HAL
archives-ouvertes.fr

HIV cure research: advances and prospects.

Caroline P Passaes, Asier Sáez-Cirión

▶ To cite this version:

Caroline P Passaes, Asier Sáez-Cirión. HIV cure research: advances and prospects.. Virology, Elsevier, 2014, 454-455, pp.340-52. <10.1016/j.virol.2014.02.021>. <pasteur-01420527>

HAL Id: pasteur-01420527
https://hal-pasteur.archives-ouvertes.fr/pasteur-01420527

Submitted on 24 Apr 2017

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Distributed under a Creative Commons Attribution - NonCommercial - ShareAlike| 4.0 International License

HIV cure research: advances and prospects

Caroline P. Passaes[a,b], Asier Saez-Cirion[a]

[a] Unité de Régulation des Infections Rétrovirales, Institut Pasteur, 25–28 rue du Dr Roux, 75724 Paris Cedex 15, France.

[b] CEA, Division of Immuno-Virology, iMETI/DSV, 18 Route du Panorama, 92265 Fontenay-aux-Roses, France.

Email addresses:

caroline.pereira-bittencourt@pasteur.fr/caroline.passaes@cea.fr

asier.saez-cirion@pasteur.fr

Corresponding author:

Asier Saez-Cirion

Unité de Régulation des Infections Rétrovirales - Institut Pasteur

25–28 rue du Dr Roux, 75724 Paris Cedex 15, France

Tel: +33 145688944; Fax: +33 145688957

E-mail: asier.saez-cirion@pasteur.fr

Abstract

Thirty years after the identification of HIV, a cure for HIV infection is still to be achieved. Advances of combined antiretroviral therapy (cART) in recent years have transformed HIV infection into a chronic disease when treatment is available. However, in spite of the favorable outcomes provided by the newer therapies, cART is not curative and patients are at risk of developing HIV-associated disorders. Moreover, universal access to antiretroviral treatment is restricted by financial obstacles. This review discusses the most recent strategies that have been developed in the search for an HIV cure and to improve life quality of people living with HIV.

Keywords: HIV cure, eradication, remission of HIV infection, HIV reservoirs, reactivation of latent virus, repression of provirus, control of infection.

Highlights:

- Some cases of cure or remission of infection have boosted the search for an HIV cure
- cART intensification has not shown significant impact in the reservoirs, but early cART may limit them
- Strategies to purge the reservoirs face difficulties linked to the complexity of latency mechanisms and drug non-specificity
- Repression of reservoirs or cell manipulation to render them less permissive to HIV may facilitate HIV remission
- HIV cure/remission may require boosting immune responses while keeping inflammation in check

Preamble

The introduction of improved combined antiretroviral therapy (cART) has dramatically improved the clinical outcome and life expectancy of HIV infected patients. The development of drugs that inhibit different steps of viral replication allows clinicians to successfully manage the disease, improving immunologic parameters, and avoiding drug resistance and side effects. Due to advances in antiretroviral development, HIV infection can nowadays be handled as a complex chronic disease (Deeks et al., 2013). Nonetheless, despite all of the clinical benefits provided by drug therapy, cART alone is not able to eradicate the virus, which persists in reservoirs that are thought to be the source for viral reemergence after treatment interruption (Chun et al., 2010; Chun et al., 1997). In addition, cART does not fully restore health – it increases the risk of non-AIDS disorders such as cardiovascular, kidney, liver and neurological diseases. Moreover, persistent immune dysfunction and inflammation increase the risk of non-AIDS morbidity and mortality (Clifford and Ances, 2013; Lake and Currier, 2013). Undoubtedly, a cure for HIV infection is needed to bypass the limitations of the current therapy and restore health. Although a vaccine against HIV remains an unachieved aspiration, several recent findings suggest that either a cure or a durable remission of infection might be possible.

Is a cure for HIV possible?

Since the isolation and characterization of the HIV as the etiologic agent of AIDS (Barre-Sinoussi et al., 1983), the search for a cure has been considered a major research priority. The description of a unique case of HIV cure after hematopoietic stem cell (HSC) transplantation has boosted remarkable optimism in the field and rekindled the hope that a cure for HIV infection is possible. In 2007, the so-called

“Berlin patient” - HIV positive and diagnosed with acute myeloid leukemia - received double allogeneic HSC transplant from an HLA-matched and unrelated donor screened for homozygosity for the *CCR5* Δ32 allele (Hutter et al., 2009). This patient discontinued ART the day before the first transplantation and, after 6 years of follow up in the absence of therapy, he shows no trace of HIV in blood and tissue samples (Figure 1A), revealing no evidence for persistent HIV. Levels of HIV-specific antibodies have also declined, suggesting that HIV antigen stimulation was very low or absent after transplantation (Allers et al., 2011; Hutter et al., 2009; Yukl et al., 2013).

Several studies have aimed to use autologous or allogeneic HSC transplantation in association with antiretroviral therapy as a strategy to eradicate HIV in seropositive patients diagnosed with leukemia and/or lymphomas (Table 1). Nevertheless, in most of these studies HIV was detected after transplantation, either following therapy withdrawal or because the therapeutic regimen was not able to completely eliminate the viral reservoirs. In addition, in several cases, the patients died after transplantation. The most recent study investigating the impact of cART on viral reservoirs in two patients who received HSC transplantation – known as “the Boston patients” – described an important reduction of HIV DNA in long term, reaching undetectable levels (Henrich et al., 2013). These observations are in agreement with another study which described that HIV DNA levels at month 24 post transplantation in HSC transplanted patients are lower than those observed at baseline (Simonelli et al., 2010). Altogether, these data suggest that HSC transplantation in association with cART may reduce viral reservoirs in HIV infected patients. However, a recent report during the 6th International Workshop on HIV Persistence, Reservoirs and

Eradication Strategies revealed that the Boston patients experienced a strong rebound in plasma viremia several months after analytic treatment interruption (ATI) (Figures 1B and 1C)(http://es.scribd.com/doc/189931630/12-06-13-Statement-From-Dr-Henrich-Regarding-HIV-Patients). These results suggest that HIV hides in yet unidentified sanctuaries or at levels that are not detectable by current available techniques.

So far, HSC transplantation to eradicate the virus was successful only in the Berlin patient. The mechanisms involved in HIV eradication in this patient are not yet fully understood. This patient underwent severe particular transplant conditions (Hutter et al., 2009) (Figure 1), such as double HSC transplantation from the same *CCR5* Δ32 donor, conditioning regimen (total body irradiation) and the development of graft-versus-host disease (GVHD), which may have contributed to cure. Comparison with the protocols applied in the case of the Boston patients (Henrich et al., 2013) suggests that total body irradiation or the engraftment with cells from a *CCR5* Δ32 donor may have been critical differential aspects in the case of the Berlin patient. As the homozygous *CCR5* Δ32 deletion offers a natural resistance to HIV infection (Dean et al., 1996), this unique successful experience has encouraged the search for new *CCR5*-based therapeutic approaches for HIV cure interventions (see below). It is interesting to notice that the Berlin patient and both Boston patients were originally heterozygous for the *CCR5* Δ32 allele, but this did not confer any advantage to the Boston patients once treatment was interrupted (Henrich et al., 2013; Hutter et al., 2009). A recent effort to cure HIV infection in a 12-year old boy with acute lymphoblastic leukemia consisted of an allogenic transplantation of HSC obtained from cord blood. Similar to the Berlin patient, the donor was screened for

homozygosity for the *CCR5* Δ32 allele. This procedure was performed at the University of Minnesota in April 2013, but the pediatric patient died two months after transplantation by a severe GVHD (http://www.healthtalk.umn.edu/2013/07/13/pediatric-patient-dies-after-undergoing-historic-transplant-at-u-of-m/).

Despite the impact of HSC transplantation on reducing HIV reservoirs, this kind of treatment is not a viable option for the majority of HIV infected patients, since it is a risky and expensive procedure that is recommended only for those who develop cancer. Furthermore, *CCR5* Δ32 homozygous donors are rare (1% of caucasians) (Lucotte, 2002), what makes the search for a compatible donor with the protective genotype an additional challenge.

How can HIV infected patients achieve durable remission of infection?

"HIV controllers" or "elite controllers" correspond to a small percentage of HIV infected patients that can naturally control viral replication below the levels of detection with standard clinical assays. Consequently, this group of patients is considered an important model to understand the mechanisms underlying control of infection in the absence of treatment (Hamimi et al., 2013; Saez-Cirion and Pancino, 2013). The aim of a so-called "functional cure" would be similarly to HIV controllers, that is, to allow HIV infected patients to achieve viral remission in which HIV remains in the body at low levels and it is controlled by the host in the absence of cART. This status may be achieved by 5-15% of patients treated very early during primary HIV infection (PHI) for long periods of time who experience treatment interruption afterwards (Goujard et al., 2012b; Hocqueloux et al., 2010; Lisziewicz et al., 1999;

Lodi et al., 2012; Saez-Cirion et al., 2013; Salgado et al., 2011; Steingrover et al., 2008). These patients are known as “post-treatment controllers”.

The VISCONTI study (Viro-Immunological Sustained CONtrol after Treatment Interruption) investigated whether the characteristics of 14 post-treatment controllers were similar to those observed in HIV controllers that spontaneously control HIV replication (Saez-Cirion et al., 2013). In this study, cART duration at after primary infection was 3 years, and after treatment interruption, post-treatment controllers presented a sustained control for a median of 7 years. During acute phase, post-treatment controllers had higher viremia levels and lower CD4+ T cell counts than patients who naturally control infection afterwards. In addition, these groups of patients have a different genetic background – while HIV controllers cohorts are enriched by the protective HLA-B*27 and B*57 (Migueles et al., 2000; Pereyra et al., 2008; Saez-Cirion et al., 2007), the risk alleles B*07 and B*35 (Carrington et al., 1999; Itescu et al., 1992; Pereyra et al., 2010; Peterson et al., 2013b) were prevalent among the 14 post-treatment controllers. HIV-1 specific CD8+ T cell responses and immune activation differ between post-treatment controllers and HIV controllers (post-treatment controllers have weak CD8+ T cell responses and a low level of immune activation during the control phase).

Another recent incident that suggests that a very early treatment may lead to HIV remission is the case identified as ‘the Mississipi baby” (Persaud et al., 2013). This infant born to a seropositive mother started receiving cART 30 hours after birth. HIV-1 RNA was detectable at 31 hours, days 6, 11 and 19, and reached undetectable levels at day 29. cART was discontinued sometime between month 18 to 23. At 36

months of age and after therapy withdrawal, HIV-1 RNA, proviral DNA and HIV-1 antibodies remain consistently undetectable or extremely low in blood and tissues in this pediatric patient.

The study of post-treatment controllers may give valuable information to guide the search for a successful strategy for inducing viral remission. However, some open questions remain. For instance: which are the mechanisms underlying control? and how can we increase the probability of HIV infected patients to become a post-treatment controller? Recent studies suggest that both the timing to initiate therapy (Ananworanich et al, 20th Conference on Retroviruses and Opportunistic Infections, 2013, San Francisco, USA) (Ananworanich et al., 2012; Gianella et al., 2011; Hecht et al., 2006) and the duration of cART (Fidler et al., 2013; Stohr et al., 2013) might play a key role in the achievement of a durable HIV control. In addition, baseline viral load and immune activation may predict success (Volberding et al., 2009). Whether the therapeutic regimen used during PHI may impact the outcome is still to be investigated. In any case, in the absence of markers predicting success after treatment interruption, this procedure is not recommended outside structured protocols for patients undergoing suppressive cART.

Treatment during PHI seems to result in broad and strong HIV-1 specific immune responses (Hecht et al., 2006; Kaufmann et al., 2004; Lisziewicz et al., 1999; Moir et al., 2010; Ortiz et al., 1999; Oxenius et al., 2000; Rosenberg et al., 2000), reduced immune activation (Volberding et al., 2009), immune restoration in the gastrointestinal mucosa (Guadalupe et al., 2006) and limited viral evolution (Chamberland et al., 2011). Additionally, initiation of cART during PHI may limit the

establishment of viral reservoirs (Archin et al., 2012b; Chun et al., 2010; Gianella et al., 2011; Pires et al., 2004; Schmid et al., 2010; Wyl et al., 2011). Central memory CD4+ T cells (T_{CM}) are a key component of the long-lasting HIV reservoir (Chomont et al., 2009), and recent studies have demonstrated that very early cART limits the seeding of the HIV reservoir in long-lived T_{CM} (Figure 2) (Ananworanich et al, 20th Conference on Retroviruses and Opportunistic Infections, 2013, San Francisco, USA). Reservoirs levels in post-treatment controllers during the control phase were very low and it was mostly associated to the transitional memory CD4+ T cell subset, due to a skewed distribution of quiescent CD4+ T cell subsets in these patients (Saez-Cirion et al., 2013)(Figure 2).

Treatment interruption in patients who started cART during chronic phase leads to viral rebound within weeks, with viral loads frequently reaching pretreatment set-point levels (Fernandez Guerrero et al., 2005; Steingrover et al., 2008; Wit et al., 2005). Notwithstanding, some patients that started cART during chronic phase were also described to maintain controlled levels of viremia after therapy discontinuation (Van Gulck et al., 2011). For all these studies describing cases of a potential “functional cure”, long period follow-up is needed to evaluate whether long HIV control can be maintained and the mechanisms involved in the long-term suppression after treatment interruption. Collectively, these studies suggest that HIV remission is possible to be achieved with the help of therapeutic interventions in patients without a favorable genetic background to naturally control HIV infection. Certainly, additional studies will be needed to understand the mechanisms that may lead to a long-lasting viral remission in post-treatment controllers.

Is it better if we intensify ART?

