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REVIEW

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Post-intervention control in HIV immunotherapy trials

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Purpose of review
While post-treatment control following interruption of standard-of-care antiretroviral therapy (ART) is well described, post-intervention control following immunotherapy in HIV cure-related clinical trials is less well understood. We provide an overview of recent studies that have identified post-intervention controllers and review the mechanisms that may drive this biologically important phenotype.

Recent findings
Post-intervention controllers have been identified in recent immunotherapy trials testing broadly neutralizing antibodies, immune modulators, modified T cells, checkpoint inhibitors, and gene therapy administered individually or in combination. Currently, there is substantial variability in how each trial defines post-intervention control, as well as in how the mechanisms underlying such control are evaluated. Such mechanisms include ongoing activity of both exogenous and autologous antibodies, as well as changes in HIV-specific T cell function.

Summary
While no therapeutic strategy to date has succeeded in definitively inducing HIV control, many studies have identified at least a small number of post-intervention controllers. The field would benefit from a standardized approach to defining and reporting this phenotype, as well as standardization in the approach to assessment of how it is achieved. Such efforts would allow for comparisons across clinical trials and could help accelerate efforts toward an HIV cure.

Keywords
HIV, HIV cure, immunotherapy, post-intervention control

INTRODUCTION

There is a global effort aimed at eradicating or inducing durable viral control of HIV. To achieve this, we need therapeutic strategies that reduce the reservoir and enhance the ability of the immune system to control HIV by stimulating or expanding existing immune responses and creating new ones. Although no trial has achieved this in all participants, many have observed what is termed "post-intervention control" (PIC) in at least some individuals. Post-intervention controllers are a proof-of-principle, can improve our understanding of the mechanisms underlying control, and may provide clues as to how future interventions can be targeted to achieve this outcome more broadly [1]. Here, we review what has been learned about post-intervention control from recent HIV immunotherapy trials with a view toward informing future cure research.

WHAT IS POST-INTERVENTION CONTROL?

HIV invariably rebounds within weeks of antiretroviral therapy (ART) interruption, usually with an exponential increase in viral load, although some individuals exhibit post-treatment control (PTC; see accompanying reviews). A variety of approaches have been evaluated for their ability to induce HIV control after an analytic treatment interruption (ATI) in which ART is paused in a monitored setting to observe the dynamics of HIV rebound [2]. However, there is no standardized definition for what constitutes post-intervention control, and most

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KEY POINTS

- Several approaches are being evaluated for their ability to induce post-intervention control of HIV after ART is paused; combined interventions are likely needed to address the complexity and diversity of the mechanisms that promote HIV persistence.
- Although the definition of post-intervention control has varied by study, it is typically characterized by factors such as the degree, duration, and pattern of control during an analytic treatment interruption.
- Mechanisms of post-intervention control may include residual direct antiviral effects, slowing of HIV re-emergence, and potentiation of HIV-specific T and B cell responses.
- Standardization of case definitions, a central database of post-intervention controllers, and an established infrastructure to share biospecimens across studies for posthoc analyses would be of tremendous value to the field.

studies use their own definition. There are several considerations:

Degree of control

The ultimate goal is likely to be the induction of complete suppression [3], even if eradication is not achieved. This would mean that plasma virus is no longer detectable on standard clinical assays. Since progress toward this goal will likely be incremental, it may be appropriate initially to set a liberal goal for post-intervention control in research studies, based on lowering the viral load set point below what is expected for most people with HIV (PWH). The set point reflects the average viral load off of ART at steady-state and is variably defined across studies. We define the post-ART set point as the median plasma HIV RNA level between the first measurement available 2 or more weeks following peak viremia and the time when ART is restarted. Although the pre-ART viral load set point can vary by several orders of magnitude, low set points are rare, and even relative changes in the set point of an individual (say, from a level of >10 000 copies/ml prior to ART and the intervention to one that is <1000 copies/ml post-intervention) may be informative [4]. As progress is made, a more restrictive target may be set, similar to current definitions of post-ART ("post-treatment") control [5]. Another target could be the level at which HIV can be transmitted (generally understood to be 200 copies/ml, although recent data indicate that the threshold may be more forgiving [6]). While the goal is to observe no virus, full suppression need not be achieved for a trial to be informative.

