40 years fighting the human immunodeficiency virus (HIV), but still no definitive cure

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Abstract

Infectious diseases continue to be a major public health problem, in addition to their impact on social and economic dynamics, which can reach global dimensions. At the turn of the millennium, we witnessed two global viral pandemics with a high social impact that exemplify this fact: the AIDS pandemic caused by the HIV-1 lentivirus towards the end of the 20th century and the COVID-19 pandemic caused by the SARS-CoV-2 coronavirus at the beginning of the 21st century. In this paper we summarize the efforts to find a cure for HIV-1, an infection which can be treated but which lacks a cure intervention that is scalable to all currently infected people.

Keywords: HIV-1, cure, viral reservoir.

40 anys de lluita contra el virus de la immunodeficiència humana (VIH), però encara sense una cura definitiva

Resum

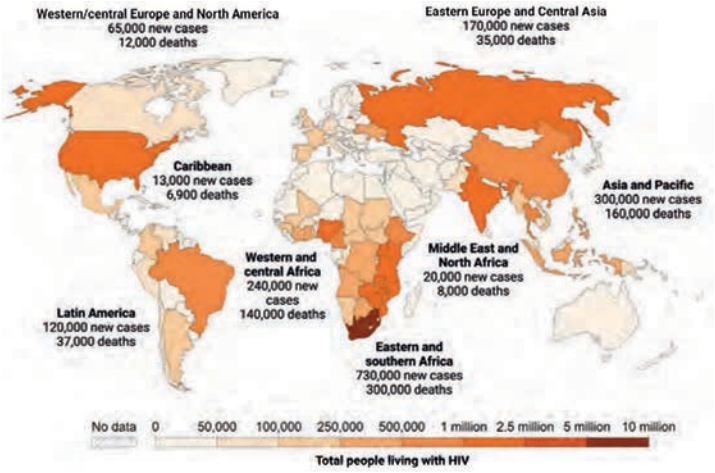
Les malalties infeccioses continuen sent un gran problema per a la salut pública i el seu impacte en la dinàmica social i econòmica pot arribar a dimensions globals. Amb el canvi de mil·lenni, hem estat testimonis de dues pandèmies víriques mundials amb un alt impacte social que exemplifiquen aquest fet: la pandèmia de la sida causada pel lentivirus del VIH-1 a la fi del segle XX i la pandèmia de la COVID-19 causada pel coronavirus SARS-CoV-2 a principis del segle XXI. En aquest article, resumim els esforços per trobar una cura per al VIH-1, una infecció que pot ser tractada, però que manca d'una intervenció curativa que sigui escalable per a totes les persones actualment infectades.

Paraules clau: VIH-1, cura, reservori viral.

1. Introduction

The HIV/AIDS pandemic is a major global health issue, involving one of the most devastating infectious diseases ever known. It has been responsible for nearly 84.2 million infections and 40.1 million people have died due to HIV/AIDS-related complications since the start of the epidemic. In 2021, the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimated that about 38.4 million people were living with HIV worldwide, 1.5 million were newly infected and more than 650,000 people had died from AIDS-related illnesses (UNAIDS, 2021).

Despite being a worldwide pandemic, its prevalence varies greatly between continents and countries, with the biggest epidemic affecting eastern and southern Africa, where 44.6% of all new infections worldwide take place. In this region, 6.2% of the adult population is living with HIV (Figure 1).



↑ Figure 1. Current epidemiological situation on HIV/AIDS pandemic. The estimated number of people living with HIV per country in 2022 is color-coded and obtained from (UNAIDS, n.d.). If epidemiological data for 2022 was not available, the most recent data for the period 2019-2021 is shown (UNAIDS, 2021; Roser and Ritchie, 2023). Estimates on the number of new cases and deaths per geographical region in 2022 are superimposed on the image and obtained from (UNAIDS, 2020*b*). Image was created with MapChart (*mapchart.net*), licensed under a Creative Commons Attribution-ShareAlike 4.0 International License, <https://creativecommons.org/licenses/by-sa/4.0/>, and then modified with BioRender (*BioRender.com*).

2. Origin of HIV/AIDS

In 1981, the epidemiological digest *Morbidity and Mortality Weekly Report* (MMWR), published by the Centers for Disease Control and Prevention (CDC) of the United States, reported an increase of unusual variants of pneumonia (*Pneumocystis jirovecii*), of aggressive cancers such as Kaposi's sarcoma, and of other opportunistic infections mainly, although not exclusively, in previously healthy young homosexual men (Centers for Disease Control, 1981; Gottlieb *et al.*, 1981). All the reported cases had in common a depletion of $CD4^+$ T cells and signs of severe immunodeficiency, a characteristic that contributed to the subsequent definition of this pathology as acquired immunodeficiency syndrome or AIDS.

In 1983, the team of Françoise Barré-Sinoussi and Luc Montagnier, at the Institut Pasteur in Paris, isolated and characterized a lymphotropic retrovirus in cultured T cells from an individual with AIDS-like symptoms (Barré-Sinoussi *et al.*, 1983).They received the Nobel Prize in Medicine for this discovery in 2008. A few months later, Robert Gallo at the National Cancer Institute in Bethesda isolated the same retrovirus from a larger group of individuals and suggested a causal involvement in AIDS (Gallo *et al.*, 1983). This T-lymphotropic retrovirus was later named *human immunodeficiency virus* (HIV) by the International Committee on Taxonomy of Viruses (Coffin *et al.*, 1986). In 1986, a virus was found in West Africa causing a morphologically similar but antigenically different AIDS and it was called *HIV type 2* (HIV-2) to distinguish it from the original type (HIV-1) (Clavel *et al.*, 1986). Epidemiological and phylogenetic analyses have shown that HIV-1 and HIV-2 are closely related to the simian immunodeficiency virus (SIV) (Chakrabarti *et al.*, 1987) found in Central African chimpanzees (SIV_{cpz}) (Huet *et al.*, 1990) and West African dark mangabeys (SIV_{sm}) (Hirsch *et al.*, 1989), respectively. These relationships, together with chrono-molecular inference analyses, provided the first evidence that HIV-1 and HIV-2 evolved from different nonhuman primate species through interspecies transmissions and were introduced into the human population between 1920 and 1940, spreading from Africa to other parts of the world (Sharp and Hahn, 2011; Faria *et al.*, 2014).

