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Broadly neutralizing antibody and the HIV reservoir in acute HIV infection: a strategy toward HIV remission?

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Abstract

Purpose of review—Infection of long-lived CD4⁺ T cells is a major obstacle to HIV remission, and antiretroviral therapy (ART) instituted during acute HIV infection restricts HIV reservoir establishment. Broadly neutralizing antibodies (bNAbs) may be employed in conjunction with early ART as strategies toward HIV remission.

Recent findings—Proof-of-concept studies *in vitro* and in animal models demonstrated bNAbs' ability to block viral entry into cells, suppress viremia and reduce cell-associated viral DNA. Combination bNAbs were more effective than single bNAbs in suppressing viremia. When bNAbs were used with ART with or without combination latency reversing agents, it prevented viral rebound after ART interruption in at least half of the animals. In one study, macaques with low baseline viral load achieved viral remission even after the blood bNAbs titer was no longer detected.

Summary—The acute HIV infection period represents a unique opportunity to explore the use of bNAbs with ART to limit the reservoir seeding that may enhance the chance of HIV remission. This article discusses the effects of early ART and bNAbs on HIV reservoirs and proposes research strategies in acute HIV infection aiming at HIV reservoir reduction and HIV remission.

Keywords

acute HIV infection; antibody; broadly neutralizing antibody; early antiretroviral therapy; HIV DNA; HIV reservoir; replication-competent virus

INTRODUCTION

Several lines of evidence indicate that immune-based therapy will be key to achieving HIV remission, that is, control of plasma viremia to undetectable levels in the absence of antiretroviral therapy (ART) [1,2,3,4,5]. Studies of broadly neutralizing antibodies

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Conflicts of interest

The authors have no conflicts of interest.

(bNAbs) *in vitro* and in animal models demonstrate the ability of these agents to reduce the frequencies of cells harboring viral DNA in the peripheral blood and in tissue, and to suppress plasma viremia, with remission achieved in a subset of animals [3■,6■,7,8■]. There are several studies planned in humans that will evaluate the effects of bNAbs on HIV viremia, reservoirs, and remission.

bNAbs' functionality lies in their ability to bind and clear both cell-free virus and viral-infected cells. How to optimally use bNAbs in humans is unclear. Although the animal models of bNAbs thus far involved chronically infected animals, bNAbs may be best used in acute HIV infection, either before ART or after viral suppression and HIV reservoir attenuation from early ART. Long-term virally suppressed, chronically infected patients have large HIV reservoirs so it seems daunting that such passive antibody administration could decrease these reservoirs enough for HIV remission to be possible. In contrast, the acute HIV infection period presents a unique opportunity to explore the use of bNAbs with ART to contain viral replication and limit the HIV reservoir seeding that may enhance the chance for HIV remission.

In this article, we discuss HIV reservoir establishment during acute HIV infection, the effects of early ART on HIV reservoirs, and the studies of bNAbs on lentivirus reservoirs in animal models and those that are planned in humans. Finally, we propose research strategies for bNAbs in acute HIV infection aiming at HIV reservoir attenuation and HIV remission.

HIV reservoir establishment during acute HIV infection and after early antiretroviral therapy

HIV preferentially infects activated CD4⁺ T cells that are then killed by effector T cells or they undergo apoptosis or pyroptosis [9–11]. However, a very small proportion of these cells reverts to a resting state that allows them to evade host immune responses to HIV infection and persist indefinitely despite many years of suppressive antiviral treatment. These resting CD4⁺ T cells, predominantly, central memory CD4⁺ T cells, may also be infected directly. Their maintenance is thought to be primarily from homeostatic proliferation [12].

It is clear that the HIV reservoir which enables persistence occurs early in infection but the precise timing is unknown [13]. A recent study in rhesus macaques showed that simian immunodeficiency virus (SIV) infection with effective ART initiated at day three and prior to detectable viremia did not prevent the development of a latent reservoir nor viral rebound when it was later removed [14]. Early ART, however, did reduce the frequencies of cells harboring SIV, which was corroborated in another study of early treated rhesus macaques showing that treatment before peak viremia was key in reducing the reservoir size [15]. Notable is that the route and dose of SIV challenge result in far more efficient transmission than HIV in humans, and the rhesus macaque model lacks certain host restriction factors and therefore this model may not be directly applicable to humans.