Therapeutic intervention during PHI appears to be valuable in inducing viral remission in a certain number of HIV infected patients. However, just a small percentage of patients are diagnosed during PHI. Most of them will know their seropositive status only during the chronic phase of HIV infection. For the great majority of HIV infected patients, other strategies to achieve viral remission must be developed. Combined antiretroviral therapy dramatically reduces viremia to levels below the detection limit of current assays (<50 copies/mL), but low-level residual viremia persists and is usually detectable by ultra-sensitive tests in patients undergoing successful ART (Palmer et al., 2008). Residual viremia may partially be the cause of persistent immune activation (Corbeau and Reynes, 2011), which increases the risk of non-AIDS morbidity and mortality in treated patients (Clifford and Ances, 2013; Lake and Currier, 2013). There are two probable sources of residual viremia (Doyle and Geretti, 2012): (i) long-lived, latently infected cells whose provirus became transcriptionally active, with intermittent or continuous viral release; (ii) ongoing low-levels of HIV replication with *de novo* viral infection, due to partial suppression and/or to inadequate drug penetration. In the latter case, therapy intensification should reduce the residual viremia and associated persistent inflammation. Moreover, in the long term, it would be expected to decrease HIV reservoir levels.

Previous studies of therapy intensification with protease and reverse transcriptase inhibitors were contradictory in determining whether or not ongoing replication is the source of persistent viremia (Dinoso et al., 2009; Havlir et al., 2003; Ramratnam et al., 2004). The development of new classes of antiretroviral drugs allowed the

exploration of the impact of treatment intensification with drugs targeting other steps of HIV replication cycle. Treatment intensification with Raltegravir (RAL), a potent integrase inhibitor, offered a unique opportunity to study the dynamic of ongoing low-level replication. As RAL blocks HIV integration, residual replication could be assessed by the increase of 2-LTR circles (Schacker, 2010). Most studies of RAL treatment intensification showed no impact on residual viremia, immune activation or in promoting CD4+ T cell reconstitution. Collectively, these data suggested that residual viremia does not originate from ongoing cycles of HIV replication (Gandhi et al., 2012; Gandhi et al., 2010; Hatano et al., 2011; McMahon et al., 2010; Negredo et al., 2013). In contrast, the study of Buzon and colleagues (Buzon et al., 2010) identified a transient increase in the levels of 2-LTR HIV DNA within two to four weeks after intensification, but no significant decrease in low-level viremia was observed. In addition, only those patients with high levels of immune activation at baseline presented a decrease in these markers. These findings strongly suggested that RAL intensification was blocking new rounds of infection in these patients and that consequently ongoing replication was taking place. Nonetheless, other studies failed to detect 2-LTR increase in RAL intensified-treated patients (Besson et al., 2012; Gandhi et al., 2012). It is possible that differences in patients' characteristics, cART regimens at baseline, and/or the time of therapy intensification with RAL had an impact in the discrepancies observed among these studies. An important observation in the Buzon et al, study was the fact that 61% of the patients with detectable 2-LTR were taking a protease inhibitor-based regimen (PI). More recently, Hatano and colleagues also detected the transient increase of 2-LTR, which was also more accentuated in patients taking PI (Hatano et al., 2013). In addition, a significant

reduction in D-Dimer levels, a coagulation biomarker, was observed, indicating that RAL intensification may lead to reduction in inflammation/activation markers.

Because HIV-1 might replicate in tissue reservoirs where drug concentrations are suboptimal (Fletcher et al., 2014), such as lymph nodes, gut associated lymphoid tissues, bone marrow and the central nervous system, some RAL intensification studies assessed the immunologic and virologic responses in tissues. Yukl et al showed reduction in unspliced HIV RNA, T cell activation and a trend towards CD4+ T cell increases in ileum, suggesting that this tissue may be an important site for ongoing replication in some patients on cART (Yukl et al., 2010). In contrast, therapy intensification with RAL did not impact cerebrospinal viral loads (Dahl et al., 2011) or isolated HIV semen shedding (Osborne et al., 2013).

Based on previous observations that Maraviroc (MVC), a CCR5 antagonist, promotes a gain of CD4+ T cells in viremic HIV-infected patients (Cooper et al., 2010; Wilkin et al., 2010), it was hypothesized that the immunomodulatory effects of this drug could decrease immune activation and improve CD4+ T cell counts in patients under suppressive cART with insufficient immunological restoration. As observed in RAL intensification trials, no impact in residual viremia or HIV reservoir was achieved. Data regarding CD4+ T cell gain was also controversial in these trials (Cuzin et al., 2012; Hunt et al., 2013; Rusconi et al., 2013; Wilkin et al., 2012). Some unexpected effects, however, were observed in MVC intensification trials, such as increased activation levels in blood and rectal mucosa (Hunt et al., 2013; Rusconi et al., 2013), increase in plasma LPS, sCD14 and sCD163 (Gutierrez et al., 2011; Hunt et al., 2013) and increased 2-LTR levels (Gutierrez et al., 2011), suggesting that MVC

intensification might induce viral replication. The mechanisms underlying these effects are still unclear, but some evidences suggest that MVC promotes an increase in the circulating levels of CCL3 (MIP-1α), CCL4 (MIP-1β) and CCL5 (RANTES), natural ligands of CCR5, which may activate T cells and monocytes/neutrophils through CCR3/CCR4 and CCR1 signaling, respectively (Guan et al., 2002; Sarau et al., 1997). Further studies are necessary to carefully evaluate the immunomodulatory effects of MVC *in vivo* and the benefits of therapy intensification with CCR5 antagonists in HIV-infected patients.

Despite some evidence that therapy intensification may have positive effects on residual replication, its potential to eradicate the virus appears limited. These results highlight the importance of designing new strategies to eliminate persistent HIV reservoirs.

HIV persistence as a challenge for a cure

HIV replication and persistence depend on the integration of the viral DNA in the host genome. Although most proviruses integrate in transcriptionally active genomic regions, in most cases these proviruses remained repressed (Ho et al., 2013). Our knowledge of the complex mechanisms underlying establishment and maintenance of HIV latency has been enormously improved in the last years (see (Mbonye and Karn, 2014) in this issue of Virology for a thorough review). Repressed HIV proviruses integrated in long-lived cells constitute the persistent HIV reservoir, which is not recognized by immune responses, not eliminated under cART, and is the main obstacle to achieving an HIV cure. Since the description of HIV reservoirs despite long-term cART, attempts to purge this reservoir have been tried. The first one consisted in the infusion in three patients under cART of the anti-CD3 OKT3 antibody

in the presence of IL2, in an effort to mimic in vivo a well-established in vitro reactivation protocol (Prins et al., 1999). OKT3+IL2 treatment was accompanied by very strong activation of T cells, and transient increases of HIV RNA levels were observed in plasma or lymph nodes of these patients. However, no decrease in the frequency of infected cells could be reported and the treatment had many undesirable effects, associated with exacerbated immune activation and cytokine release, induction of anti-OKT3 antibodies and severe long-lasting depletion of CD4+ T cells (Prins et al., 1999; van Praag et al., 2001).

HDAC inhibitors were next proposed as optimal candidate to flush HIV reservoirs due to their potential to activate HIV transcription without inducing generalized immune activation. Chromatin condensation is regulated by the level of acetylation/deacetylation of the histones that constitute the core of the nucleosomes. Histone acetyl transferases (HAT) mediate the addition of acetyl groups to histones, reducing chromatin condensation and promoting transcription. Histone deacetylases (HDAC) remove the acetyl groups and repress transcription. The balance of HAT/HDAC activities is thus thought to be a key component of HIV latency. The first molecule with HDAC inhibitory activity to be assayed in vivo was valproic acid (VPA). A first study reported a decrease in the frequency of circulating resting CD4+ T cells carrying replication competent HIV-1 in four patients receiving cART after 16 weeks of additional treatment with VPA (Lehrman et al., 2005). However, subsequent randomized clinical studies could not confirm these results and no significant effects of VPA were evidenced (Archin et al., 2010; Routy et al., 2012; Sagot-Lerolle et al., 2008; Steel et al., 2006). Failure of VPA was eventually associated to a poor capacity of this molecule to inhibit HDAC3, the HDAC isoform that is thought to play a

preponderant role in HIV latency (Huber et al., 2011). In a proof of concept study, the more potent HDAC inhibitor vorinostat has shown capacity to increase levels of HIV mRNA transcripts after a single dose, without affecting overall HIV DNA cellular levels (Archin et al., 2012a). Preliminary results of the NCT01365065 trial presented in the 20th Conference on Retrovirus and Opportunistic Infections (Lewin S, et al 2013, San Francisco, USA) also reported an increase of cell associated unspliced HIV mRNAs in 15/17 patients on cART who received daily doses of vorinostat for 14 days. Another clinical trial (NCT01680094) is evaluating the impact on HIV reservoirs of panobinostat, which has been described as an even more potent HDAC inhibitor (Rasmussen et al., 2013).

The use of HDAC inhibitors in the context of HIV cure face several hurdles. Among them, the lack of specificity of HDAC inhibitors may impact the transcription of a large fraction of all cellular genes (Glaser et al., 2003). Also, it has been recently shown (Shan et al., 2012) that viral reactivation with HDAC inhibitors will not necessarily be followed by viral-induced cell death, and that immune responses may need to be boosted in parallel to recognize and eliminate these new viral-producing cells (see below). It is also unlikely that HDAC inhibition by itself will be able to induce efficient viral reactivation in the absence of the factors necessary to ensure full viral transcription. The current belief is that it will be necessary to combine treatment of HDAC inhibitors with other molecules able to provide the additional stimuli required for HIV transcription. PKC agonists, such as prostratin (Kulkosky et al., 2001; Reuse et al., 2009) and bryostatin (Perez et al., 2010), or TLR agonists (Novis et al., 2013), that activate NF-kB have been proposed as good potential combinatorial candidates.

Purging viral reservoirs is undoubtedly the only solution to achieve HIV eradication. However, letting aside the mechanistic issues, activating every single latently infected cell in the organism still appears a gargantuan endeavor. Taking the example of natural HIV controllers or the post-treatment controllers from the VISCONTI study, durable HIV remission may be a more reasonable goal in the medium term. In this setting, limiting and controlling the viral reservoirs would be the main objectives. With this in mind, our current knowledge, albeit incomplete, of HIV latency and transcription might be turned to devise strategies aiming to repress, rather than activate, viral transcription. As alternatives to HDAC inhibitors, HAT inhibitors such as garcinol derivatives (Mantelingu et al., 2007) and curcumin (Zhang et al., 2011) have been shown to inhibit HIV transcription in vitro. Transcriptional elongation of the viral promoter depends on the recruitment of the HIV transactivator factor Tat to the transactivation-responsive element (TAR) located at the end of initial HIV transcripts (D'Orso and Frankel, 2010). Compounds such as Celastrol (Narayan et al., 2011) directly block Tat function by altering its structure. An analogue of Cortistatin A, a natural steroidal alkaloid, has shown to block HIV transcription initiation and elongation by binding specifically to the TAR-binding domain of Tat and impairing the interaction of Tat with viral RNAs (Mousseau et al., 2012). This promising molecule showed potent inhibitory capacity in vitro at very low concentrations (nM-pM). Zinc-finger domains, small protein domains that can be designed to bind specific DNA sequences, can be fused to appropriate effector domains of transcription factors to specifically regulate the expression of targeted genes. Zinc-finger transcription factors targeting different regions of the LTR promoter and carrying the repression domain of the KOX1 protein were able to repress transcription from the LTR in infected cells in vitro (Reynolds et al., 2003). Overall these results suggest that

different opportunities exist and may be exploited to specifically repress HIV transcription.

Gene therapy

The apparent cure of the Berlin patient after receiving HSCT from a *CCR5Δ32* homozygous donor and the impossibility of applying this protocol in a large scale have inspired attempts to generate HIV-resistant cells through gene therapy (Peterson et al., 2013a). One of the most promising gene therapy strategies against HIV infection aims to disrupt the *CCR5* gene by expressing an engineered zinc-finger nuclease (ZFN). Evidence that ZFN could inactivate *CCR5* in primary human CD4+ T cells and in CD34+ hematopoietic stem cells limiting HIV replication was first obtained in mouse models (Holt et al., 2010; Perez et al., 2008). The results of a Phase I clinical trial showed that HIV-infected patients treated with ZFN *CCR5* modified CD4+ T cells (SB-728-T) have sustained increases in the CD4+ T cells, mostly T_{CM} and T_{TM} with low PD-1 expression. Viremia was controlled after treatment interruption for some patients, but cART was resumed by most of them due to dual-tropic infection or viral load rebound (Ando D. et al 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy, 2013, Denver, CO, USA). Phase II clinical trials are currently ongoing to evaluate the efficacy of SB-728-T. In a recent development of these studies, ZFNs have been designed to be combined and simultaneously target *CCR5* and *CXCR4.* This approach resulted in human primary CD4+ T cells that were resistant to R5 and X4 viruses in vitro and also in vivo when introduced in humanized mice (Didigu et al., 2014). This strategy would tackle the risk of tropism switching.

Other strategies consist of transducing CD34+ or CD4+ T cells with vectors expressing (i) shRNA interfering with *CCR5* or other key factors associated with the HIV life cycle (Kiem et al., 2012), including its promoter (Suzuki et al., 2013); (ii) small peptides with capacity to inhibit HIV entry into the cells (Younan et al., 2013). Another encouraging gene therapy approach directly targets the viral reservoir and is based on the ability of a tailored site-specific recombinase (Tre) to excise HIV provirus from host genome (Sarkar et al., 2007). Recently, successful expression of Tre-recombinase in human cells was demonstrated. In addition, an important antiviral effect was observed in humanized mice, suggesting that this approach may be valuable for future HIV eradication strategies (Hauber et al., 2013).

