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Cellular determinants of HIV-1 persistence

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Abstract

The era of anti-retroviral therapy has made HIV-1 infection a manageable chronic disease for those with access to treatment. Despite treatment, virus persists in tissue reservoirs seeded with long-lived infected cells that are resistant to cell death and immune recognition. Which cells contribute to this reservoir and which factors determine their persistence are central questions that need to be answered to achieve viral eradication. In this chapter, we describe how cell susceptibility to infection, resistance to cell death and immune-mediated killing as well as natural cell life-span and turnover potential are central components that allow persistence of different lymphoid and myeloid cell subsets that were recently identified as key players in harbouring latent and actively replicating virus. The relative contribution of these subsets to persistence of viral reservoir is described and the open questions are highlighted.

Keywords: HIV reservoirs, CD4+ T cell subsets, macrophages, dendritic cells, HIV susceptibility, cell survival, turnover potential
Introduction

Current antiretrovirals (ARVs) have achieved impressive success in preventing progression of HIV-1 infection. However, ARVs, although highly efficient in blocking diverse steps of HIV-1 replication cycle, do not eliminate cells containing proviruses. Thus, despite long-lasting suppressed viremia on ARVs, HIV-1 persists in viral reservoirs (1) that are at the origin of viral rebound if antiretroviral treatment (ART) is discontinued. A better characterisation of the factors governing these reservoirs is fundamental in the search for an HIV cure (2, 3). HIV-1 persistence under ART has been associated to (i) low level viral replication, in particular in deep tissues where concentration of ARVs may not always reach optimal action levels (4-6), and (ii) long half live and self-renewal of latently HIV-1 infected cells (7). Although it is likely that HIV-1 persistence is a consequence of the combination of these two processes, we will focus here on intrinsic cell properties that determine the maintenance of infected cells.

HIV-1 infects cells from the myeloid and T cell lineages but not all cell populations contribute equally to HIV persistence (1). Most of the HIV-1 reservoir is constituted in CD4+ T cells (7, 8), while macrophages and dendritic cells play a critical role as early targets for HIV infection and as vehicles for HIV-1 dissemination throughout the body (9, 10). CD4+ T cells are typically described as cellular subsets that follow a gradient of maturation stages including naïve (TNA), stem cell memory (TSCM), central memory (TCM), transitional memory (TTM), effector memory (TEM), and terminally differentiated (TTD) cells (11). Under ART most persistent HIV-1 DNA is contained within memory CD4+ T cells, and in particular TCM and TTM (7). However the relative contribution of these subpopulations to the HIV reservoir may vary depending on whether the
treatment was initiated in primary or chronic infection, and long periods of treatment appears to enrich the contribution of very long lived cells such as TSCM (12-15).

The establishment and maintenance of HIV-1 reservoirs is a multifaceted process that depends (i) on the relative cell susceptibility to HIV infection, (ii) the capacity of the infected cell to resist HIV induced apoptosis and escape immune surveillance, (iii) the infected cell’s life span and turnover potential (figure 1). All these processes are determined by each cell type’s program and regulated by tissue location, activation and differentiation state of the cells in response to environmental conditions and stress signals. This chapter analyses each of these processes and relates them to the different cell subsets that are thought to more critically contribute to HIV reservoirs.

**Being a good or a bad host to the virus**

HIV-1 cell tropism is determined by the expression on the cell surface of the main HIV-1 receptor CD4 and at least one additional co-receptor, mainly CCR5 or CXCR4 (16). CD4+ T cells, monocytes/macrophages and dendritic cells are the major targets of HIV-1 (17, 18). The rate of viral replication largely diverges from one cell type to another, and even within a cell type depending on activation and differentiation. Thus, HIV-1 replicates strongly in activated CD4+ T cells and less efficiently in macrophages and immature dendritic cells while resting CD4+ T cells, monocytes and mature dendritic cells are strongly resistant to HIV-1 infection (19-23). These differences are mostly explained by the relative abundance of cell factors that intervene in the virus life cycle. Several studies have identified hundreds of cellular factors potentially required
for HIV-1 to complete each step of its replication cycle (HIV dependency factors, HDF) (24-28). The expression of chemokine receptors varies with T cell differentiation, impacting the susceptibility of the cells to HIV-1 (29, 30). Among CD4+ T helper lineages, Th2 cells are relatively resistant to HIV-1 infection (in particular to R5 viruses due to low CCR5 expression) (31, 32) although they might be targeted by X4 viruses late in infection (33). Th1 are susceptible to both R5 and X4 viruses but to a lower extent than Th1/Th17 or Th17 CCR6 expressing cells (31, 32, 34). The enhanced susceptibility of CCR6+ CD4+ T cells to HIV-1 infection was linked to an enhanced expression of HDF in these cells (28). Beside entry receptors some of the best known HDF include: cyclophilin, which binds to HIV-1 capsid and facilitates decapsidation/reverse transcription through a mechanisms that is still unclear (35); cytoskeleton, which is required for intracellular trafficking of the virus (36, 37); LEDGF/p75, which interacts with integrase and is responsible for the tethering and selective integration of HIV into active transcription units of the chromatin and possibly also in the regulation of HIV Latency (38, 39); P-TEFb (composed of cyclin-dependent kinase 9 (CDK9) and of cyclin T1 or T2 (CycT1/T2)) and NFκb and NAFT transcription factors, which are required for HIV-1 transcription (40); Endosomal Sorting Complex Required for Transport (ESCRT), which participates in HIV-1 budding (41). While relying on numerous cellular factors, HIV-1 needs to overcome restriction factors devised as intrinsic immunity by the cells to counteract infections (42). Although several cellular factors have been suggested to potentially inhibit HIV-1 infection (43), to date only a handful of restriction factors have been clearly validated. SERINC3 and SERINC5 interfere with the delivery of viral particles to target cells (44, 45); APOBEC3G, TRIM5alpha and SAMHD1 impair reverse transcription (46, 47); Mx2 hinders nuclear accumulation and integration of
proviral DNA into the host chromatin (48); BST-2 retains newly produced viral particles at the surface of infected cells (49). The strong expression of HDF present in immune cells suggests that HIV-1 has evolved to replicate in cells performing activities optimally matching the requirements of its replication cycle and has adapted to circumvent the action of restriction factors (24, 28). Thus, the susceptibility of host cells to HIV-1 infection is largely dictated by the availability of HDF rather than the expression of restriction factors, with the exception of SAMHD1.

