special considerations for phlebotomy, specimen labeling, whole blood processing, HIV screening/diagnostic testing, and general screening and safety testing.

Tube types for blood collection are specified in [Appendix E](#), [Appendix F](#), and [Appendix G](#). For tests performed locally, the local lab may assign appropriate tube types.

In specific situations, the blood collection tubes may be redirected to another laboratory or may require study-specific processing techniques. In these cases, laboratory special instructions will be posted on the protocol-specific section of the HVTN website.

Of note, all assays described below with the exception of HIV antiretroviral resistance testing are performed as research assays and are not approved for use in medical care. Results from these assays are not made available to participants or medical professionals to guide treatment decisions.

8.2 Assay timepoints

Endpoint assays for immunologic and virologic responses will be performed on a subset of participants to be determined by the outcome of primary objectives and endpoints.

8.3 Endpoint assays: cellular

8.3.1 Intracellular cytokine staining (ICS) assay

Flow cytometry will be used to examine HIV-specific CD4+ and CD8+ T-cell responses following stimulation of PBMCs with synthetic HIV peptides that span the HIV-1 viral proteins. ICS parameters will include cytokines such as interferon gamma (IFN- γ), interleukin (IL)-2, and TNF- α , and may include other cytokines (such as cytokines relevant to Th2 and Th17 responses) to identify T cells of specific functionality. Data will be reported as percentages of CD4+ and CD8+ T cells responding to a specific peptide pool. Additional cell surface markers, cytokines, or functional markers may also be analyzed.

8.4 Phenotyping of cell populations

Phenotyping of dendritic cells, monocytes, NK cells, B cells, T cells, or other leukocytes for lineage, maturation, and activation markers by flow cytometry may be performed on PBMCs. Data will be reported as percent of cells positive for each marker at the various timepoints.

8.5 Endpoint assays: humoral

8.5.1 Neutralizing antibody assay

HIV-1–specific nAb assays will be performed on serum samples from study participants. The TZM-bl assay will test neutralization of the autologous transmitted/founder virus and a panel of heterologous tier 2 viruses (126, 127). Autologous neutralization escape may also be assessed at the discretion of the HVTN Laboratory Center, contingent on the results of the nAb assays.

8.5.2 Antibody-dependent cellular cytotoxicity (ADCC)

ADCC activity may be assessed using serum samples from study participants. For the Luciferase-based cytotoxicity assay, participant sera are incubated with infectious molecular clone (IMC)-infected cells and percent killing is measured by evaluating the reduction in the luminescence signal after incubation of infected-target and effector cells in presence of serum Ab.

8.5.3 Antibody-dependent cellular phagocytosis (ADCP)

To assess the ability of antibodies to engage cellular FcR for potential antiviral function, ADCP may be measured using serum samples from study participants. ADCP is measured by assessing the ability of antibodies to mediate monocyte phagocytosis of HIV-1 antigen coated fluorescent beads by flow cytometry (128, 129). An array of antigens or viruses may also be analyzed at the discretion of the HVTN Laboratory Center, which may be contingent on the results of the primary antigens or viruses.

8.5.4 Virion capture

The ability of purified IgG from participant serum to mediate infectious virion capture will be measured by infectious virion capture assay (IVCA). The test uses a Protein G column-based capture of Ig-virion immune complexes.

8.6 HIV viral reservoir

Changes in the HIV reservoir will be quantitated in CD4+ T cells purified from PBMCs at designated timepoints, using testing methods such as the Intact Proviral

DNA Assay (IPDA), *Tat/rev* Induced Limiting Dilution Assay (TILDA), assays detecting replication-competent virus-bearing cells (eg, virus outgrowth assays), and/or measures of total proviral DNA. Cell-associated HIV-RNA may be quantitated as a measure of the transcriptionally active reservoir.

8.7 Host genomics

Molecular human leukocyte antigen (HLA) and CCR5 genotyping may be performed on samples from this study or HVTN 704/HPTN 085 using cryopreserved PBMC. Other genes, including those associated with immune responses (eg, immunoglobulin or T-cell receptor genes) or HIV-1 disease progression may also be assessed.

8.8 HIV antiretroviral resistance testing

HIV antiretroviral resistance testing will be performed by RNA PCR for resistance mutations in participants whose plasma viremia shows limited suppression after ART re-initiation.

8.9 ARV detection

Blood specimens will be collected during treatment interruption for ARV detection and drug level testing. ARV drug levels may be assessed at the discretion of the protocol team for participants who have not met virologic and non-virologic criteria for transition from monitoring ATI (Schedule 1) to monitoring ATI with viremia (Schedule 2) or for ART re-initiation (from Schedule 2 to Schedule 3). Assay methods may include HPLC-mass spectrometry, reverse-phase HPLC coupled with tandem mass spectrometry, or another similar method.

8.10 Biohazard containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the CDC and the NIH or other applicable agencies.

All dangerous goods materials, including Biological Substances, Category A or Category B, must be transported according to instructions detailed in the International Air Transport Association Dangerous Goods Regulations.

9 Research use of stored human samples and/or data

9.1 Specimen storage and other use of specimens

The HVTN and HPTN store specimens from all study participants indefinitely, unless a participant requests that specimens be destroyed or if required by IRB/EC, or RA.

Other use of specimens is defined as studies not covered by the protocol or the informed consent form for the main study (see [Appendix A](#) and [Appendix C](#)).

This research may relate to HIV, vaccines, antibodies, the immune system, and other diseases. This could include genetic testing and, potentially, genome-wide studies. This research is done only to the extent authorized in each study site's informed consent form, or as otherwise authorized under applicable law. Other research on specimens ("other use") will occur only after review and approval by the Networks, the IRB/EC of the researcher requesting the specimens, and the IRBs/ECs/REs of the CRSs if required.

As part of consenting for the study, participants document their initial decision to allow or not allow their specimens to be used in other research, and they may change their decision at any time. The participant's initial decision about other use of their specimens, and any later change to that decision, is recorded by their CRS in a Web-based tool that documents their current decisions for other use of their specimens. The Networks will only allow other research to be done on specimens from participants who allow such use.

CRSs must notify HVTN Regulatory Affairs if institutional or local governmental requirements pose a conflict with or impose restrictions on specimen storage or other use of specimens.

9.2 Exploratory studies

Samples may be used for other testing and research related to furthering the understanding of HIV, immunology, antibodies, or vaccines. In addition, cryopreserved samples may be used to perform additional assays to support standardization and validation of existing or newly developed methods.

10 Potential risks and benefits

10.1 Potential risks

10.1.1 Risks of ATI

The risks from a closely monitored ATI are minimal in this study population. There is a theoretical risk that such an interruption could lead to the development of HIV drug resistance (130). This may be a particular concern for individuals taking NNRTIs. However, this potential risk is substantially mitigated by the procedures described in Section 6.1.1. Given the study population as restricted by the eligibility criteria, the frequency of immunological and virologic monitoring, and the criteria for restarting ART, it is extremely unlikely that such an ART interruption will lead to the development of any opportunistic infections or AIDS-defining conditions.

Rarely, viremic rebound may be associated with acute retroviral syndrome (see Section 6.7.2).

During the ATI phase, participants may transmit HIV infection if they do not adhere to safe sex practices.

10.1.2 Phlebotomy

Drawing blood may be associated with discomfort, bruising, local hematoma formation and, on rare occasions, infections, lightheadedness, and fainting.

The amount of blood drawn for research purposes will be within regulatory limits (see 21 CFR 630.15).

10.2 Potential benefits

Study participants should expect no direct health benefits from study participation. Knowledge gained in this study may aid in development of better interventions against HIV.

11 Monitoring of safety

11.1 Safety monitoring and oversight

11.1.1 HVTN 804/HPTN 095 PSRT

The HVTN 804/HPTN 095 PSRT is composed of the following members:

- DAIDS medical officer representatives
- Protocol chairs
- Protocol Team leaders
- Core medical monitor
- Clinical safety specialist
- Regional medical liaison

The Protocol Team clinic coordinator, clinical data manager, study product developer representative, clinical trial manager, clinical research manager, and others may also be included in HVTN 804/HPTN 095 PSRT meetings.

The clinician members of HVTN 804/HPTN 095 PSRT are responsible for decisions related to participant safety.

The PSRT will review laboratory parameters (HIV-RNA, CD4+ T-cell count), adverse events, and a summary of the distribution of time to meeting ART re-initiation criteria every 2 weeks.

The PSRT will also review the distribution of time to meeting ART re-initiation criteria in the first 20 HVTN 804/HPTN 095 participants and assess whether the distribution is comparable to that observed in an NIH intramural therapeutic HIV vaccine study that enrolled HIV-infected participants who initiated ART early with similar ART re-initiation criteria to those proposed here. Based on the NIH intramural therapeutic HIV vaccine study results, we expect that the median time to meeting ART re-initiation criteria in HVTN 804/HPTN 095 will be at ATI week 15 and that the 75% percentile for time to meeting ART re-initiation criteria will be around week 12-18. If the spread in the distribution time to meeting ART re-initiation criteria is less than expected, then the HVTN 804/HPTN 095 PSRT, in consultation with the NIAID DSMB, will consider strategies for modifying the study (eg, to alter the eligibility criteria) with the aim to further enrich for potential controllers.

The HVTN 804/HPTN 095 PSRT will also monitor specifically for failure to re-suppress or to demonstrate a 2-log viral load reduction within 12 weeks after ART re-initiation. Any such failure and/or any AE \geq Grade 4 deemed related to the study procedures will be reviewed by the HVTN 804/HPTN 095 PSRT promptly and, if indicated, by the NIAID DSMB to evaluate whether and how the study should be modified.

11.1.2 NIAID DSMB

The NIAID DSMB assesses the study conduct during the trial and may give advice to the HVTN 804/HPTN 095 Protocol Team leadership.

Approximately 6 months after enrollment of the first participant or after the 10th participant has completed 12 weeks of ATI (whichever comes first), an interim review of the study will occur. The DSMB will review accrual; retention; AE summaries, including all reported AEs \geq Grade 3 and all STIs; summaries of the time to meeting ART re-initiation criteria; and longitudinal summaries of HIV-1 RNA and CD4+ T-cell count. Subsequent DSMB reviews will occur at least annually while participants remain on study. A DSMB may also be convened if a reason is identified by the DAIDS MO, study Co-chairs, or study statisticians in consultation with the HVTN 804/HPTN 095 Protocol Team leadership.

11.1.3 Roles and responsibilities in safety monitoring

The roles and responsibilities of the SDMC in relation to safety monitoring include:

- Maintaining a central database management system for clinical data;
- Providing reports of clinical data to appropriate groups such as the HVTN 804/HPTN 095 PSRT and NIAID DSMB (see Section [11.1.2](#));

The roles and responsibilities of the HVTN CSS, HVTN RML, or HVTN Core designee in relation to safety monitoring include:

- Daily monitoring of clinical data;
- Querying CRSs for additional information regarding reported clinical data; and
- Providing support to the HVTN 804/HPTN 095 PSRT.

11.2 Safety reporting

11.2.1 Submission of safety forms to SDMC

CRS staff must submit all safety forms (eg, AEs, local lab results, concomitant medications) before the end of the next business day, excluding federal or bank holidays. The forms should not be held in anticipation of additional information at a later date. If additional information is received at a later date, the forms should be updated and resubmitted before the end of the next business day after receiving the new information. For the case of a longer CRS holiday closure, CRS staff must submit the data by the end of the 5th day (local time) after receiving the information even if this day is a holiday.

For example: If the CRS becomes aware of an AE on Thursday (Day 0), the CRS must submit the data by the end of the next business day, on Friday. If there is a longer CRS holiday closure, then this AE must be reported no later than the end of the fifth day, Monday (Day 4). If Monday is a holiday as well, all safety forms still need to be submitted by the end of Monday (Day 4).

11.2.2 Serious adverse event (SAE)

An SAE is an AE that results in one or more of the following outcomes:

- Death
- A life-threatening (ie, an immediate threat to life) event
- Requires in-patient hospitalization or prolongation of an existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- A medically important event (medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization, but which may jeopardize the individual or may require intervention to prevent one of the outcomes listed above.)

11.2.3 AE reporting

An AE is any untoward medical occurrence in a clinical investigation participant, including an abnormal laboratory finding, symptom, or disease temporally

associated with the individual's participation in the research, whether or not related to the research.

The study intervention for which adverse event attribution reporting is required is ATI.

At designated visits, information regarding AEs will be elicited by appropriate questioning and examinations and will be documented in the medical record and in the electronic database.

All AEs are graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017, available on the RSC website at <https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables>, except:

- Unintentional Weight Loss is required to be reported as an AE only if it is considered to be potentially deleterious to the participant's health (see HVTN 804/HPTN 095 Study Specific Procedures); and
- Creatinine is required to be reported as an AE only if it is gradable per the increase from local lab ULN parameter. Do not grade elevated creatinine based on the change from the baseline parameter.

All AEs are reported to the SDMC on the appropriate CRF.

Sites are expected to notify HVTN clinical safety staff of any serious safety concern requiring their attention. Telephone numbers and email addresses are found on the protocol home page on the HVTN Members' site (<https://members.hvtn.org/protocols/hvtn804-hptn095>). Concerns requiring immediate attention should be communicated by calling the clinical safety phone. In the case of email notification, clinical safety staff will reply within one business day.

In addition, CRS investigators are required to submit AE information in accordance with IRB/EC and any applicable RE requirements.

12 Ethics/protection of human subjects

12.1 Informed consent process

Informed consent is a process where information is presented to enable persons to voluntarily decide whether or not to participate in a clinical trial. It is an ongoing conversation between the prospective or enrolled research participant and the researchers that begins before consent is given and continues through the decision-making process and until the end of the participant's involvement in the research. Discussions about the research will provide essential information about the study and include: purpose, duration, experimental procedures, alternatives, risks, and benefits. Participants will be given the opportunity to ask questions and to have them answered.

The participant will sign the informed consent document prior to undergoing any research procedures. The participant may withdraw consent at any time throughout the course of the study. A copy of the informed consent document will be given to participants for their records. Documentation of the signing of the consent form will be retained in the participant's medical record. The rights and welfare of participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. These rights and responsibilities are further elaborated upon in the Participants Bill of Rights and Responsibilities developed by the HVTN and HPTN for their jointly conducted trials.