Innovative approaches to eliminate HIV reservoirs

Several experimental and proof-of-concept studies aim to interfere with cell cycle and survival of HIV infected cells to facilitate their elimination or avoid their persistence by homeostatic proliferation. Rapamycin is an immunosuppresor that blocks the mammalian target of rapamycin (mTOR), a protein kinase that control cell cycle, proliferation and survival, and plays a critical role in the differentiation of T cells. Rapamycin has been shown to be able to block HIV infection in vitro (Donia et al., 2010) by decreasing the expression of CCR5, and also interferes with the synthesis of HIV transcripts (Roy et al., 2002). Through its capacity to suppress activation and proliferation of T cells, rapamycin has also the potential to block HIV infection by reducing the number of target cells and to dodge the maintenance of viral reservoirs through homeostatic proliferation. Rapamycin is commonly used to avoid organ rejection in kidney transplantation when there are complications associated with

calcineurin inhibitors. Interestingly, a clinical report on a group of 14 HIV infected patients who received kidney transplantation showed that the patients who switched to rapamycin monotherapy after transplantation were able to better control HIV replication than those who kept calcineurin inhibitors (Di Benedetto et al., 2010). Another recent study, which analyzed a larger group of HIV-infected kidney recipients, has shown that those who received rapamycin experienced, two years after transplantation, some reduction in the levels of cell associated DNA when compared to patients receiving other immunosuppresors (Stock P, et al, 19th International AIDS Society conference, 2013, Kuala Lumpur, Malaysia).

Another compound with cytostatic activities that has been tried in the context of HIV infection is hydroxyurea. Hydroxyurea is an inhibitor of ribonucleotide reductase (RNR) (Koc et al., 2004), a key enzyme responsible for dNTP synthesis that has been shown to play an important role in regulating HIV infection (Allouch et al., 2013). Hydroxyurea, other than maintaining cells in a quiescent state, reduces the levels of intracellular dNTPs thus inhibiting HIV DNA synthesis during reverse transcription. Although the impact of hydroxyurea in HIV reservoirs has not been evaluated, hydroxyurea was shown to act synergically with the nucleoside analogue didanosine to reduce HIV viral loads in patients (Lori et al., 2005; Lori and Lisziewicz, 2000). Despite its promises, hydroxyurea treatment was shown to provoke complications, such as blunted CD4+ T cell recovery and severe toxicity, in HIV infected patients (Bloch et al., 2006; Zala et al., 2002). Recent studies suggest that these undesirable effects were due to a too high dose of the drug, and that both the antiviral and the cytostatic activities of hydroxyurea may contribute to control HIV when used at lower concentrations (Lori et al., 2012).

JQ1 is an agonist of the bromodomain protein BRD4, which promotes cell cycle progression (Yang et al., 2008). BRD4 is also a positive regulator of P-TEFb that competes with Tat for binding to this complex at the HIV promoter (Bisgrove et al., 2007). JQ1 dissociates BRD4 from the HIV promoter and allows Tat recruitment and subsequent HIV elongation (Li et al., 2013). In addition, JQ1 appears also to alter chromatin organization and downregulates T cell activation genes (Banerjee et al., 2012).

A different strategy has been explored with auranofin, a gold-based compound that has been evaluated in vivo in SIV infected macaques. This compound was shown in vitro to promote differentiation of CD27+ memory CD4+ T cells to more terminal short-lived stages (Lewis et al., 2011) preceding increased cell death. Administration of auranofin to a group of SIVmac251 infected rhesus macaques with viral loads suppressed by cART, induced indeed a decreased in the frequency of T_{CM} and T_{TM} CD4+ T cells, the cells thought to contribute the most to persistent reservoirs (Chomont et al., 2009). Interestingly, auranofin treatment was accompanied by a transient decrease of viral reservoirs and a delayed rebound of viremia after interruption of auranofin and antiretroviral treatment (Lewis et al., 2011). In a follow-up study, auranofin treatment in two macaques combined with cART and buthionine sulfoximine, a glutathione-depleting agent that has been proposed to favor selective death of infected cells in vitro (Savarino et al., 2009), favored control of infection at relatively low levels after treatment interruption (Shytaj et al., 2013).

How these interventions may impact (positively or negatively) T cell immune defenses against HIV has not been thoroughly addressed, and the translation of current formulations of these drugs to clinical intervention is unlikely due to toxicity and possible harmful unspecific effects. However, the proof-of-principle studies described above suggest that targeting T cell proliferation and survival deserves further attention in the search for an HIV cure.

Immunotherapies to treat HIV infection

There is a consensus in the scientific community on the need to potentiate immune responses in the context of combinatory approaches to reach an HIV cure. Such responses would contribute to either control or eliminate HIV infected cells. A study performed by the Siliciano group showed that reactivation of latent viruses would not automatically entail the elimination of the infected cells by viral-replication-driven apoptosis (Shan et al., 2012). Efficient CD8+ T cell responses, such as those found in HIV controllers, react to very small amounts of antigens and eliminate HIV producing cells (Almeida et al., 2007; Saez-Cirion et al., 2007; Shan et al., 2012). In contrast, responses from non-controller patients would not have such capacity. Anti-exhaustion strategies try to reverse negative signaling provided by immunoregulatory molecules such as PD-1 to restore T cell function, in particular, the capacity to kill infected cells (Porichis and Kaufmann, 2012). Blockage of PD-1 interactions with PD-1 ligands on SIV-infected macaques resulted in the expansion of CD8+ T cells with improved functionality, longer survival, lower viral loads and delayed viral rebound after antiretroviral treatment interruption (Velu et al., 2009). However, another report suggests that mere expansion of polyfunctional CD8+ T cell responses through PD-1 blockade may not suffice to sustainably decrease viremia (Amancha et al., 2013). A

key aspect may be the association of the efficient responses found in HIV controllers with the selection of particular TCR clonotypes in these cells. In this sense, PD-1 blockade may be a useful adjuvant in vaccination protocols (Finnefrock et al., 2009) helping to induce efficient responses. This review will not summarize therapeutic vaccine strategies currently in development. However, recent results showing that (i) non-conventional CD8+ T cell responses were associated with control of infection and viral clearance in a group of macaques vaccinated with a cytomegalovirus vector (Hansen et al., 2013a; Hansen et al., 2013b) despite profound viral dissemination during primary infection; and that (ii) passive transfer of broadly neutralising antibodies allows control of infection in chronically SIV-infected macaques (Barouch et al., 2013), suggest that therapeutic vaccines should be an important element in the global plan to achieve HIV cure or remission.

So far, interventions based on the administration of gamma-chain cytokines such as IL-2, IL-7 or IL-15, which tried to improve T cell function and restore T cell homeostasis (Leone et al., 2009; Levy et al., 2009; Levy et al., 2012; Vanham and Van Gulck, 2012), have not shown, at least by themselves, significant benefits in HIV treatment. Indeed, improved immune reconstitution with IL-7 is also accompanied by a significant increase in the total number of HIV-harbouring CD4+ T cells (Levy et al., 2009; Vandergeeten et al., 2013). It is not excluded, however, that these cytokines may have an important adjuvant effect in vaccine strategies. Therapies based on IFNα administration have been shown to decrease viremia during chronic infection and reduce viral reservoirs after treatment interruption (Asmuth et al., 2010; Azzoni et al., 2013; Pillai et al., 2012). However, these effects were not observed in all

situations (Boue et al., 2011; Goujard et al., 2012a), which may be due to the dual role that IFNα (and immune activation) may play at different stages of infection.

Immune activation is a major determinant of HIV pathogenesis, and increased levels of inflammation markers are associated with faster progression to disease and CD4+ T cell loss (Liovat et al., 2012) including in HIV controllers with undetectable viremia (Hunt et al., 2008; Noel et al., 2014). Therefore, targeting the harmful immune activation appears to be a necessary element in ensuring a long-life remission of HIV infection. Some of the molecules targeting HIV reservoirs described in this review have also immunosuppressive effects, and their impact is being evaluated. Other molecules such as chloroquine analogues or statins specifically target inflammation. So far, studies employing these and other anti-inflammatory molecules have rendered contrasting results (Hatano, 2013). Thus, chloroquine administration has been shown to decrease levels of T cell activation (Murray et al., 2010) but produce faster CD4+ T cell loss when used for longer periods of time (Paton et al., 2012). A better knowledge of the best timing to implement interventions aimed at decreasing persistent immune activation is warranted.

Concluding remarks

Achieving HIV cure at a global scale through the eradication of HIV reservoirs seems still far off. In contrast, durable HIV remission with low levels of infected cells being controlled by host mechanisms seems more plausible at medium-term horizon. The first step in such strategy would be to limit the size of the viral reservoirs. Early treatment initiation has been shown to provide immunological and virological benefits to HIV infected patients, and early treated patients may be more prone to positively

respond to cure therapies. Moreover, treatment is prevention (Cohen et al., 2011) and, thus, early diagnosis and treatment initiation appears as a priority in the global fight against HIV. Approaches trying to purge the viral reservoirs, including activation with HDAC inhibitors or PKC agonists face the difficulty of trying to circumvent complex mechanisms of repression with non-specific drugs that may cause undesirable effects. An alternative strategy may be to further reinforce latency and repression mechanisms with specific molecules targeting Tat-dependent transcription of HIV products. Gene therapy offers also the possibility to target specific genes to render cells resistant to HIV infection and even to excise integrated provirus. Enhancing susceptibility to apoptosis of HIV infected cells or impairing homoeostatic proliferation and persistence of these cells are also proposed as potential strategies to tackle HIV reservoirs. However, such approaches need to carefully evaluate the impact they may have in immune responses of treated individuals. HIV remission will require efficient host responses to control infected cells and to prevent harmful HIV-related inflammation. These areas of research need to be explore in parallel to strategies targeting the reservoirs.

Acknowledgments

Our work receives financial support from the ANRS, Sidaction, amfAR and Total Foundation. C.P.B.P. has postdoctoral funding from the ANRS.

References

Allers, K., Hutter, G., Hofmann, J., Loddenkemper, C., Rieger, K., Thiel, E., Schneider, T., 2011. Evidence for the cure of HIV infection by CCR5Delta32/Delta32 stem cell transplantation. Blood 117, 2791-2799.

Allouch, A., David, A., Amie, S.M., Lahouassa, H., Chartier, L., Margottin-Goguet, F., Barre-Sinoussi, F., Kim, B., Saez-Cirion, A., Pancino, G., 2013. p21-mediated RNR2 repression restricts HIV-1 replication in macrophages by inhibiting dNTP biosynthesis pathway. Proc Natl Acad Sci U S A 110, E3997-4006.

Almeida, J.R., Price, D.A., Papagno, L., Arkoub, Z.A., Sauce, D., Bornstein, E., Asher, T.E., Samri, A., Schnuriger, A., Theodorou, I., Costagliola, D., Rouzioux, C., Agut, H., Marcelin, A.G., Douek, D., Autran, B., Appay, V., 2007. Superior control of HIV-1 replication by CD8+ T cells is reflected by their avidity, polyfunctionality, and clonal turnover. J Exp Med 204, 2473-2485.

Amancha, P.K., Hong, J.J., Rogers, K., Ansari, A.A., Villinger, F., 2013. In vivo blockade of the programmed cell death-1 pathway using soluble recombinant PD-1-Fc enhances CD4+ and CD8+ T cell responses but has limited clinical benefit. J Immunol 191, 6060-6070.

Ananworanich, J., Schuetz, A., Vandergeeten, C., Sereti, I., de Souza, M., Rerknimitr, R., Dewar, R., Marovich, M., van Griensven, F., Sekaly, R., Pinyakorn, S., Phanuphak, N., Trichavaroj, R., Rutvisuttinunt, W., Chomchey, N., Paris, R., Peel, S., Valcour, V., Maldarelli, F., Chomont, N., Michael, N., Phanuphak, P., Kim, J.H., 2012. Impact of multi-targeted antiretroviral treatment on gut T cell depletion and HIV reservoir seeding during acute HIV infection. PLoS One 7, e33948.

Archin, N.M., Cheema, M., Parker, D., Wiegand, A., Bosch, R.J., Coffin, J.M., Eron, J., Cohen, M., Margolis, D.M., 2010. Antiretroviral intensification and valproic acid lack sustained effect on residual HIV-1 viremia or resting CD4+ cell infection. PLoS One 5, e9390.

Archin, N.M., Liberty, A.L., Kashuba, A.D., Choudhary, S.K., Kuruc, J.D., Crooks, A.M., Parker, D.C., Anderson, E.M., Kearney, M.F., Strain, M.C., Richman, D.D., Hudgens, M.G., Bosch, R.J., Coffin, J.M., Eron, J.J., Hazuda, D.J., Margolis, D.M., 2012a. Administration of vorinostat disrupts HIV-1 latency in patients on antiretroviral therapy. Nature 487, 482-485.

Archin, N.M., Vaidya, N.K., Kuruc, J.D., Liberty, A.L., Wiegand, A., Kearney, M.F., Cohen, M.S., Coffin, J.M., Bosch, R.J., Gay, C.L., Eron, J.J., Margolis, D.M., Perelson, A.S., 2012b. Immediate antiviral therapy appears to restrict resting CD4+ cell HIV-1 infection without accelerating the decay of latent infection. Proc Natl Acad Sci U S A 109, 9523-9528.

Asmuth, D.M., Murphy, R.L., Rosenkranz, S.L., Lertora, J.J., Kottilil, S., Cramer, Y., Chan, E.S., Schooley, R.T., Rinaldo, C.R., Thielman, N., Li, X.D., Wahl, S.M., Shore, J., Janik, J., Lempicki, R.A., Simpson, Y., Pollard, R.B., 2010. Safety, tolerability, and mechanisms of antiretroviral activity of pegylated interferon Alfa-2a in HIV-1-monoinfected participants: a phase II clinical trial. J Infect Dis 201, 1686-1696.