SAMHD1 possesses dNTPase and nuclease activities and can potentially interfere with HIV-1 reverse transcription by reducing the pool of intracellular dNTP and by degrading incoming viral nucleic acids (50-52), although the relative contribution of each of these activities is still unclear. This may vary as a function of cell type and cell cycle. SAMHD1 efficiently blocks HIV-1 infection in quiescent CD4+ T cells and monocytes, strongly decreases HIV-1 dynamics in differentiated myeloid cells but it is inefficient in cycling CD4+ T cells (51, 53). The differences in the antiviral activity of SAMHD1 between these cell types are not related to its relative expression, but SAMHD1 antiviral activity is ablated by the phosphorylation of its threonine 592 (T592) residue (53, 54). Phosphorylation of SAMHD1 is regulated by cyclin-dependent kinases (CDK) 1/2, which coordinate T cell division and differentiation in response to antigen recognition (55). A recent report shows that tissue resident macrophages susceptible to HIV-1 infection such as microglial cells, which are responsible for HIV-1 persistence and compartmentalisation in the brain (56), are in a G1-like status and express high levels of phosphorylated (inactive) SAMHD1 (57). The influence of the cell cycle on HIV-1 replication is well known (58). P21, a CDK inhibitor which regulates cell cycle arrest and is involved in
monocyte differentiation (59, 60), is a potent inhibitor of HIV-1 infection (61). On one hand, p21 controls the de novo synthesis of dNTPs by regulating the expression of the main enzymes involved in this process (62). Through its CDK inhibitor activity, p21 also controls the phosphorylation state of SAMHD1 (63, 64). p21 has also been shown to interfere with HIV-1 replication in hematopoietic stem cells (65) and with CDK9-dependent transcription of HIV-1 in CD4+ T cells (66).

The differentiation state of the cells also influences the relative capacity of HIV-1 to replicate. HIV-1 replicates less well in naïve CD4+ T cells and monocytes than in memory CD4+ T cells and macrophages, and this is not only related to differential expression of HIV-1 co-receptors. Successful HIV infection requires stable integration of viral cDNA into the host cell genome. HIV integration occurs preferentially within transcription units of transcriptionally active genes (67, 68). However several mechanisms including epigenetic gene silencing, transcription gene silencing, and post-transcriptional gene silencing have been described to explain the establishment and maintenance of latency in target cells (reviewed in (69)). Although these mechanisms are described in detail elsewhere in this book, it is interesting to note here that HIV gene expression is heavily dependent on the presence of several transcription factors, such as NFAT and NFκB. These factors are critical regulators of T cell activation and differentiation and their expression is necessary for rapid production of cytokines or effector molecules (70, 71). Accordingly, NFAT and NFκB are expressed at very low levels in naïve and resting T cells and strongly expressed in activated and differentiated T cells. In vitro studies suggest that latency can be established in both resting and activated CD4+ T cells (72). However, it is reasonable to think that HIV-1 latency per integration event may be achieved more frequently
in less differentiated CD4+ T cells subsets than in effector cells, but this remains to be proven. The mammal target of rapamycin (mTOR) is a pivotal regulator of cell differentiation, cell cycle, proliferation and survival (73). mTOR directly regulates many HDF (e.g. cytoskeleton, NFAT) and it has been shown to control HIV-1 latency (74). mTOR also regulates the metabolic activity of the cells (75) and it is worth noting that expression of the glucose transporter Glut1 is required for HIV-1 replication (76). Thus, it is likely that mTOR has an important part in the regulation of HIV-1 infection in different cell subsets.

Much less evidence is available about the establishment of HIV latency in infected macrophages. As in CD4+ T cells, in macrophages HIV preferentially integrates into the transcriptionally active region of the chromatin (18). However, it is not clear whether the mechanisms driving latency on CD4+ T cells act similarly in macrophages. Latency can be established in macrophages in vitro (77) and HIV transcription is regulated in response to external signals and macrophage activation (78). Moreover, the transcription factor CTIP2, which is involved in multiple cellular processes including cell proliferation and survival, has been shown to repress HIV gene transcription in microglial cells by inhibiting the elongation factor P-TEFb and by inducing a compact, transcriptionally inactive, heterochromatic environment at the HIV promoter (79).

Although HIV-1 has evolved mechanisms to avoid the action of restriction factors such as APOBEC3G, it is interesting to notice that this factor is expressed at very high levels in the cells that are more susceptible to HIV-1 infection and this may come at a cost for the virus in terms
replication capacity of viruses produced in more differentiated cell subsets (80). Finally, some cells, such as dendritic cells, are poorly or not susceptible to HIV-1 replication but can internalize free virions in non-cytolytic vesicles and transfer them at high concentrations to CD4 T cells upon interaction (81). Along these lines, follicular DCs have been shown to trap and retain infective HIV-1 particles for extended periods of time (82).