The HVTN 804/HPTN 095 Sample Informed Consent Form (SICF) is modeled on previously-approved treatment interruption consent forms and, specifically, emphasizes the cautionary points noted above (see Section 2.9) with respect to the uncertainties, risks and lack of anticipated individual benefits; the fact that treatment interruptions are not recommended in clinical care; and the fact that ART guidelines recommend lifelong treatment. While the SICF is a crucial starting point, the quality of informed consent also relies on the process and other tools employed to supplement that document. With respect to these supplementary measures the team is building upon each Network's longstanding efforts to build rigorous informed consent into trial implementation (131). These efforts begin with the community engagement described above (see Section 2.11) and go on to include: drafting of the SICF by and with local community representatives who reflect the target population and the sites that will be conducting the study; review of translated materials by local staff and community representatives who are native speakers of each language to help ensure accuracy and appropriateness; the provision of a Frequently Asked Questions information sheet; the development and use of visual aids to convey some concepts, such as blood draw volumes; the development of materials and processes to engage sexual partners, if participants and their partners so choose; the use of an Assessment of Understanding and re-review of any misunderstandings as part of

the initial and ongoing informed consent process; and ongoing community engagement throughout the trial, including local education and engagement activities, Community Advisory Board (CAB) meetings and study-specific stakeholder meetings, among other forums.

For HVTN 804/HPTN 095, the team will develop additional tools to facilitate optimal informed consent and decision-making. Specifically, the team will develop decision aids, such as those found to improve the quality of shared decision making and consent in preference-sensitive healthcare decisions (132, 133) and will partner with participant advocates—nonteam members, ideally peers, familiar with the AMP Study, treatment interruption, and the HVTN 804/HPTN 095 study—who could work with the AMP participant to further facilitate optimal decision-making regarding potential HVTN 804/HPTN 095 participation. The latter model has been used, for example, in the setting of organ transplantation between HIV-positive donors and recipients (134, 135). Clinic staff will also be in consultation with each participant’s primary HIV care provider to ensure their understanding and ability to support the participants. Any such materials developed for participants will be submitted for review and approval to the IRB/EC prior to using with participants.

12.2 Participant confidentiality

All records will be kept confidential to the extent provided by federal, state, and local law. Study monitors and other authorized representatives of the Sponsor may inspect all documents and records required to be retained by the investigator, including but not limited to medical records. Records will be kept locked and all computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the developer of VRC01, IRB, NIH/NIAID/DAIDS or the sponsor’s designee, OHRP, or another regulatory authority.

In the United States, research participants are protected by a Certificate of Confidentiality from the US NIH, which can prevent disclosure of study participation even when that information is requested by subpoena. Participants are told of the use and limits of the certificate in the study consent form.

13 Protocol conduct

This protocol and all actions and activities connected with it will be conducted in compliance with Good Clinical Practice (GCP) (ICH6), the HVTN and HPTN network-specific *Manuals of Operations*, and DAIDS Clinical Research Policies and Standard Procedures Documents, including procedures for the following:

- Protocol registration, activation, and implementation;
- Informed consent, screening, and enrollment;
- Study participant reimbursement;
- Clinical and safety assessments;
- Safety monitoring and reporting;
- Data collection, documentation, transfer, and storage;
- Participant confidentiality;
- Study follow-up and close-out;
- Quality control;
- Protocol monitoring and compliance;
- Advocacy and assistance to participants regarding negative social impacts associated with the trial;
- Risk reduction counseling;
- Specimen collection, processing, and analysis;
- Exploratory and ancillary studies and sub-studies, and
- Destruction of specimens.

Any policies or procedures that vary from DAIDS, HVTN, or HPTN standards or require additional instructions (eg, instructions for randomization specific to this study) will be described in the HVTN 804/HPTN 095 SSP.

13.1 Emergency communication with study participants

As in all clinical research, this study may generate a need to reach participants quickly to avoid imminent harm, or to report study findings that may otherwise concern their health or welfare.

When such communication is needed, the CRS will request that its IRB/EC and any applicable RE expedite review of the message. If this review cannot be completed in a timeframe consistent with the urgency of the required communication, the site should contact the participant first, and then notify the IRB/EC and any applicable RE of the matter as soon as possible.

14 Acronyms and abbreviations

ACTG	AIDS Clinical Trials Group
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AE	adverse experience
AIDS	acquired immune deficiency syndrome
B-HCG	beta human chorionic gonadotropin
AMP	antibody mediated prevention
ALT	alanine transaminase
ANC	absolute neutrophil count
ANOVA	analysis of variance
ARS	acute retroviral syndrome
ART	antiretroviral therapy
ATI	analytical treatment interruption
AUC	area under the curve
bnAb	broadly neutralizing antibody
CAB	community advisory board
cART	combination antiretroviral therapy
caRNA	cell-associated HIV-1 RNA
CBC	complete blood count
CDC	(U.S.) Centers for Disease Control and Prevention
CHF	congestive heart failure
CRF	case report form
CVA	cerebrovascular accident
DAIDS	Division of AIDS
DNA	deoxyribonucleic acid
DSMB	data safety monitoring board
EAE	adverse event requiring expedited reporting
EC	ethics committee
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
FcγR	fragment crystallizable gamma receptor
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
HPTN	HIV Prevention Trials Network
HVTN	HIV Vaccine Trials Network
ICS	intracellular cytokine staining
IgG	immunoglobulin G
INSTI	integrase strand transfer inhibitor
IoR	investigator of record
IPDA	intact proviral DNA assay
IRB	institutional review board
IUPM	infectious units per million

LLOQ	lower limit of quantitation
LTR	long terminal repeat
mAb	monoclonal antibody
MDC CAB	Martin Delaney Collaboratory Community Advisory Board
MedDRA	Medical Dictionary for Regulatory Activities
nAb	neutralizing antibody
NHP	nonhuman primate
NIAID	National Institute of Allergy and Infectious Diseases
NICD	National Institute for Communicable Diseases
NNRTI	nonnucleoside reverse transcriptase inhibitor
NIH	National Institutes of Health
OHRP	Office of Human Research Protection
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PHI	primary HIV infection
PI	protease inhibitor
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PrEP	pre-exposure prophylaxis
PSRT	protocol safety review team
PTC	post-treatment controller
QVOA	quantitative viral outgrowth assay
RE	regulatory entity
RNA	ribonucleic acid
RSC	Regulatory Support Center
SAE	serious adverse event
SAP	statistical analysis plan
SDMC	statistics and data management center
SHIV	simian/human immunodeficiency virus
SICF	sample informed consent form
SIVIG	specific intravenous immunoglobulin
SMART	Strategies for Management of Antiretroviral Therapy
SSP	study specific procedures
T/F	transmitter/founder
TILDA	Tat/Rev induced limiting dilution assay
TMLE	targeted minimum loss-based estimation
T _{reg}	regulatory T cell
ULN	upper limit of normal
VQA	Virology Quality Assurance

15 Protocol version history

Date: November 13, 2019

Protocol version: 1.0

Protocol modification: Original protocol

16 Document references (other than literature citations)

Other documents referred to in this protocol, and containing information relevant to the conduct of this study, include:

- Antiretroviral Pregnancy Registry. Available at <http://www.apregistry.com/>.
- Assessment of Understanding. Accessible through the HVTN protocol-specific website.
- Division of AIDS (DAIDS) Clinical Research Policies and Standard Procedures Documents. Available at <https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures>
- Division of AIDS Protocol Registration Manual. Available at <https://www.niaid.nih.gov/sites/default/files/prmanual.pdf>
- Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. Version 2.1, dated March 2017. Available at <https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables>
- The Manual for Expedited Reporting of Adverse Events to DAIDS. Version 2.0, January 2010. Available at <https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids>
- HVTN Certificate of Confidentiality. Accessible through the HVTN website.
- HVTN 804/HPTN 095 Study Specific Procedures. Accessible through the HVTN protocol-specific website.
- HVTN Manual of Operations. Accessible through the HVTN website.
- Dangerous Goods Regulations (updated annually), International Air Transport Association. Available for purchase at <http://www.iata.org/publications/dgr/Pages/index.aspx>
- International Conference on Harmonisation (ICH) E6 (R1), Guideline for Good Clinical Practice: Section 4.8, Informed consent of trial subjects. Available at <http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html>
- HVTN 804/HPTN 095 Participants' Bill of Rights and Responsibilities. Accessible through the HVTN website.

- NIH Policy on Reporting Race and Ethnicity Data: Subjects in Clinical Research. Available at <http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html>
- Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. Available at <https://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/ClinicalSite.aspx>
- Title 21, Code of Federal Regulations, Part 50. Available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50>
- Title 45, Code of Federal Regulations, Part 46. Available at <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>

See Section 17 for literature cited in the background and statistics sections of this protocol.

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Appendix A Sample informed consent form

Title: Antiretroviral analytical treatment interruption (ATI) to assess immunologic and virologic responses in participants who received VRC01 or placebo and became HIV-infected during HVTN 704/HPTN 085

Protocol number: HVTN 804/HPTN 095

Site: [Insert site name]

Thank you for your interest in our research study. Please read this consent form or ask someone to read it to you. If you decide to join the study, we will ask you to sign or make your mark on this form. We will offer you a copy to keep. We will ask you questions to see if we have explained everything clearly. You can also ask us questions about the study.

Research is not the same as treatment or medical care. The purpose of a research study is to answer scientific questions. These answers can help find new medicines, treatments, vaccines, and knowledge about how the human body works.

You are being asked to take part in this study because you got HIV while you were enrolled in the AMP Study, have been taking HIV medication (also known as “ART” or anti-retroviral treatment) and because your HIV has been kept at a very low level or “undetectable” for at least the past year. We will enroll people who got the study antibody and people who got placebo. Since the AMP Study is still blinded, we don’t know whether you got the study antibody or not.

We expect that between 16 and 46 people will join this study.

Key information

These are some of the things you should know about this study:

- The purpose of the study is to learn whether having the AMP Study antibody in a person’s body might help the immune system control HIV better if that person gets HIV. Another goal is to test the safety of stopping HIV medications in a research study.
- If you are eligible and choose to join, we will ask you to stop taking your HIV medication.
- After you stop taking HIV medication, you will have regular clinic visits to carefully track your HIV and your health. If your viral load goes up to 200 or higher, you will continue to stay off your HIV medication, and we will check on your health more often.

- If your viral load goes up to 1,000 or more and stays that high for 4 weeks, or if your CD4 count drops below 350, or if you show any symptoms of HIV-related illness, you will restart taking HIV medication. If your viral load at the end of 6 months is 200 or higher, you will restart taking HIV medication. If your immune system maintains control of your HIV for the entire 6 months, you may choose to keep going without taking HIV medication for as long as your viral load remains below 200 and you don't meet the other restart criteria within this study.
- Once you restart taking HIV medication, you will have follow-up visits for up to a year to see how your body responds to restarting HIV medication and to make sure that your viral load returns to very low or undetectable levels.
- At clinic visits we will give you physical exams, ask about your physical and mental health, and collect blood for laboratory tests.
- Stopping your HIV medication is an experimental procedure that is only used in carefully monitored research. It is not recommended as part of routine healthcare for people living with HIV. Healthcare guidelines recommend that people living with HIV take HIV medication for the rest of their lives. Some of the risks when you stop taking HIV medication include having a high viral load and acute retroviral syndrome, having a low CD4 count, transmitting HIV to your partner(s), developing HIV drug resistance, and having to switch to a new HIV medication, which could have additional side effects. The study is designed to make it unlikely that any of these things will happen.
- There may also be risks we don't know about, even serious ones, including death.
- There is no direct benefit to you from being in the study.
- Whether to join this study is your choice. You do not have to join and you are free to leave at any time. Your choice will not affect the care you receive at this clinic.

The rest of this form provides a more complete description of this study. Please read it carefully and ask questions at any time.

Why is this study being done?

Researchers know that when people stop taking their HIV medication, the amount of HIV in their blood (known as “viral load”) usually goes up quickly, and they must restart taking their medication. This quick increase does not always happen. Very rarely, for only a few people, it stays low, or even undetectable for many months.

We do not expect this study to benefit you directly, even if you received the study antibody in the AMP study. You should not expect to control the virus while you are off of your HIV medication.

Researchers think having an anti-HIV antibody like the one used in the AMP Study in the body at the time when HIV infection happens may improve how the body's immune system responds to HIV. This could happen even if the antibody didn't prevent HIV acquisition.

Animal studies suggest that having an anti-HIV antibody in the body at the time of HIV infection may help the immune system keep viral load low for a longer period of time without taking HIV medication. Researchers want to find out if this will happen in people. And if it happens in people, researchers want to know how and why this happens.

1. We are doing this study to answer several questions.

- Are people who got the study antibody in the AMP Study more likely to keep HIV under control longer without taking HIV medication than people who got the placebo?
- Is it safe for people to stop taking their HIV medication in a carefully monitored research study?
- Do people who got the study antibody in the AMP Study and got HIV develop and maintain an immune system that is more capable of controlling HIV viral load than people who got the placebo and get HIV?
- Do people who got the study antibody or placebo in the AMP Study and get HIV have a difference in the number of cells that are infected with HIV but do not reproduce before and after stopping their HIV treatment?

2. To answer these questions, study participants will stop taking their HIV medications.

To answer the study questions, we will ask you to stop taking your HIV medication for up to 24 weeks (about 6 months). Stopping HIV medication is an experimental procedure that is only used in carefully monitored research. It is not recommended as part of routine healthcare for people living with HIV. Healthcare guidelines recommend that people living with HIV take HIV medication for the rest of their lives. We will tell you more about the risks of stopping your HIV medication in Section 19 of this form. During the time that you do not take your HIV medication we will check your health and HIV frequently to minimize the chance of harm to you. If your viral load goes up, your CD4 count goes down, you show signs of HIV-related illness, or you and/or your primary HIV care provider decide to, you will restart taking HIV medication right away.