Avettand-Fenoel, V., Mahlaoui, N., Chaix, M.L., Milliancourt, C., Burgard, M., Cavazzana-Calvo, M., Rouzioux, C., Blanche, S., 2007. Failure of bone marrow transplantation to eradicate HIV reservoir despite efficient HAART. Aids 21, 776-777.

Azzoni, L., Foulkes, A.S., Papasavvas, E., Mexas, A.M., Lynn, K.M., Mounzer, K., Tebas, P., Jacobson, J.M., Frank, I., Busch, M.P., Deeks, S.G., Carrington, M., O'Doherty, U., Kostman, J., Montaner, L.J., 2013. Pegylated Interferon alfa-2a monotherapy results in suppression of HIV type 1 replication and decreased cell-associated HIV DNA integration. J Infect Dis 207, 213-222.

Banerjee, C., Archin, N., Michaels, D., Belkina, A.C., Denis, G.V., Bradner, J., Sebastiani, P., Margolis, D.M., Montano, M., 2012. BET bromodomain inhibition as a novel strategy for reactivation of HIV-1. J Leukoc Biol 92, 1147-1154.

Barouch, D.H., Whitney, J.B., Moldt, B., Klein, F., Oliveira, T.Y., Liu, J., Stephenson, K.E., Chang, H.W., Shekhar, K., Gupta, S., Nkolola, J.P., Seaman, M.S., Smith, K.M., Borducchi, E.N., Cabral, C., Smith, J.Y., Blackmore, S., Sanisetty, S., Perry, J.R., Beck, M., Lewis, M.G., Rinaldi, W., Chakraborty, A.K., Poignard, P., Nussenzweig, M.C., Burton, D.R., 2013. Therapeutic efficacy of potent neutralizing HIV-1-specific monoclonal antibodies in SHIV-infected rhesus monkeys. Nature 503, 224-228.

Barre-Sinoussi, F., Chermann, J.C., Rey, F., Nugeyre, M.T., Chamaret, S., Gruest, J., Dauguet, C., Axler-Blin, C., Vezinet-Brun, F., Rouzioux, C., Rozenbaum, W., Montagnier, L., 1983. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science 220, 868-871.
Besson, G.J., McMahon, D., Maldarelli, F., Mellors, J.W., 2012. Short-course raltegravir intensification does not increase 2 long terminal repeat episomal HIV-1 DNA in patients on effective antiretroviral therapy. Clin Infect Dis 54, 451-453.
Bisgrove, D.A., Mahmoudi, T., Henklein, P., Verdin, E., 2007. Conserved P-TEFb-interacting domain of BRD4 inhibits HIV transcription. Proc Natl Acad Sci U S A 104, 13690-13695.
Bloch, M.T., Smith, D.E., Quan, D., Kaldor, J.M., Zaunders, J.J., Petoumenos, K., Irvine, K., Law, M., Grey, P., Finlayson, R.J., McFarlane, R., Kelleher, A.D., Carr, A., Cooper, D.A., 2006. The role of hydroxyurea in enhancing the virologic control achieved through structured treatment interruption in primary HIV infection: final results from a randomized clinical trial (Pulse). J Acquir Immune Defic Syndr 42, 192-202.
Boue, F., Reynes, J., Rouzioux, C., Emilie, D., Souala, F., Tubiana, R., Goujard, C., Lancar, R., Costagliola, D., 2011. Alpha interferon administration during structured interruptions of combination antiretroviral therapy in patients with chronic HIV-1 infection: INTERVAC ANRS 105 trial. Aids 25, 115-118.
Buzon, M.J., Massanella, M., Llibre, J.M., Esteve, A., Dahl, V., Puertas, M.C., Gatell, J.M., Domingo, P., Paredes, R., Sharkey, M., Palmer, S., Stevenson, M., Clotet, B., Blanco, J., Martinez-Picado, J., 2010. HIV-1 replication and immune dynamics are affected by raltegravir intensification of HAART-suppressed subjects. Nat Med 16, 460-465.
Carrington, M., Nelson, G.W., Martin, M.P., Kissner, T., Vlahov, D., Goedert, J.J., Kaslow, R., Buchbinder, S., Hoots, K., O'Brien, S.J., 1999. HLA and HIV-1: heterozygote advantage and B*35-Cw*04 disadvantage. Science 283, 1748-1752.
Chamberland, A., Sylla, M., Boulassel, M.R., Baril, J.G., Cote, P., Thomas, R., Trottier, B., Rouleau, D., Routy, J.P., Tremblay, C., 2011. Effect of antiretroviral therapy on HIV-1 genetic evolution during acute infection. Int J STD AIDS 22, 146-150.
Chomont, N., El-Far, M., Ancuta, P., Trautmann, L., Procopio, F.A., Yassine-Diab, B., Boucher, G., Boulassel, M.R., Ghattas, G., Brenchley, J.M., Schacker, T.W., Hill, B.J., Douek, D.C., Routy, J.P., Haddad, E.K., Sekaly, R.P., 2009. HIV reservoir size and persistence are driven by T cell survival and homeostatic proliferation. Nat Med 15, 893-900.
Chun, T.W., Justement, J.S., Murray, D., Hallahan, C.W., Maenza, J., Collier, A.C., Sheth, P.M., Kaul, R., Ostrowski, M., Moir, S., Kovacs, C., Fauci, A.S., 2010. Rebound of plasma viremia following cessation of antiretroviral therapy despite profoundly low levels of HIV reservoir: implications for eradication. Aids 24, 2803-2808.
Chun, T.W., Stuyver, L., Mizell, S.B., Ehler, L.A., Mican, J.A., Baseler, M., Lloyd, A.L., Nowak, M.A., Fauci, A.S., 1997. Presence of an inducible HIV-1 latent reservoir during highly active antiretroviral therapy. Proc Natl Acad Sci U S A 94, 13193-13197.
Cillo, A.R., Krishnan, A., Mitsuyasu, R.T., McMahon, D.K., Li, S., Rossi, J.J., Zaia, J.A., Mellors, J.W., 2013. Plasma viremia and cellular HIV-1 DNA persist despite autologous hematopoietic stem cell transplantation for HIV-related lymphoma. J Acquir Immune Defic Syndr 63, 438-441.
Clifford, D.B., Ances, B.M., 2013. HIV-associated neurocognitive disorder. Lancet Infect Dis 13, 976-986.
Cohen, M.S., Chen, Y.Q., McCauley, M., Gamble, T., Hosseinipour, M.C., Kumarasamy, N., Hakim, J.G., Kumwenda, J., Grinsztejn, B., Pilotto, J.H., Godbole, S.V., Mehendale, S., Chariyalertsak, S., Santos, B.R., Mayer, K.H., Hoffman, I.F., Eshleman, S.H., Piwowar-Manning, E., Wang, L., Makhema, J., Mills, L.A., de Bruyn, G., Sanne, I., Eron, J., Gallant, J., Havlir, D., Swindells, S., Ribaudo, H., Elharrar, V., Burns, D., Taha, T.E., Nielsen-Saines, K., Celentano, D., Essex, M., Fleming, T.R., 2011. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 365, 493-505.

Contu, L., La Nasa, G., Arras, M., Pizzati, A., Vacca, A., Carcassi, C., Ledda, A., Boero, R., Orru, S., Pintus, A., et al., 1993. Allogeneic bone marrow transplantation combined with multiple anti-HIV-1 treatment in a case of AIDS. Bone Marrow Transplant 12, 669-671.
Cooper, D.A., Heera, J., Goodrich, J., Tawadrous, M., Saag, M., Dejesus, E., Clumeck, N., Walmsley, S., Ting, N., Coakley, E., Reeves, J.D., Reyes-Teran, G., Westby, M., Van Der Ryst, E., Ive, P., Mohapi, L., Mingrone, H., Horban, A., Hackman, F., Sullivan, J., Mayer, H., 2010. Maraviroc versus efavirenz, both in combination with zidovudine-lamivudine, for the treatment of antiretroviral-naive subjects with CCR5-tropic HIV-1 infection. J Infect Dis 201, 803-813.
Corbeau, P., Reynes, J., 2011. Immune reconstitution under antiretroviral therapy: the new challenge in HIV-1 infection. Blood 117, 5582-5590.
Cuzin, L., Trabelsi, S., Delobel, P., Barbuat, C., Reynes, J., Allavena, C., Peytavin, G., Ghosn, J., Lascoux-Combe, C., Psomas, C., Corbeau, P., Flandre, P., 2012. Maraviroc intensification of stable antiviral therapy in HIV-1-infected patients with poor immune restoration: MARIMUNO-ANRS 145 study. J Acquir Immune Defic Syndr 61, 557-564.
D'Orso, I., Frankel, A.D., 2010. RNA-mediated displacement of an inhibitory snRNP complex activates transcription elongation. Nat Struct Mol Biol 17, 815-821.
Dahl, V., Lee, E., Peterson, J., Spudich, S.S., Leppla, I., Sinclair, E., Fuchs, D., Palmer, S., Price, R.W., 2011. Raltegravir treatment intensification does not alter cerebrospinal fluid HIV-1 infection or immunoactivation in subjects on suppressive therapy. J Infect Dis 204, 1936-1945.
Dean, M., Carrington, M., Winkler, C., Huttley, G.A., Smith, M.W., Allikmets, R., Goedert, J.J., Buchbinder, S.P., Vittinghoff, E., Gomperts, E., Donfield, S., Vlahov, D., Kaslow, R., Saah, A., Rinaldo, C., Detels, R., O'Brien, S.J., 1996. Genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the CKR5 structural gene. Hemophilia Growth and Development Study, Multicenter AIDS Cohort Study, Multicenter Hemophilia Cohort Study, San Francisco City Cohort, ALIVE Study. Science 273, 1856-1862.
Deeks, S.G., Lewin, S.R., Havlir, D.V., 2013. The end of AIDS: HIV infection as a chronic disease. Lancet 382, 1525-1533.
Di Benedetto, F., Di Sandro, S., De Ruvo, N., Montalti, R., Ballarin, R., Guerrini, G.P., Spaggiari, M., Guaraldi, G., Gerunda, G., 2010. First report on a series of HIV patients undergoing rapamycin monotherapy after liver transplantation. Transplantation 89, 733-738.
Didigu, C.A., Wilen, C.B., Wang, J., Duong, J., Secreto, A.J., Danet-Desnoyers, G.A., Riley, J.L., Gregory, P.D., June, C.H., Holmes, M.C., Doms, R.W., 2014. Simultaneous zinc-finger nuclease editing of the HIV coreceptors ccr5 and cxcr4 protects CD4+ T cells from HIV-1 infection. Blood 123, 61-69.
Dinoso, J.B., Kim, S.Y., Wiegand, A.M., Palmer, S.E., Gange, S.J., Cranmer, L., O'Shea, A., Callender, M., Spivak, A., Brennan, T., Kearney, M.F., Proschan, M.A., Mican, J.M., Rehm, C.A., Coffin, J.M., Mellors, J.W., Siliciano, R.F., Maldarelli, F., 2009. Treatment intensification does not reduce residual HIV-1 viremia in patients on highly active antiretroviral therapy. Proc Natl Acad Sci U S A 106, 9403-9408.
Donia, M., McCubrey, J.A., Bendtzen, K., Nicoletti, F., 2010. Potential use of rapamycin in HIV infection. Br J Clin Pharmacol 70, 784-793.
Doyle, T., Geretti, A.M., 2012. Low-level viraemia on HAART: significance and management. Curr Opin Infect Dis 25, 17-25.
Fernandez Guerrero, M.L., Rivas, P., Molina, M., Garcia, R., De Gorgolas, M., 2005. Long-term follow-up of asymptomatic HIV-infected patients who discontinued antiretroviral therapy. Clin Infect Dis 41, 390-394.
Fidler, S., Porter, K., Ewings, F., Frater, J., Ramjee, G., Cooper, D., Rees, H., Fisher, M., Schechter, M., Kaleebu, P., Tambussi, G., Kinloch, S., Miro, J.M., Kelleher, A., McClure, M., Kaye, S., Gabriel, M., Phillips, R., Weber, J., Babiker, A., 2013. Short-course antiretroviral therapy in primary HIV infection. N Engl J Med 368, 207-217.
Finnefrock, A.C., Tang, A., Li, F., Freed, D.C., Feng, M., Cox, K.S., Sykes, K.J., Guare, J.P., Miller, M.D., Olsen, D.B., Hazuda, D.J., Shiver, J.W., Casimiro, D.R., Fu, T.M., 2009. PD-1 blockade in rhesus macaques: impact on chronic infection and prophylactic vaccination. J Immunol 182, 980-987.