Duration of control

The duration of control observable in a trial is dependent on several factors, including the length of the ATI, frequency of monitoring, and duration and magnitude of viremia permitted. The definition of post-intervention control may also be dependent upon the trial's therapeutic strategy. Trials using immunotherapies with antiviral properties that have long half-lives, such as studies of long-acting bNAbs, may require longer durations of observation off of ART before a participant can be classified as a post-intervention controller.

Pattern of control

Several patterns of post-intervention control have been observed (see Fig. 1). These include delayed time to rebound, nonexponential viral rebound, waxing and waning periods of control (which we and others have termed "oscillations"), or no rebound. Although all patterns are characterized by a low viral load set point, each pattern may be associated with a distinct mechanism of control.

While the eventual goal is to identify a strategy that can achieve sustained control at levels at which the virus cannot be transmitted and does not confer any ill health consequences, the definition of post-intervention control does not need to be this strict. Rather, important lessons can be learned from interventions that alter the expected degree, duration, and pattern of HIV control after ART is stopped.

RECENT AND ONGOING TRIALS AIMED AT INDUCING POST-INTERVENTION CONTROL

Here, we review HIV cure immunotherapy trials in adults that reported the frequency of post-intervention control in a manuscript or conference presentation from 2022 to 2024, Table 1. These recent studies were built on two decades of investment in this area and impactful clinical trials testing novel immunotherapeutic approaches [7–13,14▪,15,16▪,17,18]. After describing each study, we discuss the proportion in the interventional arm achieving the study's definition of post-intervention control and what, if anything, is known about the mechanisms that may have contributed to control in these individuals.

Therapeutic vaccines

Because effective T cell and antibody responses have been associated with spontaneous and PTC of HIV,