Joining the study

3. It is completely up to you whether or not to join the study.

Take your time in deciding. If it helps, talk to people you trust, such as your primary HIV care provider, friends or family. We will be happy to help you explain this study to anyone you wish. If you decide not to join this study, or if you leave it after you have joined, your other care at this clinic and the benefits or rights you would normally have will not be affected.

You cannot be in this study while you are in another study where you get a study product. Being in more than one study may not be safe.

If you choose not to join this study, you may be able to join another study.

4. If you want to join the study, we will screen you to see if you are eligible.

Screening involves a physical exam, checking your mental health, an HIV test, and asking about your health history. A physical exam may include, but is not limited to:

- Checking your weight, temperature and blood pressure,
- Looking in your mouth and throat,
- Listening to your heart and lungs, and
- Feeling your abdomen (stomach and liver).

We will also do blood and urine tests. These tests tell us about some aspects of your health, such as how healthy your kidneys, liver, and immune system are. We will also test you for hepatitis B, hepatitis C, tuberculosis (TB), gonorrhea, chlamydia, and syphilis. We will ask you about medications you are taking. If you were assigned female sex at birth and can become pregnant, we will test you for pregnancy. If you are pregnant, you cannot join the study.

We will communicate with your primary HIV care provider to coordinate your care during this study. We will check to make sure your HIV has been well controlled by your HIV medications for at least one year.

We will ask if you are willing to use condoms every time you have sex for an extended period during the study, until you restart your HIV medications and your viral load returns to being very low or undetectable.

We will review the screening results with you. The screening results may show you are not eligible to join the study, even if you want to.

5. If we find that you have a health problem during screening or during the study, we will tell you about the care that we can give here for free.

For the care that we cannot give, we will explain how we will help you get care elsewhere. We will not pay for care for health problems that are unrelated to the study.

Site: Appendix B, Approved contraception methods (for sample informed consent form), contains supplemental information. If you want to include Appendix B in this consent form, paste it below.

6. If you were assigned female sex at birth and can become pregnant, you must agree to use effective contraception to join this study.

Current HIV treatment guidelines recommend using HIV medication during pregnancy to prevent transmission to the baby. Since you will stop taking your HIV medication in this study, you should not become pregnant. In addition to using condoms every time you have sex, we will ask you to use another method of contraception. These include a diaphragm or cervical cap with a cream or gel that kills sperm, IUD, hormone-based contraception, or another method approved by the researchers.

If you become pregnant or start breastfeeding after you stop taking your HIV medication, you will have to restart taking it, but you can remain in the study. We would like you to come for clinic visits for up to 6 months after your HIV viral load returns to very low or undetectable. If you become pregnant or start breastfeeding after you have restarted your HIV medication, you will continue taking it. We would like you to come for clinic visits for up to 6 months after your HIV viral load returns to very low or undetectable.

The study staff would like to obtain information from you about the outcome of the pregnancy (even if it is after your participation in the study ends). If you are taking your HIV medication when you become pregnant, your pregnancy will be reported to an international database that collects information about pregnancies in people using these HIV medications. This report will not use your name or other information that could be used to identify you.

Being in the study

If you meet the study requirements and want to join, here is what will happen.

7. We will make sure you are on the right HIV medication for this study.

You may have to change some of the HIV medication you are taking. If you are taking HIV medications that stay in the blood for a long time even after you stop taking them, we will have you switch to a different HIV medication for at least one month before you stop taking all of your HIV medication. We will provide

this new medication to you for free. This is to reduce the already small chance that you may develop drug resistance. Drug resistance means the HIV medication you have been taking might not control your HIV when you restart it. We will check on you after about two weeks to see how you are doing on the new HIV medication. If you have any problems after starting the new HIV medication, please let us know.

If the new HIV medication does not bring your HIV to very low or undetectable within about 3 months, you will not be able to continue with the rest of the study.

8. If you join the study, we will collect some basic information.

We will record your medical history and give you a physical examination, including checking your weight and vital signs. We will ask about other medications you are taking and about any illnesses you may have. We will also collect blood and urine, and if you were assigned female sex at birth and can become pregnant, we will give you a pregnancy test. We will test you for gonorrhea and chlamydia using urine, rectal swabs, and oral swabs. We will test you for syphilis using a blood sample.

9. In Part 1 of the study, you will stop taking your HIV medication.

After you stop taking your HIV medication, for the first 8 weeks (about 2 months) you will visit the clinic every week (8 visits). For the next 16 weeks (months 2-6), you will visit the clinic every 2 weeks (8 visits). For the next 6 months, if you are still in Part 1 of the study, you will visit the clinic about every month (7 visits). One reason for these frequent clinic visits is to carefully track your HIV and your health.

At these visits we will ask about anything new in your medical history and give you a brief physical exam. We will collect blood. When we collect blood the amount will depend on the lab tests we need to do. It will be some amount between 10 mL and 160 mL (2 teaspoons and 2/3 cup). Your body will make new blood to replace the blood we take out.

We will check to make sure you are using condoms for all sexual activity.

If you were assigned female sex at birth and can become pregnant, we will check to make sure you are using effective contraception. We will also give you a pregnancy test.

We will test you for gonorrhea and chlamydia at some visits using urine, and oral and rectal swabs.

Some of the blood we collect will be used for lab tests of your general health (including syphilis testing) and to check your immune system. We will also check to see if you still have any HIV medications in your blood.

Some of the blood collected at each visit will be used to test your viral load and your CD4 count. If your viral load goes up to 200 or higher, you will move to Part 2 of the study.

If any of the following happens, you will restart your HIV medication as soon as possible and move to Part 3 of the study.

- Your CD4 count drops below 350,
- You show any symptoms of HIV-related illness,
- You decide to restart your HIV medication, or
- Your primary HIV care provider or the doctor at the study clinic decides that you should restart your HIV medication.

If none of these things happens, a person can stay in Part 1 for a year or longer. Most people will be in Part 1 of the study for less than 6 months.

10. Here is what will happen in Part 2 of the study.

In Part 2, you will continue to stay off your HIV medication. When you start Part 2, for the first 8 weeks (about 2 months), you will visit the clinic every week (8 visits). For the next 28 weeks (months 2-8), you will visit the clinic every 2 weeks (14 visits). After that, if you still have not met the criteria to restart your HIV medication, for the next 4 months, you will visit the clinic once a month (4 visits). One reason for these frequent clinic visits is to carefully track your HIV and your health.

At these visits we will ask about anything new in your medical history. At the first visit in Part 2, we will give you a complete physical exam. At all other visits in Part 2 we will give you a brief physical exam. We will collect blood. When we collect blood the amount will depend on the lab tests we need to do. It will be some amount between 10 mL and 130 mL (2 teaspoons and a little more than ½ cup). Your body will make new blood to replace the blood we take out.

We will check to make sure you are using condoms for all sexual activity.

If you were assigned female sex at birth and can become pregnant, we will check to make sure you are using effective contraception. We will also give you a pregnancy test.

We will test you for gonorrhea and chlamydia at some visits using urine, oral swabs, and rectal swabs.

Some of the blood we collect will be used for lab tests of your general health (including syphilis testing) and to check your immune system. We will also check to see if you have any HIV medications in your blood.

Some of the blood collected at each visit will be used to test your viral load and your CD4 count.

During the first 24 weeks (about 6 months) in Part 2, if any of the following happens, you will restart your HIV medication as soon as possible and move to Part 3 of the study.

- Your viral load goes up to 1,000 or higher and stays there for 4 weeks without dropping very quickly,
- Your CD4 count drops below 350,
- You show any symptoms of HIV-related illness,
- You decide to restart your HIV medication, or
- Your primary HIV care provider or the doctor at the study clinic decides that you should restart your HIV medication.

After 24 weeks (6 months), if any of the following happens, you will restart your HIV medication as soon as possible and move to Part 3 of the study.

- Your viral load is 200 or higher,
- Your CD4 count drops below 350,
- You show any symptoms of HIV-related illness,
- You decide to restart your HIV medication, or
- Your primary HIV care provider or the doctor at the study clinic decides that you should restart your HIV medication.

If you do not meet these restart criteria, you can stay in Part 2 of the study for as long as your viral load stays below 200. Most people will be in Part 2 for a few weeks to a few months. Some people may stay in Part 2 for a year or longer.

11. After you restart taking HIV medication, you will have follow-up clinic visits for about another year. This is Part 3 of the study.

This follow-up period is to see how your body responds to restarting your HIV medication and to make sure that your HIV returns to very low or undetectable

levels. For most people, we expect that your viral load will drop within about 12 weeks (about 3 months).

Once you restart taking HIV medication, for the first 12 weeks (about 3 months) you will have clinic visits every 2 weeks (7 visits). For the next 16 weeks (about 4 months), you will have clinic visits once a month (4 visits). For the next 24 weeks (about 6 months) you will have 2 visits scheduled 3 months apart. At these visits we will ask about anything new in your medical history and give you a brief physical exam. We will collect blood. When we take blood, the amount will depend on the lab tests we need to do. It will be some amount between 10 mL and 225 mL (2 teaspoons and a little less than 1 cup).

At some visits, we will test you for gonorrhea and chlamydia using urine, rectal swabs, and oral swabs. We will also do a blood test for syphilis.

Until we have confirmed that your viral load has returned to very low or undetectable levels, you will still need to use condoms every time you have sex. We will check to make sure you are doing so.

Until we have confirmed that your viral load has returned to very low or undetectable levels, if you were assigned female sex at birth and can become pregnant, we will check to make sure you are using effective contraception. We will also give you a pregnancy test at some visits.

12. If you stay in Part 1 or Part 2 of the study for more than a year, you will have visits every 3 months.

At these visits we will ask about anything new in your medical history and give you a brief physical exam. We will collect blood. Some of that blood gets used for viral load and CD4 testing.

At some visits, we will test you for gonorrhea and chlamydia using urine, rectal swabs, and oral swabs. At these same visits, we will test you for syphilis using blood samples.

We will continue to check to make sure you are using condoms every time you have sex.

Also, if you were assigned female sex at birth and can become pregnant, we will check to make sure you are using effective contraception. We will also give you a pregnancy test at each visit.

If you meet the restart criteria at any time, you will restart your HIV medication and move to Part 3 of the study as described above in Section 11.

13. Most participants will be in the study about 13-18 months.

This depends on whether you need to switch your HIV medications and how long it takes before you meet the criteria to restart your HIV medication. If your immune system controls your HIV for a long time without medication, then you might be in the study longer. The longest we expect anyone to be in the study is about 3 years.

14. Some of the blood we collected previously in the AMP Study or that we collect in this study might be used for limited genetic testing in this study.

Your genes are passed to you from your birth parents. They affect how you look and how your body works. Differences in genes can explain why some people get a disease and others don't. The genetic testing that might be done in this study involves only some of your genes related to how your immune system works to fight HIV. The testing will not involve all of your genes (your genome). We want to understand whether your genes affect your ability to control HIV in combination with whether or not you got the AMP Study antibody.

In some cases, researchers may take cells from your samples and grow more of them over time, so that your samples can continue to contribute to this study.

These tests done on your samples are for research purposes, not to check your health. The labs will not give the results to you or this clinic because their tests are not approved for use in making health care decisions. These labs are only approved to do research tests.

When your samples are no longer needed for this study, the HVTN will continue to store them.

Site: Delete next section if using separate consent for use of samples and information in other studies.

15. When samples are no longer needed for this study, the HVTN and HPTN may want to use them in other studies and share them with other researchers.

These samples are called "extra samples". The HVTN and HPTN will only allow your extra samples to be used in other studies if you agree to this. You will mark your decision at the end of this form. If you have any questions, please ask.

Do I have to agree? No. You are free to say yes or no, or to change your mind after you sign this form. At your request, we will destroy all extra samples that we have. Your decision will not affect your being in this study or have any negative consequences here.

Where are the samples stored? Extra samples are stored in a secure central place called a repository. Your samples will be stored in the HVTN repository in the United States.

How long will the samples be stored? There is no limit on how long your extra samples will be stored. *[Site: Revise the previous sentence to insert limits if your regulatory authority imposes them.]*

Will I be paid for the use of my samples? No. Also, a researcher may make a new scientific discovery or product based on the use of your samples. If this happens, there is no plan to share any money with you. The researcher is not likely to ever know who you are.

Will I benefit from allowing my samples to be used in other studies? Probably not. Results from these other studies are not given to you, this clinic, or your doctor. They are not part of your medical record. The studies are only being done for research purposes.

Will the HVTN or HPTN sell my samples and information? No, but the HVTN and HPTN may share your samples with other researchers. Once we share your samples and information, we may not be able to get them back.

How do other researchers get my samples and information? When a researcher wants to use your samples and information, their research plan must be approved by the HVTN and HPTN. Also, the researcher's institutional review board (IRB) or ethics committee (EC) will review their plan. *[Site: If review by your institution's IRB/EC/RE is also required, insert a sentence stating this.]* IRBs/ECs protect the rights and well-being of people in research. If the research plan is approved, the HVTN will send your samples to the researcher's location.

What information is shared with HVTN, HPTN, or other researchers? The samples and information will be labeled with a code number. The key to the code will stay at this clinic. It will not be shared with the HVTN, HPTN, or other researchers or with anyone else who does not need to know your name. Your name will not be part of the information. However, some information that the HVTN and HPTN share may be personal, such as your race, ethnicity, sex, health information from the study, and HIV status. The HVTN and HPTN may share information about the study product you received and how your body responded to the study product.

What kind of studies might be done with my extra samples and information? The studies will be related to HIV, vaccines, monoclonal antibodies, the immune system, and other diseases.

Researchers may also do genetic testing on your samples.

In some cases, researchers may take cells from your samples and grow more of them over time, so that they can continue to do research with them.

If you agree, your samples could also be used for genome wide studies. In these studies, researchers will look at all your genes (your genome). The researchers compare the genomes of many people, looking for common patterns of genes that could help them understand diseases. The researchers may put the information from the genome-wide studies into a protected database so that other researchers can access it. Usually, no one would be able to look at your genome and link it to you as a person. However, if another database exists that also has information on your genome and your name, someone might be able to compare the databases and identify you. If others found out, it could lead to discrimination or other problems. The risk of this happening is extremely small.

Who will have access to my information in studies using my extra samples?

