Beyond antiretroviral therapy: early interventions to control HIV-1 infection

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The HIV-1 reservoir is established very early after transmission when proviruses become integrated in the genome of long-lived immune cells. Three to 6 days after infection, intracellular HIV-1 DNA in $CD4^+$ T cells and virions attached to antigen-presenting cells can be detected in regional draining lymph nodes [1]. The rapid dissemination of HIV-1 in humans corresponds to observations in nonhuman primates (NHPs) in which simian immunodeficiency virus (SIV) DNA is detectable in lymph nodes and gastrointestinal mucosa on day 3 following infection, even in the absence of detectable plasma viremia [2]. Significantly, antiretroviral therapy (ART) initiated day 3 postinfection in NHPs delayed but did not prevent viral rebound following treatment interruption after 24 weeks of ART [2]. Thus, although ART effectively suppresses SIV/HIV-1 replication, it has no effect on already integrated proviruses and cannot prevent the establishment of a latent viral reservoir.

Current HIV-1 treatment guidelines recommend initiation of ART in all infected individuals as soon as possible after confirmatory HIV-1 diagnosis. In addition to the clinical benefits of starting ART early (e.g. lower morbidity and reduced risk of HIV-1 transmission), the initiation of ART during the earliest phases of infection also limits the size of the viral reservoir, results in faster rate of HIV-1 DNA decay, limits viral diversification and preserves immune competences [3,4].

Although limiting the size of the viral reservoir is believed to be a critical step toward curing HIV-1 infection, the exact mechanisms and sequence of events that may lead to control of viral replication in the absence of ART are currently unknown. Real-life examples of durable HIV-1 control in the absence of ART are rare but have been reported in so-called posttreatment controllers (PTCs) and elite controllers. PTCs are individuals who generally initiated ART during primary HIV-1 infection (within 6 months of infection) were maintained on ART for more than 12 months and subsequently displayed durable viral control after ART interruption. The mechanisms responsible for virological control in PTCs remains unclear, but in contrast to elite controllers, who spontaneously control viral replication without ever having been exposed to ART, PTCs tend to have a more severe symptomatic primary HIV-1 infection with higher plasma viral loads and lower $CD4^+$ T-cell counts [5]. Also, contrary to elite controllers, whom often carry protective class I human leukocyte antigen alleles (e.g. HLA-B57 and HLA-B27), most PTCs carry neutral or risk class I HLA alleles (e.g. HLA-B07 or HLA-B35) and have relatively weak HIV-1-specific $CD8^+$ T-cell responses [5]. Levels of $CD8^+$ T-cell activation are often lower in PTCs compared with elite controllers; however, PTCs may have enhanced natural killer cell-mediated immunity [5,6]. Collectively, PTCs and elite controllers offer two different models – which are not necessarily mutually exclusive – of how durable HIV-1 control can be achieved.

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Although early ART seems insufficient to induce durable virological control in the majority of individuals, who subsequently interrupt ART, early ART is being promoted as an important stepping stone in HIV-1 curative efforts. Initiation of ART prevents *de novo* infection of cells, but ART-induced decline in T-cell activation and general inflammation may also stabilize the pool of already infected $CD4^+$ T cells by promoting their transition from an activated to a resting and/or transcriptional silent state, thus influencing the establishing of the HIV-1 reservoir with a long half-life. In fact, studies have shown that the plasma viruses present at ART initiation are genetically very similar to the viral population in the HIV-1 reservoir found at later time points [4]. The pressing issue is whether additional early interventions such as latency reversal agents (LRA) and/or immunotherapy alone or in combination with early ART could increase the chances of achieving durable HIV-1 control?