Fletcher, C.V., Staskus, K., Wietgrefe, S.W., Rothenberger, M., Reilly, C., Chipman, J.G., Beilman, G.J., Khoruts, A., Thorkelson, A., Schmidt, T.E., Anderson, J., Perkey, K., Stevenson, M., Perelson, A.S., Douek, D.C., Haase, A.T., Schacker, T.W., 2014. Persistent HIV-1 replication is associated with lower antiretroviral drug concentrations in lymphatic tissues. Proc Natl Acad Sci U S A 111, 2307-2312.
Gabarre, J., Marcelin, A.G., Azar, N., Choquet, S., Levy, V., Levy, Y., Tubiana, R., Charlotte, F., Norol, F., Calvez, V., Spina, M., Vernant, J.P., Autran, B., Leblond, V., 2004. High-dose therapy plus autologous hematopoietic stem cell transplantation for human immunodeficiency virus (HIV)-related lymphoma: results and impact on HIV disease. Haematologica 89, 1100-1108.
Gandhi, R.T., Coombs, R.W., Chan, E.S., Bosch, R.J., Zheng, L., Margolis, D.M., Read, S., Kallungal, B., Chang, M., Goecker, E.A., Wiegand, A., Kearney, M., Jacobson, J.M., D'Aquila, R., Lederman, M.M., Mellors, J.W., Eron, J.J., 2012. No effect of raltegravir intensification on viral replication markers in the blood of HIV-1-infected patients receiving antiretroviral therapy. J Acquir Immune Defic Syndr 59, 229-235.
Gandhi, R.T., Zheng, L., Bosch, R.J., Chan, E.S., Margolis, D.M., Read, S., Kallungal, B., Palmer, S., Medvik, K., Lederman, M.M., Alatrakchi, N., Jacobson, J.M., Wiegand, A., Kearney, M., Coffin, J.M., Mellors, J.W., Eron, J.J., 2010. The effect of raltegravir intensification on low-level residual viremia in HIV-infected patients on antiretroviral therapy: a randomized controlled trial. PLoS Med 7.
Gianella, S., von Wyl, V., Fischer, M., Niederoest, B., Battegay, M., Bernasconi, E., Cavassini, M., Rauch, A., Hirschel, B., Vernazza, P., Weber, R., Joos, B., Gunthard, H.F., 2011. Effect of early antiretroviral therapy during primary HIV-1 infection on cell-associated HIV-1 DNA and plasma HIV-1 RNA. Antivir Ther 16, 535-545.
Glaser, K.B., Staver, M.J., Waring, J.F., Stender, J., Ulrich, R.G., Davidsen, S.K., 2003. Gene expression profiling of multiple histone deacetylase (HDAC) inhibitors: defining a common gene set produced by HDAC inhibition in T24 and MDA carcinoma cell lines. Mol Cancer Ther 2, 151-163.
Goujard, C., Emilie, D., Roussillon, C., Godot, V., Rouzioux, C., Venet, A., Colin, C., Pialoux, G., Girard, P.M., Boilet, V., Chaix, M.L., Galanaud, P., Chene, G., 2012a. Continuous versus intermittent treatment strategies during primary HIV-1 infection: the randomized ANRS INTERPRIM Trial. Aids 26, 1895-1905.
Goujard, C., Girault, I., Rouzioux, C., Lecuroux, C., Deveau, C., Chaix, M.L., Jacomet, C., Talamali, A., Delfraissy, J.F., Venet, A., Meyer, L., Sinet, M., 2012b. HIV-1 control after transient antiretroviral treatment initiated in primary infection: role of patient characteristics and effect of therapy. Antivir Ther 17, 1001-1009.
Guadalupe, M., Sankaran, S., George, M.D., Reay, E., Verhoeven, D., Shacklett, B.L., Flamm, J., Wegelin, J., Prindiville, T., Dandekar, S., 2006. Viral suppression and immune restoration in the gastrointestinal mucosa of human immunodeficiency virus type 1-infected patients initiating therapy during primary or chronic infection. J Virol 80, 8236-8247.
Guan, E., Wang, J., Roderiquez, G., Norcross, M.A., 2002. Natural truncation of the chemokine MIP-1 beta /CCL4 affects receptor specificity but not anti-HIV-1 activity. J Biol Chem 277, 32348-32352.
Gutierrez, C., Diaz, L., Vallejo, A., Hernandez-Novoa, B., Abad, M., Madrid, N., Dahl, V., Rubio, R., Moreno, A.M., Dronda, F., Casado, J.L., Navas, E., Perez-Elias, M.J., Zamora, J., Palmer, S., Munoz, E., Munoz-Fernandez, M.A., Moreno, S., 2011. Intensification of antiretroviral therapy with a CCR5 antagonist in patients with chronic HIV-1 infection: effect on T cells latently infected. PLoS One 6, e27864.
Hamimi, C., Pancino, G., Barre-Sinoussi, F., Saez-Cirion, A., 2013. Will it be possible to live without antiretroviral therapy? Curr Opin HIV AIDS 8, 196-203.
Hansen, S.G., Piatak, M., Jr., Ventura, A.B., Hughes, C.M., Gilbride, R.M., Ford, J.C., Oswald, K., Shoemaker, R., Li, Y., Lewis, M.S., Gilliam, A.N., Xu, G., Whizin, N., Burwitz, B.J., Planer, S.L., Turner, J.M., Legasse, A.W., Axthelm, M.K., Nelson, J.A., Fruh, K., Sacha, J.B., Estes, J.D., Keele, B.F., Edlefsen, P.T., Lifson, J.D., Picker, L.J., 2013a. Immune clearance of highly pathogenic SIV infection. Nature 502, 100-104.
Hansen, S.G., Sacha, J.B., Hughes, C.M., Ford, J.C., Burwitz, B.J., Scholz, I., Gilbride, R.M., Lewis, M.S., Gilliam, A.N., Ventura, A.B., Malouli, D., Xu, G., Richards, R., Whizin, N., Reed, J.S., Hammond, K.B.,

Fischer, M., Turner, J.M., Legasse, A.W., Axthelm, M.K., Edlefsen, P.T., Nelson, J.A., Lifson, J.D., Fruh, K., Picker, L.J., 2013b. Cytomegalovirus vectors violate CD8+ T cell epitope recognition paradigms. Science 340, 1237874.
Hatano, H., 2013. Immune activation and HIV persistence: considerations for novel therapeutic interventions. Curr Opin HIV AIDS 8, 211-216.
Hatano, H., Hayes, T.L., Dahl, V., Sinclair, E., Lee, T.H., Hoh, R., Lampiris, H., Hunt, P.W., Palmer, S., McCune, J.M., Martin, J.N., Busch, M.P., Shacklett, B.L., Deeks, S.G., 2011. A randomized, controlled trial of raltegravir intensification in antiretroviral-treated, HIV-infected patients with a suboptimal CD4+ T cell response. J Infect Dis 203, 960-968.
Hatano, H., Strain, M.C., Scherzer, R., Bacchetti, P., Wentworth, D., Hoh, R., Martin, J.N., McCune, J.M., Neaton, J.D., Tracy, R.P., Hsue, P.Y., Richman, D.D., Deeks, S.G., 2013. Increase in 2-long terminal repeat circles and decrease in D-dimer after raltegravir intensification in patients with treated HIV infection: a randomized, placebo-controlled trial. J Infect Dis 208, 1436-1442.
Hauber, I., Hofmann-Sieber, H., Chemnitz, J., Dubrau, D., Chusainow, J., Stucka, R., Hartjen, P., Schambach, A., Ziegler, P., Hackmann, K., Schrock, E., Schumacher, U., Lindner, C., Grundhoff, A., Baum, C., Manz, M.G., Buchholz, F., Hauber, J., 2013. Highly significant antiviral activity of HIV-1 LTR-specific tre-recombinase in humanized mice. PLoS Pathog 9, e1003587.
Havlir, D.V., Strain, M.C., Clerici, M., Ignacio, C., Trabattoni, D., Ferrante, P., Wong, J.K., 2003. Productive infection maintains a dynamic steady state of residual viremia in human immunodeficiency virus type 1-infected persons treated with suppressive antiretroviral therapy for five years. J Virol 77, 11212-11219.
Hecht, F.M., Wang, L., Collier, A., Little, S., Markowitz, M., Margolick, J., Kilby, J.M., Daar, E., Conway, B., Holte, S., 2006. A multicenter observational study of the potential benefits of initiating combination antiretroviral therapy during acute HIV infection. J Infect Dis 194, 725-733.
Henrich, T.J., Hu, Z., Li, J.Z., Sciaranghella, G., Busch, M.P., Keating, S.M., Gallien, S., Lin, N.H., Giguel, F.F., Lavoie, L., Ho, V.T., Armand, P., Soiffer, R.J., Sagar, M., Lacasce, A.S., Kuritzkes, D.R., 2013. Long-term reduction in peripheral blood HIV type 1 reservoirs following reduced-intensity conditioning allogeneic stem cell transplantation. J Infect Dis 207, 1694-1702.
Ho, Y.C., Shan, L., Hosmane, N.N., Wang, J., Laskey, S.B., Rosenbloom, D.I., Lai, J., Blankson, J.N., Siliciano, J.D., Siliciano, R.F., 2013. Replication-competent noninduced proviruses in the latent reservoir increase barrier to HIV-1 cure. Cell 155, 540-551.
Hocqueloux, L., Prazuck, T., Avettand-Fenoel, V., Lafeuillade, A., Cardon, B., Viard, J.P., Rouzioux, C., 2010. Long-term immunovirologic control following antiretroviral therapy interruption in patients treated at the time of primary HIV-1 infection. Aids 24, 1598-1601.
Holland, H.K., Saral, R., Rossi, J.J., Donnenberg, A.D., Burns, W.H., Beschorner, W.E., Farzadegan, H., Jones, R.J., Quinnan, G.V., Vogelsang, G.B., et al., 1989. Allogeneic bone marrow transplantation, zidovudine, and human immunodeficiency virus type 1 (HIV-1) infection. Studies in a patient with non-Hodgkin lymphoma. Ann Intern Med 111, 973-981.
Holt, N., Wang, J., Kim, K., Friedman, G., Wang, X., Taupin, V., Crooks, G.M., Kohn, D.B., Gregory, P.D., Holmes, M.C., Cannon, P.M., 2010. Human hematopoietic stem/progenitor cells modified by zinc-finger nucleases targeted to CCR5 control HIV-1 in vivo. Nat Biotechnol 28, 839-847.
Huber, K., Doyon, G., Plaks, J., Fyne, E., Mellors, J.W., Sluis-Cremer, N., 2011. Inhibitors of histone deacetylases: correlation between isoform specificity and reactivation of HIV type 1 (HIV-1) from latently infected cells. J Biol Chem 286, 22211-22218.
Hunt, P.W., Brenchley, J., Sinclair, E., McCune, J.M., Roland, M., Page-Shafer, K., Hsue, P., Emu, B., Krone, M., Lampiris, H., Douek, D., Martin, J.N., Deeks, S.G., 2008. Relationship between T cell activation and CD4+ T cell count in HIV-seropositive individuals with undetectable plasma HIV RNA levels in the absence of therapy. J Infect Dis 197, 126-133.
Hunt, P.W., Shulman, N.S., Hayes, T.L., Dahl, V., Somsouk, M., Funderburg, N.T., McLaughlin, B., Landay, A.L., Adeyemi, O., Gilman, L.E., Clagett, B., Rodriguez, B., Martin, J.N., Schacker, T.W., Shacklett, B.L., Palmer, S., Lederman, M.M., Deeks, S.G., 2013. The immunologic effects of maraviroc

intensification in treated HIV-infected individuals with incomplete CD4+ T-cell recovery: a randomized trial. Blood 121, 4635-4646.
Hutter, G., Nowak, D., Mossner, M., Ganepola, S., Mussig, A., Allers, K., Schneider, T., Hofmann, J., Kucherer, C., Blau, O., Blau, I.W., Hofmann, W.K., Thiel, E., 2009. Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. N Engl J Med 360, 692-698.
Itescu, S., Mathur-Wagh, U., Skovron, M.L., Brancato, L.J., Marmor, M., Zeleniuch-Jacquotte, A., Winchester, R., 1992. HLA-B35 is associated with accelerated progression to AIDS. J Acquir Immune Defic Syndr 5, 37-45.
Kaufmann, D.E., Bailey, P.M., Sidney, J., Wagner, B., Norris, P.J., Johnston, M.N., Cosimi, L.A., Addo, M.M., Lichterfeld, M., Altfeld, M., Frahm, N., Brander, C., Sette, A., Walker, B.D., Rosenberg, E.S., 2004. Comprehensive analysis of human immunodeficiency virus type 1-specific CD4 responses reveals marked immunodominance of gag and nef and the presence of broadly recognized peptides. J Virol 78, 4463-4477.
Kiem, H.P., Jerome, K.R., Deeks, S.G., McCune, J.M., 2012. Hematopoietic-stem-cell-based gene therapy for HIV disease. Cell Stem Cell 10, 137-147.
Koc, A., Wheeler, L.J., Mathews, C.K., Merrill, G.F., 2004. Hydroxyurea arrests DNA replication by a mechanism that preserves basal dNTP pools. J Biol Chem 279, 223-230.
Kulkosky, J., Culnan, D.M., Roman, J., Dornadula, G., Schnell, M., Boyd, M.R., Pomerantz, R.J., 2001. Prostratin: activation of latent HIV-1 expression suggests a potential inductive adjuvant therapy for HAART. Blood 98, 3006-3015.
Lake, J.E., Currier, J.S., 2013. Metabolic disease in HIV infection. Lancet Infect Dis 13, 964-975.
Lehrman, G., Hogue, I.B., Palmer, S., Jennings, C., Spina, C.A., Wiegand, A., Landay, A.L., Coombs, R.W., Richman, D.D., Mellors, J.W., Coffin, J.M., Bosch, R.J., Margolis, D.M., 2005. Depletion of latent HIV-1 infection in vivo: a proof-of-concept study. Lancet 366, 549-555.
Leone, A., Picker, L.J., Sodora, D.L., 2009. IL-2, IL-7 and IL-15 as immuno-modulators during SIV/HIV vaccination and treatment. Curr HIV Res 7, 83-90.
Levy, Y., Lacabaratz, C., Weiss, L., Viard, J.P., Goujard, C., Lelievre, J.D., Boue, F., Molina, J.M., Rouzioux, C., Avettand-Fenoel, V., Croughs, T., Beq, S., Thiebaut, R., Chene, G., Morre, M., Delfraissy, J.F., 2009. Enhanced T cell recovery in HIV-1-infected adults through IL-7 treatment. The Journal of clinical investigation 119, 997-1007.
Levy, Y., Sereti, I., Tambussi, G., Routy, J.P., Lelievre, J.D., Delfraissy, J.F., Molina, J.M., Fischl, M., Goujard, C., Rodriguez, B., Rouzioux, C., Avettand-Fenoel, V., Croughs, T., Beq, S., Morre, M., Poulin, J.F., Sekaly, R.P., Thiebaut, R., Lederman, M.M., 2012. Effects of recombinant human interleukin 7 on T-cell recovery and thymic output in HIV-infected patients receiving antiretroviral therapy: results of a phase I/IIa randomized, placebo-controlled, multicenter study. Clin Infect Dis 55, 291-300.
Lewis, M.G., DaFonseca, S., Chomont, N., Palamara, A.T., Tardugno, M., Mai, A., Collins, M., Wagner, W.L., Yalley-Ogunro, J., Greenhouse, J., Chirullo, B., Norelli, S., Garaci, E., Savarino, A., 2011. Gold drug auranofin restricts the viral reservoir in the monkey AIDS model and induces containment of viral load following ART suspension. Aids 25, 1347-1356.
Li, Z., Guo, J., Wu, Y., Zhou, Q., 2013. The BET bromodomain inhibitor JQ1 activates HIV latency through antagonizing Brd4 inhibition of Tat-transactivation. Nucleic Acids Res 41, 277-287.
Liovat, A.S., Rey-Cuille, M.A., Lecuroux, C., Jacquelin, B., Girault, I., Petitjean, G., Zitoun, Y., Venet, A., Barre-Sinoussi, F., Lebon, P., Meyer, L., Sinet, M., Muller-Trutwin, M., 2012. Acute plasma biomarkers of T cell activation set-point levels and of disease progression in HIV-1 infection. PLoS One 7, e46143.
Lisziewicz, J., Rosenberg, E., Lieberman, J., Jessen, H., Lopalco, L., Siliciano, R., Walker, B., Lori, F., 1999. Control of HIV despite the discontinuation of antiretroviral therapy. N Engl J Med 340, 1683-1684.
Lodi, S., Meyer, L., Kelleher, A.D., Rosinska, M., Ghosn, J., Sannes, M., Porter, K., 2012. Immunovirologic control 24 months after interruption of antiretroviral therapy initiated close to HIV seroconversion. Arch Intern Med 172, 1252-1255.
Lori, F., De Forni, D., Katabira, E., Baev, D., Maserati, R., Calarota, S.A., Cahn, P., Testori, M., Rakhmanova, A., Stevens, M.R., 2012. VS411 reduced immune activation and HIV-1 RNA levels in 28

