Immune Control of HIV

Muthukumar Balasubramaniam[1,2*], Jui Pandhare[1,3], and Chandravanu Dash[1,2,3*]
[1]Center for AIDS Health Disparities Research, [2]Department of Biochemistry and Cancer Biology, [3]School of Graduate Studies and Research, Meharry Medical College, Nashville, TN – 37208. USA.
[*]Corresponding Authors Correspondence:
cdash@mmc.edu, muthukumarb@mmc.edu

ABSTRACT The **h**uman **i**mmunodeficiency **v**irus (HIV) infection of the immune cells expressing the **c**luster of **d**ifferentiation **4** cell surface glycoprotein (CD4$^+$ cells) causes progressive decline of the immune system and leads to the **a**cquired **i**mmuno**d**eficiency **s**yndrome (AIDS). The ongoing global HIV/AIDS pandemic has already claimed over 35 million lives. Even after 37 years into the epidemic, neither a cure is available for the 37 million **p**eople **l**iving with **HIV** (PLHIV) nor is a vaccine discovered to avert the millions of new HIV infections that continue to occur each year. If left untreated, HIV infection typically progresses to AIDS and, ultimately, causes death in a majority of PLHIV. The recommended **c**ombination **a**nti**r**etroviral **t**herapy (cART) suppresses virus replication and viremia, prevents or delays progression to AIDS, reduces transmission rates, and lowers HIV-associated mortality and morbidity. However, because cART does not eliminate HIV, and an enduring pool of infected resting memory CD4$^+$ T cells (latent HIV reservoir) is established early on, any interruption to cART leads to a relapse of viremia and disease progression. Hence, strict adherence to a life-long cART regimen is mandatory for managing HIV infection in PLHIV. The HIV-1-specific **c**yto**t**oxic **T** cells expressing the CD8 glycoprotein (CD8$^+$ CTL) limit the virus replication *in vivo* by recognizing the viral antigens presented by **h**uman **l**eukocyte **a**ntigen (HLA) class I molecules on the infected cell surface and killing those cells. Nevertheless, CTLs fail to durably control HIV-1 replication and disease progression in the absence of cART. Intriguingly, <1% of cART-naive HIV-infected individuals called elite controllers/**H**IV **c**ontrollers (HCs) exhibit the core features that define a HIV-1 “functional cure” outcome in the absence of cART: durable viral suppression to below the limit of detection, long-term non-progression to AIDS, and absence of viral transmission. Robust HIV-1-specific CTL responses and prevalence of protective HLA alleles associated with enduring HIV-1 control have been linked to the HC phenotype. An understanding of the molecular mechanisms underlying the CTL-mediated suppression of HIV-1 replication and disease progression in HCs carrying specific protective HLA alleles may yield promising insights towards advancing the research on HIV cure and prophylactic HIV vaccine.
Keywords: HIV, PLHIV, AIDS, cART, CD4$^+$ T cells, CD8$^+$ T cells, Latency, HLA, CTL, Functional cure, HIV controllers, Elite Controllers.

INTRODUCTION

The **h**uman **i**mmunodeficiency **v**irus (HIV) targets immune cells expressing the **c**luster of **d**ifferentiation **4** cell surface glycoprotein (CD4$^+$ cells), which include T cells [1-3], macrophages [4-7], and dendritic cells [8-10], and establishes a permanent infection by inserting the double-stranded DNA copy (vDNA) of its RNA genome into the target cell chromosome [11]. The chromosomally-integrated vDNA (termed “provirus”) persists for the lifetime of the host cell and gives rise to progeny viruses. If left untreated, in majority of HIV-infected individuals (**c**hronic **p**rogressors, CPs), continuous production of progeny virus from the provirus causes *de novo* infections and target cell death [12-14]. The resulting progressive failure of the immune system leads to the development of **a**cquired **i**mmunodeficiency **s**yndrome (AIDS) and, ultimately, death [15]. Consequently, HIV has already claimed over 35 million lives due to AIDS-related opportunistic infections and cancers. There are two types of HIV: type 1 (HIV-1) and type 2 (HIV-2) [16, 17]. The HIV-1, which accounts for over 95% infections worldwide, is the virus responsible for the ongoing HIV/AIDS pandemic, whereas the relatively less pathogenic HIV-2 is endemic to West Africa. The lack of an effective preventive HIV vaccine [18-20], despite decades of intense research, is

resulting in millions of new HIV infections every year; globally, 1.8 million people were infected with HIV in 2017.

Anti**r**etro**v**iral drugs (ARVs) that target and inhibit the function of specific HIV-1 proteins and, consequently, certain stages of virus life cycle are currently the only treatment option for the 37 million **p**eople **l**iving with **HIV** (PLHIV) [21]. The standard of care is a **c**ombination **a**nti**r**etroviral **t**herapy (cART) involving a cocktail of ARVs aimed to manage pre-existing or minimize post-therapy emergence of drug-resistant viral strains [22-27], which result from the low fidelity HIV-1 replication process and/or host factor-induced mutations in viral genome [28-30]. Since its introduction in 1996, cART has been highly effective in suppressing HIV-1 replication, impeding disease progression, partially preserving or restoring the immune competence, and minimizing the risk of transmission [31-33]. Yet, cART blocks only the *de novo* infection of susceptible cells, but not the virus production from proviruses in the infected cells. Aggravatingly, a population of long-lived **r**esting memory **CD4**$^{+}$ T cells (rCD4s) harboring transcriptionally silent, and consequently non-replicating, provirus (latent HIV reservoir) is established very early in HIV-1 infection [34-37]. The cART does not eliminate the provirus [38], and hence any interruption of cART leads to rapid resumption of HIV-1 replication within days to weeks [39, 40]. Therefore, cART is not curative and must be administered uninterrupted for life. HIV-1-specific cytotoxic T-lymphocytes (CTL) expressing the **cl**uster of **d**ifferentiation **8** cell surface glycoprotein (CD8^{+}) represent the most critical host immune response limiting HIV-1 replication *in vivo* [41]. The CTLs eliminate HIV-infected cells by first recognizing specific viral peptides presented by **h**uman **l**eukocyte **a**ntigen (HLA) class I molecules on the cell surface and then activating effector mechanisms that cause cell killing. Nevertheless, in the case of untreated CPs, CTLs fail to durably control virus replication and prevent progression to AIDS. This failure of the CTL-mediated viral control stems from a combination of viral strategies designed to pre-empt or evade the CTL response. Prominent among them is the establishment of latent HIV reservoirs that are deficient in viral antigen production and hence are impervious to CTL-mediated immune responses [42]. Therefore, the latent HIV reservoirs present the greatest barrier to HIV cure [43].