People who may see your information are:

- Researchers who use your extra samples and information for other research,
- Government agencies that fund or monitor the research using your extra samples and information,
- Any regulatory agency that reviews clinical trials,
- The researcher's Institutional Review Board or Ethics Committee, or
- The people who work with the researcher/

All these people will do their best to protect your information. The results of any new studies that use your extra samples and information may be published. No publication will use your name or identify you personally.

16. We will give you [Site: Insert compensation] for each study visit you complete.

This amount is to cover the costs of [Site: Insert text]

Site: Insert any costs to participants (eg, contraception costs for participants who could become pregnant).

US sites: Include the following paragraph. You can remove the box around the text.

Payments you receive for being in the study may be taxable. We may need to ask you for your Social Security number for tax reasons.

You do not have to pay anything to be in this study.

17. We will do our best to protect your private information.

US sites: Check HIPAA authorization for conflicts with this section.

Your study records and samples will be kept in a secure location. We will label all of your samples and most of your records with a code number, not your name or other personal information. However, it is possible to identify you, if necessary. We will not share your name with the lab that does the tests on your samples, or with anyone else who does not need to know your name.

Clinic staff will have access to your study records. Your records may also be reviewed by groups who watch over this study to see that we are protecting your rights, keeping you safe, and following the study plan. These groups include:

- The US National Institutes of Health and its study monitors,
- The Perú Instituto Nacional de Salud (INS),
- Any regulatory agency that reviews clinical trials,
- [Insert name of local IRB/EC] ,
- [Insert name of local and/or national regulatory authority as appropriate],
- The Dale and Betty Bumpers Vaccine Research Center and people who work for them,
- The HVTN, HPTN and people who work for them,
- The US National Institute of Allergy and Infectious Diseases Data and Safety Monitoring Board, and
- The US Office for Human Research Protections.

All reviewers will take steps to keep your records private.

We cannot guarantee absolute privacy. If you are found to have a medical condition that we are required to report by law, then some of your information may be shared. At this clinic, we have to report the following information:

Site: Include any public health or legal reporting requirements. Bulleted examples should include all appropriate cases (reportable communicable disease, risk of harm to self or others, etc.). If your site does not have public health or legal reporting requirements, you may delete the last sentence in the paragraph above, along with the bullets below.

- [Item 1]

- [Item 2]
- [Item 3]

US sites: Include the following boxed text. You can remove the box.

We have a Certificate of Confidentiality from the US government, to help protect your privacy. With the certificate, we do not have to release information about you to someone who is not connected to the study, such as the courts or police. Sometimes we can't use the certificate. Since the US government funds this research, we cannot withhold information from it. Also, you can still release information about yourself and your study participation to others.

The results of this study may be published. No publication will use your name or identify you personally.

We may share information from the study with other researchers. We will not share your name or information that can identify you.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

18. We may take you out of the study even if you want to stay in the study.

This may happen if:

- You move away from the study site and transfer to another study site is not possible,
- Clinic staff cannot contact you,
- We think, or your primary HIV care provider thinks, that staying in the study might harm you,
- You do not follow study instructions,
- You enroll in a different research study where you get a study product,
- You become pregnant or are breastfeeding,
- You tell us you intend to get pregnant or begin breastfeeding, or
- The study is stopped for any reason.

Risks

19. There are risks to being in this study.

This study is designed to minimize the risks of stopping your HIV medication. This depends on you following the instructions from the clinic staff and attending all your study visits.

This section describes the risks we know about. There may also be risks we don't know about, even serious ones. We will tell you if we learn anything new that may affect your willingness to stay in the study.

Risks of stopping your HIV medication

Staying off HIV medication is not recommended for routine healthcare for people living with HIV. Stopping your HIV medication is an experimental procedure. It can increase the risk of serious health complications, including death.

High viral load

At some point after you stop taking your HIV medication, your viral load will probably rise. During this time, you probably will not have any symptoms. However, it is possible that you could have symptoms of what is called “acute retroviral syndrome.” We think that having this syndrome is rare because you started taking HIV medication soon after your HIV diagnosis. The symptoms could include:

- Fever,
- Weight loss,
- Sore throat,
- Swollen lymph nodes,
- Headache,
- Body or joint aches,
- Tiredness,
- Night sweats,
- Oral yeast infection,
- Diarrhea, or

- Rash.

If you have any of these symptoms, tell the study staff right away. These symptoms should go away or become less severe once you restart your HIV medication.

If your viral load increases, this could lead to inflammation. High levels of inflammation over many years are associated with heart disease and other medical conditions. Starting your HIV medication again should reduce inflammation.

Low CD4 count

If your viral load rises, your CD4 count could drop. This could increase your risk for other HIV-related illnesses. In about 60 people studied to date, there has not been a significant difference in CD4 counts before and 6-12 months after stopping HIV medication. However, it is possible that your CD4 count might not return to its original level, even after you restart taking your HIV medication.

Transmitting HIV to your partner

While your viral load is controlled, the risk that you could transmit HIV to a sexual partner is very low, known as U = U (undetectable = untransmittable). Once you stop taking HIV medication that risk gets higher.

That is why you must use condoms for all sexual activity after you stop taking your HIV medication.

If your sexual partners do not have HIV, they should get regular HIV testing until you have restarted your HIV medication and we have confirmed that your viral load has returned to very low or undetectable levels. Testing for your partners is not part of this study. If your partners are interested, we can tell you about a program we have for providing pre-exposure prophylaxis (PrEP) to them during the time that you are in the study. You are also welcome to bring partners to the clinic for education and risk reduction counseling.

Transmitting HIV to your baby

Once you stop taking HIV medication, the risk of transmitting HIV to your baby gets higher if you become pregnant. That is why you must keep using contraception from when you stop taking HIV medication until you restart and your viral load returns to very low or undetectable. If you become pregnant, it is extremely important to take your HIV medication throughout the entire pregnancy.

Developing HIV drug resistance

As we described in Section 7 above, when you stop taking HIV medication, the HIV in your body might mutate in ways that make it resistant to the HIV medication you have been taking. This means the HIV medication you were taking may not control your HIV when you start taking it again. To make this less likely, we may ask you to switch to a different HIV medication before beginning the study.

After you restart your HIV medication, you will have very frequent viral load tests. If your viral load is not returning to its original level within 8-12 weeks of restarting your HIV medication, we will test to see if the HIV is resistant to your HIV medications. If resistance is found, we will recommend more effective HIV medications to you and your primary HIV care provider.

Side effects from new HIV medications or non-study medications:

If you need to switch your HIV medications, there may be some new side effects from the new HIV medications. We or your primary HIV care provider can explain those side effects to you.

There may also be a risk of serious or even life-threatening side effects from non-study medications taken during the study. For your safety, tell the study doctor or nurse about all medications you are taking before you start the study, and also before starting any new medications during the study.

Routine medical procedures:

In this study, we will take blood. This can cause bruising, pain, fainting, soreness, redness, swelling, itching, a sore, bleeding, and (rarely) muscle damage or infection where the needle was inserted. In some people, taking blood can cause a low blood cell count (anemia), making you feel tired.

Risks of disclosure of your personal information:

We will take several steps to protect your personal information. Although the risk is very low, it is possible that your personal information could be given to someone who should not have it. If that happened, you could face discrimination, stress, and embarrassment. We can tell you more about how we will protect your personal information if you would like.

Risks of other people learning your HIV status:

We will keep your participation in this study and your HIV status confidential. However, if others learn that you are in a study for people living with HIV, you could face discrimination, stress, embarrassment, or stigma.

Risk of limitations to research participation:

As a result of being in this study, you may not be eligible to participate in other HIV treatment or cure studies that require you to have an undetectable viral load for a period of time. After you restart taking your HIV medication and your viral load becomes undetectable again, this limitation will go away over time.

Risks of genetic testing:

It is unlikely, but the genetic tests that might be done on your samples could show you may be at risk for certain diseases. If others found out, it could lead to discrimination or other problems. However, it is almost impossible for you or others to know your test results from the genetic testing. The results are not part of your study records and are not given to you.

US Sites, include the following paragraph In the very unlikely event that your genetic information becomes linked to your name, a federal law called the Genetic Information Nondiscrimination Act (GINA) helps protect you. GINA keeps health insurance companies and employers from seeing results of genetic testing when deciding about giving you health insurance or offering you work. GINA does not help or protect you against discrimination by companies that sell life, disability or long-term care insurance.

Benefits

20. We do not expect the study to benefit you directly.

However, information learned from this study may help others who have HIV and being in the study might still help you in some ways. The lab tests and physical exams that you get while in this study might detect health problems you don't yet know about. You may also learn whether you are one of the rare people who can control HIV without taking HIV medications. This study may help in the search for a vaccine or other ways to prevent HIV.

Your rights and responsibilities

21. If you join the study, you have rights and responsibilities.

You have many rights that we will respect. You also have responsibilities. We list these in the Participant's Bill of Rights and Responsibilities. We will give you a copy of it.

Leaving the study

22. Tell us if you decide to leave the study.

You are free to leave the study at any time and for any reason. Your care at this clinic and your legal rights will not be affected, but it is important for you to let us know.

We may ask you to come back to the clinic one last time for a physical exam, and we may ask to take some blood and urine samples. We will also ask about any personal problems or benefits you have experienced from being in the study. We will counsel you about the importance of taking your HIV medications and following up with your primary HIV care provider. We believe these steps are important to protecting your health, but it is up to you whether to complete them.

Injuries

Sites: Approval from HVTN Regulatory Affairs (at vtn.core.reg@hvtn.org) is needed for any change (other than those that the instructions specifically request or those previously approved by HVTN Regulatory Affairs) to the boxed text

23. If you get sick or injured during the study, contact us immediately.

Your health is important to us. *(Sites: adjust the following 2 sentences if applicable to the care available at your site)* We will tell you about the care that we can give here. For the care that we cannot provide, we will explain how we will help you get care elsewhere.

If you become sick or injured in this study, the HVTN has a process to decide if it is related to the procedures. If it is, we call it a study-related injury. There are funds to pay for treatment of study-related injuries if certain conditions are met.

This paragraph for non-US sites only. Sites: adjust the language in this paragraph so it is applicable to your site. In this study, our clinic has insurance to cover your medical treatment in the case of a study-related injury. In rare cases, the insurance funds may not be enough.

Some injuries are not physical. For example, you might be harmed emotionally by being in a study where you stop taking your HIV medication. Or you might lose wages because you cannot go to work. However, there are no funds to pay for these kinds of injuries, even if they are study related.

You may disagree with the decision about whether your injury is study related. If you wish, the HVTN will ask independent experts to review the decision. You always have the right to use the court system if you are not satisfied.

Questions

24. If you have questions or problems at any time during your participation in this study, use the following important contacts.

If you have questions about this study, contact
[name or title and telephone number of the investigator or other study staff].

If you have any symptoms that you think may be related to this study, contact [name or title and telephone number of the investigator or other study staff].

This study has been reviewed and approved by a committee called the [name of local IRB/EC]. If you have questions about your rights as a research participant, or problems or concerns about how you are being treated in this study, contact [name or title and telephone number of person on IRB/EC] , at the committee.

If you want to leave this study, contact [name or title and telephone number of the investigator or other study staff].

Your permissions and signature

25. In Section 15 of this form, we told you about possible other uses of your extra samples and information, outside this study. Please choose only one of the options below and write your initials or make your mark in the box next to it. Whatever you choose, the HVTN keeps track of your decision about how your samples and information can be used. You can change your mind after signing this form.

I allow my extra samples and information to be used for other studies related to HIV, vaccines, the immune system, and other diseases. This may include genetic testing and keeping my cells growing over time.

OR

I agree to the option above *and* also to allow my extra samples and information to be used in genome wide studies.

OR

I do not allow my extra samples to be used in any other studies. This includes not allowing genetic testing, growing more of my cells, or genome wide studies.

26. If you agree to join this study, you will need to sign or make your mark below. Before you sign or make your mark on this consent form, make sure of the following:

- You have read this consent form, or someone has read it to you.
- You feel that you understand what the study is about and what will happen to you if you join. You understand what the possible risks and benefits are.
- You have had your questions answered and know that you can ask more.

- You agree to join this study.

You will not be giving up any of your rights by signing this consent form.

Participant's name (print)	Participant's signature or mark	Date	Time
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Clinic staff conducting consent discussion (print)	Clinic staff signature	Date	Time
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For participants who are unable to read or write, a witness should complete the signature block below:

Witness's name (print)	Witness's signature	Date	Time
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*Witness is impartial and was present for the entire discussion of this consent form.

Appendix B Approved contraceptive methods for transgender men (for sample informed consent form)

If you were assigned female at birth and are sexually active in a way that could lead to pregnancy, you must agree to use effective birth control from 21 days before stopping your HIV medication until your viral load drops to undetectable after you start taking HIV medication again.

While you are not taking HIV medication, there is a risk that you could transmit HIV to your developing baby. So, you must be careful not to become pregnant.

Although taking testosterone can lower the chances of becoming pregnant, it is not considered an effective method of contraception.

In addition to using condoms every time you have sex, you must also use one of the following contraceptive methods every time you have sex:

- Drugs that are prescribed specifically for contraception and intended to prevent pregnancy—these include pills, shots, patches, vaginal rings, or inserts under the skin;
- Diaphragm or cervical cap with a cream or gel that kills sperm;
- Intrauterine device (IUD); or
- Any other contraceptive method approved by the researchers.

You do not have to use birth control if:

- You have had a hysterectomy (your uterus removed);
- You have had an oophorectomy (your ovaries removed); or
- You are only having sex with a partner or partners who have had a vasectomy. (We will ask you some questions to confirm that the vasectomy was successful.);
- You have a tubal ligation (your “tubes tied”) or confirmed successful placement of a product that blocks the fallopian tubes; or
- You are sexually abstinent (no sex at all).

If you join the study, we will test you for pregnancy at some visits.

Appendix C Sample consent form for use of samples and information in other studies

Title: Antiretroviral analytical treatment interruption (ATI) to assess immunologic and virologic responses in participants who received VRC01 or placebo and became HIV-infected during HVTN 704/HPTN 085

Protocol number: HVTN 804/HPTN 095

Site: [Insert site name]

When samples are no longer needed for this study, the study sponsors want to keep them for use in other studies by HVTN, HPTN, or other researchers. We will call these “extra samples.”