days: randomized proof-of-concept study for antiviral-hyperactivation limiting therapeutics. PLoS One 7, e47485.
Lori, F., Foli, A., Groff, A., Lova, L., Whitman, L., Bakare, N., Pollard, R.B., Lisziewicz, J., 2005. Optimal suppression of HIV replication by low-dose hydroxyurea through the combination of antiviral and cytostatic ('virostatic') mechanisms. Aids 19, 1173-1181.
Lori, F., Lisziewicz, J., 2000. Rationale for the use of hydroxyurea as an anti-human immunodeficiency virus drug. Clin Infect Dis 30 Suppl 2, S193-197.
Lucotte, G., 2002. Frequencies of 32 base pair deletion of the (Delta 32) allele of the CCR5 HIV-1 co-receptor gene in Caucasians: a comparative analysis. Infect Genet Evol 1, 201-205.
Mantelingu, K., Reddy, B.A., Swaminathan, V., Kishore, A.H., Siddappa, N.B., Kumar, G.V., Nagashankar, G., Natesh, N., Roy, S., Sadhale, P.P., Ranga, U., Narayana, C., Kundu, T.K., 2007. Specific inhibition of p300-HAT alters global gene expression and represses HIV replication. Chem Biol 14, 645-657.
Mbonye, U., Karn, J., 2014. Transcriptional control of HIV latency: Cellular signaling pathways, epigenetics, happenstance and the hope for a cure. Virology, In this issue.
McMahon, D., Jones, J., Wiegand, A., Gange, S.J., Kearney, M., Palmer, S., McNulty, S., Metcalf, J.A., Acosta, E., Rehm, C., Coffin, J.M., Mellors, J.W., Maldarelli, F., 2010. Short-course raltegravir intensification does not reduce persistent low-level viremia in patients with HIV-1 suppression during receipt of combination antiretroviral therapy. Clin Infect Dis 50, 912-919.
Migueles, S.A., Sabbaghian, M.S., Shupert, W.L., Bettinotti, M.P., Marincola, F.M., Martino, L., Hallahan, C.W., Selig, S.M., Schwartz, D., Sullivan, J., Connors, M., 2000. HLA B*5701 is highly associated with restriction of virus replication in a subgroup of HIV-infected long term nonprogressors. Proc Natl Acad Sci U S A 97, 2709-2714.
Moir, S., Buckner, C.M., Ho, J., Wang, W., Chen, J., Waldner, A.J., Posada, J.G., Kardava, L., O'Shea, M.A., Kottilil, S., Chun, T.W., Proschan, M.A., Fauci, A.S., 2010. B cells in early and chronic HIV infection: evidence for preservation of immune function associated with early initiation of antiretroviral therapy. Blood 116, 5571-5579.
Mousseau, G., Clementz, M.A., Bakeman, W.N., Nagarsheth, N., Cameron, M., Shi, J., Baran, P., Fromentin, R., Chomont, N., Valente, S.T., 2012. An analog of the natural steroidal alkaloid cortistatin A potently suppresses Tat-dependent HIV transcription. Cell Host Microbe 12, 97-108.
Murray, S.M., Down, C.M., Boulware, D.R., Stauffer, W.M., Cavert, W.P., Schacker, T.W., Brenchley, J.M., Douek, D.C., 2010. Reduction of immune activation with chloroquine therapy during chronic HIV infection. J Virol 84, 12082-12086.
Narayan, V., Ravindra, K.C., Chiaro, C., Cary, D., Aggarwal, B.B., Henderson, A.J., Prabhu, K.S., 2011. Celastrol inhibits Tat-mediated human immunodeficiency virus (HIV) transcription and replication. J Mol Biol 410, 972-983.
Negredo, E., Massanella, M., Puertas, M.C., Buzon, M.J., Puig, J., Perez-Alvarez, N., Perez-Santiago, J., Bonjoch, A., Molto, J., Jou, A., Echeverria, P., Llibre, J.M., Martinez-Picado, J., Clotet, B., Blanco, J., 2013. Early but limited effects of raltegravir intensification on CD4 T cell reconstitution in HIV-infected patients with an immunodiscordant response to antiretroviral therapy. J Antimicrob Chemother 68, 2358-2362.
Noel, N., Boufassa, F., Lecuroux, C., Saez-Cirion, A., Bourgeois, C., Dunyach-Remy, C., Goujard, C., Rouzioux, C., Meyer, L., Pancino, G., Venet, A., Lambotte, O., 2014. Elevated IP10 levels are associated with immune activation and low CD4+ T-cell counts in HIV controller patients. Aids 28, 467-476.
Novis, C.L., Archin, N.M., Buzon, M.J., Verdin, E., Round, J.L., Lichterfeld, M., Margolis, D.M., Planelles, V., Bosque, A., 2013. Reactivation of latent HIV-1 in central memory CD4(+) T cells through TLR-1/2 stimulation. Retrovirology 10, 119.
Ortiz, G.M., Nixon, D.F., Trkola, A., Binley, J., Jin, X., Bonhoeffer, S., Kuebler, P.J., Donahoe, S.M., Demoitie, M.A., Kakimoto, W.M., Ketas, T., Clas, B., Heymann, J.J., Zhang, L., Cao, Y., Hurley, A., Moore, J.P., Ho, D.D., Markowitz, M., 1999. HIV-1-specific immune responses in subjects who

temporarily contain virus replication after discontinuation of highly active antiretroviral therapy. The Journal of clinical investigation 104, R13-18.
Osborne, B.J., Sheth, P.M., Yi, T.J., Kovacs, C., Benko, E., Porte, C., Huibner, S., Le, A.Q., Danroth, R., Baraki, B., Mazzulli, T., Brumme, Z.L., Kaul, R., 2013. Impact of antiretroviral therapy duration and intensification on isolated shedding of HIV-1 RNA in semen. J Infect Dis 207, 1226-1234.
Oxenius, A., Price, D.A., Easterbrook, P.J., O'Callaghan, C.A., Kelleher, A.D., Whelan, J.A., Sontag, G., Sewell, A.K., Phillips, R.E., 2000. Early highly active antiretroviral therapy for acute HIV-1 infection preserves immune function of CD8+ and CD4+ T lymphocytes. Proc Natl Acad Sci U S A 97, 3382-3387.
Palmer, S., Maldarelli, F., Wiegand, A., Bernstein, B., Hanna, G.J., Brun, S.C., Kempf, D.J., Mellors, J.W., Coffin, J.M., King, M.S., 2008. Low-level viremia persists for at least 7 years in patients on suppressive antiretroviral therapy. Proc Natl Acad Sci U S A 105, 3879-3884.
Paton, N.I., Goodall, R.L., Dunn, D.T., Franzen, S., Collaco-Moraes, Y., Gazzard, B.G., Williams, I.G., Fisher, M.J., Winston, A., Fox, J., Orkin, C., Herieka, E.A., Ainsworth, J.G., Post, F.A., Wansbrough-Jones, M., Kelleher, P., 2012. Effects of hydroxychloroquine on immune activation and disease progression among HIV-infected patients not receiving antiretroviral therapy: a randomized controlled trial. Jama 308, 353-361.
Pereyra, F., Addo, M.M., Kaufmann, D.E., Liu, Y., Miura, T., Rathod, A., Baker, B., Trocha, A., Rosenberg, R., Mackey, E., Ueda, P., Lu, Z., Cohen, D., Wrin, T., Petropoulos, C.J., Rosenberg, E.S., Walker, B.D., 2008. Genetic and immunologic heterogeneity among persons who control HIV infection in the absence of therapy. J Infect Dis 197, 563-571.
Pereyra, F., Jia, X., McLaren, P.J., Telenti, A., de Bakker, P.I., Walker, B.D., Ripke, S., Brumme, C.J., Pulit, S.L., Carrington, M., Kadie, C.M., Carlson, J.M., Heckerman, D., Graham, R.R., Plenge, R.M., Deeks, S.G., Gianniny, L., Crawford, G., Sullivan, J., Gonzalez, E., Davies, L., Camargo, A., Moore, J.M., Beattie, N., Gupta, S., Crenshaw, A., Burtt, N.P., Guiducci, C., Gupta, N., Gao, X., Qi, Y., Yuki, Y., Piechocka-Trocha, A., Cutrell, E., Rosenberg, R., Moss, K.L., Lemay, P., O'Leary, J., Schaefer, T., Verma, P., Toth, I., Block, B., Baker, B., Rothchild, A., Lian, J., Proudfoot, J., Alvino, D.M., Vine, S., Addo, M.M., Allen, T.M., Altfeld, M., Henn, M.R., Le Gall, S., Streeck, H., Haas, D.W., Kuritzkes, D.R., Robbins, G.K., Shafer, R.W., Gulick, R.M., Shikuma, C.M., Haubrich, R., Riddler, S., Sax, P.E., Daar, E.S., Ribaudo, H.J., Agan, B., Agarwal, S., Ahern, R.L., Allen, B.L., Altidor, S., Altschuler, E.L., Ambardar, S., Anastos, K., Anderson, B., Anderson, V., Andrady, U., Antoniskis, D., Bangsberg, D., Barbaro, D., Barrie, W., Bartczak, J., Barton, S., Basden, P., Basgoz, N., Bazner, S., Bellos, N.C., Benson, A.M., Berger, J., Bernard, N.F., Bernard, A.M., Birch, C., Bodner, S.J., Bolan, R.K., Boudreaux, E.T., Bradley, M., Braun, J.F., Brndjar, J.E., Brown, S.J., Brown, K., Brown, S.T., Burack, J., Bush, L.M., Cafaro, V., Campbell, O., Campbell, J., Carlson, R.H., Carmichael, J.K., Casey, K.K., Cavacuiti, C., Celestin, G., Chambers, S.T., Chez, N., Chirch, L.M., Cimoch, P.J., Cohen, D., Cohn, L.E., Conway, B., Cooper, D.A., Cornelson, B., Cox, D.T., Cristofano, M.V., Cuchural, G., Jr., Czartoski, J.L., Dahman, J.M., Daly, J.S., Davis, B.T., Davis, K., Davod, S.M., DeJesus, E., Dietz, C.A., Dunham, E., Dunn, M.E., Ellerin, T.B., Eron, J.J., Fangman, J.J., Farel, C.E., Ferlazzo, H., Fidler, S., Fleenor-Ford, A., Frankel, R., Freedberg, K.A., French, N.K., Fuchs, J.D., Fuller, J.D., Gaberman, J., Gallant, J.E., Gandhi, R.T., Garcia, E., Garmon, D., Gathe, J.C., Jr., Gaultier, C.R., Gebre, W., Gilman, F.D., Gilson, I., Goepfert, P.A., Gottlieb, M.S., Goulston, C., Groger, R.K., Gurley, T.D., Haber, S., Hardwicke, R., Hardy, W.D., Harrigan, P.R., Hawkins, T.N., Heath, S., Hecht, F.M., Henry, W.K., Hladek, M., Hoffman, R.P., Horton, J.M., Hsu, R.K., Huhn, G.D., Hunt, P., Hupert, M.J., Illeman, M.L., Jaeger, H., Jellinger, R.M., John, M., Johnson, J.A., Johnson, K.L., Johnson, H., Johnson, K., Joly, J., Jordan, W.C., Kauffman, C.A., Khanlou, H., Killian, R.K., Kim, A.Y., Kim, D.D., Kinder, C.A., Kirchner, J.T., Kogelman, L., Kojic, E.M., Korthuis, P.T., Kurisu, W., Kwon, D.S., LaMar, M., Lampiris, H., Lanzafame, M., Lederman, M.M., Lee, D.M., Lee, J.M., Lee, M.J., Lee, E.T., Lemoine, J., Levy, J.A., Llibre, J.M., Liguori, M.A., Little, S.J., Liu, A.Y., Lopez, A.J., Loutfy, M.R., Loy, D., Mohammed, D.Y., Man, A., Mansour, M.K., Marconi, V.C., Markowitz, M., Marques, R., Martin, J.N., Martin, H.L., Jr., Mayer, K.H., McElrath, M.J., McGhee, T.A., McGovern, B.H., McGowan, K., McIntyre, D., McLeod, G.X., Menezes, P., Mesa, G., Metroka, C.E., Meyer-Olson, D., Miller, A.O., Montgomery, K., Mounzer, K.C., Nagami, E.H., Nagin, I., Nahass, R.G., Nelson, M.O., Nielsen, C., Norene, D.L.,