Disconcertingly, 37 years into the epidemic, no curative treatment is currently available for the 37 million PLHIV. Consequently, close to a million people continue to die of AIDS-related illnesses every year. The "HIV care continuum"- a framework outlining the recommended steps of medical care for PLHIV, entails testing and diagnosis, linkage to and retention in clinical care, initiation of and adherence to cART, and viral suppression [44, 45]. However, 1 in 4 of the PLHIV (i.e. over 9 million individuals) are unaware of their HIV-1 status, and only around 60% of the PLHIV (~21 million individuals) are currently accessing cART. Further, two-thirds of the PLHIV (over 25 million individuals) reside in resource-limited settings of sub-Saharan Africa, which presents significant barriers to effective implementation of the HIV care continuum. Therefore, the HIV/AIDS pandemic is likely to continue to be a significant public health crisis in the foreseeable future for the following reasons: (1) requirement of and strict adherence to life-long cART regimen, even in the face of significant long-term side effects, (2) increasing rates of comorbid non-AIDS-related diseases (cardiovascular, liver, kidney) and disorders (neurocognitive) in PLHIV due to persistent and elevated immune activation and inflammation despite cART-induced viral suppression, and (3) the uncertainty of the timeline, let alone the prospects, of the availability of effective, viable, and scalable curative strategies targeting HIV. Hence, despite the associated scientific and logistical challenges, it is imperative that the scientific community and the funding agencies pursue the path towards developing curative strategies to tackle HIV [46].

Remarkably, the HIV-1 replication is robustly and durably suppressed, the viral load is maintained below the clinical detection limit, and the

disease progression is prevented over long-term in a small subset (<1%) of untreated (cART-naïve) HIV-infected individuals called elite controllers/**H**IV **c**ontrollers (HCs) [47, 48]. Despite the reported genetic and immunologic heterogeneity amongst HCs, robust HIV-1-specific CTL responses have been demonstrated to play a key role in controlling HIV-1 infection in HCs. Further, certain HLA alleles associated with enduring control of HIV-1 replication and long-term non-progression to AIDS are prevalent in HCs, whose CTLs display superior functional avidity (ability to recognize very low concentrations of HIV-specific antigens) and polyfunctionality (ability to secrete multiple cytokines) in countering HIV-infected cells. This illustrates that the human immune response, albeit in select human population, can mount a robust and enduring control of HIV-1 replication and prevent progression to AIDS, even in the absence of cART. Because HCs exhibit the core features that define a HIV-1 "functional cure" outcome, i.e. durable suppression of viral replication, absence of viral transmission, and non-progression to AIDS- all in the absence of cART, they have been proposed as a model for HIV cure research.

This review is directed at a broader readership in life sciences with the primary aim of providing an overview of the evolving challenges and opportunities in the ongoing research activities directed towards HIV cure. In this review, we start by drawing the reader's attention to the origin and types of HIV because any discussion on HIV cure or elimination at the clinical or population level must be cognizant of the existence of animal reservoirs (40 different simian immune deficiency viruses, two of which gave rise to HIV) [16, 49, 50], and the clinically-significant HIV subtype-specific variances in the HIV pathogenesis, transmission, and drug resistance [51-54]. We then provide a primer on the architecture, genome, and proteome of HIV-1, an outline of the HIV-1 replication cycle in the host cell, and a rundown on HIV-1 pathogenesis, so as to highlight how the virus make-up, replication strategy, and pathogenesis is geared towards establishing a permanent and immune-evasive infection in the host. The overviews of the HIV-1 latency, the ongoing research on HIV-1 cure, and the HIV-specific CTL response are leads to the discussion about how specific HLA alleles in the HCs contribute to the CTL-mediated durable suppression of virus replication and disease progression, and how a better understanding of the underlying molecular mechanisms may help advance scientific research efforts towards an HIV cure.

ORIGIN AND TYPES OF HIV

AIDS was diagnosed and recognized as a new disease in 1981 in the USA [55, 56] with the subsequent discovery of HIV-1 as the causative agent in 1983 [57]. The two types of HIV identified to date, HIV-1 and HIV-2, display similar morphology, tropism, and modes of transmission; however, they are genetically and antigenically divergent [58, 59]. HIV-1 is responsible for over 95% infections worldwide, and the different strains of HIV-1 are classified into four groups: **m**ajor (M), **n**on-outlier (N), **o**utlier (O), and P [60-63]. The group M HIV-1 is the predominant circulating strain responsible for >90% infections worldwide, and hence, for the global HIV/AIDS epidemic; viruses belonging to the other three groups are endemic in certain African countries and cause fewer infections. HIV arose from cross-species zoonotic transmissions of **s**imian **i**mmunodeficiency **v**iruses (SIV) from monkeys to great apes and ultimately to humans [16, 64, 65]. Four independent cross-species transmissions of SIV from chimpanzees (SIVcpz) or gorillas (SIVgor) to humans gave rise to the four HIV-1 groups: M and N from SIVcpz, and O and P from SIVgor. Notably, the pandemic HIV-1 group M strain arose in Cameroon almost a century ago from a single transmission event involving an SIVcpz-infected chimpanzee and a human. The group M strains are further classified into nine subtypes (A, B, C, D, F, G, H, J, and K); each subtype is genetically distinct but phylogenetically equidistant from each other. Two or more of these subtypes can further recombine their genetic material to generate mosaic strains known as **c**irculating **r**ecombinant **f**orms (CRFs); around 97 CRFs have been reported to date. The globally dominant HIV-1

subtype C accounts for nearly 50% infections worldwide and is concentrated in Southern Africa and India. The HIV-1 subtype B is dominant in the Americas, Western Europe, and Australasia, and accounts for around 10% global infections. Unlike HIV-1, HIV-2 is largely endemic in West Africa [16, 66, 67], although the virus has spread to other parts of world in the past decade [17]. Approximately 1-2 million of the PLHIV are infected with HIV-2. The different strains of HIV-2 are classified into nine different groups- A to I, which arose from nine independent cross-species transmission events involving the SIV from **s**ooty **m**angabey **m**onkeys (SIVsmm). Relative to HIV-1 infection, HIV-2 infection is generally marked by lower viral load, longer asymptomatic period, slower target cell depletion and disease progression, and lower transmission rates [68-75]. However, in the absence of cART, HIV-2 infection eventually leads to AIDS and, ultimately, death [76].