This form gives you information so you can decide if you want your extra samples and information used in other studies. You will mark your decision at the end of the form. If you have any questions, please ask.

Key information

These are some of the things you should know about the use of your samples and information for other studies:

- The extra samples will be labeled with a code number and some personal information. They will not be labeled with your name. The extra samples are stored in a secure place. At your request, the HVTN and HPTN will destroy all your extra samples. You can still join the main study even if you do not agree to the use of your extra samples in other studies.
- Researchers may do genetic testing on your samples, which could include genome wide studies. It is unlikely, but these tests could show you may be at risk for certain diseases. In the very unlikely event that others found out, this could lead to discrimination or other problems.
- You will not be paid or otherwise benefit from allowing your extra samples to be used in other studies.

The rest of this form gives more information about use of your extra samples for other studies. Please read it carefully.

1. Do I have to agree?

No. You are free to say yes or no, or to change your mind after you sign this form. At your request, we will destroy all extra samples that we have. Your decision will not affect your being in this study or have any negative consequences here.

2. Where are the samples stored?

Extra samples are stored in a secure central place called a repository. Your samples will be stored in the HVTN repository in the United States.

3. How long will the samples be stored?

There is no limit on how long your extra samples will be stored. *[Site: Revise the previous sentence to insert limits if your regulatory authority imposes them.]*

4. Will I benefit from allowing my samples to be used in other studies?

We do not expect this to benefit you directly. Results from these other studies are not given to you, this clinic, or your doctor. They are not part of your medical record. The studies are only being done for research purposes.

5. Will I be paid for the use of my samples?

No. Also, a researcher may make a new scientific discovery or product based on the use of your samples. If this happens, there is no plan to share any money with you. The researcher is not likely to ever know who you are.

6. Will the HVTN or HPTN sell my samples and information?

No, but the HVTN and HPTN may share your samples with other researchers. Once we share your samples and information, we may not be able to get them back.

7. How do other researchers get my samples and information?

When a researcher wants to use your samples and information, their research plan must be approved by the HVTN and HPTN. Also, the researcher's institutional review board (IRB) or ethics committee (EC) will review their plan. *[Site: If review by your institution's IRB/EC/RE is also required, insert a sentence stating this.]* IRBs/ECs protect the rights and well-being of people in research. If the research plan is approved, the HVTN and HPTN will send your samples to the researcher's location.

8. What information is shared with HVTN, HPTN, or other researchers?

The samples and information will be labeled with a code number. The key to the code will stay at this clinic. It will not be shared with the HVTN, HPTN, other researchers or with anyone else who does not need to know your name. Your name will not be part of the information. However, some information that the HVTN and HPTN share may be personal, such as your race, ethnicity, gender, health information from the study, and HIV status. The HVTN and HPTN may

share information about the study product you received and how your body responded to the study product.

9. What kind of studies might be done with my extra samples and information?

The studies will be related to HIV, vaccines, monoclonal antibodies, the immune system, and other diseases.

Researchers may also do genetic testing on your samples.

In some cases, researchers may take cells from your samples and grow more of them over time, so that they can continue to contribute to this study.

If you agree, your samples could also be used for genome wide studies. In these studies, researchers will look at all of your genes (your genome). The researchers compare the genomes of many people, looking for common patterns of genes that could help them understand diseases. The researchers may put the information from the genome-wide studies into a protected database so that other researchers can access it, but your name and other personal information will not be included. Usually, no one would be able to look at your genome and link it to you as a person. However, if another database exists that also has information on your genome and your name, someone might be able to compare the databases and identify you. If others found out, it could lead to discrimination or other problems. The risk of this is very small.

10. What are the risks of genetic testing?

It is unlikely, but the genetic tests done on your samples could show you may be at risk for certain diseases. If others found out, it could lead to discrimination or other problems. However, it is almost impossible for you or others to know your test results from the genetic testing. The results are not part of your study records and are not given to you.

US Sites, include the following paragraph

In the very unlikely event that your genetic information becomes linked to your name, a federal law called the Genetic Information Nondiscrimination Act (GINA) helps protect you. GINA keeps health insurance companies and employers from seeing results of genetic testing when deciding about giving you health insurance or offering you work. GINA does not help or protect you against discrimination by companies that sell life, disability or long-term care insurance.

11. Who will have access to my information in studies using my extra samples?

People who may see your information are:

- Researchers who use your extra samples and information for other research

- Government agencies that fund or monitor the research using your extra samples and information
- Any regulatory agency that reviews clinical trials
- The researcher's Institutional Review Board or Ethics Committee
- The people who work with the researcher

All of these people will do their best to protect your information. The results of any new studies that use your extra samples and information may be published. No publication will use your name or identify you personally.

Questions

12. If you have questions or problems about allowing your samples and information to be used in other studies, use the following important contacts.

If you have questions about the use of your samples or information or if you want to change your mind about their use, contact
[name or title and telephone number of the investigator or other study staff].

If you think you may have been harmed because of studies using your samples or information, contact
[name or title and telephone number of the investigator or other study staff].

If you have questions about your rights as a research participant, contact
[name or title and telephone number of person on IRB/EC .

13. Please choose only one of the options below and write your initials or make your mark in the box next to it. Whatever you choose, the HVTN and HPTN keep track of your decision about how your samples and information can be used. You can change your mind after signing this form.

I allow my extra samples and information to be used for other studies related to HIV prevention, the immune system, and other diseases. This may include genetic testing and keeping my cells growing over time.

OR

I agree to the option above *and* also to allow my extra samples and information to be used in genome wide studies.

OR

I do not allow my extra samples to be used in any other studies. This includes not allowing genetic testing, growing more of my cells, or genome wide studies.

Participant's name (print)	Participant's signature or mark	Date	Time
_____ Clinic staff conducting consent discussion (print)	_____ Clinic staff signature	_____ Date	_____ Time

For participants who are unable to read or write, a witness should complete the signature block below:

Witness's name (print)	Witness's signature	Date	Time
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*Witness is impartial and was present for the entire discussion of this consent form.

Appendix D Tables of procedures for sample informed consent form

Table of procedures for Part 1: Screening and stopping your HIV medications

	Screening	HIV medication switch ^a	Pre-stop visit about 4 weeks later	Time after stopping HIV medications													
				Day 0	Week 1	Week 2	Week 3	~1 month	Week 5	Week 6	Week 7	~2 months	Week 10	~3 months	Week 14	~4 months	Week 18
Study procedures																	
HIV medication switch (if required)		✓	✓														
Medical history	✓																
Complete physical exam	✓			✓													
Brief physical exam		✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pregnancy test and contraception review ^b	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Blood drawn	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
STI testing (blood, urine, and oral & rectal swabs) ^c	✓			✓				✓				✓		✓		✓	
Transmission risk reduction counseling	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Interview/questionnaire	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
TB test	✓																
Blood drawn	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Procedures in gray only for participants switching HIV medications.

^a We will contact you about 2 weeks after you start the new HIV medication to check to see if you have had any side effects or have other concerns.

^b Persons assigned female sex at birth who have reached menopause or who had a hysterectomy, oophorectomy, or tubal ligation verified by medical records are not required to have a pregnancy test or contraception review.

^c In addition to STI testing at the checked visits, we will test at other visits if you show symptoms of an STI.

^d Extra visits every 3 months for people do not meet criteria for moving to Part 2 or Part 3.

Table of procedures for Part 1: Screening and stopping your HIV medications (continued)

	Time after stopping HIV medications							Extra visits ^d	
	~6 months	Week 28	Week 32	Week 36	~ 9 months	Week 44	Week 48		1 year
Study procedures									
Complete physical exam									
Brief physical exam	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pregnancy test and contraception review ^b	✓	✓	✓	✓	✓	✓	✓	✓	✓
Transmission risk reduction counseling	✓	✓	✓	✓	✓	✓	✓	✓	✓
Interview/questionnaire	✓	✓	✓	✓	✓	✓	✓	✓	✓
STI testing (blood, urine, and oral & rectal swabs) ^c	✓	✓	✓	✓	✓	✓	✓	✓	✓
Blood Drawn	✓	✓	✓	✓	✓	✓	✓	✓	✓

^a We will contact you about 2 weeks after you start the new HIV medication to check to see if you have had any side effects or have other concerns.

^b Persons assigned female sex at birth who have reached menopause or who had a hysterectomy, oophorectomy, or tubal ligation verified by medical records are not required to have a pregnancy test or contraception review.

^c In addition to STI testing at the checked visits, we will test at other visits if you show symptoms of an STI.

^d Extra visits every 3 months for people do not meet criteria for moving to Part 2 or Part 3.

Table of procedures for Part 2: Monitoring your health and your HIV

	Time after stopping HIV medications															
	Day 0	Week 1	Week 2	Week 3	~1 month	Week 5	Week 6	Week 7	~2 months	Week 10	~3 months	Week 14	~4 months	Week 18	~5 months	Week 22
Study procedures																
Complete physical exam	✓															
Brief physical exam		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pregnancy test and contraception review ^a	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Blood drawn	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
STI testing (blood, urine, and oral & rectal swabs) ^b	✓				✓				✓		✓		✓		✓	
Transmission risk reduction counseling	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Interview/questionnaire	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Blood drawn	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

^a Persons assigned female sex at birth who have reached menopause or who had a hysterectomy, oophorectomy, or tubal ligation verified by medical records are not required to have a pregnancy test or contraception review.

^b In addition to STI testing at the checked visits, we will test at other visits if you show symptoms of an STI.

^c Extra visits every 3 months for people do not meet criteria for moving to Part 3.

Table of procedures for Part 2: Monitoring your health and your HIV (continued)

	Time after stopping HIV medications										Extra visits ^c	
	Week 24	6 months	Week 28	Week 30	Week 32	Week 34	Week 36	~9 months	Week 44	Week 48		1 year
Study procedures												
Complete physical exam												
Brief physical exam	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pregnancy test and contraception review ^a	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Blood drawn	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
STI testing (blood, urine, and oral & rectal swabs) ^b	✓		✓		✓		✓	✓	✓	✓	✓	✓
Transmission risk reduction counseling	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Interview/questionnaire	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Blood drawn	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

^a Persons assigned female sex at birth who have reached menopause or who had a hysterectomy, oophorectomy, or tubal ligation verified by medical records are not required to have a pregnancy test or contraception review.

^b In addition to STI testing at the checked visits, we will test if you show symptoms of an STI.

^c Extra visits every 3 months for people do not meet criteria for moving to Part 3.

Table of procedures for Part 3: Restart HIV medications

	Time after restarting HIV medications												
	Week 0	Week 2	~1 month	Week 6	~2 months	Week 10	Week 12	~4 months	Week 20	~6 months	Week 28	~9 months	1 year
Study procedures													
Complete physical exam													✓
Brief physical exam	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Pregnancy test & contraception review ^a	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Transmission risk reduction counseling	✓	✓	✓		✓		✓		✓		✓		✓
Interview/Questionnaire	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
STI testing (blood, urine, and oral & rectal swabs) ^b	✓		✓		✓		✓	✓ ^c	✓ ^c	✓	✓ ^c	✓	
Blood Drawn	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

^a Persons assigned female sex at birth who have reached menopause or who had a hysterectomy, oophorectomy, or tubal ligation verified by medical records are not required to have a pregnancy test or contraception review. Pregnancy test and contraceptive review are not required once viral load drops to undetectable after restarting HIV medication.

^b In addition to STI testing at the checked visits, we will test if you show symptoms of an STI.

^c STI testing is not required at this visit if viral load has returned to undetectable.

Appendix E Laboratory procedures—Schedule 1: Monitoring ATI

Procedure	Ship to ¹	Assay location ^{1,2}	Tube Type ³	Tube size (vol. capacity) ³	Visit:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	
					Days on ATI:	Screening visit ¹⁵	ART Switch ⁸	ATI qualification ⁹	D0 W0	D7 W1	D14 W2	D21 W3	D28 W4	D35 W5	D42 W6	D49 W7	D56 W8	D70 W10	D84 W12	D98 W14	D112 W16	D126 W18	D140 W20	D154 W22	
BLOOD COLLECTION																									
Screening or diagnostic assays																									
HIV PCR viral load ¹³	Local labs	Local labs	EDTA	6mL	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
CD4+/CD8+ T-cell count ¹⁴	Local labs	Local labs	EDTA	4mL	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
HBsAg/anti-HCV ⁴	Local labs	Local labs	SST	5mL	10	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
QuantiFERON TB testing ⁵	Local labs	Local labs	QFT Gold/Gold-Plus	1mL	4	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Safety labs																									
Hgb / ANC / PLT	Local labs	Local labs	EDTA	4mL	4	4	4	4	4	—	—	—	4	—	—	—	4	—	4	—	4	—	4	—	4
ALT / direct bilirubin / eGFR	Local labs	Local labs	SST	5mL	5	5	5	5	5	—	—	—	5	—	—	—	5	—	5	—	5	—	5	—	5
Syphilis ¹⁰	Local labs	Local labs	SST	5mL	5	—	—	—	5	—	—	—	5	—	—	—	5	—	5	—	5	—	5	—	5
Drug levels																									
ARV detection	CSR	TBD	EDTA	4mL	—	—	—	—	—	—	—	—	4	—	—	—	4	—	4	—	4	—	4	—	4
Immunogenicity & Virologic Assays																									
Cellular assays																									
ICS	CSR	HVTN labs	ACD	8.5mL	—	—	—	—	42.5	z	—	—	42.5	z	—	—	42.5	z	42.5	z	—	42.5	z	—	42.5
Phenotyping	CSR	HVTN labs	ACD	8.5mL	—	—	—	—	z	—	—	—	z	—	—	—	z	—	z	—	z	—	z	—	z
Humoral assays																									
Neutralizing antibody	CSR	HVTN labs	SST	8.5mL	—	—	—	—	8.5	—	—	—	8.5	—	—	—	8.5	—	8.5	—	8.5	—	8.5	—	8.5
FcR-mediated effector functions ⁶	CSR	HVTN labs	SST	8.5mL	—	—	—	—	y	—	—	—	y	—	—	—	y	—	y	—	y	—	y	—	y
HIV reservoir assays	CSR	TBD	ACD	8.5mL	—	—	—	—	51	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Storage																									
Serum	CSR		SST	8.5mL	—	—	—	—	8.5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Plasma	CSR		EDTA	10mL	—	—	—	—	—	—	—	—	—	—	—	—	10	—	10	—	10	—	10	—	10
PBMC	CSR		ACD	8.5mL	—	—	—	—	—	—	—	—	—	—	—	—	17	—	17	—	17	—	17	—	17
Visit total					38	19	19		134.5	6	10	6	79	6	10	6	106	6	106	6	106	6	106	6	106
56-Day total					38	57	76		210.5	216.5	226.5	232.5	311.5	317.5	327.5	333.5	401.5	229	319	240	330	230	330	230	
URINE COLLECTION																									
Pregnancy Test ¹⁶	Local labs	Local labs			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chlamydia/gonorrhea ^{7,10}	Local labs	Local labs			X	—	—	—	X	—	—	—	X	—	—	—	X	—	X	—	X	—	X	—	X
RECTAL SWAB COLLECTION																									
Chlamydia/gonorrhea ^{7,10}	Local labs	Local labs			X	—	—	—	X	—	—	—	X	—	—	—	X	—	X	—	X	—	X	—	X
OROPHARYNGEAL SWAB COLLECTION																									
Chlamydia/gonorrhea ^{7,10}	Local labs	Local labs			X	—	—	—	X	—	—	—	X	—	—	—	X	—	X	—	X	—	X	—	X

¹ CSR = central specimen repository.