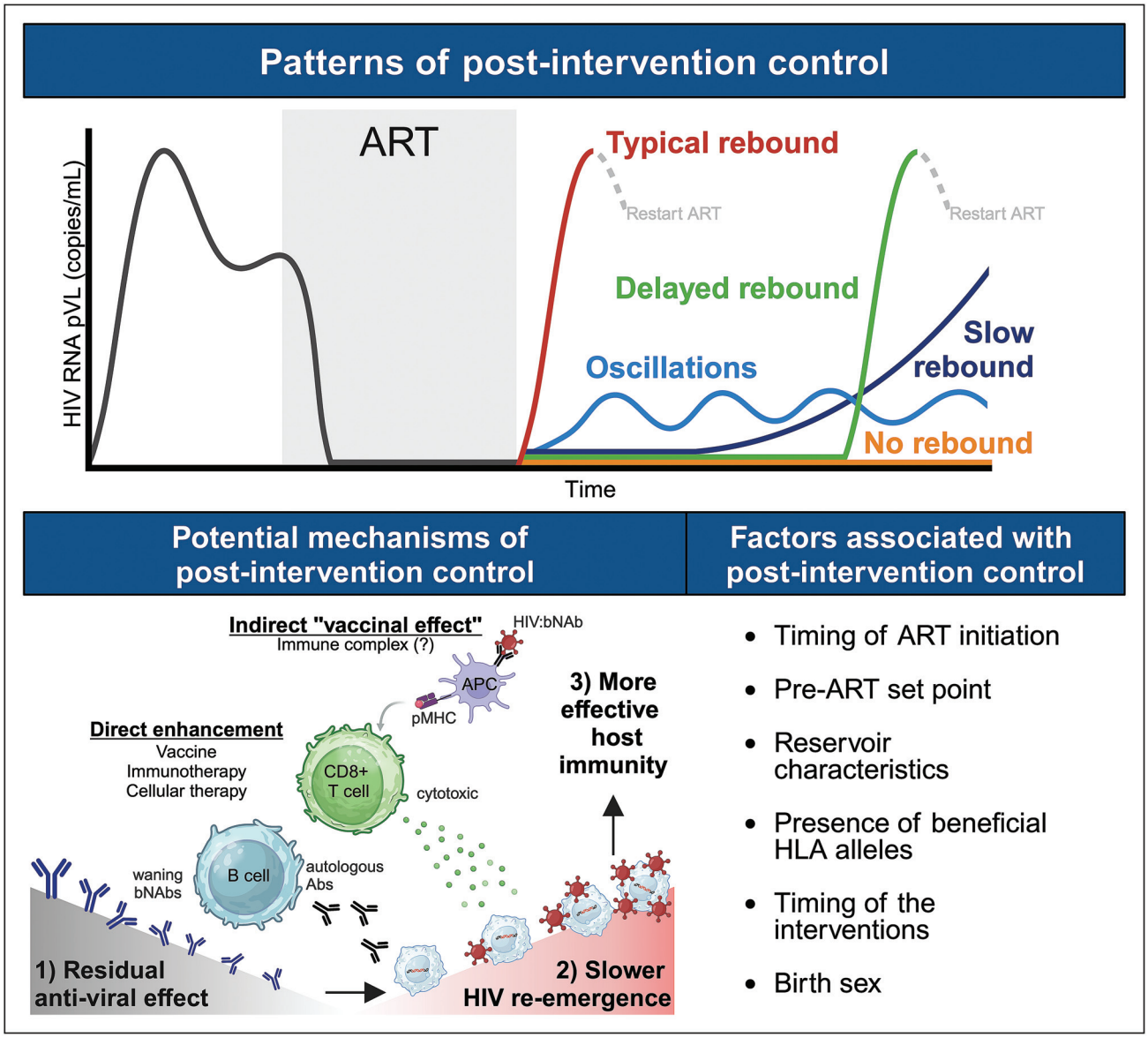

FIGURE 1. Patterns, potential mechanisms, and factors associated with post-intervention control. ART, antiretroviral therapy. HLA, human leukocyte antigen. APC, antigen presenting cell; bNAbs, broadly neutralizing antibodies; pMHC, peptide:major histocompatibility complex. Created in BioRender. Rutishauser, R. (2024) BioRender.com/t75c224.

most cure strategies seek to harness HIV-specific immunity to control the virus [19,20]. Endogenous HIV-specific T and B cells can be directly targeted by therapeutic vaccination, and therapeutic vaccines are an important component of many cure strategies. Most therapeutic vaccines for HIV seek to elicit new or to boost preexisting HIV-specific $CD8^+$ T cell responses [21], and studies are underway to evaluate the effect of boosting endogenous antibodies via vaccination (see NCT06006546). To be effective in a cure strategy, it is thought that T cell based therapeutic vaccines must elicit long-lived, highly functional HIV-specific $CD8^+$ T cells and overcome preexisting HIV-specific T cell immunodominance hierarchies to redirect T cells to target epitopes derived from relatively un-mutable viral sequences [21].

AELIX-002

AELIX-002 studied the administration of a vaccine regimen intended to induce T cell responses against viral antigens targeted in spontaneous controllers (HTI: HIVACAT T cell Immunogen formulated with DNA, modified vaccinia ankara [MVA], and chimp adenovirus [ChAd]) given to early-treated PWH to determine if they could elicit cellular immune responses [22▪▪]. Participants received either eight doses of vaccine or placebo and stopped ART for up to 24 weeks. In a posthoc analysis of participants without beneficial HLA class I alleles, eight of 20

Table 1. Summary of HIV cure immunotherapy trials that evaluated post-intervention control reported in 2022 to 2024