Latency reversal aims to (re)activate HIV-1 transcription in latently infected $CD4^+$ T cells consequently leading to viral cytopathic and/or immune-mediated killing of the cells. Proof-of-concept clinical trials testing the 'shock and kill' approach to eradicate the HIV-1 reservoir have demonstrated that latently infected cells can be shocked, as evidenced by enhanced transcription of HIV-1 RNA and increased plasma viremia following treatment with LRA [7]. Importantly, these clinical trials have found no, or only modest, reductions in the size of the HIV-1 reservoir, possibly due to the presence of a very stable latent proviral HIV-1 reservoir. Thus, LRA initiated at or shortly after ART initiation when the viral reservoir may be more volatile due to the rapid turnover have been proposed to be more effective at eliminating infected cells than interventions targeting the stable reservoir observed after years of ART [8]. The clinical importance of the size of the viral reservoir has been investigated in patients who interrupt ART. Patients with small viral reservoirs experience viral rebound later than patients with larger reservoirs following ART interruption. However, unless every single replication-competent proviral HIV-1 DNA is eradicated/inactivated reducing the size of the HIV-1 reservoir without improving HIV-1-specific immunity will likely be insufficient in achieving durable HIV-1 control. Several case reports have documented that even among patients with extremely small or undetectable viral reservoirs (such as those receiving very early ART or hematopoietic stem cell transplantation), HIV-1 replication rebounds to high levels after periods of months to years off ART [9]. Thus, in addition to reducing the size of the viral reservoir, potent HIV-1-specific immunity that persistently surveys tissues and effectively kills infected $CD4^+$ T cells is probably needed to achieve durable HIV-1 control.

To this end, inducing potent $CD8^+$ T-cell immunity has been proposed as strategy to induce durable control of the infection. Two recently published NHP studies elegantly addressed this issue using broadly neutralizing antibodies (bNAbs). Similarly to ART, bNAbs are capable of suppressing viral replication but in contrast to ART, bNAbs also act as immunotherapy by directly engaging the host immune system through antibody-dependent cytotoxicity and by producing immune complexes that activate dendritic cells to become antigen presenting cells generating potent $CD8^+$ T-cell responses. Nishimura *et al.* [10] administered three weekly combinations of the bNAbs 10−1074 and 3BNC117 starting day 3 post-simian/human immunodeficiency virus (SHIV) infection. Viral rebound occurred between days 56 and 177 among all bNAbs-treated NHP, whereas ART-treated NHP had rapid viral rebound following treatment interruption likely due to the longer half-life of bNAbs relative to ART. As previously observed, ART-treated animals were unable to control viral replication following treatment interruption, but intriguingly bNAbs-treated animals maintained high $CD4^+$ T-cell counts upon viral rebound and subsequently resuppressed viral replication in the absence of any treatment. $CD8^+$ T-cell depletion resulted in rapid viral rebound at 2 and 3 years of follow-up strongly suggesting that the bNAbs induced $CD8^+$-mediated control of viral replication. In a different study, Iseda *et al.* [11] administered bNAbs (anti-SIV-IgG) to NHP on day 7 postinfection, and the animals subsequently suppressed viremia for up to 2 years. Virus-specific $CD8^+$ T-cell responses from bNAbs-treated compared with control IgG-treated animals were able to suppress SIV with escape mutants in the acute phase, whereas during the chronic phase no viral escape mutants accumulated and the SIV-specific $CD8^+$ T-cell responses converged on a pattern of immunodominant preservation. Both studies demonstrated that early immunotherapy with bNAbs alone as opposed to ART alone can lead to durable $CD8^+$ T-cell-mediated virological control [10,11].

Another strategy to induce long-lasting $CD8^+$-mediated immunity is by therapeutic immunization. In a NHP study, Borducchi *et al.* [12] administered a therapeutic vaccine with Ad26/modified vaccinia Ankara (MVA) [recombinant adenovirus serotype 26 (Ad26) prime, MVA boost] with a Toll-like receptor (TLR) 7 agonist after 24 weeks of suppressive ART. During follow-up, vaccine/TLR 7-treated NHP had reduced viral set points and delayed time to viral rebound compared with controls. Three of nine animals receiving this combination demonstrated virologic control to undetectable levels in the absence of ART. The breadth of the SIV-specific cellular immunity was negative correlated with viral set point and delayed time to viral rebound. Even though this intervention was administered 24 weeks after the initiation of ART, their findings highlight the potential impact of a therapeutic vaccine in the early phase of infection as a tool to induce potent HIV-specific $CD8^+$-mediated immunity.