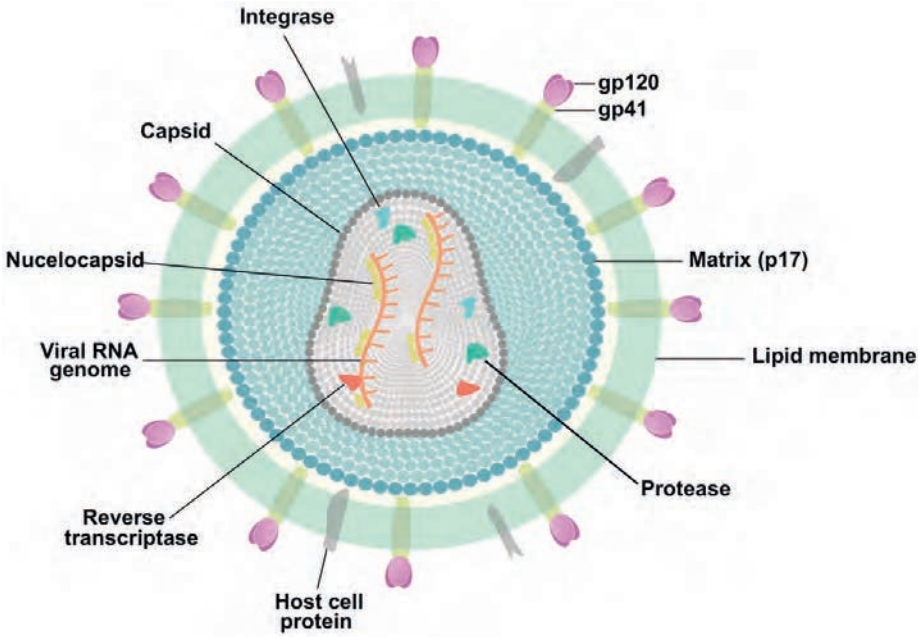
3. HIV virology

3.1. HIV classification

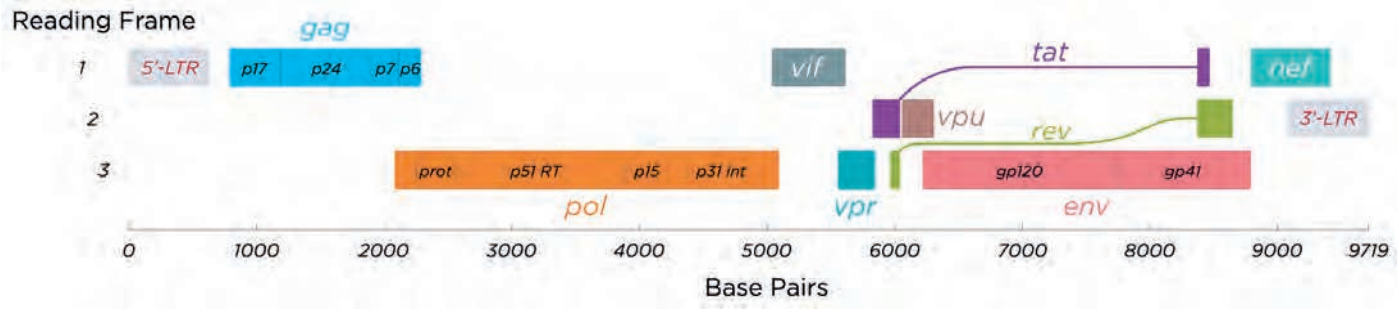
HIV belongs to the group VI reverse transcribing viruses, Retroviridae family, Orthoretrovirinae subfamily, *Lentivirus* genus (International Committee on Taxonomy of Viruses, 2012). Two types of HIV have been characterized: HIV-1 and HIV-2. Despite being similar, these two species differ in their replicative and pathogenic capacity, their viral evolution and their target of infection. The most prevalent virus is HIV-1, accounting for around 95% of all infections worldwide, while HIV-2 is mainly restricted to West Africa.

3.2. HIV-1 structure and genome

HIV-1 virions are spherical particles of about 119-207 nm in diameter (Briggs *et al.*, 2004) wrapped within an envelope (Figure 2). This is formed by a lipid bilayer derived from the host cell that contains embedded trimers of the envelope glycoproteins (Env; gp160), the only virus-encoding determinants on the virus surface, which are responsible for attachment and



↑ Figure 2. Schematic structure of the HIV-1 virion. Prepared by the authors.



↑ Figure 3. Schematic structure of the HIV-1 genome. Reproduced from Splettstoesser (n.d.) and published under the license Creative Commons Attribution-Share Alike 3.0 (CC BY-SA 3.0), <https://creativecommons.org/licenses/by-sa/3.0/>.

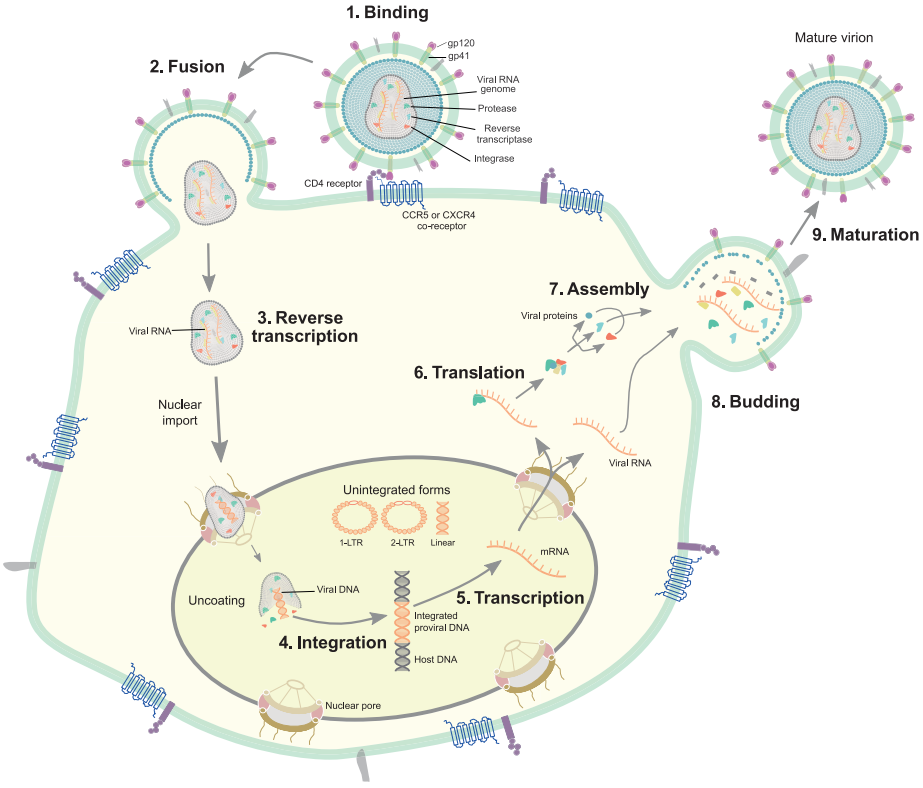
fusion to the host cell. Attached to the inside of the envelope is the matrix (MA), which provides the virion with structural and mechanical support. The matrix surrounds the conical-shaped capsid core (CA) and the nucleocapsid (NC). Within the capsid, there is the viral ribonucleic acid (RNA) protected by the closely associated NC. The CA also contains the protease, reverse transcriptase and integrase enzymes (Turner and Summers, 1999).

The viral genome is composed of two copies of positive single-stranded RNA (ssRNA) of approximately 9.8 kb in length (Muesing *et al.*, 1985), flanked by a repeated sequence known as the long terminal repeats (LTRs). The LTR regions contain sites important for viral integration, packaging, and transcription regulation. The HIV-1 genome encodes for nine genes: three major genes encoding for structural proteins (*gag*, *pol* and *env*), two regulatory genes (*tat* and *rev,* and four accessory genes (*vif, vpr*, *vpu* and *nef)* (Figure 3).

3.3. HIV-1 replication cycle

The HIV-1 replication cycle includes several stages and all of them can be potentially inhibited by antiretroviral drugs (Figure 4). First, the viral protein gp120 binds with the cellular receptor CD4, which is present on the surface of target cells (Maddon *et al.*, 1986), causing a conformational change in gp120 that exposes the co-receptor binding site allowing gp120 to interact with the co-receptor CCR5 or CXCR4 (Rizzuto *et al.*, 1998). The co-receptor used for cellular entry determines the tropism of the virus, which is termed R5-, X4- or dual-tropic, depending on each case. Individuals lacking the CCR5 co-receptor due to a homozygous Δ32 deletion in the *CCR5* gene are resistant to infection by R5-tropic strains (Samson *et al.*, 1996; Marmor *et al.*, 2001). The binding of gp120 to CD4 and the co-receptor causes a conformational change in gp41, leading to a fusion between the viral and cellular membrane. Subsequently, the viral capsid core is internalized and the ss-RNA is retrotranscribed by the reverse transcriptase enzyme into linear double-stranded DNA (dsDNA) (Hu and Hughes, 2012). Due to the absence of a proofreading mechanism, this process introduces high rates of DNA base-pair mutations, contributing to the high rate of viral evolution (Smyth *et al.*, 2012).

Then the viral capsid enters the nucleus through the nuclear pore, where the capsid uncoats, releasing the enzymes and dsDNA. The dsDNA is integrated into the host cell genome by the viral enzyme integrase (Engelman *et al.*, 1991). Once the virus is integrated into the host genome, the HIV-1 DNA is called *provirus* and the host cell is permanently and irreversibly infected. Since the integration process is not entirely efficient, aborted integration events may also be found in the nucleus. The unintegrated DNA can be found as linear or circularized DNA. Circularization is performed by host DNA repair enzymes to form episomes that contain two copies of the LTR (2-LTR circles) or that undergo recombination to form 1-LTR circles (Varmus, 1988). When the host cell receives a signal to become activated, the provirus transcribes to mRNA transcripts, which are transported to the cytoplasm to be translated into viral proteins (Karn and Stoltzfus, 2012). Lastly, the new HIV virions and HIV-RNA move to the surface of the cell and assemble into immature noninfectious particles. Once the immature virions bud out of the cell, the viral protease is activated, converting the immature virion into its mature infectious form (Sundquist and Kräusslich, 2012).