Category	Study name	NCT ID	Interventions	Loss of virologic control definition	Weeks post-ATI PIC assessed/ reported	Rate of PIC or placebo-arm PTC[a]	ART initiated early (<6 months) vs. late after HIV acquisition	References
Therapeutic vaccines	AELIX-002	NCT03204617; NCT04385875 (extension)	Controller-associated epitope (HTI)-based therapeutic vaccine regimen (DNA, MVA, ChAd) prior to ATI, vs placebo	pVL >100 000 copies/ml (once) or >10 000 copies/ml for 8 consecutive weeks	22	8/20 (40%; 0 NR) of vaccinated participants without beneficial HLA (vs. placebo: 1/12 [8%])	Early	[22▪▪,23]
Antibody-based interventions	Dual bNAbs	NCT03526848	2 bNAbs (3BNC117 + 10-1074) prior to ATI (group 2) or during ATI (group 1) (7 doses every 2-4 weeks)	2 consecutive pVLs >200 copies/ml	22	Group 1: 2/17 (12%; 2 NR)[a] Group 2: 0/6 (0%)	Late	[14▪]
	T003	NCT03721510	3 bNAbs (PGT121 + VRC07-523LS + PGDM1400) prior to and following ATI	2 consecutive pVLs ≥1000 copies/ml	44	4/11 (36%; 4 NR)	Not specified	[26,27]
	RIO	NCT04319367	2 bNAbs (3BNC117-LS + 10-1074-LS) prior to ATI vs. placebo; placebo group with option for bNAbs at time of ART re-initiation => 2nd ATI	6 consecutive pVLs >1000 copies/ml or 2 pVLs >100 000 copies/ml	8 and 32	2/4 (50%; 0 NR) of reported participants in the placebo=>bNAbs at ART re-initiation group (2nd ATI)	Early	[29]
Immune modulators	M19-939	NCT04223804	anti-PD-1 (Budigalimab) on ART prior to ATI (stage I), or during ATI (stage II, 4 doses), vs. placebo	pVL >200 copies/ml	29	Stage I: 0/17 (0%) Stage II: 2/9 (22%; 0 NR) (vs placebo: 0/9 [0%])	Not specified	[32,33]
Combination approaches	eCLEAR	NCT03041012	HDAC inhibitor (Romidepsin), bNAb (3BNC117), or Romidepsin + 3BNC117 at time of ART initiation, vs. placebo; followed by an ATI	2 consecutive pVLs >5000 copies/ml	12	5/16 (31%; 1 NR) of participants across intervention arms (vs. placebo: 2/4 [50%, 0 NR])	Early and late	[37▪,38,39]
	TITAN	NCT03837756	TLR9 agonist (Lefitolimod) plus 2 bNAbs (3BNC117 + 10-1074) prior to and during an ATI, vs. placebo	pVL >1000 copies/ml for 4 weeks or 4 consecutive pVL measurements >100 000 copies/ml	25	6/33 (18%; 2 NR) of participants across intervention arms (vs. placebo: 0/11 [0%])	Early and late	[41▪,42]
	BEAT2	NCT03588715	Pegylated IFNα-2b + 2 bNAbs (3BNC117 + 10-1074) prior to and during ATI	pVL >1000 copies/ml for 6 weeks	48	2/12 (17%; 0 NR)	Late	[43–52]
	AELIX-003	NCT04364035	Controller-associated epitope (HTI)-based therapeutic vaccine regimen (DNA, MVA, ChAd) + TLR7 agonist (Vesatolimod)	pVL >100 000 copies/ml (once) or >10 000 copies/ml for 8 consecutive weeks	24	10/30 (33%; 2 NR) (vs. placebo: 4/17 [24%; 0 NR])	Early	[23]
	UCSF-amfAR combination study	NCT04357821	conserved element (CE)-based DNA+IL-12/MVA therapeutic vaccine regimen + 2 bNAbs (10-1074 + VRC07-523LS) + TLR9 agonist (Lefitolimod) followed by 2nd round of bNAbs at the time of ATI	ART re-start criteria: pVL >50 000 copies/ml for 4 weeks, >10 000 copies/ml for 6 weeks, >2000 copies/ml for 12 weeks, or >400 copies/ml for 24 weeks	>20	7/10 (70%; 1 NR)	Early and late	[53–55]