HIV-1 ARCHITECTURE, GENOME, AND PROTEOME

The infectious HIV-1 (virion) is a spherical-shaped particle measuring ~120 nm in diameter and consisting of an outer host cell-derived lipid bilayer membrane and an inner core [77]. The viral core comprises of a conical-shaped protein shell termed capsid [78] that encases a **r**ibo**n**ucleo**p**rotein (RNP) complex of two non-covalently attached copies of the ~9.7 kb-sized positive-sense **s**ingle-**s**tranded (ss) **v**iral **RNA** genome (vRNA), certain viral and host proteins, and the host cellular $tRNA^{Lys}$ [79]. The highly structured vRNA harbors several cis-acting structural elements and nine **o**pen-**r**eading **f**rames (ORF) [80]. The three major ORFs- *gag*, *pol*, and *env*, code for the polyprotein precursors of structural proteins [**ma**trix (MA), **ca**psid (CA), **n**ucleo**c**apsid (NC), and p6], enzymes [**pr**otease (PR), **r**everse **t**ranscriptase (RT), and **in**tegrase (IN)], and envelope proteins [**g**lyco**p**rotein **120** (gp120) and **g**lyco**p**rotein **41** (gp41)], respectively. The remaining six ORFs encode regulatory [**t**rans-**a**ctivator of **t**ranscription protein (tat) and **r**egulator of **e**xpression of **v**iral proteins (Rev)] or accessory [**ne**gative **f**actor (Nef), **v**iral **p**rotein **R** (Vpr), **v**iral **p**rotein **U** (Vpu), and **v**irion **i**nfectivity **f**actor (Vif)] viral proteins. These viral proteins are synthesized only after the DNA copy of the HIV genome is integrated into the host chromosome and then transcribed into viral mRNAs. The polymorphic capsid is composed of ~200-250 hexamers and 12 pentamers of the 24 kDa CA protein, and contains multiple copies of RT, IN, PR, NC, MA, and Vpr [81]. Approximately 7-14 Env spikes, each comprised of three copies of non-covalently linked heterodimers of viral gp120 and gp41, are anchored in the outer viral membrane [82-84]. The Env spike determines the HIV-1 target cell tropism, i.e. $CD4^+$ cells [85-88] and, being the only viral protein exposed on the surface of the virus particle, is the primary target of the neutralizing antibodies [20, 89-93].

HIV-1 REPLICATION

HIV-1 primarily targets and infects the $CD4^+$ T helper cells, macrophages, and dendritic cells in humans. HIV-1 replication in target cells is broadly categorized into two phases: early and late [94]. Besides the virus-encoded proteins, HIV-1 is extensively dependent on the host cell machinery and proteins for productive replication [95]. Remarkably, over 2000 host cellular proteins, termed **h**ost-**d**ependency **f**actors (HDFs), have been implicated in HIV-1 replication cycle [96]. Conversely, HIV-1 also employs its genome and proteome to effectively thwart the barriers imposed by host-encoded restriction factors [97]. The early phase begins with the Env-mediated adhesion of the virus particle onto certain cell attachment factors present on the surface of the target cells. The viral Env has been shown to adhere to the heparan sulfate proteoglycans on macrophages [98], $\alpha4\beta7$ integrin on T cells [99, 100], and **d**endritic **c**ell-**s**pecific **i**ntercellular adhesion molecule-3-**g**rabbing **n**on-integrin (DC-SIGN) on dendritic cells [101, 102]. This enables the viral surface subunit protein gp120 to sequentially bind to the CD4 receptor [85, 87] and one of the chemokine receptors, **C**-**C** **c**hemokine **r**eceptor type **5** (CCR5)- the preferred coreceptor of the transmitted form of HIV-1, or **C**-**X**-**C** **c**hemokine receptor type **4** (CXCR4), on the target cell surface [103-106]. The ensuing conformational

changes in the Env spike triggers the viral transmembrane protein gp41 to drive the fusion of the viral and cellular membranes, thus leading to the release of the viral core into the target cell cytoplasm [107]. This initiates the subsequent series of events of the early phase: reverse transcription, nuclear entry, and integration.

The capsid, by itself or by recruiting cellular cofactors, is being recognized as the master regulator of the early phase of viral replication [108-111]. The reverse transcription process- a defining feature of the replication of retroviruses such as HIV, takes place within the confines of the capsid in the cytoplasm, potentially to avoid exposure of the vRNA and/or the vDNA to the innate immune sensors [112-114]. Reverse transcription occurs in the context of a ribonucleoprotein complex of vRNA, viral proteins, and host factors- termed **r**everse **t**ranscription **c**omplex (RTC). The RT enzyme uses the host cellular $tRNA^{Lys}$ to prime the reverse transcription of the vRNA into a double-stranded DNA copy (vDNA) containing **l**ong **t**erminal **r**epeat (LTR) sequences at the 5′ and 3′ ends [115]. Importantly, the tendency of the RT to accommodate transfers of the growing DNA strand between the two copies of the vRNA during the reverse transcription process leads to the generation of recombinant progeny viruses. The capsid-binding cellular cofactor **cy**clo**p**hilin **A** (CypA) has been demonstrated to promote the viral reverse transcription process in a target cell type-dependent manner [116, 117]. Subsequently, the RTC transitions into another nucleoprotein complex termed **p**re-**i**ntegration **c**omplex (PIC), and the PIC-resident vDNA LTR ends are bound by the viral IN enzyme molecules [118]. The PIC, in concert with capsid and cellular cofactors, orchestrates the nuclear entry and integration of the vDNA into the host chromosome [119-122]. As a member of the lentivirus genus of retroviruses, HIV-1 can infect both dividing (activated $CD4^+$ T cells) and non-dividing (macrophages and quiescent T cells) target cells. Because an intact capsid is too big (~60 nm in diameter at the broad end of the cone) to navigate the **n**uclear **p**ore **c**omplex (NPC, ~40 nm in diameter at the central opening) [123], the reverse transcription process was generally considered to be synchronized with the disassembly of the capsid (aka uncoating) in the cytoplasm [124]. However, accumulating evidence suggest that uncoating may also occur at the NPC and/or in the nucleoplasm; the latter scenario likely involves capsid and/or NPC remodeling [125, 126]. For instance, the capsid-binding host proteins CypA, **Nu**cleo**p**orin **153** (Nup153), **Nu**cleo**p**orin **358** (Nup358), and, more recently, **c**leavage and **p**olyadenylation **s**pecificity **f**actor **6** (CPSF6) have been demonstrated to facilitate the viral nuclear entry [116, 126-129]. Once inside the nucleus, the PIC-resident viral IN, in concert with host factors such as the CA-recruited CPSF6 [130] and the IN-recruited **l**ens **e**pithelium-**d**erived **g**rowth **f**actor (LEDGF/p75) [131-133], mediates the preferential integration of the vDNA into transcriptionally active gene-dense regions of the human chromosomal DNA [11, 134-138]. The integrated vDNA (provirus) persists for the life of the cell [11]. The establishment of the provirus culminates the early phase of HIV replication.