It has been shown since the 1990s that latently infected cells were readily detected in people with recent HIV infection, that is those infected within the past 6–12 months [13]. What was lacking, however, was information on HIV reservoir establishment during very early stages of HIV or acute HIV infection when HIV immunoglobulin (Ig)G is not yet detected. This is

due in part to the challenge of identifying acute HIV infection that requires testing to be done during a short-window period prior to antibody detection by routine methods, and the expense of algorithmic testing using sensitive antigen– antibody combo testing and/or nucleic acid testing. Recent data demonstrated a gradual increase in cell-associated HIV DNA in blood and gut during the first month of infection, with the lowest reservoir size observed in individuals diagnosed before HIV IgM developed, which roughly corresponded to the first 2–3 weeks of infection [16] These individuals also exhibit the lowest reservoir size following early ART [17,18].

ART instituted during acute HIV infection does not eliminate HIV persistence, but it significantly restricts infection and facilitates a faster decay of latently infected cells [19–21]. Importantly, it attenuates infection of long-lived central memory CD4⁺ T cells [18,22] and may skew the distribution of latently infected cells to shorter-lived memory CD4⁺ T cells that are more prone to immune clearance, a profile observed in posttreatment controllers in the VISCONTI cohort [23] and in long-term non-progressors [24].

Broadly neutralizing antibody and the HIV reservoir

Single or combination administration of bNAbs has the potential to combat HIV infection by preventing viral spread, facilitating viral clearance, and mediating destruction of virus-producing cells, which, in turn, decreases the viral reservoir and reduces immune activation [25].

Proof-of-concept studies *in vitro* [26], in humanized mice [6,7,8] and in rhesus macaques [2,3] are summarized in Table 1. They demonstrated that bNAbs are capable of blocking viral entry into cells [26] and suppressing viremia [2,3,6,7,8,26]. Some studies also showed reduction in cell-associated viral DNA [3,6] and RNA [2] in peripheral blood mononuclear cells (PBMCs) and tissues. Combination bNAbs with at least three antibodies were more effective than a single bNAbs in suppressing viremia in humanized mice, and after the bNAbs were removed, the time to viral rebound was longer in the combination bNAbs group [6,7,8]. Interestingly, when combination bNAbs were given with combination latency reversing agents (LRAs) in virally suppressed mice, it prevented viral rebound in half of the mice [8]. Administering bNAbs with ART to reduce the initial viral load followed by bNAbs monotherapy during ART interruption helped prevent viral rebound in all mice, illustrating the role bNAbs might play in maintaining HIV remission [6]. In chimeric SIV/HIV (SHIV)-infected macaques, combination bNAbs with two antibodies was more effective in lowering viremia than monotherapy [2]. Significant reduction in cell-associated SHIV DNA in gut and lymph node tissues after bNAbs was also observed [3]. Remarkably, PGT121 bNAbs administration resulted in SHIV remission in macaques with low baseline viral load ($n = 3$) that persisted even after PGT121 titers were no longer detected in the blood [3].

Phase I dose-finding and safety studies in humans are being performed for Vaccine Research Center (VRC)01 [27,28] and 3BNC117 bNAbs [29]. Several planned studies in adults and children will evaluate the effects of VRC01 bNAbs on the HIV reservoirs including two by the U.S. Military HIV Research Program that will evaluate the use of VRC01 in acutely infected individuals (Retrovirology (RV)397 and RV398 studies).

How might broadly neutralizing antibody be tested in acute HIV infection to achieve HIV reservoir reduction and remission?

The recent identification and characterization of several classes of bNAbs provides an opportunity to study these agents for HIV treatment. Figure 1 illustrates two research strategies that unified in their focus on individuals identified during acute HIV infection but direct those interventions at different timepoints in the disease course. First, bNAbs could be used in combination with ART during acute HIV infection when viral load rise is rapid and extreme, based on the hypothesis that the bNAbs could exhibit a synergistic effect with ART on reducing viral burden. This may quickly suppress plasma viral load and limit establishment of latent viral reservoirs across multiple compartments. Secondly, individuals who were identified and treated with ART during acute HIV infection could be administered bNAbs to facilitate clearance of HIV-infected, and, presumably latently infected cells, in order to enhance their ability to control viremia post-ART interruption. Such individuals may have limited HIV-specific immunity because of efficient suppression of HIV viremia with early ART, and may benefit from adjunct immunotherapy like bNAbs. It is conceivable that administering LRAs, such as histone deacetylase inhibitors or newer drug classes, prior to bNAbs could reactivate viral production from, and HIV expression on, the latently infected cells to further promote the elimination of these reactivated cells by bNAbs. Other immune-based therapies such as T-cell-based therapies, therapeutic HIV vaccines, or immune checkpoint blockers [4] could also be tested in combination with bNAbs at the time of acute HIV infection or after viral suppression.