² HVTN Laboratories include: Duke University Medical Center (Durham, North Carolina, USA).

Non-HVTN laboratories: TBD.

³ Local labs may assign appropriate alternative tube types for locally performed tests.

⁴ HCV RNA PCR testing will be performed as a reflex test if indicated by anti-HCV antibody results.

⁵ Tuberculin skin test (TST) will be performed if QuantiFERON TB testing is not available. See Procedures at CRS ([Appendix H](#)).

⁶ FcR-mediated effector function assays may include ADCC, virion capture, and phagocytosis assays.

⁷ Chlamydia/gonorrhea testing will be done on urine, and rectal and oropharyngeal swabs.

⁸ The "ART switch" phase will only be performed for participants on NNRTIs. These participants will be considered enrolled on the first day of the new ART medication.

⁹ The ATI Qualification visit specimens must be obtained at least 28 days after ART switch. If needed, VL retesting may continue until viral suppression has been achieved (up to 84 days after ART switch). The last ATI qualification procedures must take place no more than 14 days prior to visit 4 (see HVTN 804/HPTN 095 SSP for more information).

¹⁰ In addition to STI testing at the marked visits, STI testing may occur at any visit if clinically indicated.

¹¹ Extended follow-up visit type A will occur every 6 months starting with 3 months after visit 27 continuing up to 3 years of this schedule. This follow-up visit may be performed for participants who have not met criteria to transition to Schedule 2 or Schedule 3 (see Protocol Section 3.3 and HVTN 804/HPTN 095 SSP for details).

¹² Extended follow-up visit type B will occur every 6 months starting with 6 months after visit 27 continuing up to 3 years of this schedule, and then every 3 months thereafter. This follow-up visit may be performed for participants who have not met criteria to transition to Schedule 2 or Schedule 3 (see Protocol Section 3.3 and HVTN 804/HPTN 095 SSP for details).

¹³ A confirmatory sample should be drawn as soon as possible following the first VL result ≥ 200 copies/mL. See Protocol Section 3.3.1 for details.

¹⁴ A confirmatory sample should be drawn as soon as possible following the first CD4+ T-cell count < 350 cells/mm³. See Protocol Section 3.3.2 for details.

¹⁵ Screening visit specimens for participants not undergoing an NNRTI switch should be obtained no later than 2 weeks before Visit 4; see HVTN 804/HPTN 095 for more information.

¹⁶ For persons capable of becoming pregnant, pregnancy test may be performed on urine or blood specimens.

¹⁷ At an early termination visit for a withdrawn or terminated participant (see Section 6.5), blood should be drawn as shown for Extended follow-up visit type A (see HVTN 804/HPTN 095 SSP for more information).

y = SST blood collected for neutralizing antibody will also cover specimen needs for FcR-mediated effector functions; no separate blood draw is needed.

z = PBMC blood collected for ICS will also cover specimen needs for phenotyping; no separate blood draw is needed.

Laboratory procedures—Schedule 1: Monitoring ATI (continued)

Procedure	Ship to ¹	Assay location ^{1,2}	Tube Type ³	Tube size (vol. capacity) ³	Visit:	20	21	22	23	24	25	26	27	Visit Type A ^{11,17}	Visit Type B ¹²	Total
					Days on ATI:	D168	D196	D224	D252	D280	D308	D336	D364			
					Weeks on ATI:	W24	W28	W32	W36	W40	W44	W48	W52			
BLOOD COLLECTION																
Screening or diagnostic assays																
HIV PCR viral load ¹³	Local labs	Local labs	EDTA	6mL	6	6	6	6	6	6	6	6	6	6	6	174
CD4+/CD8+ T-cell count ¹⁴	Local labs	Local labs	EDTA	4mL	4	4	4	4	—	4	—	4	4	4	4	76
HBsAg/anti-HCV	Local labs	Local labs	SST	5mL	—	—	—	—	—	—	—	—	—	—	—	10
QuantiFERON TB testing ⁵	Local labs	Local labs	QFT Gold/Gold-Plus	1mL	—	—	—	—	—	—	—	—	—	—	—	4
Safety labs																
Hgb / ANC / PLT	Local labs	Local labs	EDTA	4mL	4	4	4	4	—	4	—	4	4	4	4	68
ALT / direct bilirubin / eGFR	Local labs	Local labs	SST	5mL	5	5	5	5	—	5	—	5	5	5	5	85
Syphilis ¹⁰	Local labs	Local labs	SST	5mL	5	5	5	5	5	5	5	5	5	5	5	85
Drug levels																
ARV detection	CSR	TBD	EDTA	4mL	4	4	4	4	4	4	4	4	4	4	4	60
Immunogenicity & Virologic Assays																
Cellular assays																
ICS	CSR	HVTN labs	ACD	8.5mL	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5	—	—	595
Phenotyping	CSR	HVTN labs	ACD	8.5mL	z	z	z	z	z	z	z	z	z	—	—	0
Humoral assays																
Neutralizing antibody	CSR	HVTN labs	SST	8.5mL	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	—	—	119
FcR-mediated effector functions ⁶	CSR	HVTN labs	SST	8.5mL	y	y	y	y	y	y	y	y	y	—	—	0
HIV reservoir assays	CSR	TBD	ACD	8.5mL	—	—	—	—	—	—	—	—	—	—	—	51
Storage																
Serum	CSR		SST	8.5mL	—	—	—	—	—	—	—	—	—	8.5	—	17
Plasma	CSR		EDTA	10mL	10	10	10	10	10	10	10	10	10	10	—	130
PBMC	CSR		ACD	8.5mL	17	17	17	17	17	17	17	17	17	59.5	—	263.5
Visit total					106	106	106	106	93	106	93	106	106	106	28	
56-Day total					330	324	318	318	305	305	292	305	106	28		
URINE COLLECTION																
Pregnancy Test ¹⁶	Local labs	Local labs			X	X	X	X	X	X	X	X	X	X	X	
Chlamydia/gonorrhea ^{7,10}	Local labs	Local labs			X	X	X	X	X	X	X	X	X	X	X	
RECTAL SWAB COLLECTION																
Chlamydia/gonorrhea ^{7,10}	Local labs	Local labs			X	X	X	X	X	X	X	X	X	X	X	
OROPHARYNGEAL SWAB COLLECTION																
Chlamydia/gonorrhea ^{7,10}	Local labs	Local labs			X	X	X	X	X	X	X	X	X	X	X	

¹ CSR = central specimen repository.

² HVTN Laboratories include: Duke University Medical Center (Durham, North Carolina, USA).

Non-HVTN laboratories: TBD.

³ Local labs may assign appropriate alternative tube types for locally performed tests.

⁴ HCV RNA PCR testing will be performed as a reflex test if indicated by anti-HCV antibody results.

⁵ Tuberculin skin test (TST) will be performed if QuantiFERON TB testing is not available. See Procedures at CRS [Appendix H](#).

⁶ FcR-mediated effector function assays may include ADCC, virion capture, and phagocytosis assays.

⁷ Chlamydia/gonorrhea testing will be done on urine, and rectal and oropharyngeal swabs.

⁸ The "ART switch" phase will only be performed for participants on NNRTIs. These participants will be considered enrolled on the first day of the new ART medication.

⁹ The ATI Qualification visit specimens must be obtained at least 28 days after ART switch. If needed, VL retesting may continue until viral suppression has been achieved (up to 84 days after ART switch). The last ATI qualification procedures must take place no more than 14 days prior to visit 4 (see HVTN 804/HPTN 095 SSP for more information).

- ¹⁰ In addition to STI testing at the marked visits, STI testing may occur at any visit if clinically indicated.
- ¹¹ Extended follow-up visit type A will occur every 6 months starting with 3 months after visit 27 continuing up to 3 years of this schedule. This follow-up visit may be performed for participants who have not met criteria to transition to Schedule 2 or Schedule 3 (see Protocol Section 3.3 and HVTN 804/HPTN 095 SSP for details).
- ¹² Extended follow-up visit type B will occur every 6 months starting with 6 months after visit 27 continuing up to 3 years of this schedule, and then every 3 months thereafter. This follow-up visit may be performed for participants who have not met criteria to transition to Schedule 2 or Schedule 3 (see Protocol Section 3.3 and HVTN 804/HPTN 095 SSP for details).
- ¹³ A confirmatory sample should be drawn as soon as possible following the first VL result ≥ 200 copies/mL. See Protocol Section 3.3.1 for details.
- ¹⁴ A confirmatory sample should be drawn as soon as possible following the first CD4+ T-cell count < 350 cells/mm³. See Protocol Section 3.3.2 for details.
- ¹⁵ Screening visit specimens for participants not undergoing an NNRTI switch should be obtained no later than 2 weeks before Visit 4; see HVTN 804/HPTN 095 SSP for more information.
- ¹⁶ For persons capable of becoming pregnant, pregnancy test may be performed on urine or blood specimens.
- ¹⁷ At an early termination visit for a withdrawn or terminated participant (see Section 6.5), blood should be drawn as shown for Extended follow-up visit type A (see HVTN 804/HPTN 095 SSP for more information).
- y = SST blood collected for neutralizing antibody will also cover specimen needs for FcR-mediated effector functions; no separate blood draw is needed.
- z = PBMC blood collected for ICS will also cover specimen needs for phenotyping; no separate blood draw is needed.

¹² For persons capable of becoming pregnant, pregnancy test may be performed on urine or blood specimens.

¹³ At an early termination visit for a withdrawn or terminated participant (see Section 6.5), blood should be drawn as shown for Extended follow-up visit type A (see HVTN 804/HPTN 095 SSP for more information).

y = SST blood collected for neutralizing antibody will also cover specimen needs for FcR-mediated effector functions; no separate blood draw is needed.

z = PBMC blood collected for ICS will also cover specimen needs for phenotyping; no separate blood draw is needed.

Laboratory procedures—Schedule 2: Monitoring ATI with viremia (continued)

Procedure	Ship to ¹	Assay location ^{1,2}	Tube Type ³	Tube size (vol. capacity) ³	Visit:	56	57	58	59	60	61	62	63	64	65	66	Visit Type A ^{8,13}	Visit type B ⁹	Total
					Days on ATI with viremia	D168	D182	D196	D210	D224	D238	D252	D280	D308	D336	D364			
					Weeks on ATI with viremia	W24	W26	W28	W30	W32	W34	W36	W40	W44	W48	W52			
BLOOD COLLECTION																			
Screening or diagnostic assays																			
HIV PCR viral load ¹⁰	Local labs	Local labs	EDTA	6mL	6	6	6	6	6	6	6	6	6	6	6	6	6	6	174
CD4+/CD8+ T-cell count ¹¹	Local labs	Local labs	EDTA	4mL	4	—	4	—	4	—	4	—	4	—	4	—	4	4	64
Safety labs																			
Hgb / ANC / PLT	Local labs	Local labs	EDTA	4mL	4	—	4	—	4	—	4	—	4	—	4	—	4	4	56
ALT / direct bilirubin / eGFR	Local labs	Local labs	SST	5mL	5	—	5	—	5	—	5	—	5	—	5	—	5	5	70
Syphilis ⁷	Local labs	Local labs	SST	5mL	5	—	5	—	5	—	5	5	5	5	5	5	5	5	80
Drug levels																			
ARV detection	CSR	TBD	EDTA	4mL	4	—	4	—	4	—	4	4	4	4	4	4	4	4	60
Immunoassays & Virologic Assays																			
Cellular assays																			
ICS	CSR	HVTN labs	ACD	8.5mL	42.5	—	42.5	—	42.5	—	42.5	42.5	42.5	42.5	42.5	42.5	—	—	637.5
Phenotyping	CSR	HVTN labs	ACD	8.5mL	z	—	z	—	z	—	z	z	z	z	z	z	—	—	0
Humoral assays																			
Neutralizing antibody	CSR	HVTN labs	SST	8.5mL	8.5	—	8.5	—	8.5	—	8.5	8.5	8.5	8.5	8.5	8.5	—	—	127.5
FcR-mediated effector functions ⁴	CSR	HVTN labs	SST	8.5mL	y	—	y	—	y	—	y	y	y	y	y	y	—	—	0
Storage																			
Serum	CSR		SST	8.5mL	—	—	—	—	—	—	—	—	—	—	—	—	8.5	—	17
Plasma	CSR		EDTA	10mL	10	—	10	—	10	—	10	10	10	10	10	10	10	—	140
PBMC	CSR		ACD	8.5mL	17	—	17	—	17	—	17	17	17	17	17	17	59.5	—	263.5
Visit total					106	6	106	6	106	6	106	93	106	93	106	106	106	28	
56-Day total^{6,10,11}					330	230	330	230	330	230	330	311	305	292	305	106	28		
URINE COLLECTION																			
Pregnancy Test ¹²	Local labs	Local labs			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chlamydia/gonorrhea ^{5,7}	Local labs	Local labs			X	—	X	—	X	—	X	X	X	X	X	X	X	X	
RECTAL SWAB COLLECTION																			
Chlamydia/gonorrhea ^{5,7}	Local labs	Local labs			X	—	X	—	X	—	X	X	X	X	X	X	X	X	
OROPHARYNGEAL SWAB COLLECTION																			
Chlamydia/gonorrhea ^{5,7}	Local labs	Local labs			X	—	X	—	X	—	X	X	X	X	X	X	X	X	

¹ CSR = central specimen repository.