ART, antiretroviral therapy; ATI, analytic treatment interruption; NR, no rebound; PIC, post-intervention control; PTC, post-treatment control; pVL, plasma HIV viral load; TLR, toll-like receptor.
[a]Post-intervention control with no rebound indicated with (NR).

vaccinated participants (40%) versus one of 12 placebo participants (8%) remained off ART up to 22 weeks post-ATI, with plasma HIV RNA levels less than 2000 copies/ml in five vaccinated and one placebo recipient. Of these, three vaccinated individuals who underwent an ATI extension demonstrated sustained control for 72 weeks [23]. While HIV reservoir measurements did not relate to time off ART, the magnitude of the HTI T cell response at ATI start was significantly associated with prolonged time off ART and lower plasma viral load at ART restart amongst vaccinated participants.

Antibody-based interventions

Combinations of HIV-specific bNAbs are in development for use in HIV prevention and treatment, and are now a core element of many HIV cure studies [24]. Previous studies in which bNAbs were administered at the time of ATI reported occasional post-intervention controllers [25]. In addition to their direct antiviral effects, bNAbs may also promote other effective immune responses, as discussed below.

Dual bNAbs

Seven doses of two bNAbs (3BNC117 and 10–1074) were given over 20 weeks to PWH on ART prior to an ATI [14▪]. Rebound occurred in most participants when antibodies reached serum concentrations below 10 μg/ml, or if rebound viral isolates lost sensitivity to the bNAbs; two individuals (of 23 followed to 22 weeks) remained suppressed off ART at least 1 year (including one heterozygous for the controller-associated HLA allele, B∗57). There was a modest decrease in the overall size of the intact HIV reservoir.

T003

This trial tested three bNAbs (PGT121, VRC07–523LS, PGDM1400) administered at days 0, 28, and 56 following during an ATI [26,27]. While most of the 12 participants rebounded in the context of resistance or waning antibody levels, four participants continued to exhibit post-intervention control, defined as having no consecutive plasma HIV RNA measurements at least 1000 copies/ml, up to week 44 despite serum bNAb levels waning below the threshold at which they are thought likely to continue to have antiviral activity (typically defined as 10 μg/ml [14▪,28]).

RIO

The RIO trial tested two bNAbs 3BNC117-LS and 10–1074-LS in PWH who had started ART within six months of HIV acquisition [29]. Participants were randomized to receive bNAbs versus placebo at the time of an ATI. Following the ATI, participants who were in the placebo group had the option to receive open-label bNAbs at the time of ART restart and subsequently complete a second ATI. As of December 2022, post-intervention control was reported after the second ATI in two of four participants in the open-label group.

Immune modulators

There is interest in the use of checkpoint inhibition (e.g., anti-PD-1 therapy) as a component of HIV immunotherapy regimens to overcome dysfunction and exhaustion of HIV-specific $CD8^+$ T cells. Recent studies in SIV-infected NHPs have suggested that checkpoint inhibition administered during suppressive ART may not boost virus-specific $CD8^+$ T cells and affect viral kinetics after an ATI [30]; however, there may be some efficacy if they are administered at the time of an ATI and in combination with other immunomodulators [31].

M19-939

After finding that administration of the monoclonal PD-1 inhibitor, budigalimab, prior to an ATI did not alter viral rebound dynamics, investigators administered four doses of budigalimab versus placebo every 2 weeks during an ATI [32,33]. Among nine participants who received the intervention, six exhibited atypical rebound kinetics including delayed time to rebound or some degree of post-ART control, compared to none of the five participants in the placebo group. Two individuals exhibited strict post-intervention control (plasma HIV RNA levels <200 copies/ml) for up to 29 weeks post-ATI (one with HLA-B∗57 allele). Exploratory studies suggested that participants with low viral loads had a trend towards greater expansion of $CXCR5^+$ $CD8^+$ T cells in the peripheral blood, which may preferentially home to lymph node B cell follicles, a putative site of HIV reservoir persistence.