Many questions arise from these research designs. How do we optimally quantify the changes in HIV reservoir size and composition following bNAbs? What types of sampling should be done? How often and how long should the bNAbs be given? At this time, there are no clear answers. Quantifying the HIV reservoir in PBMCs are limited by the sensitivity of available assays [30,31]. Lessons are learned from the reemergence of virus in three patients after several months to 2.5 years off treatment, who previously had no detectable HIV DNA or replication-competent virus [32–34]. The absence of predictive markers for rebound in the plasma or PBMC suggests the need to measure HIV in tissue, which is more difficult because of limitations in sampling and low viable cell yield. In these early trials, it seems prudent to measure cell-associated HIV DNA and HIV RNA, replication-competent virus and low-level viremia in the peripheral blood and tissue compartments, and store samples for future testing.

The bNAbs are currently administered intravenously or subcutaneously, and their half-lives vary. It is possible that administration as frequent as every 2–4 weeks may be needed. The duration of bNAbs will depend on trial designs. When given in addition to ART during acute HIV infection to reduce viral burden, one to two doses may be adequate. When the goal is to achieve HIV remission, more doses may be required to control viremia following ART interruption. Frequent administrations, however, could promote viral escape or elicit antibody to bNAbs, rendering bNAbs ineffective [2■,7,35]. The use of multiple bNAbs with different specificities is attractive and some data indicate these combinations will be superior. Notably though, the potency and breadth of bNAbs are HIV clade-specific, for

example, glycan-dependent bNAbs such as PGT121 have little activity against HIV CRF01_AE recombinant that circulates in Thailand and some Asian countries.

FUTURE RESEARCH

The fundamental research question is whether bNAbs can kill latently infected cells. The conventional belief is that latently infected resting cells express no HIV on their surface rendering them incapable of being detected and bound by bNAbs, as observed with natural immune surveillance. However, reduction in cell-associated viral DNA by bNAbs has been shown in some studies [32,62], but that may be due to shortening of infected cell half-life and blocking of viral spread [62]. Research to extensively characterize cells able to be cleared by bNAbs will help to elucidate this important question. Another critical question is the extent to which bNAbs can affect tissue reservoirs. Although these antibodies are believed to have poor tissue penetration, containment of reservoirs in these compartments was observed in one study in macaques [32]. For bNAbs to have a significant effect on HIV reservoir and remission, understanding their activities in lymphoid-associated tissues (e.g. lymph nodes and gut), and in the central nervous system, is a high priority research area.

CONCLUSION

Intervening during acute HIV infection with ART has been one of the most effective ways to attenuate HIV reservoir seeding. HIV reservoir size (frequency of cells harboring HIV DNA or replication-competent virus) is to date, the best, albeit imperfect, surrogate marker for time to viral load rebound in the absence of ART [36–38]. However, early ART alone is inadequate in achieving sustained viral remission as illustrated in the Mississippi child [32,33]. Therefore, combination cure therapy, akin to combination ART for HIV, will likely be required to achieve this goal. Perhaps, the most important research question facing the HIV cure field is the choices of combination therapy to advance into clinical trials. ART will continue to be the main stay of HIV treatment but bNAbs may have an important contributing role toward an HIV remission, particularly when given in the setting of low HIV reservoirs, such as in acute HIV infection. Research into delivering durable bNAbs by active immunization with novel viral-like particle immunogens or adeno-associated virus vector is underway [39,40]. The bNAbs could also be tested in combination with LRAs or other immune-based therapies. However, testing more than one novel therapy in HIV cure research is challenging at many levels. Understanding the contribution of individual agents to the efficacy and safety outcomes will be difficult and agents with no effect alone may provide synergy in combination strategies. The risk to trial participants would be theoretically greater with combination agents, but the likelihood of success may also be higher. Requirements for approval of combination cure therapies by regulator agencies are unclear. Partnership between companies may be complicated based on intellectual property and marketing considerations. Finally, measurement of success requires an interruption of suppressive treatment and observation. Defining a surrogate marker for rebound will greatly accelerate the evaluation of cure strategies including those using bNAbs.