In the late phase of HIV-1 replication, the proviral DNA may be transcribed by the cellular transcriptional machinery or, under certain circumstances, remain silent (latent provirus) [139]. After transcription and posttranscriptional processing, the completely spliced viral mRNAs are transported to the cytoplasm by the canonical host exportin 1 (XPO1)-RanGTP nuclear export pathway, whereas the transport of the unspliced full-length and partially spliced viral mRNAs is facilitated by the viral Rev protein in concert with XPO1-RanGTP [140]. In the cytoplasm, the viral mRNAs are translated into polyprotein **pr**ecursors [Pr55Gag, Pr160GagPol, and gp160], regulatory proteins (Rev and Tat), and accessory proteins (Nef, Vif, Vpu, and Vpr). Next, the viral proteins and full-length vRNAs needed for the generation of progeny virus traffic to the virus assembly site (typically, the plasma membrane) where the Gag protein binds to the membrane *via* its MA domain, dimerizes *via* it CA domain, and coordinates the assembly of an immature virus particle bound by the cell membrane [141-143]. The Gag NC domain binds

to the packaging signal (ψ) sequence of two copies of full-length vRNA and ensures their packaging into assembling virus particle. The cell membrane enclosing the nascent virus particle is embedded with trimeric complexes of non-covalently linked heterodimers of the viral gp120 and gp41 proteins that are derived from the viral gp160 protein by the action of cellular endopeptidases [144]. This non-infectious immature virus particle is then released from the producer cell by the action of the Gag p6 domain-recruited cellular **e**ndosomal **s**orting **c**omplexes **r**equired for **t**ransport (ESCRT) machinery. During the concomitant viral maturation process, the viral PR enzyme, itself encoded as part of the Gag-Pol, first matures *via* auto-processing and subsequently processes the Gag into MA, CA, NC, and p6, and the Gag-Pol into RT and IN, mature functional proteins [145]. The resulting mature infectious virus particle is termed virion, the transmission of which, as a cell-free virus particle or *via* cell-cell contacts, to a new target cell leads to the establishment of a new infection [146, 147].

HIV-1 PATHOGENESIS

HIV-1 transmission at the mucosal membrane- the main portal of virus entry, generally results from a single free or cell-bound virion (transmitted/founder virus) infecting a single target cell [147-150]. The current understanding of the earliest events during acute HIV-1 infection *in vivo* mainly derives from studies involving HIV-1 infection of human tissue explants *ex vivo* [151], and SIV infection of the non-human primate rhesus macaque [152, 153]. A typical time course of HIV-1 infection progresses through 4 phases: eclipse, acute infection, chronic infection, and AIDS [154]. The first one or two weeks after the virus transmission mark the eclipse phase during which HIV-1 is actively replicating at the site of infection and spreading to distant susceptible tissues and organs, all without detectable viremia or symptoms or immune response. The first detection of viral RNA in the blood marks the end of the eclipse phase. The acute/primary infection phase (weeks 2-4) is marked by high levels of viremia (>10^7 copies of viral RNA/mL of blood), large pools of infected $CD4^+$ T cells in blood and lymphoid tissues, and, consequently, acute depletion of $CD4^+$ T cells [155]. This phase is also frequently characterized by flu or mononucleosis-like symptoms. Both humoral (antibodies targeting viral proteins) and cell-mediated ($CD8^+$ cytotoxic T cells targeting viral antigen-expressing infected cells) host immune response is initiated at the time of peak viremia [42]. Majority of the productively infected $CD4^+$ T cells die from **a**ctivation-**i**nduced **c**ell **d**eath (AICD), viral **c**yto**p**athic **e**ffects (CPE), or CTL-mediated cell killing. A significant proportion of non-productively infected resting $CD4^+$ T cells in the susceptible lymphoid tissues have been shown to undergo pyroptosis, a form of programmed cell death. The resulting decline in $CD4^+$ T cell numbers and viremia, arising from the eventual catch-up by the host immune system and the exhaustion of available target cell pool, mark the end of the acute phase. This is followed by the chronic infection phase during which the viremia levels stabilize to a set point, which can vary by orders of magnitude between individuals. The $CD4^+$ T cell levels continue to steadily decrease due to the death of sizeable number of infected cells, and there is chronic immune activation and inflammation. If untreated with ARV, the HIV infection advances to the fourth and final AIDS phase anytime between months to 20 years (10 years on average). The AIDS phase is marked by significantly declining $CD4^+$ T cell numbers and increasing viremia levels; the consequent loss of immune control leads to opportunistic infections, cancers, and, ultimately, to the death of the infected individual [15]. The AIDS is generally considered to result from the HIV-infection associated loss of the $CD4^+$ T cells. However, because the turnover rate of SIV-infected cells in natural hosts who do not progress to AIDS is comparable to that of HIV-infected cells in humans who do progress to AIDS in the absence of cART, it has been suggested that the infection-associated $CD4^+$ T cell loss may not be the sole driver of disease progression to AIDS in humans [154]. Hence, two

characteristics distinguishing HIV-1 infection in humans from SIV infections in their natural hosts, namely the chronic immune activation and the robust infection of diverse subsets of $CD4^+$ T cells, has been postulated to contribute to the development of AIDS in humans, by causing immune exhaustion and depleting immune cells protective against opportunistic infections, respectively [154].

HIV-1 LATENCY

The current cART regimens suppress viral replication, reduce plasma virus levels to below the clinical detection limit (~50 copies of HIV-1 RNA/mL), and prevent disease progression. However, cART does not eliminate proviruses; traces of HIV-1 RNA can still be detected in the plasma by using ultrasensitive assays [37, 156]. This is primarily due to HIV-1 establishing a stable reservoir of non-productively infected and long-lived rCD4s (referred to as latent virus reservoir) harboring proviruses, within days of virus transmission and before detectable viremia [2, 35, 157, 158]. Notably, only around 2-7% of those proviruses in the rCD4s are replication-competent and thus constitute the relevant or bona fide population of latent reservoir [159]; the other predominant population comprises of defective proviruses [43, 159-161]. The latent reservoirs have been shown to be present in different anatomical compartments including the peripheral blood, lymph nodes, gut-associated lymphoid tissue (GALT), and central nervous system (CNS) [162-167], and, besides the $CD4^+$ T cells, other types of immune cells, especially of the myeloid lineage, have also been reported to contribute to the generation and maintenance of the latent reservoirs. However, the rCD4s from the peripheral blood continue to represent the most extensively characterized latent reservoir. These latent virus reservoirs are remarkably stable [168]. The resting and memory state of these infected cells largely precludes proviral gene expression and viral protein production [160]. Consequently, these latent virus reservoirs are generally invisible to CTL-mediated host immune response and also immune to cART, thus presenting the greatest barrier to HIV cure. HIV-1 can persist in different subsets of memory T cells including central (T_{CM}), effector (T_{EM}), transitional (T_{TM}), and the stem cell-like memory T cells. However, the T_{CM} cells, which display diverse tissue distribution profile, are generally regarded as the HIV-preferred latent cell reservoirs [169]. The latent HIV-1 reservoir, first evidenced *in vivo* in 1995 [34], displays an extremely slow decay rate (t1/2 = 3.7 years) in PLHIV on cART [168]; for instance, natural clearance of a million latently-infected cells may take ~73 years. Preempting the establishment of such latent HIV reservoirs in infected individuals continues to remain a formidable therapeutic challenge.