² HVTN Laboratories include: Duke University Medical Center (Durham, North Carolina, USA).

Non-HVTN laboratories: TBD.

³ Local labs may assign appropriate alternative tube types for locally performed tests.

⁴ FcR-mediated effector function assays may include ADCC, virion capture, and phagocytosis assays.

⁵ Chlamydia/gonorrhea testing will be done on urine, and rectal and oropharyngeal swabs.

⁶ The 56-day blood draw limit does not include visits from Schedule 1; please see HVTN 804/HPTN 095 SSP for details on prioritizing collections to avoid exceeding the 56-day limit.

⁷ In addition to STI testing at the marked visits, STI testing may occur at any visit if clinically indicated.

⁸ Extended follow-up visit type A will occur every 6 months starting with 3 months after visit 66, continuing up to 3 years of this schedule. This follow-up visit may be performed for participants who have not met ART re-initiation criteria (see Protocol Section 3.3 and HVTN 804/HPTN 095 SSP for details).

⁹ Extended follow-up visit type B will occur every 6 months starting with 6 months after visit 66, continuing up 3 years of this schedule and then every 3 months thereafter. This follow-up visit may be performed for participants who have not met ART re-initiation criteria (see Protocol Section 3.3 and HVTN 804/HPTN 095 SSP for details).

¹⁰ Additional weekly viral load monitoring may be required between weeks 8 and 24; after week 24, a confirmatory sample should be drawn as soon as possible following the first VL result ≥ 200 copies/mL. See Protocol Section 3.3.3 for details. The 56-day blood draw limit does not include up to 10mL blood collected per visit for this additional monitoring; however, the 56-day limit is not exceeded at any visit by these collections.

¹¹ A confirmatory sample should be drawn as soon as possible following the first CD4+ T-cell count < 350 cells/mm³. See Protocol Section 3.3.3 for details.

¹² For persons capable of becoming pregnant, pregnancy test may be performed on urine or blood specimens.

¹³ At an early termination visit for a withdrawn or terminated participant (see Section 6.5), blood should be drawn as shown for Extended follow-up visit type A (see HVTN 804/HPTN 095 SSP for more information).

y = SST blood collected for neutralizing antibody will also cover specimen needs for FcR-mediated effector functions; no separate blood draw is needed.

z = PBMC blood collected for ICS will also cover specimen needs for phenotyping; no separate blood draw is needed.

Appendix G Laboratory procedures—Schedule 3: Follow-up on ART

Procedure	Ship to ¹	Assay location ^{1,2}	Tube Type ³	Tube size (vol. capacity) ³	Visit:	80 ⁷	81	82	83	84	85	86	87	88	89	90	91 ¹²	92	Total	
					Days post ART re-initiation	D0	D14	D28	D42	D56	D70	D84	D112	D140	D168	D196	D280	D364		
					Weeks post ART re-initiation:	W0	W2	W4	W6	W8	W10	W12	W16	W20	W24	W28	W40	W52		
					ART re-initiation visit															
BLOOD COLLECTION																				
Screening or diagnostic assays																				
HIV PCR viral load	Local labs	Local labs	EDTA	6mL	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	78
CD4+/CD8+ T-cell count	Local labs	Local labs	EDTA	4mL	4	—	4	—	4	—	4	—	4	—	4	—	4	4	4	32
Safety labs																				
Hgb / ANC / PLT	Local labs	Local labs	EDTA	4mL	—	—	4	—	4	—	4	—	—	—	4	—	4	—	—	20
ALT / direct bilirubin / eGFR	Local labs	Local labs	SST	5mL	—	—	5	—	5	—	5	—	—	—	5	—	5	—	—	25
Syphilis ⁹	Local labs	Local labs	SST	5mL	5	—	5	—	5	—	5	—	5 ¹³	5 ¹³	5	5 ¹³	5	—	—	45
HIV genotypic antiretroviral resistance ⁸	CSR	TBD	EDTA	5mL	—	—	—	—	15	—	—	—	—	—	—	—	—	—	—	15
Immunogenicity & Virologic Assays																				
Viral isolation/sequencing	CSR	HVTN Labs	EDTA	10mL	10	10	—	—	—	—	10	—	—	—	10	—	10	10	60	
Cellular assays																				
ICS	CSR	HVTN Labs	ACD	8.5mL	—	—	—	—	—	—	42.5	—	—	—	42.5	—	42.5	42.5	170	
Phenotyping	CSR	HVTN Labs	ACD	8.5mL	—	—	—	—	—	—	z	—	—	—	z	—	z	z	0	
Humoral assays																				
Neutralizing antibody	CSR	HVTN Labs	SST	8.5mL	—	—	—	—	—	—	8.5	—	—	—	8.5	—	8.5	8.5	34	
FcR-mediated effector functions ⁴	CSR	HVTN Labs	SST	8.5mL	—	—	—	—	—	—	y	—	—	—	y	—	y	y	0	
HIV reservoir assays	CSR	TBD	ACD	8.5mL	34	—	—	—	—	—	—	—	—	—	51	—	51	51	187	
Storage																				
Serum	CSR		SST	8.5mL	8.5	—	—	—	—	—	8.5	—	—	—	8.5	—	8.5	8.5	42.5	
Plasma	CSR		EDTA	10mL	—	—	—	—	—	—	10	—	—	—	10	—	10	10	40	
PBMC	CSR		ACD	8.5mL	42.5	—	—	—	—	—	102	—	—	—	51	—	51	51	297.5	
Visit total					110	16	24	6	39	6	205.5	11	15	201.5	15	205.5	191.5			
56-Day total⁵						126	150	156	195	91	280.5	261.5	231.5	227.5	231.5	205.5	191.5			
URINE COLLECTION																				
Pregnancy Test ¹¹	Local labs	Local labs			X	X ¹⁰	X ¹⁰	X ¹⁰	X ¹⁰	X ¹⁰	X	X ¹⁰	X ¹⁰	X	X ¹⁰	X	X	X	X	
Chlamydia/gonorrhea ^{6,9}	Local labs	Local labs			X	—	X	—	X	—	X	—	—	X	—	X	—	X	—	
RECTAL SWAB COLLECTION																				
Chlamydia/gonorrhea ^{6,9}	Local labs	Local labs			X	—	X	—	X	—	X	X ¹³	X ¹³	X	X ¹³	X	X	X	—	
OROPHARYNGEAL SWAB COLLECTION																				
Chlamydia/gonorrhea ^{6,9}	Local labs	Local labs			X	—	X	—	X	—	X	X ¹³	X ¹³	X	X ¹³	X	X	X	—	

¹ CSR = central specimen repository.

² HVTN Laboratories include: Duke University Medical Center (Durham, North Carolina, USA).

Non-HVTN laboratories: TBD

³ Local labs may assign appropriate alternative tube types for locally performed tests.

⁴ FcR-mediated effector function assays may include ADCC, virion capture, and phagocytosis assays.

⁵ 56-day totals do not include visit totals from Schedule 1 or 2. Please see HVTN 804/HPTN 095 SSP for details on prioritizing collections to avoid exceeding the 56-day limit.

⁶ Chlamydia/gonorrhea testing will be done on both urine, and rectal and oropharyngeal swabs; in addition, testing may occur at any visit if clinically indicated.

⁷ Samples for visit 80 should be collected after ART re-initiation criteria have been met, but prior to ART re-initiation.

⁸ HIV antiretroviral resistance testing will be tested only if indicated by viral load results.

⁹ In addition to STI testing at the marked visits, STI testing may occur at any visit if clinically indicated.

¹⁰ Pregnancy testing is not required if viral load has returned to undetectable.

¹¹ For persons capable of becoming pregnant, pregnancy test may be performed on urine or blood specimens.

¹² At an early termination visit for a withdrawn or terminated participant (see Section 6.5), blood should be drawn as shown for Visit 91 (see HVTN 804/HPTN 095 SSP for more information).

¹³ Syphilis, chlamydia, and gonorrhea testing is not required at this visit if viral load has returned to undetectable.

y = SST blood collected for neutralizing antibody will also cover specimen needs for FcR-mediated effector functions; no separate blood draw is needed.

z = PBMC blood collected for ICS will also cover specimen needs for phenotyping; no separate blood draw is needed.

Appendix H Procedures at CRS—Schedule 1: Monitoring ATI

	Visit:	01 ¹	02	03	04 ³	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	
	Days on ATI:	Screening	ART Switch ²	ATI qualification	D0	D7	D14	D21	D28	D35	D42	D49	D56	D70	D84	D98	D112	D126	D140	D154	
	Weeks on ATI:				W0	W1	W2	W3	W4	W5	W6	W7	W8	W10	W12	W14	W16	W18	W20	W22	
Study procedures																					
Screening consent (if used)		✓																			
Protocol consent		✓																			
Assessment of understanding		✓																			
Medical history		✓																			
Complete physical exam		✓			✓																
Targeted physical exam ⁴			✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant medications ⁴		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Intercurrent illness/adverse experience ⁴			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ART re-initiation assessment ⁴						✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Transmission risk reduction counseling ⁴		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Contraception status assessment ⁵		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Decision aid		✓																			
Decision-making assessment			✓		✓											✓					
Psychosocial assessment			✓		✓										✓						
Social impact assessment ⁴					✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Social impact assessment questionnaire															✓						
QuantiFERON tuberculosis test ⁶		✓																			
Confirm eligibility		✓																			
Specimen collection⁷		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

¹ Screening procedures may occur over the course of several contacts/visits up to and including the day of enrollment, except for blood collection for participants not on NNRTIs, which may occur up to 14 days before enrollment, as defined in Section 6.1.2.

² For participants undergoing switch from NNRTI-based to protease- or integrate-based ART regimen. Participants undergoing an “ART switch” will be considered enrolled on first day of the new ART medication. The “ART switch” phase will not be performed for participants not on NNRTIs. For procedure timing during the “ART switch,” see Section 6.1.3 and HVTN 804/HPTN 095 SSP.

³ Enrollment visit for participants who do not undergo ART switch.

⁴ Procedure to be performed at interim visits held to draw confirmatory viral load samples or confirmatory samples for CD4+ T cell counts (see Sections 3.3.1, 3.3.2, and 3.3.3).

⁵ Contraception status assessment is required only for participants who were assigned female sex at birth and who can become pregnant (does not include those persons not of reproductive potential due to having undergone hysterectomy or bilateral oophorectomy [verified by medical records]).

⁶ If QuantiFERON TB testing cannot be performed, a tuberculin skin test (TST) should be conducted. Additional risk/clinical/diagnostic assessment may be performed at the discretion of the clinician to meet institutional standard of care for evaluation and treatment of latent TB.

⁷ For specimen collection requirements, see Appendix E.

⁸ Extended follow-up visit type A will occur every 6 months starting with 3 months after visit 66, continuing up to 3 years of this schedule. This follow-up visit may be performed for participants who have not met ART re-initiation criteria (see Protocol Section 3.3 and HVTN 804/HPTN 095 SSP for details).

⁹ Extended follow-up visit type B will occur every 6 months starting with 6 months after visit 66, continuing up 3 years of this schedule and then every 3 months thereafter. This follow-up visit may be performed for participants who have not met ART re-initiation criteria (see Protocol Section 3.3 and HVTN 804/HPTN 095 SSP for details).

¹⁰ At an early termination visit for a withdrawn or terminated participant, CRS staff should consider performing procedures specified for Extended follow-up visit Type A (see Section 6.5 and HVTN 804/HPTN 095 SSP for details).

Procedures at CRS—Schedule 1: Monitoring ATI (continued)

	Visit:	20	21	22	23	24	25	26	27	Visit Type A ^{8,10}	Visit Type B ⁹
	Days on ATI:	D168	D196	D224	D252	D280	D308	D336	D364		
	Weeks on ATI:	W24	W28	W32	W36	W40	W44	W48	W52		
Study procedures											
Screening consent (if used)											
Protocol consent											
Assessment of understanding											
Medical history											
Complete physical exam											
Targeted physical exam ⁴		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant medications ⁴		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Intercurrent illness/adverse experience ⁴		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ART re-initiation assessment ⁴		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Transmission risk reduction counseling ⁴		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Contraception status assessment ⁵		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Decision aid											
Decision-making assessment		✓			✓				✓		✓
Psychosocial assessment		✓			✓				✓		✓
Social impact assessment ⁴		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Social impact assessment questionnaire		✓			✓				✓		✓
QuantiFERON tuberculosis test ⁶											
Confirm eligibility											
Specimen collection⁷		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

¹ Screening procedures may occur over the course of several contacts/visits up to and including the day of enrollment, except for blood collection for participants not on NNRTIs, which may occur up to 14 days before enrollment, as defined in Section 6.1.2.

² For participants undergoing switch from NNRTI-based to protease- or integrate-based ART regimen. Participants undergoing an “ART switch” will be considered enrolled on first day of the new ART medication. The “ART switch” phase will not be performed for participants not on NNRTIs. For procedure timing during the “ART switch,” see Section 6.1.3 and HVTN 804/HPTN 095 SSP.

³ Enrollment visit for participants who do not undergo ART switch.

⁴ Procedure to be performed at interim visits held to draw confirmatory viral load samples or confirmatory samples for CD4+ T cell counts (see Sections 3.3.1, 3.3.2, and 3.3.3).

⁵ Contraception status assessment is required only for participants who were assigned female sex at birth and who can become pregnant (does not include those persons not of reproductive potential due to having undergone hysterectomy or bilateral oophorectomy [verified by medical records]).