Eradicating every cell capable of producing HIV is extremely difficult and currently unachievable in the absence of extreme measures such as the cancer treatment and bone

marrow transplantation with HIV resistant cells used in the Berlin patient [41]. The alternate goal of HIV remission is realistic and achievable. Early ART in conjunction with immune-based interventions such as bNAbs offers hope in realizing this goal and warrants their advancement into clinical trials.

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KEY POINTS

- Infection of resting and long-lived CD4⁺ T cells occurs during acute HIV infection. These cells can persist indefinitely, posing a major obstacle to HIV remission. ART instituted during acute HIV infection can restrict the HIV reservoir size in the peripheral blood and tissues.
- bNAbs clear cell-free virus and infected cells that express HIV. They have been shown in animal models to reduce viremia and frequencies of infected cells in the peripheral blood and tissue compartments. If, and how, bNAbs can eliminate latently infected cells is not well understood.
- Research strategies could include employing bNAbs in conjunction with ART in acute HIV infection to reduce HIV viral burden. They could also be given to virally suppressed individuals who initiated ART during acute HIV infection with a goal to eliminate persistently infected cells and prolong time to viral rebound in the absence of ART.

FIGURE 1.

Proposed research strategies for using broadly neutralizing antibody (bNAb) in acute HIV infection. In the typical course of HIV infection (grey line), HIV RNA peaks during acute infection, penetrates various body compartments to establish a latent reservoir, and ultimately reaches a steady level of viremia. Antiretroviral therapy (ART) initiated during chronic infection reduces HIV RNA, often to undetectable levels, but the virus rebounds when ART is stopped. bNAb's can be administered with ART during acute infection in order to possibly achieve a more rapid viral suppression (black line) and prevent establishment of a significant HIV reservoir. In people treated with ART during acute HIV infection, bNAb's could be given in attempt to eliminate HIV-infected cells to an extent that, thereby, viremic control posttreatment interruption can be achieved (dark grey line). It is also possible to give latency reversing agents (LRAs) to reactivate the expression of HIV on infected cells to facilitate the bNAb's function in eliminating these reactivated cells.

Table 1

Proof-of-concept studies of broadly neutralizing antibodies' effects on HIV viremia and reservoirs