An early initiation of cART has been shown to minimize the size of this latent viral reservoir but is incapable of preventing its establishment. For instance, initiating the cART very early (3rd day post infection) in the SIV-infected rhesus macaque non-human primate model still did not prevent the establishment of the latent viral reservoirs [170]. In the case of HIV-1 infection, initiating cART extremely early during infection (10 days post transmission) led to undetectable virus levels in the infected individual for up to 2 years on cART; however, the virus rebounded 32 weeks after interruption of cART [171]. Further, these long-lived latently-infected rCD4s are maintained by homeostatic proliferation, antigen-driven proliferation, and integration site-driven clonal expansion, and thus persist despite long-term cART in PLHIV [169, 172-176]. The homeostatic proliferation is mediated by common gamma chain family of cytokines (IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21), the antigen-stimulated proliferation may be mediated by specific antigens (**c**yto**m**egalo**v**irus, CMV; **h**uman **p**apilloma**v**irus, HPV, **E**pstein-**B**arr **v**irus, EBV) or non-specific immune activators (bacteria), and the integration site-driven clonal expansion could result from viral integration into cell growth or cell cycle-related genes [177]. Especially, recent findings indicate that the clonally-expanded population of the latent reservoir containing replication-competent provirus [178, 179], a fraction of which are transcriptionally active even during cART [180], may account for over 50% of the latent reservoir

[172, 181, 182] and are more dynamic that previously anticipated [161, 176].

Despite cART-mediated suppression of ongoing virus replication, transient bursts of virus production from such latently infected cells, potentially upon exposure to antigens or cytokines, may contribute to the residual plasma HIV-1 RNA. Alternatively, ongoing virus replication in tissue compartments ineffectually targeted by, or inaccessible to, cART may also contribute to the residual plasma HIV-1. However, the resident virus populations in such inaccessible tissue compartments evolve differently and thus display reduced diversity than those of the latent HIV reservoirs. Direct cell-to-cell transmission of virus *via* virological synapses has also been proposed to contribute to the residual ongoing virus replication and establishment of latent HIV reservoir [183, 184]. Any disruption of cART will enable resumption of virus production from proviruses in latently-infected cells, thus leading to a relapse of pre-treatment level viremia within days to weeks [37, 39, 185]. Hence, an uninterrupted and life-long cART is essential for effectively managing HIV in PLHIV.

If untreated, HIV evades both the humoral and cell-mediated host immune response by acquiring escape mutations in its genome [186-192] and continues to actively replicate in infected individuals throughout their lifetime [193]. This discounts any need for HIV to establish latency as a means to persist in infected individuals. The prevalent theory proposed [46] to explain the incidence of HIV-1 latency invokes the transmitted viruses' preference for CCR5 tropism [150] and, consequently, for activated $CD4^+$ T cells capable of transitioning into rCD4s. The activated $CD4^+$ T cells are marked by the activation-induced upregulation and increased availability of CCR5, completion of the early events of virus replication leading to the critical step of vDNA integration (i.e. establishment of provirus) within few hours post infection, and the ready availability of the cellular factors required for the transcription of the proviral DNA. Conversely, the rCD4s are deficient in the expression or levels of the cellular cofactors required for optimal virus replication; for instance, completion of the reverse transcription process may take up to 3 days in rCD4s. Though the activated $CD4^+$ T cells infected by HIV-1 have a very short half-life ($t_{1/2}$ of ~1day) and die of one of the many proposed cell death pathways, if HIV-1 stochastically infects activated $CD4^+$ T cells that are in the process of transitioning into memory phenotype [194], a sufficient window of time may be available for completion of the early events of virus replication culminating in the establishment of the provirus. The transition into memory phenotype causes sequestration of host transcription factors that are essential for virus gene expression from the provirus, and the resulting transcriptionally-silent provirus [195] may further be subjected to certain epigenetic modifications that sustain the latent phenotype [158, 196].

Recent reports suggest that HIV-1 can directly infect resting $CD4^+$ T cells [197]. Though HIV can enter resting $CD4^+$ T cells [198], certain host restriction factors present significant blocks to steps in the early phase of virus replication. For instance, the host-encoded protein **s**terile **a**lpha-**m**otif (SAM) and **h**istidine-aspartate (HD) domain-containing protein **1** (SAMHD1) [199, 200] is highly expressed in resting $CD4^+$ T cells and impairs viral reverse transcription by limiting the availability of the nucleotides essential for vDNA synthesis [201, 202]. The resulting incomplete vDNA products are sensed by **i**nter**f**eron-γ **i**nducible protein **16** (IFI16), which leads to pyroptosis, release of pro-inflammatory cytokines, and ultimately the depletion of $CD4^+$ T cells. Occasionally, HIV infection in some resting $CD4^+$ T cells progresses through reverse transcription and nuclear import of the ensuing vDNA, which may or may not be integrated into the host chromosome. The unintegrated vDNA is typically circularized by end-to-end joining of the viral DNA LTR ends into 2-LTR circles by the host **n**on-**h**omologous **e**nd **j**oining (NHEJ) pathway or into 1-LTR circles *via* homologous recombination [203], and these unintegrated circular forms of vDNA persist for extended periods of time [204]. Recent demonstration of cellular activation-

induced and IN-dependent linearization of the 2-LTR circles and their subsequent integration into host chromosome suggests that the 2-LTR circles may also serve as a reserve supply for integration-competent vDNA [205, 206]. Taken together, the generation and maintenance of latent HIV reservoirs, which are not, or poorly, targeted by CTLs and cART represent a major hurdle to HIV cure efforts [174].

HIV-1 CURE

Two pathways have been proposed for achieving cART-free HIV cure: sterilizing cure and functional cure [46, 207]. The "sterilizing cure" refers to complete elimination of HIV from the patient's body by purging the latent reservoirs of replication-competent proviruses. The "functional cure" aims for immune system-mediated durable suppression of viral replication, in the absence of cART and without completely eliminating replication-competent HIV [208].