O'Connor, D.H., Ojikutu, B.O., Okulicz, J., Oladehin, O.O., Oldfield, E.C., 3rd, Olender, S.A., Ostrowski, M., Owen, W.F., Jr., Pae, E., Parsonnet, J., Pavlatos, A.M., Perlmutter, A.M., Pierce, M.N., Pincus, J.M., Pisani, L., Price, L.J., Proia, L., Prokesch, R.C., Pujet, H.C., Ramgopal, M., Rathod, A., Rausch, M., Ravishankar, J., Rhame, F.S., Richards, C.S., Richman, D.D., Rodes, B., Rodriguez, M., Rose, R.C., 3rd, Rosenberg, E.S., Rosenthal, D., Ross, P.E., Rubin, D.S., Rumbaugh, E., Saenz, L., Salvaggio, M.R., Sanchez, W.C., Sanjana, V.M., Santiago, S., Schmidt, W., Schuitemaker, H., Sestak, P.M., Shalit, P., Shay, W., Shirvani, V.N., Silebi, V.I., Sizemore, J.M., Jr., Skolnik, P.R., Sokol-Anderson, M., Sosman, J.M., Stabile, P., Stapleton, J.T., Starrett, S., Stein, F., Stellbrink, H.J., Sterman, F.L., Stone, V.E., Stone, D.R., Tambussi, G., Taplitz, R.A., Tedaldi, E.M., Theisen, W., Torres, R., Tosiello, L., Tremblay, C., Tribble, M.A., Trinh, P.D., Tsao, A., Ueda, P., Vaccaro, A., Valadas, E., Vanig, T.J., Vecino, I., Vega, V.M., Veikley, W., Wade, B.H., Walworth, C., Wanidworanun, C., Ward, D.J., Warner, D.A., Weber, R.D., Webster, D., Weis, S., Wheeler, D.A., White, D.J., Wilkins, E., Winston, A., Wlodaver, C.G., van't Wout, A., Wright, D.P., Yang, O.O., Yurdin, D.L., Zabukovic, B.W., Zachary, K.C., Zeeman, B., Zhao, M., 2010. The major genetic determinants of HIV-1 control affect HLA class I peptide presentation. Science 330, 1551-1557.

Perez, E.E., Wang, J., Miller, J.C., Jouvenot, Y., Kim, K.A., Liu, O., Wang, N., Lee, G., Bartsevich, V.V., Lee, Y.L., Guschin, D.Y., Rupniewski, I., Waite, A.J., Carpenito, C., Carroll, R.G., Orange, J.S., Urnov, F.D., Rebar, E.J., Ando, D., Gregory, P.D., Riley, J.L., Holmes, M.C., June, C.H., 2008. Establishment of HIV-1 resistance in CD4+ T cells by genome editing using zinc-finger nucleases. Nat Biotechnol 26, 808-816.

Perez, M., de Vinuesa, A.G., Sanchez-Duffhues, G., Marquez, N., Bellido, M.L., Munoz-Fernandez, M.A., Moreno, S., Castor, T.P., Calzado, M.A., Munoz, E., 2010. Bryostatin-1 synergizes with histone deacetylase inhibitors to reactivate HIV-1 from latency. Curr HIV Res 8, 418-429.

Persaud, D., Gay, H., Ziemniak, C., Chen, Y.H., Piatak, M., Jr., Chun, T.W., Strain, M., Richman, D., Luzuriaga, K., 2013. Absence of detectable HIV-1 viremia after treatment cessation in an infant. N Engl J Med 369, 1828-1835.

Peterson, C.W., Younan, P., Jerome, K.R., Kiem, H.P., 2013a. Combinatorial anti-HIV gene therapy: using a multipronged approach to reach beyond HAART. Gene Ther 20, 695-702.

Peterson, T.A., Kimani, J., Wachihi, C., Bielawny, T., Mendoza, L., Thavaneswaran, S., Narayansingh, M.J., Kariri, T., Liang, B., Ball, T.B., Ngugi, E.N., Plummer, F.A., Luo, M., 2013b. HLA class I associations with rates of HIV-1 seroconversion and disease progression in the Pumwani Sex Worker Cohort. Tissue Antigens 81, 93-107.

Pillai, S.K., Abdel-Mohsen, M., Guatelli, J., Skasko, M., Monto, A., Fujimoto, K., Yukl, S., Greene, W.C., Kovari, H., Rauch, A., Fellay, J., Battegay, M., Hirschel, B., Witteck, A., Bernasconi, E., Ledergerber, B., Gunthard, H.F., Wong, J.K., 2012. Role of retroviral restriction factors in the interferon-alpha-mediated suppression of HIV-1 in vivo. Proc Natl Acad Sci U S A 109, 3035-3040.

Pires, A., Hardy, G., Gazzard, B., Gotch, F., Imami, N., 2004. Initiation of antiretroviral therapy during recent HIV-1 infection results in lower residual viral reservoirs. J Acquir Immune Defic Syndr 36, 783-790.

Porichis, F., Kaufmann, D.E., 2012. Role of PD-1 in HIV pathogenesis and as target for therapy. Curr HIV/AIDS Rep 9, 81-90.

Prins, J.M., Jurriaans, S., van Praag, R.M., Blaak, H., van Rij, R., Schellekens, P.T., ten Berge, I.J., Yong, S.L., Fox, C.H., Roos, M.T., de Wolf, F., Goudsmit, J., Schuitemaker, H., Lange, J.M., 1999. Immuno-activation with anti-CD3 and recombinant human IL-2 in HIV-1-infected patients on potent antiretroviral therapy. Aids 13, 2405-2410.

Ramratnam, B., Ribeiro, R., He, T., Chung, C., Simon, V., Vanderhoeven, J., Hurley, A., Zhang, L., Perelson, A.S., Ho, D.D., Markowitz, M., 2004. Intensification of antiretroviral therapy accelerates the decay of the HIV-1 latent reservoir and decreases, but does not eliminate, ongoing virus replication. J Acquir Immune Defic Syndr 35, 33-37.

Rasmussen, T.A., Schmeltz Sogaard, O., Brinkmann, C., Wightman, F., Lewin, S.R., Melchjorsen, J., Dinarello, C., Ostergaard, L., Tolstrup, M., 2013. Comparison of HDAC inhibitors in clinical

development: effect on HIV production in latently infected cells and T-cell activation. Hum Vaccin Immunother 9, 993-1001.
Resino, S., Perez, A., Seoane, E., Serrano, D., Berenguer, J., Balsalobre, P., Gomez-Chacon, G.F., Diez-Martin, J.L., Munoz-Fernandez, M.A., 2007. Short communication: Immune reconstitution after autologous peripheral blood stem cell transplantation in HIV-infected patients: might be better than expected? AIDS Res Hum Retroviruses 23, 543-548.
Reuse, S., Calao, M., Kabeya, K., Guiguen, A., Gatot, J.S., Quivy, V., Vanhulle, C., Lamine, A., Vaira, D., Demonte, D., Martinelli, V., Veithen, E., Cherrier, T., Avettand, V., Poutrel, S., Piette, J., de Launoit, Y., Moutschen, M., Burny, A., Rouzioux, C., De Wit, S., Herbein, G., Rohr, O., Collette, Y., Lambotte, O., Clumeck, N., Van Lint, C., 2009. Synergistic activation of HIV-1 expression by deacetylase inhibitors and prostratin: implications for treatment of latent infection. PLoS One 4, e6093.
Reynolds, L., Ullman, C., Moore, M., Isalan, M., West, M.J., Clapham, P., Klug, A., Choo, Y., 2003. Repression of the HIV-1 5' LTR promoter and inhibition of HIV-1 replication by using engineered zinc-finger transcription factors. Proc Natl Acad Sci U S A 100, 1615-1620.
Rosenberg, E.S., Altfeld, M., Poon, S.H., Phillips, M.N., Wilkes, B.M., Eldridge, R.L., Robbins, G.K., D'Aquila, R.T., Goulder, P.J., Walker, B.D., 2000. Immune control of HIV-1 after early treatment of acute infection. Nature 407, 523-526.
Routy, J.P., Tremblay, C.L., Angel, J.B., Trottier, B., Rouleau, D., Baril, J.G., Harris, M., Trottier, S., Singer, J., Chomont, N., Sekaly, R.P., Boulassel, M.R., 2012. Valproic acid in association with highly active antiretroviral therapy for reducing systemic HIV-1 reservoirs: results from a multicentre randomized clinical study. HIV Med 13, 291-296.
Roy, J., Paquette, J.S., Fortin, J.F., Tremblay, M.J., 2002. The immunosuppressant rapamycin represses human immunodeficiency virus type 1 replication. Antimicrob Agents Chemother 46, 3447-3455.
Rusconi, S., Vitiello, P., Adorni, F., Colella, E., Foca, E., Capetti, A., Meraviglia, P., Abeli, C., Bonora, S., D'Annunzio, M., Di Biagio, A., Di Pietro, M., Butini, L., Orofino, G., Colafigli, M., d'Ettorre, G., Francisci, D., Parruti, G., Soria, A., Buonomini, A.R., Tommasi, C., Mosti, S., Bai, F., Di Nardo Stuppino, S., Morosi, M., Montano, M., Tau, P., Merlini, E., Marchetti, G., 2013. Maraviroc as intensification strategy in HIV-1 positive patients with deficient immunological response: an Italian randomized clinical trial. PLoS One 8, e80157.
Saez-Cirion, A., Bacchus, C., Hocqueloux, L., Avettand-Fenoel, V., Girault, I., Lecuroux, C., Potard, V., Versmisse, P., Melard, A., Prazuck, T., Descours, B., Guergnon, J., Viard, J.P., Boufassa, F., Lambotte, O., Goujard, C., Meyer, L., Costagliola, D., Venet, A., Pancino, G., Autran, B., Rouzioux, C., 2013. Post-treatment HIV-1 controllers with a long-term virological remission after the interruption of early initiated antiretroviral therapy ANRS VISCONTI Study. PLoS Pathog 9, e1003211.
Saez-Cirion, A., Lacabaratz, C., Lambotte, O., Versmisse, P., Urrutia, A., Boufassa, F., Barre-Sinoussi, F., Delfraissy, J.F., Sinet, M., Pancino, G., Venet, A., 2007. HIV controllers exhibit potent CD8 T cell capacity to suppress HIV infection ex vivo and peculiar cytotoxic T lymphocyte activation phenotype. Proc Natl Acad Sci U S A 104, 6776-6781.
Saez-Cirion, A., Pancino, G., 2013. HIV controllers: a genetically determined or inducible phenotype? Immunol Rev 254, 281-294.
Sagot-Lerolle, N., Lamine, A., Chaix, M.L., Boufassa, F., Aboulker, J.P., Costagliola, D., Goujard, C., Pallier, C., Delfraissy, J.F., Lambotte, O., 2008. Prolonged valproic acid treatment does not reduce the size of latent HIV reservoir. Aids 22, 1125-1129.
Salgado, M., Rabi, S.A., O'Connell, K.A., Buckheit, R.W., 3rd, Bailey, J.R., Chaudhry, A.A., Breaud, A.R., Marzinke, M.A., Clarke, W., Margolick, J.B., Siliciano, R.F., Blankson, J.N., 2011. Prolonged control of replication-competent dual- tropic human immunodeficiency virus-1 following cessation of highly active antiretroviral therapy. Retrovirology 8, 97.
Sarau, H.M., Rush, J.A., Foley, J.J., Brawner, M.E., Schmidt, D.B., White, J.R., Barnette, M.S., 1997. Characterization of functional chemokine receptors (CCR1 and CCR2) on EoL-3 cells: a model system to examine the role of chemokines in cell function. J Pharmacol Exp Ther 283, 411-418.