Combination approaches

There is a growing consensus that sustained control of HIV will not be achieved with a single therapeutic modality; combination approaches may be needed [24]. Previously published studies in SHIV-infected nonhuman primates (NHPs; a less stringent model with a lower barrier to control) that used a combination of an innate-targeting toll-like receptor (TLR) 7 agonist and a bNAb were associated with long-term virologic suppression or delayed viral rebound [34–36]. A number of trials have tested different

combinations of therapeutics (bNAbs, therapeutic vaccines, immune modulators, and reservoir-targeting agents such as latency reversal agents [LRAs]) in an attempt to replicate these findings in people.

eCLEAR

eCLEAR investigated the administration of a bNAb, 3BNC117, with or without a subsequent HDAC inhibitor, romidepsin, given at the time of ART initiation in newly diagnosed PWH (versus ART-only; [37▪,38,39]). Five of 16 participants in the interventional arms who completed an ATI exhibited post-intervention control, defined as no consecutive plasma HIV RNA measurements more than 5000 copies/ml over 12 weeks. Two of four in the ART-only group achieved similar levels of control. Sensitivity to 3BNC117 predicted control amongst those receiving the bNAb, and amongst participants with 3BNC117-sensitive virus, some may have had an increased magnitude of Gag-specific $CD8^+$ T cells (measured 90 days after ART initiation by an activation-induced marker assay [37▪]). None of the seven total post-intervention controllers had a protective HLA class I allele, and five of the seven post-intervention controllers had started ART within 6 months of the estimated date of infection. Notably, one participant without protective alleles demonstrated sustained control for 5 years and was found to have the majority of sequenced intact proviruses in heterochromatin (as has been seen in some spontaneous controllers [40]).

TITAN

TITAN evaluated the impact of combining a TLR9 agonist (lefitolimod) with two bNAbs (3BNC117 and 10–1074) given in two doses to PWH on ART (early and late treated) immediately prior to an ATI and 3 weeks into the ATI [41▪,42]. Although all 11 participants in the placebo group had typical rebound, varying degrees of post-intervention control were observed in one individual in the lefitolimod group, four individuals in the bNAb-only group, and one individual in the combination group. This included two participants with no virologic rebound for 18 months. A post-bNAb increase in HIV-specific $CD8^+$ T cell responses was not observed.

BEAT2

BEAT2 studied a combination of weekly pegylated interferon-alpha 2b with two bNAbs, 3BNC117 and 10–1074, administered multiple times prior to and during an ATI in people who had initiated ART during chronic HIV infection [43–52]. Four out of 12 participants that completed the study exhibited post-intervention control (plasma viral load did not reach >1000 copies/ml for >6 weeks) for up to 33 weeks. Although the interventions did not enhance T cell responses, change the size of the reservoir, or induce a "vaccinal effect" boosting of HIV-specific T cells, pre-intervention neutralizing antibody titers of autologous antibodies were found to inversely correlate with time to rebound.

AELIX-003

AELIX-003 further investigated the HTI vaccination strategy (ChAdOx1.HTI and MVA.HTI) combined with TLR7 agonist vesatolimod prior to an ATI in early treated PWH [23]. Randomization was stratified based upon the presence of protective HLA alleles. The vaccine regimen was immunogenic. During the ATI, 10/30 participants in the intervention arm and 4/17 in the placebo arm remained off ART for 24 weeks. Despite similar proportions of control between the placebo and intervention groups, the magnitude of HTI-specific T cells at study entry correlated with time to plasma viral load more than 50 copies/ml only in the vaccinated group.