**Dodging cell death upon infection**

Although apoptosis is a major mechanism of defense against infection, viruses have evolved means to influence the balance of death and survival of the host cell in order to promote efficient virus replication and persistence of infection. Progressive CD4+ T cell loss is a defining characteristic of uncontrolled HIV-1 infection. HIV-1 can provoke direct cytotoxicity on target cells. However, it is now well accepted that decline of CD4+ T cells in vivo is not solely due to direct viral cytotoxicity but to a multifactorial process that also includes apoptosis of “bystander” cells (83-85) and killing of productively infected cells by immune effectors. Yet persistence of HIV-1 infected cells for long periods of time requires avoiding all these forms of cell death. Studies performed in vitro and ex vivo have shown the contribution of many different molecules in apoptosis induction in CD4+ T cells and other HIV-1 susceptible cell subsets but not much information is available in vivo. The exact molecular mechanisms of HIV-1 induced cytotoxic or anti-apoptotic effects on infected cells that lead to the establishment of persistence are still not well understood.
Viral proteins such as tat (86, 87), env (88), vpr (89) and nef (90, 91) have been shown to have an apoptotic effect in vitro. However, the action of these proteins at physiological concentrations and in a complex immunological setting remains unclear. Moreover, the regulation of apoptosis depends on the interaction of viral factors with cell pathways and the equilibrium between pro-apoptotic and anti-apoptotic signals may vary as a function of the stage of viral replication, nature and state of the target/bystander cell and external signals. Thus, nef has been shown to prevent apoptosis in productively infected cells upon Fas and TNFalpha ligation (92) by inhibiting Fas signaling (93). Nef was also shown to inactivate pro-apoptotic Bad protein hence rendering infected T cells more resistant to apoptosis (94). On the other hand, myeloid lineage cells including monocytes and macrophages, appear less sensitive to the cytopathic effect of HIV replication than T cells, suggesting that intrinsic properties of myeloid cells may render them selectively resistant to HIV-induced apoptosis (18, 79). Along these lines, telomerase activity increases in macrophages upon infection, rendering them more resistant to DNA damage or oxidative stress (95). Macrophages were observed to be more apoptosis resistant at least in part due to env (96) and nef (97) dependent alterations in apoptotic pathways.

Under ART the contribution of direct viral cytotoxicity to cell death is likely minimal. Latently infected cells remain largely unnoticed due to lack of expression of viral products, which favors their persistence. However, infected CD4+ T cells have been reported to undergo integration-dependent cell death, linked to the recruitment of DNA-PK (98). It is also unclear that latency is an absolute phenomenon and it is possible that episodes of viral reactivation occur episodically in vivo even in the presence of effective cART (99, 100). On the other hand, recent studies have
shown that reactivation of latent HIV-1 reservoirs in cells from ART-suppressed HIV-1 subjects with HDAC inhibitors or other latency reversal agents was insufficient to promote cell death ex vivo or to decrease the proportion of integrated viral DNA or infectious units in vivo (101-105). Moreover, cells carrying latent replication competent viruses might be particularly resilient to CD8+ T cell-mediated killing even after viral reactivation (106). Therefore, long-term HIV-1 persistence may be caused by cells that are particularly resistant to cell death, either due to their intrinsic properties or because a peculiar anti-apoptotic status was induced by infection.

Until recently the characterization of latently HIV-1 infected cells has been severely hampered by the lack of a phenotypic marker allowing the identification of these cells ex vivo (107). However, different studies using in vitro models of HIV-1 latency have described that establishment of latent HIV-1 infection is accompanied by the induction of anti-apoptotic proteins (e.g. BCL-2, cFLIP, Mcl-1) (108-110) or the downregulation of pro-apoptotic proteins (e.g. BAX, FADD) (111, 112). Interestingly, in vivo, highly persistent cells carrying the virus such as TCM (113) and monocytes (114) were also observed to have an increase in anti-apoptotic gene signature in HIV+ patients vs healthy controls.

Death of non-productively infected non-activated T cells that do not express viral antigen, have been reported to result from the detection of viral reverse transcription products by DNA sensor IFI16, which leads to caspase-1 activation thereby triggering pyroptosis (83, 115). However, the contribution of this form of cell death is probably limited once ART is initiated (116). Apoptosis of bystander cells has also been linked to persistent immune activation seen in chronic infection via signaling by TNF family members (TRAIL, FasL and TNFalpha) (117-120). Death signals delivered via Fas ligation (119, 120) were shown to have an important
contribution to bystander cell depletion in HIV patients (121-123). However, these signals were observed to be counteracted, at least in part, by viral proteins expressed by infected cells. For example, Env was observed to induce resistance to TRAIL-induced apoptosis in macrophages (96).

Overall, it seems that the activation status of cells plays a role in the susceptibility to cell death during HIV infection, which is also reflected by differential loss of cell populations from different tissues, where more or less activated cell phenotypes are found. For example, in the lymph nodes of HIV-positive patients, the degree of apoptosis has been correlated with virus and microbial-driven immune activation observed in infection and not the viral load (124). It has been further shown that highly activated effector memory CD4+ T cells are depleted fastest and first from gut mucosal sites (125) and naïve T cells displaying resting phenotype are resistant to depletion in lymphoid tissues (30). Additionally, it was shown that blood-derived CD4+ T cell that display deeper resting state than lymphoid tissue derived cells are more resistant to pyroptosis despite carrying viral genetic material (126). Thus, infected naïve, central memory and stem cell like memory T cells displaying less activated phenotype could be less prone to these mechanisms of induced cell death than highly activated effector memory T cells, which would contribute to shaping the HIV-1 reservoir before treatment initiation. However, how these mechanisms play out during ART is unknown. ART undoubtedly halts loss of CD4+ T cells but some level of abnormal chronic inflammation persists (127) and it is likely that this may contribute to selective elimination during treatment of the most apoptosis-susceptible HIV-carrying cells. The susceptibility of infected cells to cell death may also vary in tissues depending on the cytokine milieu. For example, IL-7 protected resting CD4+ T cells from death
during in vitro HIV infection (128), whereas IL-12 protected while IL-10 augmented Fas-mediated cell death of CD4 T cells from HIV-1 patients (129).