Sarkar, I., Hauber, I., Hauber, J., Buchholz, F., 2007. HIV-1 proviral DNA excision using an evolved recombinase. Science 316, 1912-1915.
Savarino, A., Mai, A., Norelli, S., El Daker, S., Valente, S., Rotili, D., Altucci, L., Palamara, A.T., Garaci, E., 2009. "Shock and kill" effects of class I-selective histone deacetylase inhibitors in combination with the glutathione synthesis inhibitor buthionine sulfoximine in cell line models for HIV-1 quiescence. Retrovirology 6, 52.
Schacker, T., 2010. New tools to track HIV. Nat Med 16, 373-374.
Schmid, A., Gianella, S., von Wyl, V., Metzner, K.J., Scherrer, A.U., Niederost, B., Althaus, C.F., Rieder, P., Grube, C., Joos, B., Weber, R., Fischer, M., Gunthard, H.F., 2010. Profound depletion of HIV-1 transcription in patients initiating antiretroviral therapy during acute infection. PLoS One 5, e13310.
Shan, L., Deng, K., Shroff, N.S., Durand, C.M., Rabi, S.A., Yang, H.C., Zhang, H., Margolick, J.B., Blankson, J.N., Siliciano, R.F., 2012. Stimulation of HIV-1-specific cytolytic T lymphocytes facilitates elimination of latent viral reservoir after virus reactivation. Immunity 36, 491-501.
Shytaj, I.L., Chirullo, B., Wagner, W., Ferrari, M.G., Sgarbanti, R., Corte, A.D., LaBranche, C., Lopalco, L., Palamara, A.T., Montefiori, D., Lewis, M.G., Garaci, E., Savarino, A., 2013. Investigational treatment suspension and enhanced cell-mediated immunity at rebound followed by drug-free remission of simian AIDS. Retrovirology 10, 71.
Simonelli, C., Zanussi, S., Pratesi, C., Rupolo, M., Talamini, R., Caffau, C., Teresa Bortolin, M., Tedeschi, R., Basaglia, G., Mazzucato, M., Manuele, R., Vaccher, E., Spina, M., Tirelli, U., Michieli, M., De Paoli, P., 2010. Immune recovery after autologous stem cell transplantation is not different for HIV-infected versus HIV-uninfected patients with relapsed or refractory lymphoma. Clin Infect Dis 50, 1672-1679.
Sora, F., Antinori, A., Piccirillo, N., De Luca, A., Chiusolo, P., Cingolani, A., Laurenti, L., Rutella, S., Ortona, L., Leone, G., Sica, S., 2002. Highly active antiretroviral therapy and allogeneic CD34(+) peripheral blood progenitor cells transplantation in an HIV/HCV coinfected patient with acute myeloid leukemia. Exp Hematol 30, 279-284.
Steel, A., Clark, S., Teo, I., Shaunak, S., Nelson, M., Gazzard, B., Kelleher, P., 2006. No change to HIV-1 latency with valproate therapy. Aids 20, 1681-1682.
Steingrover, R., Pogany, K., Fernandez Garcia, E., Jurriaans, S., Brinkman, K., Schuitemaker, H., Miedema, F., Lange, J.M., Prins, J.M., 2008. HIV-1 viral rebound dynamics after a single treatment interruption depends on time of initiation of highly active antiretroviral therapy. Aids 22, 1583-1588.
Stohr, W., Fidler, S., McClure, M., Weber, J., Cooper, D., Ramjee, G., Kaleebu, P., Tambussi, G., Schechter, M., Babiker, A., Phillips, R.E., Porter, K., Frater, J., 2013. Duration of HIV-1 viral suppression on cessation of antiretroviral therapy in primary infection correlates with time on therapy. PLoS One 8, e78287.
Suzuki, K., Hattori, S., Marks, K., Ahlenstiel, C., Maeda, Y., Ishida, T., Millington, M., Boyd, M., Symonds, G., Cooper, D.A., Okada, S., Kelleher, A.D., 2013. Promoter Targeting shRNA Suppresses HIV-1 Infection In vivo Through Transcriptional Gene Silencing. Mol Ther Nucleic Acids 2, e137.
Van Gulck, E., Heyndrickx, L., Bracke, L., Coppens, S., Florence, E., Buve, A., Lewi, P., Vanham, G., 2011. Control of viral replication after cessation of HAART. AIDS Res Ther 8, 6.
van Praag, R.M., Prins, J.M., Roos, M.T., Schellekens, P.T., Ten Berge, I.J., Yong, S.L., Schuitemaker, H., Eerenberg, A.J., Jurriaans, S., de Wolf, F., Fox, C.H., Goudsmit, J., Miedema, F., Lange, J.M., 2001. OKT3 and IL-2 treatment for purging of the latent HIV-1 reservoir in vivo results in selective long-lasting CD4+ T cell depletion. J Clin Immunol 21, 218-226.
Vandergeeten, C., Fromentin, R., DaFonseca, S., Lawani, M.B., Sereti, I., Lederman, M.M., Ramgopal, M., Routy, J.P., Sekaly, R.P., Chomont, N., 2013. Interleukin-7 promotes HIV persistence during antiretroviral therapy. Blood 121, 4321-4329.
Vanham, G., Van Gulck, E., 2012. Can immunotherapy be useful as a "functional cure" for infection with Human Immunodeficiency Virus-1? Retrovirology 9, 72.
Velu, V., Titanji, K., Zhu, B., Husain, S., Pladevega, A., Lai, L., Vanderford, T.H., Chennareddi, L., Silvestri, G., Freeman, G.J., Ahmed, R., Amara, R.R., 2009. Enhancing SIV-specific immunity in vivo by PD-1 blockade. Nature 458, 206-210.

Volberding, P., Demeter, L., Bosch, R.J., Aga, E., Pettinelli, C., Hirsch, M., Vogler, M., Martinez, A., Little, S., Connick, E., 2009. Antiretroviral therapy in acute and recent HIV infection: a prospective multicenter stratified trial of intentionally interrupted treatment. Aids 23, 1987-1995.
Wilkin, T.J., Lalama, C.M., McKinnon, J., Gandhi, R.T., Lin, N., Landay, A., Ribaudo, H., Fox, L., Currier, J.S., Mellors, J.W., Gulick, R., Tenorio, A.R., 2012. A pilot trial of adding maraviroc to suppressive antiretroviral therapy for suboptimal CD4(+) T-cell recovery despite sustained virologic suppression: ACTG A5256. J Infect Dis 206, 534-542.
Wilkin, T.J., Ribaudo, H.R., Tenorio, A.R., Gulick, R.M., 2010. The relationship of CCR5 antagonists to CD4+ T-cell gain: a meta-regression of recent clinical trials in treatment-experienced HIV-infected patients. HIV Clin Trials 11, 351-358.
Wit, F.W., Blanckenberg, D.H., Brinkman, K., Prins, J.M., van der Ende, M.E., Schneider, M.M., Mulder, J.W., de Wolf, F., Lange, J.M., 2005. Safety of long-term interruption of successful antiretroviral therapy: the ATHENA cohort study. Aids 19, 345-348.
Wyl, V., Gianella, S., Fischer, M., Niederoest, B., Kuster, H., Battegay, M., Bernasconi, E., Cavassini, M., Rauch, A., Hirschel, B., Vernazza, P., Weber, R., Joos, B., Gunthard, H.F., 2011. Early antiretroviral therapy during primary HIV-1 infection results in a transient reduction of the viral setpoint upon treatment interruption. PLoS One 6, e27463.
Yang, Z., He, N., Zhou, Q., 2008. Brd4 recruits P-TEFb to chromosomes at late mitosis to promote G1 gene expression and cell cycle progression. Mol Cell Biol 28, 967-976.
Younan, P.M., Polacino, P., Kowalski, J.P., Peterson, C.W., Maurice, N.J., Williams, N.P., Ho, O., Trobridge, G.D., Von Laer, D., Prlic, M., Beard, B.C., DeRosa, S., Hu, S.L., Kiem, H.P., 2013. Positive selection of mC46-expressing CD4+ T cells and maintenance of virus specific immunity in a primate AIDS model. Blood 122, 179-187.
Yukl, S.A., Boritz, E., Busch, M., Bentsen, C., Chun, T.W., Douek, D., Eisele, E., Haase, A., Ho, Y.C., Hutter, G., Justement, J.S., Keating, S., Lee, T.H., Li, P., Murray, D., Palmer, S., Pilcher, C., Pillai, S., Price, R.W., Rothenberger, M., Schacker, T., Siliciano, J., Siliciano, R., Sinclair, E., Strain, M., Wong, J., Richman, D., Deeks, S.G., 2013. Challenges in detecting HIV persistence during potentially curative interventions: a study of the Berlin patient. PLoS Pathog 9, e1003347.
Yukl, S.A., Shergill, A.K., McQuaid, K., Gianella, S., Lampiris, H., Hare, C.B., Pandori, M., Sinclair, E., Gunthard, H.F., Fischer, M., Wong, J.K., Havlir, D.V., 2010. Effect of raltegravir-containing intensification on HIV burden and T-cell activation in multiple gut sites of HIV-positive adults on suppressive antiretroviral therapy. Aids 24, 2451-2460.
Zala, C., Salomon, H., Ochoa, C., Kijak, G., Federico, A., Perez, H., Montaner, J.S., Cahn, P., 2002. Higher rate of toxicity with no increased efficacy when hydroxyurea is added to a regimen of stavudine plus didanosine and nevirapine in primary HIV infection. J Acquir Immune Defic Syndr 29, 368-373.
Zhang, H.S., Ruan, Z., Sang, W.W., 2011. HDAC1/NFkappaB pathway is involved in curcumin inhibiting of Tat-mediated long terminal repeat transactivation. J Cell Physiol 226, 3385-3391.

Figure legends

Figure 1: Schematic representation of the clinical course before and after allogeneic hematopoietic stem cell transplantation (HSCT) in the Berlin (A) and the Boston patients (B and C) as described in (Henrich et al., 2013; Hutter et al., 2009). The most important events associated to the HSCT and HIV disease are indicated. Blue arrows represent the periods of radio/chemotherapy. Red arrows represent total body irradiation. Periods of detectable viremia are represented by orange boxes. The period that patients were under antiretroviral treatment are indicated in grey below the timeline. The period between allogeneic HSCT and ATI in Boston patients are indicated by brackets. AML: acute myeloid leukemia; ATI: analytical treatment interruption; cART: combined antiretroviral therapy; HL: Hodgkin lymphoma; HSCT: hematopoietic stem cell transplantation; GVHD: graft-versus-host disease; WT: wild type.

Figure 2: Schematic representation of the HIV acute infection and the contribution of each T cell subset to the establishment of the HIV reservoir. Early treatment during Fiebig stages I-III may limit the number of infected cells and protect T_{CM} cells from infection. Treatment during Fiebig stages IV-V may decrease the contribution of long-lived T_N and T_{CM} cells to the reservoir due to low relative abundance of these cell subsets. Frequency of T_{CM} normalizes during chronic infection increasing the contribution of these cells to the reservoir.

Table 1: Hematopoietic stem cell transplantation in HIV positive patients

Study Reference	Patients			Diagnosis	Graft type	Strategy against HIV infection	Effect on HIV persistence	Clinical Outcome
	N	Gender	Age					
(Holland et al., 1989)	1	M	41	NHL	Allogeneic (bone marrow)	High-dose zidovudine for 2 weeks before transplantation. Lower maintenance dose zidovudine after transplantation.	No detectable HIV RNA and DNA at day 32 after transplantation and at autopsy.	Death 47 days after transplantation.
(Contu et al., 1993)	1	F	25	NA	Allogeneic (bone marrow)	Zidovudine, IFN-alpha 2 and anti-HIV-1-specific T cell clones.	No detectable HIV RNA at day 30 after transplantation and at autopsy.	Death 10 months after transplantation.
(Sora et al., 2002)	1	F	33	AML	Allogeneic (bone marrow)	cART before and after transplantation, with interruptions due to side-effects.	No detectable HIV RNA on cART from day 210 after transplantation.	Alive after 42 months of follow up.
(Gabarre et al., 2004)	14	M/F	27-53	BL, HL, NHL	Autologous	cART before and after transplantation.	No detectable HIV RNA on cART in three patients who survived.	Five patients were alive.
(Resino et al., 2007)	4	NA	31-58	BL, HL, NHL	Autologous	cART before and after transplantation.	On cART No detectable HIV RNA after transplantation (two patients), viral load rebound (two patients). Detectable HIV DNA at month 12 after transplantation for all patients.	The four patients were alive after 12 months of follow up.
(Avettand-Fenoel et al., 2007)	1	M	17	BL,AML	Allogeneic (bone marrow)	cART before and after transplantation, with interruptions due to side-	Undetectable RNA and DNA on cART. Detectable HIV RNA and DNA at day 16	Death 191 days after transplantation.

						effects.	after TI.	
(Hutter et al., 2009)	1	M	40	AML	Allogeneic (bone marrow)	Donor homozygous for CCR5 Δ32.	No cART. No trace of HIV after 6 years of follow-up.	Alive after 6 years of follow up. Considered the first case of AIDS cure.
(Simonelli et al., 2010)	24	M/F	<45 (n=15) ≥45 (n=9)	HL, NHL	Autologous	cART before and after transplantation, with interruptions due to side-effects (n=8).	On cART Detectable HIV RNA and DNA after transplantation. HIV DNA significantly lower at month 24 than those at baseline.	Alive, immunologic characteristics comparable to HIV negative patients.
(Cillo et al., 2013)	10	M	24-60	BL, HL, NHL	Autologous	cART before and after transplantation, with interruptions due to side-effects (n=3).	On cART. Detectable HIV RNA (9/10 patients) and DNA (10/10 patients) after transplantation.	Alive with undetectable VL by conventional methods, but with detectable proviral DNA.
(Henrich et al., 2013)	2	M	NI	HL	Allogeneic (bone marrow)	cART before and after transplantation.	Undetectable HIV RNA on cART, detectable after TI. Detectable HIV DNA early after transplantation and undetectable in long term follow-up.	Alive 5 and 3 years after transplantation, but viremia rebounded after TI.
University of Minnesota (not published)	1	M	12	ALL	Allogeneic (cord blood)	Donor homozygous for CCR5 Δ32 deletion.	No detectable HIV after treatment discontinuation.	Died 2 months after transplantation by a severe graft-versus-host disease.

ALL: acute lymphoblastic leukemia; AML: Acute myeloid leukemia; BL: Burkitt lymphoma; BM: bone marrow; F: Female; HL: Hodgkin lymphoma; M: male; NHL: non-Hodgkin lymphoma; NA: not available; PBMC: Peripheral blood mononuclear cells; PCR: polymerase chain reaction; TI: treatment interruption; VL: viral load.