Two prominent clinical cases highlight the tantalizing prospect that HIV can be eliminated (Berlin patient) or temporarily controlled in the absence of cART (Mississippi baby). In 2006, an HIV-1-positive patient maintaining a cART-induced virologic suppression for over 10 years was diagnosed with acute myeloid leukemia that was neither associated with the HIV infection nor the treatment. This individual, later named Berlin patient, first underwent myeloablative conditioning regimen that employs chemotherapy and whole-body radiation to eliminate the host stem and immune cells. Subsequently, the patient received allogeneic hematopoietic stem cell transplantations (HSCT) from a chosen donor who carried a homozygous deletion in the *CCR5* gene that codes for the namesake co-receptor required for HIV entry. Following discontinuation of cART, neither viral RNA in the peripheral blood nor replication-competent proviral DNA in tissue compartments have been detected over the past 12 years [209, 210]. Though the underlying mechanism(s) remain unclear, three likely contributing factors include the conditioning regimen and the graft-versus-host disease (GvHD), both of which enabled the elimination of HIV-infected cells, and the non-permissiveness of the transplanted cells to new HIV infections. However, the inherent and significant risks associated with this clinical procedure makes it unsuitable for PLHIV who are negative for myeloid malignant diseases. Further, CXCR4-tropic HIV variants pre-existing in patients who receive such allogeneic transplantation with CCR5 Δ32 homozygous stem cells can breakthrough and rebound under the selection pressure [211]. The Mississippi baby was born in 2010 to an untreated HIV-1-infected mother and was started on cART 30 hours after birth. The baby tested positive for HIV up to 3 weeks of age but then the virus declined to below detectable levels by the end of 4 weeks of age. Despite the discontinuation of cART at 18 months of age, the virologic suppression was maintained [212]. However, the child experienced virologic rebound in mid 2014, and the child was placed back on cART [213]. Accumulating evidence over the years have substantiated the significant role of initiating the cART as early as feasible during the early stages of infection in containing the establishment of latent HIV reservoirs and achieving long-lasting remission in the absence of cART [214, 215]; however, the case of the Mississippi baby highlights certain limitations of this strategy. Research directed towards translating the insights gained from these clinical cases into viable curative interventions targeted at achieving cART-free remission in PLHIV are currently underway.

The mainstay of the therapeutic strategies focused on eliminating the latent virus reservoir is the kick(shock)-and-kill strategy [216-219] that relies on the use of **l**atency **r**eversing **a**gents (LRAs) to induce *de novo* production of viral proteins from the replication-competent proviruses in the latently-infected rCD4s, followed by viral cytopathic effect-induced or HIV-specific CTL-induced cell death [46, 220]. However, recent evidence suggests that the LRA-treated cells may not be cleared by cytopathic effects [220]. Hence, the first, and the most critical step, in CTL response after latency reversal is a prompt and effective recognition of

the viral antigens produced from the replication-competent proviruses [42]. *In vivo*, CTLs face multiple roadblocks to recognition of latently-infected cells. Recent evidence suggests that, unlike in the case of HIV-infected individuals who initiated cART during acute infection, almost all the replication-competent and defective proviruses from the rCD4s in patients who started cART during chronic infection contained escape mutations in certain dominant viral epitopes targeted by CTLs, and thereby are unaffected by CTL response [187]. These CTL escape mutations arise early in infection due to robust CTL response in the absence of cART and hence are archived in the latent reservoir. This necessitates the latent reservoir-targeting CTL-based therapies to be directed towards subdominant viral epitopes for which the virus hasn't acquired any escape mutations.

In HIV-infected individuals, 300 out of every 1 million rCD4s harbor a provirus [221]; nevertheless, only one among those contain an inducible replication-competent provirus, whereas the remaining rCD4s harbor defective proviruses [168, 222]. Irrespective of whether the cART is initiated during the acute infection or chronic infection phase, majority (over 90%) of the proviruses are defective [159]. Early initiation of ART limits the size of the reservoir but does not profoundly affect the proviral landscape [223]. The primary determinant of the viral IN binding to, and mediating the chromosomal integration of, the vDNA is the specific affinity between the viral enzyme and intact LTR ends of the vDNA. This permits indiscriminate integration of full-length, internally-deleted, and defective viral DNAs into host chromosome. The predominance of defective proviruses in latent reservoirs is an outcome of **apo**lipoprotein **B** **e**diting **c**omplex **3G** (APOBEC3G)-induced hypermutations, inactivating point mutations, packaging signal (ψ) deletions, major splice donor mutations, and large internal deletions [43, 159]. However, defective proviruses have been shown to be transcribed into RNAs that are spliced and translated [224]. More importantly, some CTL-targeted epitopes are produced, despite the presence of upstream lethal mutations, through aberrant translation, and such cells are recognized by HIV-specific CTLs. Because of the predominance of defective proviruses over replication-competent proviruses, the effectiveness of the CTL response can be significantly blunted by the non-productive targeting of cells harboring defective proviruses [225].

Contrary to the promising results from studies based on *in vitro* latency model systems, multiple clinical trials testing strategies based on the kick-and-kill approach have consistently failed to shrink, let alone eliminate, the latent viral reservoirs [226]. Insufficient latency reversal and suboptimal immune clearance have been frequently ascribed to such disappointing clinical outcomes. Accordingly, recent findings implicate additional barriers, present *in vivo* but absent in the *in vitro* latency models, in the inefficient CTL-mediated elimination *in vivo*. Apparently, the latency models do not fully recapitulate the complex nature of the latent virus reservoirs that are established *in vivo* over several years or decades in the face of cART [227, 228]. Nevertheless, and notably, the outcome of the sterilizing or functional curative strategies will likely depend on an effective HIV-specific CTL response- to eliminate any reactivated latently-infected rCD4s or to durably control the viremia, respectively.

HIV-1-SPECIFIC CTL RESPONSE

HIV-1-specific CTLs mount the most critical host immune response towards limiting virus replication and spread during primary HIV infection [155, 186, 229-231]. The CTLs, *via* their **T** **c**ell **r**eceptors (TCR), specifically recognize and bind to short HIV-derived peptides, which are derived from proteasomal processing of mature viral proteins [232] or truncated defective viral proteins, and presented by HLA class I molecules on the surface of the infected cells. Following this direct cell-to-cell contact, an immunological synapse is established between the two cell types that activates a cascade of effector mechanisms targeting the infected cell [233]. These include the secretion of cell death-

inducing effector molecules like granzymes, perforin, and Fas-ligand, and the release of a variety of antiviral cytokines and chemokines, which collectively orchestrate the killing of the infected cell, potentially before the biogenesis of progeny virus [234]. The significance of the CTL-mediated antiviral response to HIV-1 infection is evident from the (1) inverse correlation between the magnitude and promptness of the HIV-specific CTL response and the viral load set point during acute HIV infection, (2) rapid evolution of escape mutations within the sequences encoding the viral epitopes targeted by the CTLs, (3) robust ability of HIV-specific CTLs from infected individuals to kill HIV-infected cells *in vitro* [235], and (4) increase in viremia upon depletion of CTLs during acute SIV infection in the non-human primate animal model macaque [236]. Further, the strong selective pressure exerted on the virus to escape the CTL response, both at the individual and population level, is a major driver of HIV evolution [237-239]. The HIV-specific CTLs have also been reported to control HIV infection *via* non-cytotoxic mechanisms, especially by secreting beta-chemokines that block the HIV infection of target cells [240].