HIV-1 specific cytotoxic CD8+ T cells and NK cells are able to eliminate infected cells and these responses have been linked to protection against HIV transmission or natural control of infection (130-136). However, during progressive infection selection in vivo of viral variants that escape this immune pressure occurs progressively diminishing the capacity of these cells to counteract infection (137-140). HIV-1 reservoirs persist for many years even in the presence of highly efficient CD8+ T cell responses observed in HIV-1 elite controllers (141), suggesting that persistent infected cells are able to avoid immune surveillance. Latently infected resting CD4+ T cells that do not actively express viral epitopes escape immune surveillance although just transient expression of viral antigens may trigger their killing (100). Viral proteins such as Nef (142) and Vpu (143) downregulate MHC class I and may contribute to protect infected CD4+ cells from the CD8+ T cell response (144, 145) (although this could make these targets susceptible to NK mediated killing (142)). Infected macrophages might be more resistant than CD4+ T cells to killing by CD8+ T cells in vitro independently of nef (146, 147) although they may be eliminated by HIV-specific cytotoxic CD4+ T cells (148), which have been found to increase during acute infection (149) and in elite controllers (150). In addition, in macrophages, HIV-1 particles assembly in intracellular virus containing compartments (VCCs) (151, 152) that may provide a protective shelter from immune recognition (153).

In addition to escape mutations and latency, effective immune responses are also curtailed by the physical separation of effector cells from their targets residing in tissue sanctuaries. The
central nervous system (CNS) has long been considered an “immune privileged” site where infected macrophages, astrocytes and microglial cells are relatively inaccessible to anti-viral immune responses and variably accessible to cART (154, 155), thus constituting an important viral reservoir. Cerebrospinal fluid (CSF) of non-infected individuals contains CD4+ T cells with an activated central memory phenotype (156), which are a preferential target of HIV-1. Compared to the blood, the ratio of CD8/CD4 T cells is much lower in the CNS, and it has been suggested that antigen-specific CD8+ T cells found in the CNS do not provide durable immune surveillance in the absence of antigen (157). However, resident memory CD8+ T cells can be found in the CNS in the context of viral infection (158) and it is now recognized that functional HIV-1 specific CD8+ T cells infiltrate CNS during acute (159) and chronic (160) infection. Remarkably, CD8+ T cell responses in the CNS are detected in elite controller patients with undetectable viral load in the CSF and blood (161) and during cART therapy (162, 163) and contribute to the control of infection in the CNS (164). Similarly, several reports have shown accumulation of virus bearing Tfh cells in germinal centers of lymphoid follicles (165, 166) where CD8+ T cells are found in low frequencies as compared to T cell zones (167-170). However, recently identified follicular cytotoxic T cells (Tfc) were shown to enter B cell follicles of HIV+ subjects and to have a cytotoxic potential (171, 172). Cytotoxic CD8+ T cells displaying viral target lysis are also detected in the lamina propria (173) as well as vaginal epithelium and submucosa (174) of SIV infected rhesus macaques. Activated CD8+ T cells with cytotoxic potential were also located in adipose tissue (which carried infected CD4+ T cells and macrophages) of SIV infected monkeys (175). It is, therefore, probable that tissue CD8+ T cell responses contribute to the elimination of infected cell populations in non-lymphoid tissues.
and even the CNS, although more studies will be needed to define how they compare in terms of phenotype, function and abundancy per infected target cells when compared to lymphoid tissues.

**Endurance and renovation**

The number of cells containing HIV DNA decreases sharply during the first months following initiation of ART (176, 177). A steady state appears to be reached by 2 years after treatment, although this may occur later when treatment is initiated during primary infection (177). Modeling the dynamics of viral decrease showed that this decay occurs in several phases that have been attributed to the sequential loss of viral reservoirs of varying half-life (176, 178). In the context of ART efficiently blocking systemic HIV replication, cells with active viral replication are expected to be eliminated within a few days due to cytopathic effects or immune clearance (see above). However, some cells like macrophages can produce infectious viral particles for long periods of time without being killed and resting CD4+ T cells carrying latent provirus persist despite multiple decades of treatment. The maintenance of infected CD4+ T cells under ART is driven by survival of long-lived cells and homeostatic proliferation (7).

The lifespan of quiescent CD4+ T cell progressively decreases with differentiation. Naïve CD4+ T cells are much longer lived than memory cells, and early differentiated memory CD4+ T cells have a longer half-life than terminally differentiated cells. TNA, TSCM and TCM upregulate genes associated with survival and are less prone to undergo apoptosis, at least in vitro (11, 179). It has been estimated that one TNA has a half-life of one to several years, a TCM a few
months or a year while a TEM would last just a few weeks (180, 181). TSCM have the highest survival capacity among memory T cells in the absence of cognate antigen (179, 182). However, these estimations, largely based on the in vivo analysis of incorporation of deuterated glucose or water on CD4+ T cells, are limited by the lack of resolution on cells that migrate to the tissues. The recently described resident memory T cells are programmed to persist locally and not recirculate even in the absence of antigen (183). The role of these cells in the context of HIV-1 infection has not been clarified yet but their potential contribution to the persistence of HIV reservoirs deserves analysis.