Reference	Experimental design	Effect and/or implications for reservoir (measurement)	Main findings and/or comments
[26•]	In-vitro study involving human sample isolates from 29 HIV+ chronically infected, virally suppressed individuals bNAbs studied: B12, VRC01, VRC03, PG9, PG16, PGT121, 2G12, 2F5, and 10E8	PGT121, VRC01, and VRC03 were most potent in neutralizing HIV virus isolated from the latent viral reservoir in CD4 ⁺ T-cells, by 72, 52, and 44%, respectively, with 32% overlap between PGT121 and either VRC01 or VRC03 Abs Log suppression of HIV viral entry into uninfected CD8 ⁻ depleted CD4 ⁺ T-cells was 2.4log, 2.1log, and 1.8log for PGT121, VRC01, and VRC03, respectively	HIV-specific bNAbs can efficiently bind virions induced from the latent HIV-reservoir of CD4 ⁺ T-cells of individuals whose plasma viremia has been successfully controlled by ART HIV-specific bNAbs PGT121, VRC01, and VRC03 can dramatically suppress entry of latent-pool isolated HIV into CD4 ⁺ T-cells, and suppress HIV replication in stimulated autologous CD4 ⁺ T-cells of individuals receiving ART
[8••]	Neonatal (1–5-day-old) mice were sublethally irradiated and injected with CD34 ⁺ human hematopoietic stem cells intrahepatically. These humanized mice were used as the experimental model. Mice with 10% huCD45 ⁺ and 10% huCD4 ⁺ were selected for postexposure prophylaxis experiments in which mice were treated 4 days with either bNAbs or ART after infection of HIV-1 _{YU2} challenge virus Mice with measurable CD4 ⁺ cells by FACS analysis were selected for experiments assessing the effects of bNAbs and/or inducers. HIV-1 _{YU2} was used as the challenge virus. bNAbs were administered in mice 2–3 weeks postinfection, and viral inducers were administered once plasma-viremia and cell-associated HIV RNA dropped below the limit of detection LRAs used: Vorinostat, I-BET 151, CTLA bNAbs studied: 10-1074, PG16, and 3BNC117	After an 80-day monitoring period, 10 of 21 hu-mice showed a rebound to HIV viremia after cessation of postexposure prophylaxis of a tri-mix bNAbs (10-1074/PG16/3BNC117), as opposed to 18 of 22 hu-mice that received postexposure prophylactic ART. The hu-mice that rebounded after cessation of postexposure prophylactic bNAbs showed longer time to rebound on average (74–107 days), compared to hu-mice that rebounded after cessation of postexposure prophylactic ART (28–84 days) In chronically infected hu-mice with suppressed viremia, 10 of 23 showed viral rebound after administration of all three viral inducers simultaneously with tri-mix bNAbs, compared to 31 of 33 hu-mice exhibiting viral rebound after tri-mix therapy + any single inducer ($P = 0.0001$) or 22 of 25 mice exhibiting viral rebound that received tri-mix bNAbs alone ($P = 0.0018$)	bNAbs can interfere with the establishment of the latent HIV-1 viral reservoir as measured by time to viral rebound Combination bNAbs along with combination LRAs in virally suppressed mice can prevent viral rebound in almost half of the mice
[6••]	Neonatal (1–5-day-old) mice were sublethally irradiated and injected with CD34 ⁺ human hematopoietic stem cells intrahepatically. These humanized mice were used as the experimental model Humanized mice with measurable human graft of human lymphocytes at 8 weeks of age were injected intraperitoneally with HIV-1 _{YU2} In one arm of the study, mice were treated for 6 weeks with combination immunotherapy (PG16, 3BNC117, 10-1074) 2–3 weeks after infection	Combination bNAbs therapy 3BNC117, PG16, and 10-1074 for 6 weeks significantly reduced HIV viremia for all hu-mice and controlled viremia to undetectable levels for the majority of hu-mice studied. Combination bNAbs therapy reduced levels of cellular HIV-1 DNA an average of 0.8log DNA copies per 10 ⁶ cells When bNAbs was given with ART to lower the initial viral load followed by a tri-mix bNAbs immunotherapy during ART interruption, it prevented viral rebound in five of five hu-mice in the presence of the bNAbs mixture. Whereas the mice that only received ART, all rebounded when ART was stopped. Control of plasma viremia during period of bNAbs monotherapy correlated with bNAbs half-life	Immunotherapy with 3BNC117, PG16, and 10-1074 controls HIV-1 infection in hu-mice by reducing both plasma viral RNA and cell-associated viral HIV-1 DNA When bNAbs is given with ART to lower initial viremia, it allowed maintenance bNAbs combination immunotherapy to prevent viral load rebound when ART is discontinued