UCSF-amfAR combination study

This single-arm combination study tested the effect of a combination of an HIV Gag conserved element DNA vaccine (with an IL-12 adjuvant and followed by a boost with MVA62 [Gag, Pol, Env]), TLR9 agonist (lefitolimod), and two bNAbs (10–1074 and VRC07–523LS) over a 34-week period; at the time of ATI, a second dose of the bNAbs was administered [53–55]. Seven of 10 participants exhibited post-intervention control: one did not rebound but eventually re-started ART after approximately 72 weeks and six achieved set points of approximately 1000 copies/ml or less. Multiple patterns of control were observed. Individuals who went on to have lower plasma HIV RNA set points were found to have more robust proliferative responses of $CD8^+$ T cells in response to early rebounding virus, and their proliferating $CD8^+$ T cells expressed higher levels of TCF-1, a transcription factor important for promoting sustained HIV/SIV-specific memory T cell persistence and proliferative capacity [54,56–58].

Adoptive T cell therapy

Given the consistent association between functional HIV-specific $CD8^+$ T cell responses and spontaneous control of HIV [59], as well as the promise of CAR-T cell therapies for cancer and now other indications (e.g., autoimmunity [60]), adoptive T cell therapies are being actively evaluated as an HIV cure strategy. While no outcomes from clinical trials including adoptive transfer of anti-HIV T cells with

an ATI have been publicly reported in the past 2 years, recent studies suggest that CAR-T cells with bNAb-derived antigen binders can exert immunologic pressure and promote viral escape of rebounding virus after an ATI and even potentially shape the HIV reservoir on ART [61,62].

FACTORS ASSOCIATED WITH POST-INTERVENTION CONTROL

Studies to date have identified several clinical and virologic factors that appear to alter the likelihood that someone will achieve spontaneous or post-treatment control, and therefore may also be important for post-intervention control [5,63,64▪]. The likelihood of spontaneous and/or PTC is increased amongst cisgender women [19,20], in the presence of specific "beneficial" human leukocyte antigen (HLA) types [22▪▪,65,66▪,67], if the pre-ART viral load set point was lower, and if ART was initiated early after HIV or SIV acquisition [57]. For example, it is estimated that 10–15% of early-treated PWH may achieve some level of PTC, whereas this rate is closer to 5% or lower in people who initiate ART during chronic infection [5]. There are a number of reasons early-treated PWH may be more likely to achieve PTC, including the presence of smaller, less diverse and potentially inducible reservoirs, and the ability to mount a more robust anti-HIV immune response [40,68–72].

Because all of these factors influence the rate of spontaneous and PTC and likely affect the rates of post-intervention control, we suggest that they should be reported by HIV cure interventional studies in a standardized way, including reporting them at a participant-level (i.e., associated with viral load outcomes; see Fig. 1).

MECHANISMS OF POST-INTERVENTION CONTROL

The above-reviewed studies demonstrate that immunotherapeutic interventions in HIV cure trials have the potential to alter the time-to-rebound, the rate at which the virus increases, the peak viral load, and/or the steady-state viral load (set point). The field remains in a proof-of-concept stage, with each study providing more clues as to strategies that might definitively demonstrate post-intervention control at rates that exceed PTC following standard-of-care ART. Here, we review mechanisms that may contribute to post-intervention control (Fig. 1).

Residual direct antiviral effect

A straightforward explanation for sustained post-intervention control could be ongoing direct antiviral activity of the elicited immune responses and/or administered bNAbs (or other therapies) that directly prevents or alters the dynamics of rebound, even if levels are very low. Although the first generation of bNAbs waned relatively quickly, many bNAbs have since undergone modification to extend their biological half-lives ("LS" versions). Some are now capable of persisting following a single dose for months or longer in blood. Pharmacokinetics in tissues are poorly understood; it is unknown whether antibodies can persist in tissues after plasma levels have waned.

Slowing HIV re-emergence

Another mechanism that could contribute to post-intervention control is the ability of bNAbs (or other therapies that induce a sustained, partially effective response) to slow the typically explosive, exponential rebound of HIV following ART interruption. With modern ART, many PWH have plasma HIV RNA levels that are detectable at levels at or below the quantifiable level on conventional assays. Some studies, such as the UCSF-amfAR combination study, have noted "smoldering" HIV in which plasma levels remain detectable but unquantifiable for weeks or longer following ART interruption as bNAb levels waned. It is possible that a slow re-emergence of HIV in the presence of residual bNAbs allows host immune responses to "catch up" to control the virus without becoming overwhelmed. Thus, the fundamental balance of viral replication and host immunity is shifted, potentially allowing for a more successful response.