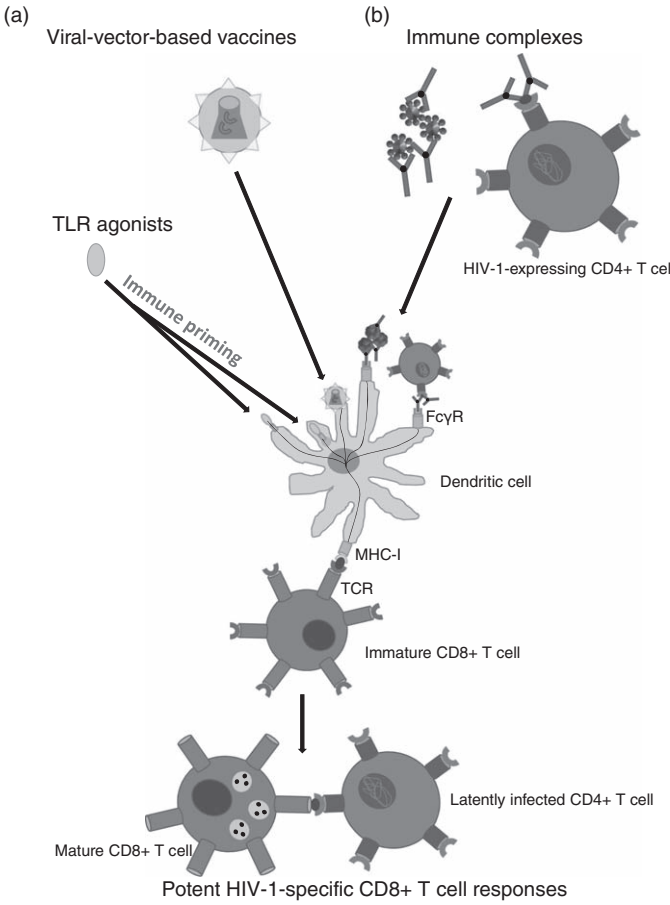

Fig. 1. Two possible mechanisms for generating potent HIV-1-specific CD8$^+$ T-cell responses that could diminish the latent HIV-1 reservoir. Antigen-presenting cells such as dendritic cells (a) display viral epitopes following transduction of target cell (here dendritic cell) with viral-vector-based vaccines and immune priming by Toll-like receptor agonists or (b) recognize immune complexes formed by opsonization of virions and/or HIV-1-expressing CD4$^+$ T cells by broadly neutralizing antibodies though their Fcγ receptors.

Collectively, these NHP studies demonstrate that it is possible to induce potent virus-specific CD8$^+$ immune responses capable of partial or complete ART-free control of SIV/SHIV infection (Fig. 1). Whether the same effects can be achieved in humans remain to been seen but these exciting findings raise the possibility that early immunological interventions aimed at boosting and/or maintaining the initial HIV-1-specific immunity with or without latency reversal could lead to durable control of the infection. In support of this concept, preliminary results from an ongoing clinical trial were presented at the 2017 CROI conference. In the BNC 02 trial (an extension of the BNC 01 trial [13]), early intervention with therapeutic HIV-1 immunization using an attenuated chimpanzee adenovirus serotype 63 (ChAdV63) prime and MVA boost was followed by latency reversal with romidepsin and MVA boost almost 3 years after the initial immunization and ART initiation. This combined intervention led to virological control in five of 13 (40%) of early ART-treated individuals that had lasted 6–28 weeks at the time of reporting [14]. Whether such ART-free HIV-1 control is durable and can be induced consistently across different populations will be an exciting focus for clinical studies in the coming years.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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