The contribution of infected macrophages to the persistent HIV reservoir during ART is debated (184). Surely resting CD4+ T cells constitute the bulk of persisting infected cells, but the potential implication of infected macrophages as source of rebounding virus if treatment is interrupted should not be overlooked (185). Although it is accepted that viral decay in monocytes/macrophages is slower than in activated CD4+ T cells, it is often assumed that the half-life of infected monocytes/macrophages is lower than that of quiescent CD4+ T cells (69, 176, 186). However, the life span of macrophages, as for CD4+ T cells, also varies greatly. Depending on their tissue location, macrophages can live from a few months to several years. Alveolar macrophages, which can be infected by HIV (187), have been found to persist for over 3 years in analyses performed after lung transplant (188, 189), and microglial cells persist for years in the CNS (190). Moreover, macrophages may be best prepared than CD4+ T cells to resist apoptosis under conditions of metabolic stress (191-193).
It was previously assumed that activation of HIV-infected CD4+ T cells driving them to proliferation would reverse viral latency and decrease the half-life of cells carrying productive viruses. However, recent phylogenetic studies using ultra deep whole genome sequencing have shown the presence of proviruses with identical sequences in clonally expanded infected CD4+ T cells (7, 194-198). Moreover, it is now clear that these expanded infected CD4+ T cells do not only carry replication incompetent virus but can also harbor intact proviruses able to spread infection (196, 199). Several reports have shown that proliferation of infected CD4+ T cells could be at least partially driven but the selective integration of HIV-1 into genes that have been associated with cell growth, division and cancer (195, 197). In addition, CD4+ T cells can divide in response to antigenic stimulation or to homeostatic signaling to balance cell numbers although capacity of self-renewal is lost with progressive differentiation of memory CD4+ T cells (11, 200). Antigenic stimulation through the T cell receptor entails the activation of the cell and triggers cell differentiation. However, naïve and early differentiated cells require higher signaling threshold and prolonged contact with antigen presenting cells and they also depend more on co-stimulatory signals than more differentiated cells to respond to antigens. Thus low levels of antigen during treated infection might provide a suboptimal signal allowing some degree of activation of these cells. It is however unknown whether, in vivo, some transiently activated cells might escape cell death despite some degree of viral production to later regain a quiescent state. In contrast in vitro studies have confirmed that infected CD4+ T cells can undergo homeostatic proliferation without significant viral production or cell death (201).

Homeostatic proliferation is governed by members of the common gamma chain family of cytokines in the absence of antigenic stimulation (202-204). In particular IL-7 plays a central role
in CD4+ T cell homeostasis and survival. In the case of naïve CD4+ T cells, IL-7 signaling and contact with self MHC-peptides complexes promotes cell survival without inducing proliferation. In contrast, IL-7 signaling can promote proliferation of memory CD4+ T cells independently of TCR signal. Responsiveness to IL-7 is not equal among all CD4+ T cell memory subsets. TSCM and TCM express high levels of the IL-7 receptor (CD127) and have strong proliferation potential while TEM express lower levels of CD127 and have a limited proliferative potential (11). Other common gamma chain cytokines (such as IL-2 or IL-15) are also going to influence the survival and turnover of the T cells in their inflammatory environment (205).

Overall, once established memory CD4+ T cells can persist for decades in the absence of antigens (206).

Macrophages and dendritic cells are terminally differentiated cell populations that cannot be propagated in vitro. However, macrophages subsets that are susceptible to HIV-1 infection are not in a quiescent state and share some characteristics of cycling cells (57, 207, 208). Although infected macrophages did not show evidence of division in vitro, it is now clear that in vivo some macrophages can proliferate locally in tissues in response to inflammatory signals (209-211). Thus the possible persistence of some infected macrophages through cell division cannot be discarded.

**Conclusion**

The persistence of HIV-1 infected cells under antiretroviral treatment depends on a combination of cell intrinsic characteristics including the susceptibility of the cells to infection
and their capacity to survive and proliferate (Figure 2). However it is also influenced by the responsiveness of these cells to external signals (such as inflammatory cytokines or contact with antigen presenting cells) or their localization and capacity to circulate. For instance, HIV-specific CD4+ T cells have been reported to be preferentially infected by HIV during treatment interruption when compared to other antigen-specific memory CD4+ T cells and this is likely due to the selective localization of activated HIV-specific cells to the sites of viral replication (212). On the other hand, while effector CD4+ T cells are highly susceptible to infection, this cell subset is quickly depleted during infection (30). In contrast, TSCM, rare among memory CD4+ T cell subsets, increase their contribution to the total pool of infected CD4+ T cells with time on treatment (13, 14). Similarly, despite their relative lower frequency, CCR6+ CD4+ T cells (with Th17 or Th1/Th17 polarization) are enriched for HIV-DNA in patients on ART when compared to other Th lineages (32, 213), and this could be the result of enhanced susceptibility to HIV-1 infection (31, 32, 34), resistance to apoptosis, long life-span and proliferation potential (214, 215). HIV-1 can thus reside in multiple cell subsets in multiple tissues while the main mechanisms of persistence may diverge from one to another. It is of the outmost importance to define whether specific cell subsets are more likely to give rise to viral rebound if treatment is discontinued and determine if some of these subsets should be preferentially targeted. In any case, tackling HIV persistence will require the combined neutralization of different mechanisms set for cell survival.
REFERENCES