↑ Figure 4. Schematic overview of the HIV-1 replication cycle. Prepared by the authors.

4. HIV-1 pathogenesis

4.1. Transmission

HIV-1 can be transmitted by the exchange of body fluids from infected people, such as blood, semen, vaginal secretion, and breast milk. Also, it can be transmitted by vertical transmission from mother to child during pregnancy or delivery. The risk of infection is dependent on different factors such as the route of infection, viral concentration in the exposed body fluid, presence of other sexually transmitted diseases, and the susceptibility of the recipient. Sexual transmission through the lower genital tract and rectal mucosa is responsible for the highest proportion of new infections (Chen *et al.*, 2019).

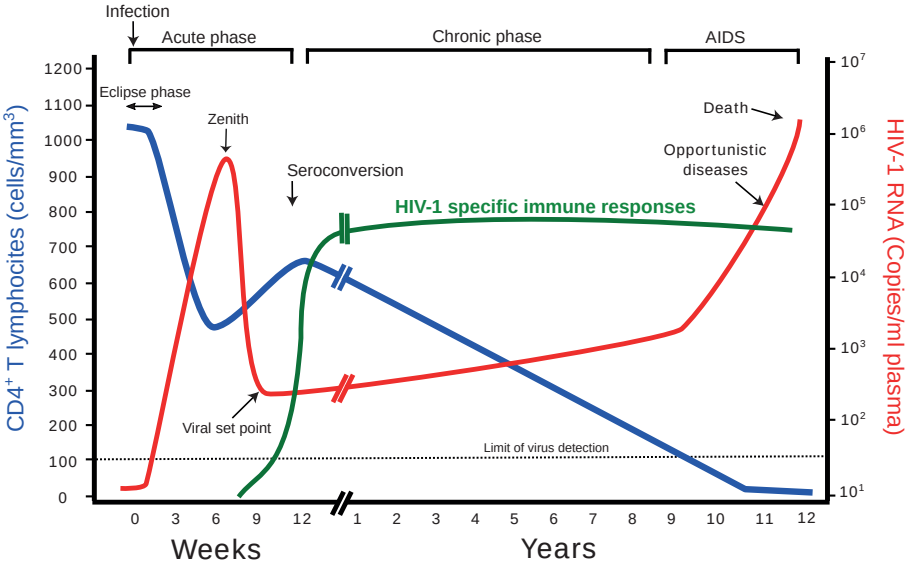
In most cases, the infection is established by a single virus, but this may vary depending on the infection route (Li *et al.*, 2010; Shaw and Hunter, 2012). Specifically, during sexual transmission, cell-free or cell-associated virions can penetrate the epithelium through microabrasions or by transcytosis. Then the virus rapidly reaches dendritic cells (DCs), Langerhans cells, intraepithelial $CD4^+$ T cells and resting $CD4^+$ T cells in the lamina propria (Haase, 2010; Hladik and Doncel, 2010). After local viral expansion, the virus disseminates to the draining LN, and subsequently reaches the bloodstream to establish the infection in secondary lymphoid organs, with particular preference for $CD4^+$ T cells located in the gut-associated lymphoid tissue (GALT) (Dandekar, 2007).

4.2. Course of HIV-1 infection

HIV-1 infection is characterized by a progressive decline in the number of CD4⁺ T cells, a rise in the HIV-1 viral load, a chronic immune activation, and exhaustion of the immune system. In the absence of treatment, an asymptomatic period of 8 to 10 years is observed before the progression to AIDS (Pantaleo and Fauci, 1996), which is associated with the development of opportunistic infections and cancers that finally lead to death (Babiker *et al.*, 2000). The natural course of infection commonly includes three different stages (Figure 5): acute phase, chronic phase, and AIDS.

Although 80-90% of HIV-1-infected individuals present a natural history of the infection as described above, a small number are able to remain clinically stable without progression to AIDS in the absence of antiretroviral treatment. These individuals represent between 5 and 15% of the total HIV-1-infected population and are called *long-term nonprogressors* (LTNPs), remaining clinically and/or immunologically stable for more than 10 years with CD4⁺ T-cell counts over 500 cells/mm^3 (Cao *et al.*, 1995; Muñoz *et al.*, 1995; Pantaleo *et al.*, 1995; Gurdasani *et al.*, 2014). A more evolved definition of long-term nonprogression includes the elite controllers (ECs), who have the ability to maintain plasma viremia at undetectable levels (<50 copies/ml) and generally maintain elevated CD4⁺ T-cell counts (200 to 1000 cells/mm^3) for at least 1 year, representing less than 1% of the total HIV-1-infected population (Hubert *et al.*, 2000; Lambotte *et al.*, 2005; Gonzalo-Gil *et al.*, 2017). Likewise, HIV-1 infected individuals have recently been described who maintain EC characteristics without disease progression, in some cases for more than 25 years, with non-functional and non-genetically evolving viral reservoirs and effective innate and adaptative immune responses (Casado *et al.*, 2020; Jiang *et al.*, 2020; Turk *et al.*, 2021). An additional progression phenotype comprises the so-called *viremic controllers* (VCs), who maintain a lower degree of virologic control (<2000 copies/ml) while showing elevated CD4⁺ T-cell counts (≤500 cells/mm^3) (Emu *et al.*, 2008; Okulicz *et al.*, 2009). At the other end of the disease spectrum, there is a small group of HIV-1-infected individuals (<0.5%) with a rapid progression to AIDS, within 2-3 years after primary infection, the rapid progressors (RPs). They may present clinically severe acute infection and are defined by a decay of CD4⁺ T cells below 350 cells/mm^3 within 3 years after seroconversion, in most cases with high levels of plasma viremia (Dalmau *et al.*, 2009; Gurdasani *et al.*, 2014).

Likewise, there are individuals termed viremic nonprogressors (VNPs) who are characterized as having high levels of HIV-1 replication during the chronic phase of infection despite remaining asymptomatic, while maintaining high CD4⁺ T-cell counts for long periods of time in the absence of antiretroviral treatment (Choudhary *et al.*, 2007).



↑ Figure 5. Schematic representation of the natural course of HIV-1 infection in the absence of antiretroviral therapy. CD4⁺ T-lymphocyte count is shown in blue, HIV-1 RNA copies/ml in red, and HIV-1 specific immune responses in green. Adapted from Splettstoesser (n.d.) and published under the license Creative Commons CC0 1.0 Universal Public Domain Dedication (CC0 1.0), <https://creativecommons.org/publicdomain/zero/1.0/>.

5. Antiretroviral treatment of HIV-1 infection

The development of antiretroviral treatment has modified the natural course of the HIV-1 infection, achieving one of the most significant advances in the HIV-1 field. AZidoThymidine (AZT) was the first antiretroviral, approved in 1987. It was the first of a family of nucleoside reverse transcriptase inhibitors (NRTIs) that interfere with HIV-1 replication by blocking reverse transcriptase (Furman and Barry, 1988). For several years, NRTIs and a parallel group of non-nucleoside reverse transcriptase inhibitors (NNRTIs) were administered as mono or dual therapy, leading to the development of drug resistances resulting from incomplete suppression of viral replication. In 1996, long-term suppression of HIV-1 was achieved by the administration of triple-drug therapy, called *highly active antiretroviral therapy (*HAART) or combined antiretroviral therapy (cART) (Staszewski *et al.*, 1996; Arts and Hazuda, 2012).