⁶ If QuantiFERON TB testing cannot be performed (see Appendix E), TST should be conducted. Additional risk/clinical/diagnostic assessment may be performed at the discretion of the clinician to meet institutional standard of care for treatment of latent TB.

⁷ For specimen collection requirements, see Appendix E.

⁸ Extended follow-up visit type A will occur every 6 months starting with 3 months after visit 66, continuing up to 3 years of this schedule. This follow-up visit may be performed for participants who have not met ART re-initiation criteria (see Protocol Section 3.3 and HVTN 804/HPTN 095 SSP for details).

⁹ Extended follow-up visit type B will occur every 6 months starting with 6 months after visit 66, continuing up 3 years of this schedule and then every 3 months thereafter. This follow-up visit may be performed for participants who have not met ART re-initiation criteria (see Protocol Section 3.3 and HVTN 804/HPTN 095 SSP for details).

¹⁰ At an early termination visit for a withdrawn or terminated participant, CRS staff should consider performing procedures specified for Extended follow-up visit Type A (see Section 6.5 and HVTN 804/HPTN 095 SSP for details).

Appendix I Procedures at CRS—Schedule 2: Monitoring ATI with viremia

Visit:	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55
Days on ATI with viremia:	D0	D7	D14	D21	D28	D35	D42	D49	D56	D70	D84	D98	D112	D126	D140	D154
Weeks on ATI with viremia:	W0	W1	W2	W3	W4	W5	W6	W7	W8	W10	W12	W14	W16	W18	W20	W22
Study procedures																
Complete physical exam	✓															
Targeted physical exam ¹		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant medications ¹	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Intercurrent illness/adverse experience ¹	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ART re-initiation assessment ¹		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Transmission risk reduction counseling ¹	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Contraception status assessment ²	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Decision-making assessment	✓															
Psychosocial assessment	✓										✓					
Social impact assessment ¹	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Social impact assessment questionnaire											✓					
Specimen collection³	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

¹ Procedure to be performed at interim visits held to draw confirmatory viral load samples or confirmatory samples for CD4+ T cell counts (see Sections 3.3.1, 3.3.2, and 3.3.3).

² Contraception status assessment is required only for participants who were assigned female sex at birth and who can become pregnant (does not include those persons not of reproductive potential due to having undergone hysterectomy or bilateral oophorectomy [verified by medical records]).

³ For specimen collection requirements, see [Appendix F](#).

⁴ Extended follow-up visit type A will occur every 6 months starting with 3 months after visit 66, continuing up to 3 years of this schedule. This follow-up visit may be performed for participants who have not met ART re-initiation criteria (see Protocol Section 3.3 and HVTN 804/HPTN 095 SSP for details).

⁵ Extended follow-up visit type B will occur every 6 months starting with 6 months after visit 66, continuing up 3 years of this schedule and then every 3 months thereafter. This follow-up visit may be performed for participants who have not met ART re-initiation criteria (see Protocol Section 3.3 and HVTN 804/HPTN 095 SSP for details).

⁶ At an early termination visit for a withdrawn or terminated participant, CRS staff should consider performing procedures specified for Extended follow-up visit Type A (see Section 6.5 and HVTN 804/HPTN 095 SSP for details).

Procedures at CRS—Schedule 2: Monitoring ATI with viremia (continued)

Visit:	56	57	58	59	60	61	62	63	64	65	66	Visit Type A ^{4,6}	Visit Type B ⁵
Days on ATI with viremia:	D168	D182	D196	D210	D224	D238	D252	D280	D308	D336	D364		
Weeks on ATI with viremia:	W24	W26	W28	W30	W32	W34	W36	W40	W44	W48	W52		
Study procedures													
Targeted physical exam ¹	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant medications ¹	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Intercurrent illness/adverse experience ¹	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ART re-initiation assessment ¹	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Transmission risk reduction counseling ¹	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Contraception status assessment ²	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Decision-making assessment	✓						✓				✓		✓
Psychosocial assessment	✓						✓				✓		✓
Social impact assessment ¹	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Social impact assessment questionnaire	✓						✓				✓		✓
Specimen collection³													
	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

¹ Procedure to be performed at interim visits held to draw confirmatory viral load samples or confirmatory samples for CD4+ T cell counts (see Sections 3.3.1, 3.3.2, and 3.3.3).

² Contraception status assessment is required only for participants who were assigned female sex at birth and who can become pregnant (does not include those persons not of reproductive potential due to having undergone hysterectomy or bilateral oophorectomy [verified by medical records]).

³ For specimen collection requirements, see [Appendix F](#).

⁴ Extended follow-up visit type A will occur every 6 months starting with 3 months after visit 66, continuing up to 3 years of this schedule. This follow-up visit may be performed for participants who have not met ART re-initiation criteria (see Protocol Section 3.3 and HVTN 804/HPTN 095 SSP for details).

⁵ Extended follow-up visit type B will occur every 6 months starting with 6 months after visit 66, continuing up 3 years of this schedule and then every 3 months thereafter. This follow-up visit may be performed for participants who have not met ART re-initiation criteria (see Protocol Section 3.3 and HVTN 804/HPTN 095 SSP for details).

⁶ At an early termination visit for a withdrawn or terminated participant, CRS staff should consider performing procedures specified for Extended follow-up visit Type A (see Section 6.5 and HVTN 804/HPTN 095 SSP for details).

Appendix J Procedures at CRS—Schedule 3: Follow-up on ART

Visit:	80 ¹	81	82	83	84	85	86	87	88	89	90	91 ⁴	92
Days after ART re-initiation:	D0	D14	D28	D42	D56	D70	D84	D112	D140	D168	D196	D280	D364
Weeks after ART re-initiation:	W0	W2	W4	W6	W8	W10	W12	W16	W20	W24	W28	W40	W52
Study procedures													
Complete physical exam													✓
Targeted physical exam	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Concomitant medications	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Intercurrent illness/adverse experience	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Transmission risk reduction counseling	✓	✓	✓		✓		✓		✓		✓		✓
Contraception status assessment ²	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Decision-making assessment	✓						✓			✓			✓
Psychosocial assessment	✓						✓			✓			✓
Social impact assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Social impact assessment questionnaire							✓			✓			✓
Specimen collection³	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

¹ ART re-initiation visit.

² Contraception status assessment is required only for participants who were assigned female sex at birth and who can become pregnant (does not include those persons not of reproductive potential due to having undergone hysterectomy or bilateral oophorectomy [verified by medical records]). Contraception status assessment is not required if participant VL has returned to undetectable.

³ For specimen collection requirements, see [Appendix G](#).

⁴ At an early termination visit for a withdrawn or terminated participant, CRS staff should consider performing procedures specified for Visit 91 (see Section 6.5 and HVTN 804/HPTN 095 SSP for more details).

Appendix K Visit Windows

Visit Windows – Schedule 1: Monitoring ATI

Visit Number	Visit Type		Lower Allowable Window	Lower Target Day	Target Day ⁴	Upper Target Day	Upper Allowable Window
			<i>Relative dates of reference are noted in individual cells below.</i>				
01.0 ¹	Participants not on NNRTIs	Screening: Blood collection only	56 days before Visit 4	-	-	-	14 days before Visit 4
		Screening: All other screening procedures	56 days before Visit 4	-	-	-	0 days before Visit 4
	Participants on NNRTIs [ART Switch Participants]	Screening	56 days before Visit 2	-	-	-	0 days before Visit 2
02.0	Participants on NNRTIs [ART Switch Participants]	ART Switch	<i>For participants on NNRTIs, Visit 2 is considered the enrollment visit.</i>				
03.0		ATI Qualification ²	28 days after Visit 2	-	-	-	84 days after Visit 2
Visit Number	Visit Type		Lower Allowable Window	Lower Target Day	Target Day ³ <i>Relative to initiation of ATI</i>	Upper Target Day	Upper Allowable Window
04.0	Week 0 Initiation of ATI		-	-	0	-	-
05.0	Week 1		-3	-2	7	+2	+3
06.0	Week 2		-3	-2	14	+2	+3
07.0	Week 3		-3	-2	21	+2	+3
08.0	Week 4		-3	-2	28	+2	+3
09.0	Week 5		-3	-2	35	+2	+3
10.0	Week 6		-3	-2	42	+2	+3
11.0	Week 7		-3	-2	49	+2	+3
12.0	Week 8		-3	-2	56	+2	+7
13.0	Week 10		-6	-4	70	+4	+7
14.0	Week 12		-6	-4	84	+4	+7
15.0	Week 14		-6	-4	98	+4	+7
16.0	Week 16		-6	-4	112	+4	+7
17.0	Week 18		-6	-4	126	+4	+7
18.0	Week 20		-6	-4	140	+4	+7

19.0	Week 22	-6	-4	154	+4	+7
20.0	Week 24	-6	-4	168	+4	+14
21.0	Week 28	-13	-8	196	+8	+14
22.0	Week 32	-13	-8	224	+8	+14
23.0	Week 36	-13	-8	252	+8	+14
24.0	Week 40	-13	-8	280	+8	+14
25.0	Week 44	-13	-8	308	+8	+14
26.0	Week 48	-13	-8	336	+8	+14
27.0	Week 52	-13	-8	364	+8	+14
Visit Type A ⁴	Follow-up (Schedule 1: Visit Type A)	-42	-28	Visit Type A will occur every 6 months starting with 3 months after visit 27 continuing up to three years of this schedule	+28	+42
Visit Type B ⁴	Follow-up (Schedule 1: Visit Type B)	-42	-28	Visit Type B will occur every 6 months starting with 6 months after visit 27 continuing up to three years of this schedule, and then every 3 months thereafter	+28	+42

¹ Screening procedures may occur over the course of several contacts/visits up to and including the day of enrollment, except for blood collection for participants not on NNRTIs, which may occur up to 14 days before enrollment, as defined in Section 6.1.2.

² If needed, VL retesting may continue up to 84 days after ART switch until viral suppression has been achieved. The final ATI qualification procedures must take place no more than 14 days prior to visit 4.

³ Viral load sample collection should occur as close to the target day as possible and must occur at least 2 days apart (this applies to both scheduled visits and interim visits). See Visit Scheduling and Coding SSP for further details.

⁴ Type A and Type B visits must be at least 8 weeks apart.

Visit Windows – Schedule 2: Monitoring ATI with viremia

Visit Number	Visit Type	Lower Allowable Window	Lower Target Day	Target Day ¹	Upper Target Day	Upper Allowable Window
40.0	First visit after confirmed ATI VL ≥ 200 copies/mL	-	-	0	-	-
41.0	Week 1	-3	-2	7	+2	+3
42.0	Week 2	-3	-2	14	+2	+3
43.0	Week 3	-3	-2	21	+2	+3
44.0	Week 4	-3	-2	28	+2	+3
45.0	Week 5	-3	-2	35	+2	+3
46.0	Week 6	-3	-2	42	+2	+3
47.0	Week 7	-3	-2	49	+2	+3
48.0	Week 8	-3	-2	56	+2	+7
49.0	Week 10	-6	-4	70	+4	+7
50.0	Week 12	-6	-4	84	+4	+7
51.0	Week 14	-6	-4	98	+4	+7
52.0	Week 16	-6	-4	112	+4	+7
53.0	Week 18	-6	-4	126	+4	+7
54.0	Week 20	-6	-4	140	+4	+7
55.0	Week 22	-6	-4	154	+4	+7
56.0	Week 24	-6	-4	168	+4	+7
57.0	Week 26	-6	-4	182	+4	+7
58.0	Week 28	-6	-4	196	+4	+7
59.0	Week 30	-6	-4	210	+4	+7
60.0	Week 32	-6	-4	224	+4	+7
61.0	Week 34	-6	-4	238	+4	+7
62.0	Week 36	-6	-4	252	+8	+14
63.0	Week 40	-13	-8	280	+8	+14
64.0	Week 44	-13	-8	308	+8	+14
65.0	Week 48	-13	-8	336	+8	+14
66.0	Week 52	-13	-8	364	+8	+14
Visit Type A ²	Follow-up (Schedule 2: Visit Type A)	-42	-28	Visit Type A will occur every 6 months starting with 3 months after visit 66 continuing up to	+28	+42

				three years of this schedule		
Visit Type B ²	Follow-up (Schedule 2: Visit Type B)	-42	-28	Visit Type B will occur every 6 months starting with 6 months after visit 66 continuing up to three years of this schedule, and then every 3 months thereafter	+28	+42

¹Viral load sample collection should occur as close to the target day as possible and must occur at least 2 days apart (this applies to both scheduled visits and interim visits). See Visit Scheduling and Coding SSP for further details.

²Type A and Type B visits must be at least 8 weeks apart.

Visit Windows – Schedule 3: Follow-up on ART

Visit Number	Visit Type	Lower Allowable Window	Lower Target Day	Target Day¹ <i>relative to ART re-initiation</i>	Upper Target Day	Upper Allowable Window
80.0	ART Re-initiation	-	-	0	-	-
81.0	Week 2	-6	-4	14	+4	+7
82.0	Week 4	-6	-4	28	+4	+7
83.0	Week 6	-6	-4	42	+4	+7
84.0	Week 8	-6	-4	56	+4	+7
85.0	Week 10	-6	-4	70	+4	+7
86.0	Week 12	-6	-4	84	+4	+14
87.0	Week 16	-13	-8	112	+8	+14
88.0	Week 20	-13	-8	140	+8	+14
89.0	Week 24	-13	-8	168	+8	+14
90.0 ¹	Week 28	-13	-8	196	+8	+14
91.0 ¹	Week 40	-42	-14	280	+14	+42
92.0 ¹	Week 52	-28	-14	364	+14	+42

¹There must be at least 8 weeks between visits 90.0 and 91.0, and visits 91.0 and 92.0.

Appendix L Protocol Signature Page

Antiretroviral analytical treatment interruption (ATI) to assess immunologic and virologic responses in participants who received VRC01 or placebo and became HIV-infected during HVTN 704/HPTN 085

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (U.S.) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (eg, U.S. National Institutes of Health, Division of AIDS) and institutional policies

Investigator of Record Name (print)

Investigator of Record Signature

Date

DAIDS Protocol Number: HVTN 804/HPTN 095

DAIDS Protocol Version: Version 1.0

Protocol Date: November 13, 2019