1. Barton K, Winckelmann A, Palmer S. 2016. HIV-1 Reservoirs During Suppressive Therapy. Trends Microbiol 24:345-355.
2. Deeks SG, Lewin SR, Ross AL, Ananworanich J, Benkirane M, Cannon P, Chomont N, Douek D, Lifson JD, Lo YR, Kuritzkes D, Margolis D, Mellors J, Persaud D, Tucker JD, Barre-Sinoussi F, International ASTaCWG, Alter G, Auerbach J, Autran B, Barouch DH, Behrens G, Cavazzana M, Chen Z, Cohen EA, Corbelli GM, Eholie S, Eyal N, Filder S, Garcia L, Grossman C, Henderson G, Henrich TJ, Jefferys R, Kiem HP, McCune J, Moodley K, Newman PA, Nijhuis M, Nsibuga MS, Ott M, Palmer S, Richman D, Saez-Cirion A, Sharp M, Siliciano J, Silvestri G, Singh J, Spire B, Taylor J, Tolstrup M, Valente S, van Lunzen J, Walensky R, Wilson I, Zack J. 2016. International AIDS Society global scientific strategy: towards an HIV cure 2016. Nat Med 22:839-850.
3. Passaes CP, Saez-Cirion A. 2014. HIV cure research: advances and prospects. Virology 454-455:340-352.
4. Fletcher CV, Staskus K, Wietgrefe SW, Rothenberger M, Reilly C, Chipman JG, Beilman GJ, Khoruts A, Thorkelson A, Schmidt TE, Anderson J, Perkey K, Stevenson M, Perelson AS, Douek DC, Haase AT, Schacker TW. 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.
5. Lorenzo-Redondo R, Fryer HR, Bedford T, Kim EY, Archer J, Kosakovsky Pond SL, Chung YS, Penugonda S, Chipman JG, Fletcher CV, Schacker TW, Malim MH, Rambaut A, Haase AT, McLean AR, Wolinsky SM. 2016. Persistent HIV-1 replication maintains the tissue reservoir during therapy. Nature 530:51-56.
6. Tobin NH, Learn GH, Holte SE, Wang Y, Melvin AJ, McKernan JL, Pawluk DM, Mohan KM, Lewis PF, Mullins JI, Frenkel LM. 2005. Evidence that Low-Level Viremias during Effective Highly Active Antiretroviral Therapy Result from Two Processes: Expression of Archival Virus and Replication of Virus. Journal of Virology 79:9625-9634.
7. Chomont N, El-Far M, Ancuta P, Trautmann L, Procopio FA, Yassine-Diab B, Boucher G, Boulassel MR, Ghattas G, Brenchley JM, Schacker TW, Hill BJ, Douek DC, Routy JP, Haddad EK, Sekaly RP. 2009. HIV reservoir size and persistence are driven by T cell survival and homeostatic proliferation. Nat Med 15:893-900.
8. Chun TW, Engel D, Berrey MM, Shea T, Corey L, Fauci AS. 1998. Early establishment of a pool of latently infected, resting CD4(+) T cells during primary HIV-1 infection. Proc Natl Acad Sci U S A 95:8869-8873.
9. Abbas W, Tariq M, Iqbal M, Kumar A, Herbein G. 2015. Eradication of HIV-1 from the Macrophage Reservoir: An Uncertain Goal? Viruses 7:1578-1598.
10. Coleman CM, Wu L. 2009. HIV interactions with monocytes and dendritic cells: viral latency and reservoirs. Retrovirology 6:51.
11. Mahnke YD, Brodie TM, Sallusto F, Roederer M, Lugli E. 2013. The who's who of T-cell differentiation: Human memory T-cell subsets. European Journal of Immunology 43:2797-2809.
12. Ananworanich J, Dube K, Chomont N. 2015. How does the timing of antiretroviral therapy initiation in acute infection affect HIV reservoirs? Curr Opin HIV AIDS 10:18-28.
13. Buzon MJ, Sun H, Li C, Shaw A, Seiss K, Ouyang Z, Martin-Gayo E, Leng J, Henrich TJ, Li JZ, Pereyra F, Zurakowski R, Walker BD, Rosenberg ES, Yu XG, Lichterfeld M. 2014. HIV-1 persistence in CD4+ T cells with stem cell-like properties. Nat Med 20:139-142.
14. Jaafoura S, de Goer de Herve MG, Hernandez-Vargas EA, Hendel-Chavez H, Abdoh M, Mateo MC, Krzysiek R, Merad M, Seng R, Tardieu M, Delfraissy JF, Goujard C, Taoufik Y. 2014.
Progressive contraction of the latent HIV reservoir around a core of less-differentiated CD4(+) memory T Cells. Nat Commun 5:5407.

15. Cheret A, Bacchus-Souffan C, Avettand-Fenoel V, Melard A, Nembot G, Blanc C, Samri A, Saez-Cirion A, Hocqueloux L, Lascoux-Combe C, Allavena C, Goujard C, Valantin MA, Leplatois A, Meyer L, Rouzioux C, Autran B, Group OA-S. 2015. Combined ART started during acute HIV infection protects central memory CD4+ T cells and can induce remission. J Antimicrob Chemother 70:2108-2120.

16. Wilen CB, Tilton JC, Doms RW. 2012. HIV: cell binding and entry. Cold Spring Harb Perspect Med 2:a006866.

17. Kandathil AJ, Sugawara S, Balagopal A. 2016. Are T cells the only HIV-1 reservoir? Retrovirology 13:86.

18. Kumar A, Abbas W, Herbein G. 2014. HIV-1 latency in monocytes/macrophages. Viruses 6:1837-1860.

19. Steinman RM, Granelli-Piperno A, Pope M, Trumpfhuber C, Ignatius R, Arrode G, Racz P, Tenner-Racz K. 2003. The interaction of immunodeficiency viruses with dendritic cells. Curr Top Microbiol Immunol 276:1-30.