To date, more than forty drugs have been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of HIV-1 (US Food and Drug Administration, US Department of Health and Human Services. HIV/AIDS Treatment - HIV Treatment Information for Adults, n.d.). These drugs are classified by their mode of action in six categories:

1. Nucleoside/nucleotide-analog reverse transcriptase inhibitors (NRTIs), which inhibit viral DNA transcription by incorporating a defective nucleotide.
2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs), which inhibit reverse transcriptase by binding to its active site.
3. Integrase inhibitors (INIs), which prevent integration of viral DNA into the host genome.
4. Protease inhibitors (PIs), which inhibit the protease enzyme, resulting in non-mature virions.
5. Fusion inhibitors, which interfere with binding, fusion, and entry of HIV-1 into the host cell.
6. Entry inhibitors, which block binding of HIV-1 to the co-receptor CCR5 or the CD4 receptor.

Typically, a standard cART consists of a combination of two NRTIs and one drug from any of the other categories. cART suppresses viremia below the clinical detection limit, restores $CD4^+$ T-cell counts, reduces the risk of comorbidities, and increases the life expectancy of HIV-1-infected individuals to nearly that of the general population (Palella *et al.*, 2014). Also, it has been shown that if a high adherence to daily therapy exists, the risk of viral transmission is reduced to negligible levels (undetectable = untransmissible) (Rodger *et al.*, 2019).

Nowadays it is recommended to start cART immediately upon diagnosis of HIV-1, regardless of $CD4^+$ T-cell counts or viral load, since it has been associated with an improved prognosis and reductions in the number of HIV transmissions in the population (Lundgren *et al.*, 2015). Furthermore, several studies indicate that starting cART during acute or early HIV-1 infection compared to starting it during chronic infection also provides additional benefits such as lower progression, preserved $CD4^+$ T-cell counts, reduced viral set point, and less destruction of lymphoid tissue (O'Brien and Markowitz, 2012).

6. HIV prevention

There are different preventive measures to avoid the acquisition of HIV, with the aim of diminishing the incidence of this pandemic.

The first type of prevention is related to HIV transmission routes (blood, mother-to-child, and sexual contact). Blood transmission can be prevented by routine blood supply screening or the use of clean syringes. Mother-to-child transmission is effectively prevented with the use of cART during pregnancy, childbirth, and puerperium (Townsend *et al.*, 2008). Lastly, sexual transmission, which is the principal driving force of this epidemic, can be prevented by a number of ways including: 1) the use of condoms, which not only prevents HIV acquisition but also other sexually transmitted infections (Remis *et al.*, 2014); 2) male circumcision (Bailey *et al.*, 2007; Farley *et al.*, 2020); 3) microbicides (Nel *et al.*, 2016), and 4) pre-exposure (Baeten *et al.*, 2012; Choopanya *et al.*, 2013) or post-exposure (Enise *et al.*, 1997) prophylaxis treatment, which consists of the use of antiretrovirals before or right after a contact risk to avoid getting HIV by preventing it from taking hold and spreading throughout the body.

Likewise, there are behavioral prevention programs to foster healthy behaviors, including HIV testing and counseling to detect undiagnosed infections, together with sexual education and treatment and prevention of drug and alcohol abuse. Lastly, a preventive HIV vaccine is under development with the goal of enhancing the immune response against HIV before exposure to the virus. Up to now, however, none of the major phase III clinical trials of preventive HIV vaccines have shown evidence of effective prevention. At present, more clinical studies are underway.

7. HIV-1 persistence during suppressive antiretroviral therapy

cART is effective and reduces HIV-1 RNA levels below the limit of detection (LOD), reconstitutes the immune system, and decreases morbidity, mortality and viral transmission (Palella *et al.*, 2014; Rodger *et al.*, 2019), but it is not able to cure the infection. In most cases, if treatment is interrupted, the HIV-1 viral load rebounds in a median of 2 to 8 weeks (Chun *et al.*, 1999), with a decrease in the $CD4^+$ T-cell count. In 1995, it was demonstrated for the first time that the reason why HIV-1 cannot be cured is that resting $CD4^+$ T cells from HIV-1-infected individuals contained integrated HIV-1 DNA (Chun *et al.*, 1995). This phenomenon is known as *latent infection*.

Latent infection is a reversibly nonproductive state of HIV-1 infection, which is characterized by the presence of infected cells that are transcriptionally silent but capable of being induced to produce replication-competent virus. Alternatively, a reservoir is defined as a cell type or anatomical site in which virus accumulates and persists (Blankson *et al.*, 2002).

The reservoir levels fluctuate and evolve during the natural and therapeutic course of HIV-1 infection. Thus, reservoirs can be detected very early after infection with median total blood HIV-1 DNA load of 3.3 log10 copies/106 PBMC after a median of 47 days after infection (Ghosn *et al.*, 2010). Once cART is started, the reservoir in blood is reduced, being variable among different individuals (Izopet *et al.*, 1998; Parisi *et al.*, 2012; Buzon *et al.*, 2014*a*; Ananworanich *et al.*, 2016*a*). Specifically, individuals who naturally control HIV-1 infection present very low and stable total HIV-1 DNA levels in the absence of cART (Lambotte *et al.*, 2005; Sajadi *et al.*, 2007; Groves *et al.*, 2012; Mendoza *et al.*, 2012). Reduced latency is also observed in post-treatment controllers (PTCs) who started cART early after infection and achieved long-term viral control after analytical treatment interruption (Sáez-Cirión *et al.*, 2013), and LoViReT individuals who were treated mostly in the chronic phase of infection but harbor extremely low reservoir levels (Gálvez *et al.*, 2020 and 2022). On the other hand, individuals who do not control HIV-1 replication or are symptomatic have significantly higher HIV-1 DNA levels (Tierney *et al.*, 2003). However, the mechanism by which the reservoir is established and why it varies among individuals is still unknown.

7.1. Cellular and anatomical HIV-1 reservoirs

Since the first description was made of resting $CD4^+$ T cells as a reservoir of HIV-1 (Chun *et al.*, 1995), different cell types and tissue compartments have been described as reservoirs. Consequently, HIV-1 reservoirs are diverse and can be conceptualized as either cellular or anatomical.

7.1.1. Cellular reservoirs

HIV-1 primarily infects $CD4^+$ T cells due to the need of specific interaction of gp120 with the CD4 receptor of virus entry. A recent study shows that the HIV-1 reservoir is composed of a mosaic of cell subpopulations, with heterogeneous proviral HIV-1 DNA, HIV-1 transcription, and activation status, thus contributing to HIV-1 persistence through different mechanisms such as susceptibility to infection, rates of intact provirus, transcriptional status, or half-life (Gálvez *et al.*, 2021). In particular, memory $CD4^+$ T cells are the largest contributor to the HIV-1 reservoir and the most widely characterized population (Chomont *et al.*, 2009). There are different types of memory $CD4^+$ T cells, based on their memory and functional status. Several studies have shown that $CD4^+$ T-cell subsets harbor different amounts of latent HIV-1 and the mechanisms by which they support viral persistence may be different. T central memory (T_{CM}), T transitional memory (T_{TM}), and T effector memory (T_{EM}) $CD4^+$ T cells contain HIV-1 DNA at higher frequencies than the more differentiated subsets, such as T terminally differentiated (T_{TD}) cells (Chomont *et al.*, 2009). A subset with stem cell-like properties, the T stem cell memory (T_{SCM}) cells have been shown to significantly contribute to the HIV-1 reservoir due to their increased proliferative capacity and self-renewal, although their levels of total HIV-1 DNA and their proportion in peripheral blood are lower than other memory

$CD4^+$ T-cell subsets (Buzon *et al.*, 2014*b*). Naïve $CD4^+$ T cells (T_N) also contain HIV-1 DNA, but at a lower frequency than the other mentioned T-cell subpopulations (Chomont *et al.*, 2009).

Other $CD4^+$ T-cell subtypes, such as T follicular helper (T_{FH}) (Perreau *et al.*, 2013; Banga *et al.*, 2016; García *et al.*, 2017), T regulatory (T_{reg}) (Dunay *et al.*, 2017; Li *et al.*, 2017), tissue resident memory (T_{RM}) (Couturier *et al.*, 2015; Cantero-Pérez *et al.*, 2019), and T migratory memory (T_{TM}) cells also contribute to the long-lived HIV-1 reservoir.