Despite the protective role played by CTLs during acute HIV infection, CTL response eventually fails to durably control virus replication and prevent disease progression in untreated HIV-infected individuals [241, 242]. This has been attributed to the virus acquiring CTL-resistant escape mutations [243, 244], virus disrupting the HLA Class I-mediated antigen presentation pathway [245], dysfunction of the $CD8^+$ T cells [246], and the rapid establishment and compartmentalization of non-replicating proviruses in rCD4s (latent virus reservoir) during primary HIV infection [42, 247]. The CTL-countering escape mutations acquired by the virus may interfere with processing of viral epitope, loading of viral epitopes onto HLA molecules, and binding of viral epitope antigens to TCR [243, 248]. Although several mother-to-child and adult transmission studies have demonstrated that the CTL escape mutant viruses are transmitted [239, 249-251], WT viruses are preferentially transmitted when an HIV-infected individual harbors a mixture of **w**ild-**t**ype (WT) and CTL-resistant mutant viruses [252]. This suggests that the CTL-escape mutations may impose a significant fitness cost on the viral variants. In untreated PLHIV, persistent exposure to HIV antigens (chronic antigenic stimulation) causes progressive dysfunction of the $CD8^+$ T cells, termed T cell exhaustion. This is marked by diminished proficiency of antigen-induced proliferation, reduced polyfunctionality, and apoptosis. The exhausted $CD8^+$ T cells also express a variety of coinhibitory molecules- the **p**rogrammed cell **d**eath-**1** (PD-1) being the central player [253, 254], which further impair their antiviral activity. Nevertheless, long-term cART has been reported to partially relieve the manifestations associated with T cell exhaustion. The proviruses in the latently-infected rCD4s are deemed transcriptionally silent and, consequently, lacking in viral antigen production- a prerequisite for CTL-mediated recognition and cell killing. This potentially renders the latently-infected rCD4s impervious to CTL-mediated host immune responses. However, because the CTLs are capable of recognizing even a single HLA-peptide antigen complex displayed on cell surface, an escape from CTLs would require the maintenance of a remarkably rigorous state of latency over a period of many years in cART-experienced individuals. Yet, available evidence indicates that episodic activation of a subset of such latently-infected cells may lead to low-level transient expression of HIV antigens [174]. Therefore, latency has been proposed to be the principle but not the exclusive barrier to CTL-mediated clearance of HIV-infected cells. Conversely, a role for CTL in limiting the expansion of viral reservoir in HIV-infected individuals on cART has been proposed. For instance, in SIV-infected macaques on cART, depletion of $CD8^+$ T-cells was shown to stimulate the levels of SIV transcripts, thus implicating a role for $CD8^+$ T-cells in suppressing viral transcription [255]. Recent research raises the possibility that the replication-competent proviruses in latent cells may be inherently resistant to CTL response [256]. For instance, treatment of $CD4^+$ T cells from HIV-infected

individuals on cART with combinations of LRAs and autologous CTLs diminished the levels of the cell-associated HIV DNA but not the replication-competent provirus. Importantly, this failing appears to neither stem from immune escape by the virus nor dysfunction of the autologous CTLs, because CD4⁺ T cells inoculated with autologous reservoir virus were eliminated by the autologous CD8⁺ T cells.

The replication strategy employed by HIV-1 is generally considered tuned towards ensuring the establishment of the provirus before the infected cell becomes the target of CTL response. This is because the incoming vRNA is not translated and the production of viral proteins, which are the *de facto* precursors for the peptide antigens targeted by CTL, requires transcription of viral mRNAs from the chromosomally-integrated provirus. However, studies in SIV-infected rhesus macaques demonstrated that the early presentation of peptide epitopes processed from the incoming viral Gag protein leads to the recognition of the target CD4⁺ T cell by the Gag-specific CTLs even before proviral DNA integration [257]. In the case of HIV-1 infection in activated CD4⁺ T cells, peptide epitopes derived from the incoming viral proteins and presented by protective HLA alleles have been reported to be recognized by HIV-specific CTLs and to confer antiviral activity [258, 259]. Notably, HIV-specific CTLs from HCs have been shown to be significantly efficient in recognizing and eliminating target CD4⁺ T cells even before the establishment of a productive infection [260, 261].

HIV-1 CONTROLLERS

A key impetus for the ongoing research focused on a functional cure for HIV is the recognition of HCs- a subgroup of untreated HIV-infected individuals with clinically undetectable viremia (<50 RNA copies/mL plasma) and normal or elevated CD4⁺ T cell counts (median levels at >500 cells per cubic millimeter of blood) for extended periods of time (many years to decades) [47, 48]. The HCs comprise <1% of untreated PLHIV, and majority of them do not progress to AIDS. Though uncommon, some HCs may eventually lose the virus control. The cART-naïve HCs differ from the **p**ost-**t**reatment **c**ontrollers (PTC)- another subgroup of PLHIV who exhibit sustained virologic control after discontinuing cART [262]. Because HIV infection in cART-naïve HCs is marked by durable suppression of viral replication, disease progression, and viral transmission, they are considered an apt model for identifying and defining the molecular mechanisms underlying these protective immunologic traits, which may significantly advance the research on HIV cure [263].

The HCs exhibit distinct genetic and immunologic characteristics, and several distinct mechanisms have been proposed to explain the HC phenotype [264]. However, robust HIV-1-specific CTL responses have been reported to be a major player and, many times, a common determinant in the manifestation of the HC phenotype [242, 265-268]. It has been suggested that a distinct host response, likely during early in infection, plays a major role in conferring the HC phenotype. Accordingly, the HIV set point-the stabilized viral load following acute infection that is considered a predictive marker for disease progression, generally correlates with the magnitude of the HIV-specific CTL response [188]. However, because sampling in HIV-infected individuals is typically after peak viremia, the current understanding of acute HIV infection dynamics is imprecise. Though the contribution of the HIV genetic variation-especially in the context of the viral accessory genes, to the HC phenotype has been studied extensively, the findings have been largely variable and many of the proposed models await verification [269]. This has led to the proposal that the host factors might play a relatively major role in conferring the robust and sustained virus control in HCs [270].