20. Wu L, KewalRamani VN. 2006. Dendritic-cell interactions with HIV: infection and viral dissemination. Nat Rev Immunol 6:859-868.

21. Izquierdo-Useros N, Naranjo-Gomez M, Erkizia I, Puertas MC, Borras FE, Blanco J, Martinez-Picado J. 2010. HIV and mature dendritic cells: Trojan exosomes riding the Trojan horse? PLoS Pathog 6:e1000740.

22. Descours B, Cribier A, Chable-Bessia C, Ayinde D, Rice G, Crow Y, Yatim A, Schwartz O, Laguette N, Benkirane M. 2012. SAMHD1 restricts HIV-1 reverse transcription in quiescent CD4(+) T-cells. Retrovirology 9:87.

23. Diamond TL, Roshal M, Jamburuthugoda VK, Reynolds HM, Merriam AR, Lee KY, Balakrishnan M, Bambara RA, Planelles V, Dewhurst S, Kim B. 2004. Macrophage tropism of HIV-1 depends on efficient cellular dNTP utilization by reverse transcriptase. J Biol Chem 279:51545-51553.

24. Brass AL, Dykxhoorn DM, Benita Y, Yan N, Engelman A, Xavier RJ, Lieberman J, Elledge SJ. 2008. Identification of host proteins required for HIV infection through a functional genomic screen. Science 319:921-926.

25. König R, Zhou Y, Elleeder D, Diamond TL, Bonamy GMC, Irelan JT, Chiang C-y, Tu BP, De Jesus PD, Lilley CE, Seidel S, Oupaluch AM, Caldwell JS, Weitzman MD, Kuhén KL, Bandyopadhyay S, Ideker T, Orth AP, Miraglia LJ, Bushman FD, Young JA, Chanda SK. 2008. Global Analysis of Host-Pathogen Interactions that Regulate Early-Stage HIV-1 Replication. Cell 135:49-60.

26. Zhou H, Xu M, Huang Q, Gates AT, Zhang XD, Castle JC, Stec E, Ferrer M, Strulovici B, Hazuda DJ, Espeseth AS. 2008. Genome-Scale RNAi Screen for Host Factors Required for HIV Replication. Cell Host & Microbe 4:495-504.

27. Chinn LW, Tang M, Kessing BD, Lautenberger JA, Troyer JL, Malasky MJ, McIntosh C, Kirk GD, Wolinsky SM, Buchbinder SP, Gomperts ED, Goedert JJ, O'Brien SJ. 2010. Genetic Associations of Variants in Genes Encoding HIV-Dependency Factors Required for HIV-1 Infection. The Journal of Infectious Diseases 202:1836-1845.

28. Cleret-Buhot A, Zhang Y, Planas D, Goulet J-P, Monteiro P, Gosselin A, Wacleche VS, Tremblay CL, Jenabian M-A, Routy J-P, El-Far M, Chomont N, Haddad EK, Sekaly R-P, Ancuta P. 2015. Identification of novel HIV-1 dependency factors in primary CCR4+CCR6+Th17 cells via a genome-wide transcriptional approach. Retrovirology 12:102.

29. Sallusto F, Lenig D, Mackay CR, Lanzavecchia A. 1998. Flexible programs of chemokine receptor expression on human polarized T helper 1 and 2 lymphocytes. J Exp Med 187:875-883.
30. **Veazey RS, Mansfield KG, Tham IC, Carville AC, Shvetz DE, Forand AE, Lackner AA.** 2000. Dynamics of CCR5 Expression by CD4+ T Cells in Lymphoid Tissues during Simian Immunodeficiency Virus Infection. Journal of Virology **74:**11001-11007.

31. **Gosselin A, Monteiro P, Chomont N, Diaz-Griffero F, Said EA, Fonseca S, Wacleche V, El-Far M, Boulassel M-R, Routy J-P, Sekaly R-P, Ancuta P.** 2010. Peripheral Blood CCR4+CCR6+ and CCRX3+CCR6+ CD4+ T Cells Are Highly Permissive to HIV-1 Infection. The Journal of Immunology **184:**1604-1616.

32. **Sun H, Kim D, Li X, Kiselnova M, Ouyang Z, Vandekerckhove L, Shang H, Rosenberg ES, Yu XG, Lichterfeld M.** 2015. Th1/17 Polarization of CD4 T Cells Supports HIV-1 Persistence during Antiretroviral Therapy. J Virol **89:**11284-11293.

33. **Maggi E, Mazzetti M, Ravina A, Annunziato F, de Carli M, Piccinni MP, Manetti R, Carbonari M, Pesce AM, del Prete G, et al.** 1994. Ability of HIV to promote a TH1 to TH0 shift and to replicate preferentially in TH2 and TH0 cells. Science **265:**244-248.

34. **El Hed A, Khaitan A, Kozhaya L, Manel N, Daskalakis D, Borkowsky W, Valentine F, Littman DR, Unutmaz D.** 2010. Susceptibility of Human Th17 Cells to Human Immunodeficiency Virus and Their Perturbation during Infection. The Journal of Infectious Diseases **201:**843-854.

35. **De Iaco A, Luban J.** 2014. Cyclophillin A promotes HIV-1 reverse transcription but its effect on transduction correlates best with its effect on nuclear entry of viral cDNA. Retrovirology **11:**11.

36. **Menager MM, Littman DR.** 2016. Actin Dynamics Regulates Dendritic Cell-Mediated Transfer of HIV-1 to T Cells. Cell **164:**695-709.

37. **Stolp B, Fackler OT.** 2011. How HIV takes advantage of the cytoskeleton in entry and replication. Viruses **3:**293-311.