Additionally, other cell types in the myeloid lineage, such as monocytes, macrophages and DCs have been proposed to be permissive for HIV-1 infection. The expression of the CD4 receptor on these cells is much lower than on $CD4^+$ T lymphocytes, and their ability to get infected remains controversial. Monocytes are derived from myeloid progenitors in the bone marrow and they are the precursors of macrophages and DCs. HIV-1 has been rarely detected in circulating monocytes of infected individuals (Ellery *et al.*, 2007; Honeycutt *et al.*, 2016). Moreover, their short half-life of a few days before their differentiation into macrophages and their high turnover suggest that they do not represent a stable reservoir but could be an important viral reservoir because of their ability to disseminate into different tissues and to differentiate into macrophages. In fact, HIV-1 DNA has also been detected in macrophages from different organs (microglial cells, alveolar macrophages, intestinal macrophages…) (Trillo-Pazos *et al.*, 2003; Zalar *et al.*, 2010; Cribbs *et al.*, 2015). However, it was not demonstrated until 2019 that macrophages harvested from urethral tissue of individuals under cART harbor replication-competent HIV-1 (Ganor *et al.*, 2019). It was subsequently shown that macrophages constitute a viral reservoir in individuals on effective cART and that macrophage-tropic variants can appear in rebounding viremia when treatment is interrupted (Andrade *et al.*, 2020). On the other hand, low levels of proviral DNA have been observed *in vivo* in DCs , but the most important contribution of DCs to the HIV-1 reservoir seems to be the ability to retain HIV-1 virions and to transfer them to $CD4^+$ T cells (Kumar *et al.*, 2014; Wong *et al.*, 2019).

7.1.2. Anatomical reservoirs

HIV-1 reservoirs have been widely analyzed in peripheral blood, but only 2% of the total amount of lymphocytes are found there (Westermann and Pabst, 1992). Therefore, the scenario could be different in tissues, underlining the importance of the study of the HIV-1 reservoir in different anatomic compartments.

The cells described above which contain HIV-1 DNA can be found in different tissues or anatomic compartments, such as lymphoid tissues, brain, kidneys, lung, liver, adipose tissue, gastrointestinal tract, genitourinary system and bone marrow (BM) (Wong and Yukl, 2016; Mzingwane and Tiemessen, 2017). The lymphoid tissues, which comprise the spleen, thymus, LN and GALT, are the most important sites of viral replication during active infection and HIV-1 DNA is still detected there after years of cART (Wong and Yukl, 2016). In many cases, these anatomical reservoirs have a less efficient drug penetration and/or poorer immune surveillance by the effector cells of the immune system (Fletcher *et al.*, 2014). Thus, viral replication and viral reseeding may occur.

GALT is the largest lymphoid tissue in the body and comprises the largest population of T cells and macrophages (Westermann and Pabst, 1992). It is thought to be the main primary site of initial HIV-1 replication and an important contributor to the overall pool of latently infected $CD4^+$ T cells during treated HIV-1 infection. Several studies have shown that it contains much higher levels of HIV-1 DNA than peripheral blood among HIV-1-infected individuals under cART (Chun *et al.*, 2008; Morón-López *et al.*, 2017). One study by Yukl *et al.* estimated that the gut contains $1.2x10^9$ infected $CD4^+$ T cells, which would represent 83-95% of all HIV-1-infected cells in the body (Yukl *et al.*, 2010).

Other secondary lymphoid tissues such as LNs or spleen represent an important HIV-1 reservoir. They are the primary site for viral replication and contain high numbers of infected cells and free virions (Pantaleo *et al.*, 1993). Although cART can decrease in 3 logs the HIV-1 RNA in LNs, HIV-1 DNA and HIV-1 RNA can still be detected in individuals after long periods of cART (Cavert *et al.*, 1997; Lafeuillade *et al.*, 2001; Deeks *et al.*, 2012). In fact, several studies have shown a higher concentration of HIV-1 DNA and HIV-1 RNA in LNs and spleen compared to peripheral blood (Günthard *et al.*, 2001). In LNs, rather than the T_{CM} and T_{TM} subsets forming the largest proportion of infected cells as in peripheral blood, the memory subset T_{FH} (characterized by the expression of C-X-C chemokine receptor type 5 (CXCR5) and programmed cell death protein 1 (PD-1) are the most enriched subpopulation for replication-competent virus and viral RNA (Banga *et al.*, 2016).

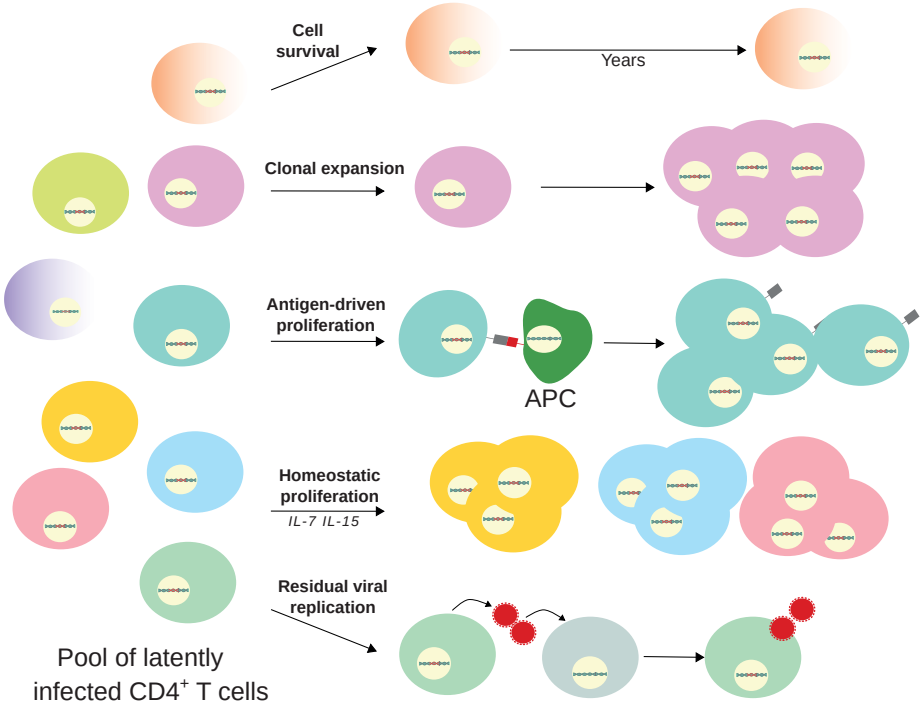
7.2. Reservoir establishment and maintenance

The HIV-1 reservoir is established in the first days of infection. Therefore, the treatment during acute HIV-1 infection does not prevent the establishment of a pool of latently infected $CD4^+$ T cells, even in the Fiebig I stage (Ananworanich *et al.*, 2016*a*).

The *in vivo* mechanisms responsible of the establishment of the HIV-1 reservoir are not completely clear yet. Two main models of latency have been described by which HIV-1 establishes a pool of latently HIV-1 infected cells: through the infection of activated $CD4^+$ T cells that survive and revert to a memory phenotype, or via direct infection and integration into the genome of resting memory $CD4^+$ T cells. *In vitro* models have shown that activated $CD4^+$ T cells that are transitioning to a resting state are more permissive to HIV-1 infection, hence escaping the rapid destruction of the infected T cells (Shen *et al.*, 2000). Therefore, latent HIV-1 infection can be established in resting and activated cells, but the probability of establishing latency could be higher in resting $CD4^+$ T cells while productive infection is more likely in activated $CD4^+$ T cells (Chavez *et al.*, 2015).