Polymorphism within the *HLA* class I locus has been reported to constitute the primary host genetic determinant of HIV infection outcome [271]. Certain HLA alleles associated with control of HIV-1 and non-progression to AIDS (e.g. HLA-B*27, HLA-B*57) are prevalent in HCs, whereas

HLA alleles associated with accelerated disease progression (e.g. HLA-B*35) are scarce in HCs [264, 272] [273]. Conversely, some PTC cohorts are marked by low incidence of the protective HLA-B*27 and HLA-B*57 alleles, and higher prevalence of HLA-B*35 allele. This suggests that the HC's ability to robustly control HIV-1 may be largely dependent on potent HLA-B-restricted HIV-specific CTLs. Interestingly, a proportion of macaques carrying MHC class I allele Mamu-B*08 or Mamu-B*17, the viral antigen-binding motifs of which resemble those of the human HLA-B*27 or HLA-B*57, respectively [274, 275], have been shown to display HC-like phenotype when infected with pathogenic SIV [276-278]. The HIV-specific CTLs in HCs are functionally superior to that in PTCs and CPs- in terms of avidity and polyfunctionality, in countering virus replication, and thus lead to better immunologic control [279-281]. Further, unlike the HIV-specific CTLs in CPs, the HIV-specific CTLs in HCs mediate a sustained response [282, 283] because they are more resistant to the persistent antigen stimulation-induced T-cell exhaustion [284], and do not lose the proliferative capacity [285] during the chronic infection phase because they are better at evading the inhibitory effect of the **reg**ulatory T cells (Treg) [286]. The HIV-specific CTLs from HCs are also more inhibitory to HIV-1 replication *in vitro* [287].

The protective HLA alleles have been reported to be distinctive in their propensity to present the most conserved viral epitopes to the HIV-specific CTLs [288]. The resulting immune pressure on the virus drives the emergence of escape mutations within the sequences that encode the CTL-restricted viral epitopes, which may consequently be impaired in processing, loading onto the HLA molecules, and binding to the TCR on CTLs. However, the evolution of the escape mutations in the most conserved regions of the HIV-1 genome invariably imposes significant fitness costs on the mutant viral variants [289]. Therefore, though the generation of viral variants may appear to have compromised the protective role of HLA alleles, the ensuing negative impact on the viral replication efficiency has been proposed to confer the characteristic immune control in HCs harboring such protective HLA alleles. Accordingly, the influence of the HLA loci on set point viremia in HIV-infected individuals is primarily mediated through its immune pressure on viral genetic variants, as evidenced from the exclusive association of HLA variants with specific viral mutants [290, 291].

Some of the most immunodominant viral epitopes targeted by CTL are derived from the viral Gag and Env proteins. Gag-specific CTLs have been shown to be more potent in viral suppression than the Env-specific CTLs [292], and, accordingly, robust CTL-mediated targeting of Gag epitopes has been associated with lower viral set point and, consequently, slower disease progression [268, 293]. For instance, the slower progression to AIDS by HLA-B*27:05-positive HIV-infected individuals has been ascribed to the CTL response toward the HLA-B*27-restricted immunodominant Gag epitope KK10 [294-296]. When viral variants harboring escape mutations (that compromise the CTL response) within the KK10 epitope and compensatory mutations (that relieve the viral fitness cost) arise, typically late in infection, it leads to rapid progression to AIDS [188, 297]. Interestingly, the human anti-HIV restriction factor tripartite motif-containing protein 5 alpha (huTRIM5α), which binds to the incoming viral capsid core and inhibits the viral reverse transcription, has been implicated in the control of HIV infection in HCs carrying the HLA-B*27 or HLA-B*57 alleles; the CTL escape HIV-1 CA mutants exhibited enhanced sensitivity to the restriction by the human huTRIM5α [298-300]. A direct comparison of the functional characteristics of the HLA-B*27-KK10-specific TCRs from the HCs and CPs indicated that the TCRs did not contribute to the differential CTL response in these two populations [301]. Further, the latent viruses in patients who initiate cART during the chronic phase of infection contain escape mutations in CTL-targeted dominant viral epitopes and thus are immune to respective CTLs [187]. Recent immune-based therapeutic studies have provided prospective evidence that CTL

responses, especially those targeting the subdominant viral epitopes that hasn't acquired any CTL escape mutations [18], may play a critical role in HIV cure. Rhesus macaques vaccinated with a replicating CMV vector expressing SIV genes and then challenged with a pathogenic SIV virus became infected, but the virus was subsequently eliminated in half of the animals. This was attributed to the vaccine-induced generation of virus-specific broad CTL responses that targeted the HLA class 1-restricted subdominant epitopes and not the immunodominant epitopes capable of mutating with ease [302, 303]

Eliminating nonproductively-infected resting $CD4^+$ T cells, i.e. after viral entry but before reverse transcription, can prevent both abortive and latent infection, thereby preempting the $CD4^+$ T cell depletion and the size of the latent virus reservoir, respectively. Interestingly, HIV-specific CTLs have been reported to be capable of recognizing cognate peptides derived directly from the incoming virus particles and presented *via* the HLA Class I molecules, both in activated $CD4^+$ T cells [258, 259] and in resting $CD4^+$ T cells [260]. More recently, incoming HIV-1 particles in resting non-productively infected $CD4^+$ T cells were reported to be processed by host proteasomes and aminopeptidases into antigens that are then displayed by the HLA-I molecules on the cell surface. Strikingly, HIV-specific CTLs from the HCs, but not the CPs, harboring at least one of the two protective HLA class I alleles- HLA-B27 or HLA-B57, were shown to recognize such virus inoculum-derived peptides, form synapses between the two cell types, and orchestrate cell death, all within few hours [261]. The identification of factor(s) that enable the $CD8^+$ T cells from HCs, but not the CPs, to better recognize and target the non-activated infected cells may provide promising avenues for not only reducing the viral reservoir but also potentially limit the establishment of the latent virus reservoir *via* T-cell based prophylactic vaccines.

The recognition of HCs has, despite the challenges discussed above, spurred the hopes of devising sustainable HIV cure strategies. Assembling large cohorts of HCs will significantly aid in identifying and characterizing their unique immune correlates. However, because the clinical outcomes of HCs can be heterogeneous and because the treatment guidelines for HCs are still inexact, it is critical to precisely define the HC phenotype that will serve as suitable model of functional cure research. The recent identification of viral properties and host factors potentially associated with natural loss of virus control in HCs can be used as predictive biomarkers to determine treatment intervention [304-306]. Studies on HC cohorts have started to reveal crucial insights on distinctive immune-control mechanisms [261, 307-309], including the observation that sustained virus suppression can be attained even in patients lacking the known protective HLA alleles. Therefore, the HCs may hold the key for immunotherapy-based HIV cure [272].

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