Reference	Experimental design	Effect and/or implications for reservoir (measurement)	Main findings and/or comments
	In the other arm of the study, HIV-1 _{YU2} infected mice were started on a 3 week course of ART, and a twice-weekly bNAb mixture (45-46 ^{G54W} , PG16, 10-1074) was initiated 5 days post-ART initiation and continued 4 weeks post-ART termination bNAbs studied: 3BNC117, PG16, 10-1074, and 45-46 ^{G54W}		
[7]	Neonatal (1–5-day-old) mice were sublethally irradiated and injected with CD34 ⁺ human hematopoietic stem cells intrahepatically. These humanized mice were used as the experimental model Mice were infected by HIV-1 _{YU2} by intraperitoneally, and chronic infection was assessed as persistent viremia as associated with progressive CD4 ⁺ T cell reduction. Mice were injected subcutaneously with 0.5 mg bNAb once or twice a week, based on the bNAb's half-life in mice Tri-mix: 3BC176, PG16, and 45-46 ^{G54W}	At 6–7 days after initiation of therapy, hu-mice receiving PGT128, 10-1074, PG16, 45-46 ^{G54W} , or 3BC176 mono-therapy showed an average decrease of 1.1log, 1.5log, 0.23log, 0.56log and no effect of HIV-1 RNA copies/ml, respectively. However, all mice (except one receiving 10-1074) rebounded to viremia after 14–16 days Of the 12 mice receiving tri-mix therapy, 3 exhibited prolonged control of viremia (two rebounding in 20–40 days, one with detectable but very low viremia in the absence of therapy for 60 days) Eleven of 12 living hu-mice receiving a penta-mix of bNAbs reduced viral load below or near the viral load limit of detection during the 60-day therapy period. Among this group, seven of eight hu-mice that survived the 100-day monitoring period post penta-mix therapy cessation, viral load rebound occurred after an average of 60 days after discontinuation of therapy	Monotherapy of bNAbs results in temporary decreases in the viral load of hu-mice Tri-mix and penta-mix therapies of bNAbs resulted in longer average time to viremic rebound in hu-mice compared to monotherapy Reemerging viruses following tri and penta-mix therapy cessation were found to remain susceptible to re-treatment by combination immunotherapy
	Penta-mix: PGT128, 10-1074, PG16, 45-46 ^{G54W} , and 3BC176 bNAbs studied: 3BC176, PGT128, 10-1074, 45-46 ^{G54W} , and PG16		
[2■]	Indian origin rhesus macaques that did not express MHC class I alleles <i>Mamu-A*01</i> , <i>Mamu-B*08</i> , <i>Mamu-B*17</i> . Monkeys were infected with intrarectally with 10 ³ TCID ₅₀ of SHIV _{AD8EO} Decreasing concentrations of bNAbs 10-1074 or 3BNC117 were administered intravenously and an intrarectal SHIV challenge followed 24-h post-bNAb passive transfer Combination bNAb therapy was administered intravenously in symptomatic, chronically infected macaques who had been infected for more than 3 years bNAbs studied: 10-1074, 3BNC117, and VRC01	Most animals treated with bNAb showed significantly reduced levels of cell-associated viral RNA from a viremic baseline to below the threshold of detection. No consistent change in cell-associated viral DNA levels occurred as a result of bNAb treatment Coadministration of 10-1074 and 3BNC117 resulted in transient increase in circulating CD4 ⁺ T-cells of chronically infected macaques	Combination bNAb therapy of 3BNC117 and 10-1074 is superior to monotherapy of either bNAb in suppressing viremia and restoring CD4 bNAb combination therapy can rapidly and potently suppress SHIV plasma viremia in chronically infected rhesus macaques. Immunotherapy alone or immunotherapy coupled with conventional ART has potential therapeutic utility Either 3BNC or 10-1074 alone can potentially block virus acquisition
[3■]	Indian origin, outbred, young adult, male and female, specific pathogen-free, rhesus monkeys that did not express MHC class I alleles <i>Mamu-A*01</i> , <i>Mamu-B*08</i> , and	A two-fold decline in proviral DNA in lymph nodes was observed and a three-fold decline in gastrointestinal mucosa proviral DNA was observed	Potent bNAb responses suppress viremia and reduce proviral DNA in tissue

Reference	Experimental design	Effect and/or implications for reservoir (measurement)	Main findings and/or comments
	<i>Mamu-B*17</i> . Monkeys were infected intrarectally with virus SHIV-SF162P3 9 months prior to mAb administration. mAbs infusions were done intravenously on day 0 and day 7		compartments without the generation of viral resistance
	bNAbs studied: PGT121, 3BNC117, and b12	PGT121 was most potent in suppressing viremia with four of four animals achieving undetectable viral load by day 7 and a prolonged time to viral load rebound correlating with the decline in PGT121 titers In 3 of 18 animals with low baseline viral loads receiving PGT121 alone or as part of a cocktail (<3.5log RNA copies/ml), long-term control of viral replication was observed even after the decline of PGT121 titers	A single infusion of PGT121 in rhesus monkeys resulted in rapid virologic control, with ability to reduce proviral DNA in tissues In macaques with low baseline viremia, PGT121 infusion led to sustained SHIV remission

ART, antiretroviral therapy; bNAbs, broadly neutralizing antibody; CTLA, cytotoxic T-lymphocyte-associated protein; FACS, fluorescence-activated cell sorting; I-BET, inhibitor-bromodomain and extraterminal; LRA, latency reversing agent; MHC, major histocompatibility complex; PG, IAVI Protocol G; SHIV, chimeric simian immunodeficiency virus/human immunodeficiency virus; TCID, tissue culture infectious dose.