Once the reservoir is established in either of these ways, the pool of latently infected cells is extremely stable, with a medium half-life of 3.7 years in HIV-1-infected individuals on cART (Finzi *et al.*, 1999; Siliciano *et al.*, 2003), estimating that it would take more than 60 years of cART to eradicate the infection. Hence, the maintenance of this remarkably stable reservoir might be the result of normal homeostatic mechanisms, among other factors, as shown in Figure 6. The first explanation of the maintenance of the reservoir is the fact that the latent reservoir is composed of long-survival cells, which are able to maintain the size of the latent reservoir for long periods of time. Also, it may be maintained by proliferation of latently infected cells due to clonal expansion of cells with an HIV-1 provirus integrated in genes associated with the cell cycle passing identical proviral copies from dividing cells to daughter cells (Maldarelli *et al.*, 2014; Wagner *et al.*, 2014; Simonetti *et al.*, 2016), by homeostatic proliferation driven by cytokines such as IL-7 (Chomont *et al.*, 2009) or IL-15 (Picker *et al.*, 2006), or by some degree of antigen-driven proliferation, which may induce

proliferation of T cells without activation of viral gene expression. Lastly, it may be maintained by the low levels of residual viral replication that are present in some HIV-1-infected individuals (Palmer *et al.*, 2008) despite being under cART. This low-level replication might be due to the insufficient drug penetration in some tissues such as LNs (Lorenzo-Redondo *et al.*, 2016), or cell-to-cell spread.

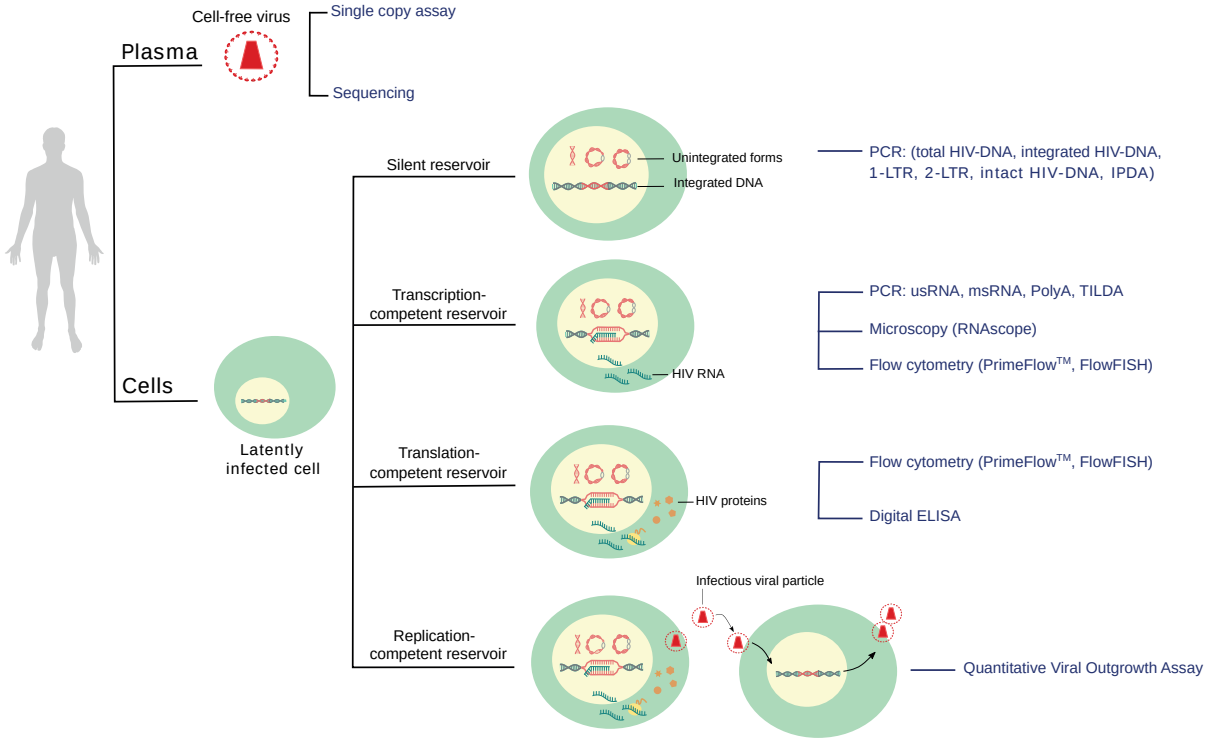


↑ Figure 6. Different mechanisms by which the HIV-1 reservoir is maintained. Each cell color represents a different HIV-1 clone, where HIV-1 is integrated in a different part of the human genome. Prepared by the authors.

7.3. Measuring the HIV-1 reservoir

In HIV-1-infected individuals, approximately 1 in 10^4-10^7 $CD4^+$ T cells are latently infected (Zhang *et al.*, 1998), with the rate of infection depending on the moment when cART was initiated after infection and on the HIV-1 viral load set point (Strain *et al.*, 2005). Given these low frequencies, the assays to measure the HIV-1 reservoirs need to be sensitive enough to detect a small number of cells in a background of a large number of cells, to be specific enough to detect that a rare event is true, to be able to distinguish between replication-competent and nonreplication-competent proviruses, and to be precise enough to detect a reduction in the HIV-1 reservoir when assessing an eradication strategy.

To date, several assays have been developed for measuring HIV-1 persistence. The different assays can measure free virus, cell-associated HIV-1 DNA (integrated or unintegrated, total or intact), the transcription-competent reservoir, the translation-competent reservoir, or the replication-competent reservoir. These assays are mainly based on polymerase chain reaction (PCR), flow cytometry, microscopy, and cell culture (Figure 7). The use of each assay



↑ Figure 7. Assays to measure the HIV-1 reservoir. Prepared by the authors.

Table 1. Characteristics of assays to measure persistent HIV-1. Prepared by the authors.

Measurement	Assay	Detection method	Cell number requirement	Specific for intact provirus	Over/under estimation	Pros	Cons
Free virus	SCA / ultrasensitive viral load	qRT-PCR	-	No	-	Measures residual virus production during cART	Time consuming and only measures productive latency. Large volume of body fluid
	Sequencing	PCR	-	Yes	-	Indication of the source viremia	Time consuming and only measures productive latency
Cell-associated HIV-1 DNA	Total HIV-1 DNA	qPCR or ddPCR	Low	No	Over	Easy, fast and cheap	Overestimates the size of the reservoir because it detects intact and defective provirus
	IPDA	ddPCR	Low	Yes	Over	Easy and gives an estimation of intact provirus	Primer mismatches in some individuals
	Integrated HIV-1 DNA	qPCR	Low	No	Over	Easy and sensitive for measurement of HIV persistence	Overestimates the size of the reservoir because it detects intact and defective provirus
	Nonintegrated forms	qPCR or ddPCR	Low	No	Over	Marker of residual viral replication	Measurement of 2-LTR at a single point does not provide information on recency of cellular infection
Transcription-competent reservoir	caHIV-1 RNA	qRT-PCR or ddPCR	Low	No	Over	Easy and cheap	May miss cells that harbor transcriptionally silent proviruses
	TILDA	qRT-PCR	Medium	No	Over	No need for outgrowth, faster than qVOA	May detect some defective provirus
	RNA scope	Microscope	Medium	No	Over	Tissue level information, highly sensitive and specific	Limited cell phenotyping
	Flow cytometry	Flow cytometry	Medium	No	Over	High throughput, in-depth phenotyping of single cells	Background in HIV-uninfected individuals, labor intensive and high starting cell number
Translation-competent reservoir	Flow cytometry	Flow cytometry	Medium	Partial	Over	High throughput, in-depth phenotyping of single cells	Labor intensive, high starting cell number
	Digital ELISA	SIMOA	Medium	Partial	Over	Highly sensitive	Can detect defective provirus
	VIP-SPOT	ELISpot	Low	Partial	Over	Sensitive, low cell number	May overestimate the "true" replication-competent viral reservoir
Replication-competent reservoir	qVOA	p24 antigen ELISA in supernatant	High	Yes	Under	Measures replication-competent provirus	Labor intensive, large number of cells and not all intact proviruses get reactivated
	mVOA	qRT-PCR	High	Yes	Under	Large number of cells can be assayed	Labor intensive and high cost. Variable levels of cell engraftment. Not all intact provirus get reactivated

depends on the aim of the study and the type and quantity of sample available, with the consequent advantages and disadvantages in each case (Table 1).