The "vaccinal effect"

It has long been suggested that bNAbs may have effects that go beyond neutralization, and that the interaction between HIV and bNAbs can potentiate HIV-specific T and B cell responses, possibly through the formation of immune complexes, in a phenomenon known as the "vaccinal effect" [73]. One human study has suggested that bNAbs may be associated with an increase in autologous HIV-specific antibody activity [14▪]. In terms of boosting autologous T cell responses, in a study of SHIV-infected nonhuman primates, treatment with bNAbs 3BNC117 and 10–1074 starting 3 days after infection promoted long-term viral control in 10 of 13 animals, and T cell depletion studies suggested that control was maintained by $CD8^+$ T cells [74]. In humans, one earlier study of dual bNAbs (3BNC117 and 10–1074) at the time of ATI demonstrated a clear, significant increase in the magnitude of Gag-specific $CD4^+$ and $CD8^+$ T cell responses at 6–7 weeks after bNAb

administration, while HIV was still suppressed [75]. This effect was accompanied by an increase in breadth of HIV-specific $CD8^+$ T cell responses. However, the boost in magnitude normalized by week 18 of the ATI and the increase in magnitude and breadth was not associated with post-intervention control. As noted above, some participants in eCLEAR who received bNAbs at ART initiation may have had a transient boost in the magnitude of HIV-specific $CD8^+$ T cell responses (although it is unclear if this related to the development of post-intervention control). In contrast, a boost in HIV-specific T cell responses was not observed in individuals who received bNAbs at the time of ATI in TITAN. While both the mechanisms and the generalizability of the "vaccinal effect" remain controversial, this remains an important area of investigation in HIV interventional trials.

Of note, both the second and third proposed mechanisms (slowing HIV re-emergence and the "vaccinal effect") are, by definition, influenced by the timing of immunologic interventions. In particular, for both bNAbs and anti-PD-1 therapy, administration of these therapies during a low antigen state (on suppressive ART) does not increase rates of post-intervention control, while there appears to be an effect of administration during higher antigen states (concurrent with ART start or at the time of stopping ART). Deep investigations into the immunology, virology, and pharmacology during these key windows will help elucidate the biological mechanisms that promote post-intervention control of HIV.

CONCLUSION

Modern HIV cure immunotherapy trials are building upon prior observations to define the mechanisms of post-intervention control and develop new strategies to achieve it. Ongoing challenges include the fact that most studies are small, only a handful of participants achieve post-intervention control, and definitions of post-intervention control differ. To enable cross-trial comparisons, we believe that the field should standardize reporting of the considerations noted in Table 2. Overall, just as prior efforts to collate exceptional controllers [76,77] and post-treatment controllers [5] led to greater standardization and insight for those phenotypes, now is the time for a similar undertaking for post-intervention controllers. A central database of post-intervention controllers from immunotherapy trials and an established mechanism to share biospecimens across studies for posthoc analyses would be of tremendous value. Such efforts are now underway and have the potential to provide new insights into the predictors and mechanisms of post-intervention control, with the goal of honing the therapeutic strategies needed to eventually achieve long-term ART-free control of HIV.

Table 2. Considerations of factors to harmonize across HIV cure interventional clinical trials to enable cross-trial comparison

• Harmonize definition(s) of post-intervention control
• Standardize the duration of treatment interruption and criteria for ART restart across trials
• Report factors associated with spontaneous and post-treatment control of HIV at a participant level, associated with post-ART viral load outcomes
• Collect biospecimens at similar/frequent time points pre and post-intervention (e.g., during early phases after ART release and/or HIV rebound; consider weekly)
• Assess immunologic, virologic, and pharmacologic measures using standardized/harmonized assays

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Conflicts of interest

M.J.P. serves on a Data Safety Monitoring Board for American Gene Technologies.

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- ■ of special interest
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