8. The search for a cure

As previously stated, cART is not able to eradicate HIV-1 due to the presence of latently infected cells. The need for life-long treatment is associated with adverse effects, social stigma, persistent inflammation, and a constant threat of emergent resistance (Deeks *et al.*, 2013). Therefore, a cure for HIV-1 infection is a major goal of research. There are two main ways of regarding HIV-1 cure, involving the sterilizing cure concept and the functional cure concept. A *sterilizing cure* would be achieved by a complete elimination of the HIV-1 virus from the body, while a *functional cure* seeks to use the immune system to keep the virus at an undetectable level without the need for antiretroviral therapy.

Several approaches are being pursued, including treatment optimization, latency reversal, latency silencing, immunotherapy, HIV-1-specific immune enhancement, and gene or cell therapy.

8.1. Treatment optimization

One of the proposed strategies to cure HIV-1 is based on treatment optimization with either intensification of treatment or early treatment initiation.

The *intensification of treatment* is based on the presence of low-level viral replication during cART, which may be due to a partial suppression or suboptimal drug concentrations in some tissues. Therefore, treatment intensification aims at targeting the source of residual replication by using additional drugs to accelerate the decay of the latent reservoir, eventually leading to a cure in some individuals. Several studies have been performed with compounds such as raltegravir (Buzón *et al.*, 2010), maraviroc (Kawana-Tachikawa *et al.*, 2014), or darunavir/ritonavir (Sayana *et al.*, 2009), with limited evidence of reducing the latent reservoir or residual plasma viremia. Nonetheless, a recent study with obefazimod (formerly ABX464) (Bernal *et al.*, 2023) offers promising results, showing a reduction in the viral reservoir and transcription initiation in suppressed individuals (Morón-López *et al.*, 2020).

On the other hand, *treatment on early infection* has been shown to lead to a lower viral reservoir in peripheral blood and tissues, less immune activation, better immune reconstitution, and lower risk of serious AIDS-related events (Ananworanich *et al.*, 2016*b*; Cao *et al.*, 2016; Leyre *et al.*, 2020). Moreover, different studies have identified a small proportion of individuals in whom the PTC started cART early after infection and achieved long-term viral control after analytical treatment interruption (Salgado *et al.*, 2011; Sáez-Cirión

et al., 2013; Namazi *et al.*, 2018; Etemad *et al.*, 2023). This effect has also been observed in different vertically infected children, who were treated early after birth and show long-term sustained virological control after treatment interruption for more than 9.5 years (Frange *et al.*, 2016; Violari *et al.*, 2019).

8.2. Latency reversal

One of the most intensively studied eradication approaches is the so-called *shock and kill approach*, which aims to combine the effect of reversing the transcriptional silencing of the integrated provirus through latency reversal agents (LRAs) (shock) with the elimination of the new virions through the combined effects of cART and/or HIV-1-specific immune responses (kill).

Many types of LRAs have been identified that successfully induce RNA production, but only some drugs induce the production of proteins and viral particles. These include histone deacetylase and histone methyltransferase inhibitors that upregulate transcription by reversing epigenetic silencing (Lehrman *et al.*, 2005; Archin *et al.*, 2012 and 2014); protein kinase C agonists (Williams *et al.*, 2004; Pérez *et al.*, 2010) and CCR5 agonists (López-Huertas *et al.*, 2017; Madrid-Elena *et al.*, 2018) that stimulate latent HIV-1 by activating NF-κb.

However, none of these interventions were capable of reducing the viral reservoirs, probably due to the limited ability of the compounds to reverse latency and/or because the immune system needed to be primed to clear antigen-expressing cells (Shan *et al.*, 2012).

A second generation of LRAs appear to show promising results in pre-clinical studies, such as the small-molecule inhibitor of apoptosis antagonists, called SMAC (second mitochondria-derived activator of caspases) mimetic compounds, that have demonstrated potent activity in different animal models by reversing HIV-1 latency (Nixon *et al.*, 2020; Pache *et al.*, 2020). Similarly, a study demonstrated that the FDA-approved retinoic acid derivative known as *acitretin* reactivates latent HIV-1 and induces preferential apoptosis of HIV-1 latently infected cells *in vitro* (Li *et al.*, 2016). Also, toll-like receptor (TLR) agonists have shown latency-reversing activity in nonhuman primates (Thibault *et al.*, 2009; Novis *et al.*, 2013; Álvarez-Carbonell *et al.*, 2017). Lastly, for the "kill", the use has been proposed of immunotherapies or therapeutic vaccinations, as will be explained in the following sections. In fact, a recent study in nonhuman primates has shown that the combination of active and passive immunization with a TLR-7 agonist may facilitate post-ART virologic control (Walker-Sperling *et al.*, 2022).

8.3. Latency silencing

Since the shock and kill strategy has not yet been proven successful, an opposite approach called *block and lock* has been proposed. This strategy aims to permanently silence the provirus, even in the absence of cART, with the use of latency-promoting agents (LPAs). These drugs target HIV-1 transcription-related viral and cellular factors to silence HIV-1 transcription in latent HIV-1 infected cells.

To date, the most advanced study involves the use of didehydro-cortistatin A (dCA), an inhibitor of the viral transcriptional activator Tat. *In vivo*, dCA has been shown to block HIV-1 transcription and to prevent viral reactivation. In humanized mice, dCA administration during cART has shown a modest delayed and reduced viral rebound upon treatment interruption (Kessing *et al.*, 2017). This approach, still pending confirmation in humans, is proof of the concept of *functional cure*.

Other promising candidates for LPAs include the LEDGINs integration inhibitor, mTOR inhibitors, kinase inhibitors, and Jak-STAT inhibitors, among others (reviewed in Vansant *et al.*, 2020). Nevertheless, these strategies are in early stages of development.

8.4. Immunotherapy

Constant antigenic stimulation during HIV-1 infection leads to chronic immune activation, inflammation, and immune exhaustion. In this context, HIV-1-specific cells diminish or become dysfunctional, losing their antiviral and proliferative capacity to eliminate productively infected cells. Therefore, immunotherapy strategies are aimed at reversing immune exhaustion to enhance anti-HIV-1 immune responses, mainly by using immune checkpoint blockers.

Immune checkpoint blockers are antibodies against immune checkpoint molecules such as PD-1 or CTLA-4. An enrichment has been shown for HIV-1 provirus in $CD4^+$ T cells expressing immune checkpoint molecules, as well as a high expression of these molecules on HIV-1-specific $CD8^+$ T cells. Therefore, these antibodies have the potential to boost T-cell function and to act as LPAs. *Ex vivo*, antibodies against immune checkpoint molecules have demonstrated an enhancement on HIV-1-specific $CD8^+$ T-cell responses (Day *et al.*, 2006; Trautmann *et al.*, 2006) and viral production by $CD4^+$ T cells (DaFonseca *et al.*, 2010; Fromentin *et al.*, 2019). Different studies have suggested that immune checkpoint blockers are safe and efficacious in HIV-1-infected individuals with advanced stage cancers (Davar *et al.*, 2015; Heppt *et al.*, 2017; Cook and Kim, 2019; Uldrick *et al.*, 2019; González-Cao *et al.*, 2020). However, the effectiveness of immune checkpoint blockers to boost the immune system or eliminate the viral reservoir in HIV-1-infected individuals is still controversial. Results from studies using different immune checkpoint blockers range from showing no changes in HIV-1-specific $CD8^+$ T-cell responses or HIV-1 reservoirs (Scully *et al.*, 2018), transient enhancement of HIV-1-specific $CD8^+$ T cells with no variation in viral persistence (Gay *et al.*, 2017; Le Garff *et al.*, 2017), transient increase in viral production without changes in viral reservoirs (Wightman *et al.*, 2015; Blanch-Lombarte *et al.*, 2019), or cases of at least transient depletion of the HIV-1 reservoir (Guihot *et al.*, 2018; Fromentin *et al.*, 2019; Uldrick *et al.*, 2022). Moreover, it has been recently reported that in nonhuman primates, the combination of PD-1/CTLA-4 blockade induces a robust latency reversal and reduction of integrated virus although this is insufficient to achieve viral control (Harper *et al.*, 2020). Overall, it appears that immune checkpoint blockade is unlikely to induce HIV-1 remission in the absence of additional interventions.

8.5. HIV-1-specific immune enhancement

To enhance HIV-1-specific immunity, the use of therapeutic vaccination, broadly neutralizing antibodies (bNAbs) and chimeric antigen receptor T cells is being developed. These strategies are aimed at eliminating or significantly reducing viral rebound when therapy is interrupted by enhancing the host immune response to HIV-1, thus achieving a functional cure.

Therapeutic vaccination aims to boost the magnitude and breadth of antigen specificities and the functionality of anti-HIV-1 T-cell responses to eliminate or control HIV-1 infected cells in the absence of cART. In therapeutic vaccine trials, the vaccine is administered during cART, followed by a period of cART interruption to assess efficacy by time to viral rebound, reservoir size and host immune responses. Different vaccine strategies have been

tried, including live attenuated virus, dead whole virus, replicating viral vectors, replication-deficient viral vectors, viral-like particles, soluble proteins, peptides and naked DNA, with different immunogenicity and safety (Ross *et al.*, 2010). Some of these vaccine strategies have shown an improvement of autologous HIV-1-specific T-cell responses but with limited success on viral control (MacGregor *et al.*, 2002; Robbins *et al.*, 2003).

Recently, several studies have assessed the combination of an LRA with a therapeutic vaccine. For instance, phase I/IIa clinical trials that used therapeutic vaccines in combination with either romidepsin or vesatolimod, led to a reduction in total HIV-1 DNA in one study (Leth *et al.*, 2016) and viremic control after cART cessation in some participants in other studies (Bailón *et al.*, 2022; Mothe Pujades *et al.*, 2023). A recent report has shown a progressive decrease in the reservoir together with recovery of the immune function after Tat based immunization (Sgadari *et al.*, 2019; Mothe *et al.*, 2023). Moreover, in nonhuman primates, other vectors that stimulate HIV-1-specific T cells look promising, including cytomegalovirus and the combination of an adenovirus vector with a TLR-7 agonist (Borducchi *et al.*, 2016; Walker-Sperling *et al.*, 2022).

bNAbs can neutralize a wide range of viral strains, enhance $CD8^+$ T-cell function, and mediate different effector functions such as ADCC (antibody-dependent cellular cytotoxicity), ADCP (antibody-dependent cellular phagocytosis), ADCDC (antibody-dependent complement-dependent cytotoxicity) or ADCT (antibody-dependent cellular trogocytosis). In nonhuman primates, the use of the monoclonal antibody PGT121 resulted in a decline of plasma viremia and reduced proviral DNA in peripheral blood, gastrointestinal mucosa, and lymph nodes (Barouch *et al.*, 2013). Furthermore, the early administration of VRC07-523 and PGT121 to 1-month-old nonhuman primates resulted in complete clearance of SHIV-infected cells (Hessell *et al.*, 2016). In clinical trials with HIV-1-infected individuals, the combination of 3BNC177 and 10-1074 showed an effective suppression of viral rebound for a median of 21 weeks (Mendoza *et al.*, 2018), with the prevention of viral replication in some individuals when cART is interrupted and a boost in CD8 cytotoxic activity (Niessl *et al.*, 2020). Also, a phase 1b/2a test of the combination of bNAb 3BNC117 with romidepsin at treatment initiation showed enhanced elimination of plasma virus and infected cells as well as sustained virologic control when cART was interrupted (Gunst *et al.*, 2022). Similarly, a phase IIA clinical trial using N6LS has shown strong antiviral efficacy and good tolerability (Leone, 2022). Alternatively, the use of synthetic molecules that mimic antibodies such as eCD4-Ig, which mimics both CD4 and CCR5 receptors, have demonstrated protection from SIV and SHIV infection in nonhuman primates (Gardner *et al.*, 2015 and 2019).

Chimeric antigen receptor T cells (CAR-Ts) are genetically engineered autologous T cells that comprise an extracellular domain (derived from the CD4 receptor or anti-HIV-1 antibodies) recognizing an HIV-1 epitope linked to an intracellular T-cell receptor domain that induces a cytotoxic T-lymphocyte response on antigen binding. Thus, when re-administered to the individual, it can direct the cytotoxic response to cells expressing the disease epitope. *In vitro* studies have demonstrated virus-clearing using anti-HIV-1 CAR-T cells (Sahu *et al.*, 2013; Ali *et al.*, 2016; Hale *et al.*, 2017). Also, CAR-T cells targeting multiple sites, called *duoCARs*, have shown a potent antiviral activity and elimination of HIV-1-infected cells in humanized mice (Anthony-Gonda *et al.*, 2019) and are being tested in a clinical phase I/IIa study (NCT04648046).

8.6. Gene and cell therapy

Lastly, gene- and cell-therapy strategies aim to replace HIV-1-infected cells with new virus-resistant hematopoietic stem or progenitor cells, thereby generating an HIV-resistant immune system. The virus-resistant cells can either be derived from a genetically HIV-1-resistant donor, by allogeneic hematopoietic stem-cell transplantation (allo-HSCT), or by genome editing of autologous cells. Usually, these strategies are focused on mimicking the 32-bp deletion in the *CCR5* gene (*CCR5*Δ32) that confers natural resistance to the R5 viral strains present in some individuals.

Allo-HSCT is the only eradication strategy that has achieved an HIV-1 remission or cure. In 2007, the "Berlin patient", who suffered from acute myeloid leukemia, received a myeloablative conditioning, two sessions of total body irradiation and two allogeneic stem-cell transplants from a donor who was homozygous for the *CCR5*Δ32 mutation (Hütter *et al.*, 2009). The individual stopped cART at the time of the transplant and remained undetectable for HIV-1 for more than 12 years, until September 2020 when he died of leukemia relapse. Also, no replication-competent HIV-1 RNA or HIV-1 DNA were detectable in peripheral blood, BM or GALT, and it is thus considered that a sterilizing cure was achieved (Yukl *et al.*, 2013). This case was unique for a decade, until the IciStem consortium, which studied people with HIV-1 who needed to undergo allo-HSCT for medical reasons (Henrich *et al.*, 2013), reported two additional cases of HIV-1 remission for 5.5 and 4 years respectively: the London (Gupta *et al.*, 2019, 2020) and Düsseldorf (Jensen *et al.*, 2023) cases. Similarly, a 1.5-year remission case has been most recently reported in a woman after a *CCR5*Δ32/Δ32 haplo-cord blood transplant (Hsu *et al.*, 2023). These cases prove that HIV-1 can be cured but the intrinsic risk of this medical intervention precludes its use on anyone with HIV.

On the other hand, *gene therapy* aims at directly modifying a specific sequence of DNA by genome-editing techniques such as zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), or clustered regularly interspaced short-palindromic repeats/CRISP-associated protein nuclease-9 (CRISP/Cas9). This approach would involve the disruption of the *CCR5* gene in autologous $CD4^+$ T cells or hematopoietic stem cells followed by the reinfusion of the modified cells, with the aim of mimicking the natural *CCR5*Δ32 mutation to make the cells resistant to new infections. Clinical trials using ZFNs showed that the modification of the *CCR5* gene was safe, but it did not prevent viral rebound in all the participants once therapy was interrupted (Tebas *et al.*, 2014, 2021). New gene strategies are currently under investigation, involving the modification of stem cells, different conditioning regimens or the use of other genome-editing tools such as CRISPR/Cas9. Alternatively, gene editing may be used to knock out or attenuate the HIV-1 provirus by targeting the LTR or *gag* genes to disrupt viral gene expression or to cleave it out entirely from the cell genome (Kaminski *et al.*, 2016; Dash *et al.*, 2019).

9. Conclusions

Since the beginning of the HIV pandemic in the early 1980s, great advances have been made, such as the development of antiretroviral therapy, making a fatal infection treatable. However, the long-awaited goal of eradicating HIV is still a chimera, partly due to the lack of a preventive vaccine, but also because there is

still a need for a safe, cost-effective and scalable cure for people living with HIV, which would reduce the long-term health, social and economic burden associated with the infection. A worldwide effort to find a cure is currently underway, and while promising strategies are being studied, the scientific challenge remains enormous.

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