38. **Gerard A, Segeral E, Naughtin M, Abdouni A, Charmeteau B, Cheynier R, Rain JC, Emiliani S.** 2015. The integrase cofactor LEDGF/p75 associates with Lws1 and Spt6 for postintegration silencing of HIV-1 gene expression in latently infected cells. Cell Host Microbe **17:**107-117.

39. **Engelman A, Cherepanov P.** 2008. The lentiviral integrase binding protein LEDGF/p75 and HIV-1 replication. PLoS Pathog **4:**e1000046.

40. **Karn J, Stoltzfus CM.** 2012. Transcriptional and posttranscriptional regulation of HIV-1 gene expression. Cold Spring Harb Perspect Med **2:**a006916.

41. **Usami Y, Popov S, Popova E, Inoue M, Weissenhorn W, G. Göttlinger H.** 2009. The ESCRT pathway and HIV-1 budding. Biochemical Society Transactions **37:**181-184.

42. **Arhel N, Kirchhoff F.** 2010. Host proteins involved in HIV infection: New therapeutic targets. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease **1802:**313-321.

43. **Liu L, Oliveira NM, Cheney KM, Pade C, Dreja H, Bergin AM, Borgdorff V, Beach DH, Bishop CL, Dittmar MT, McKnight A.** 2011. A whole genome screen for HIV restriction factors. Retrovirology **8:**94.

44. **Rosa A, Chande A, Ziglio S, De Sanctis V, Bertorelli R, Goh SL, McCauley SM, Nowosielaka A, Antonarakis SE, Luban J, Santoni FA, Pizzato M.** 2015. HIV-1 Nef promotes infection by excluding SERINC5 from virion incorporation. Nature **526:**212-217.

45. **Usami Y, Wu Y, Gottlinger HG.** 2015. SERINC3 and SERINC5 restrict HIV-1 infectivity and are counteredacted by Nef. Nature **526:**218-223.

46. **Santa-Marta M, de Brito PM, Godinho-Santos A, Goncalves J.** 2013. Host Factors and HIV-1 Replication: Clinical Evidence and Potential Therapeutic Approaches. Front Immunol **4:**343.

47. **Simon V, Bloch N, Landau NR.** 2015. Intrinsic host restrictions to HIV-1 and mechanisms of viral escape. Nat Immunol **16:**546-553.

48. **Goujon C, Moncorge O, Bauby H, Doyle T, Ward CC, Schaller T, Hue S, Barclay WS, Schulz R, Malim MH.** 2013. Human MX2 is an interferon-induced post-entry inhibitor of HIV-1 infection. Nature **502:**559-562.
59. Perez-Caballero D, Zang T, Ebrahimi A, McNatt MW, Gregory DA, Johnson MC, Bieniasz PD. 2009. Tetherin inhibits HIV-1 release by directly tethering virions to cells. Cell 139:499-511.

60. Beloglazova N, Flick R, Tchigvintsev A, Brown G, Popovic A, Nocek B, Yakunin AF. 2013. Nuclease activity of the human SAMHD1 protein implicated in the Aicardi-Goutieres syndrome and HIV-1 restriction. J Biol Chem 288:8101-8110.

61. Laguette N, Sobhian B, Casartelli N, Ringeard M, Chable-Bessia C, Segeral E, Yatim A, Emiliani S, Schwartz O, Benkirane M. 2011. SAMHD1 is the dendritic- and myeloid-cell-specific HIV-1 restriction factor counteracted by Vpx. Nature 474:654-657.

62. Lahouassa H, Daddacha W, Hofmann H, Ayinde D, Logue EC, Dragan L, Bloch N, Maudet C, Bertrand M, Gramberg T, Pancino G, Priet S, Canard B, Laguette N, Benkirane M, Transy C, Landau NR, Kim B, Margottin-Goguet F. 2012. SAMHD1 restricts the replication of human immunodeficiency virus type 1 by depleting the intracellular pool of deoxynucleoside triphosphates. Nat Immunol 13:223-228.

63. Cribier A, Descours B, Valadao AL, Laguette N, Benkirane M. 2013. Phosphorylation of SAMHD1 by cyclin A2/CDK1 regulates its restriction activity toward HIV-1. Cell Rep 3:1036-1043.

64. White TE, Brandariz-Nunez A, Valle-Casuso JC, Amie S, Nguyen LA, Kim B, Tuzova M, Díaz-Griffero F. 2013. The retroviral restriction ability of SAMHD1, but not its deoxynucleotide triphosphohydrolase activity, is regulated by phosphorylation. Cell Host Microbe 13:441-451.

65. Wells AD, Morawski PA. 2014. New roles for cyclin-dependent kinases in T cell biology: linking cell division and differentiation. Nat Rev Immunol 14:261-270.

66. Schnell G, Joseph S, Spudich S, Price RW, Swanstrom R. 2011. HIV-1 replication in the central nervous system occurs in two distinct cell types. PLoS Pathog 7:e1002286.

67. Mlcochova P, Sutherland KA, Watters SA, Bertoli C, de Bruin RA, Rehwinkel J, Neil SJ, Lenzi GM, Kim B, Khwaja A, Gage MC, Georgiou C, Chittka A, Yona S, Noursadeghi M, Towers GJ, Gupta RK. 2017. A G1-like state allows HIV-1 to bypass SAMHD1 restriction in macrophages. EMBO J 36:604-616.

68. Goh WC, Rogel ME, Kinsey CM, Michael SF, Fultz PN, Nowak MA, Hahn BH, Emerman M. 1998. HIV-1 Vpr increases viral expression by manipulation of the cell cycle: a mechanism for selection of Vpr in vivo. Nat Med 4:65-71.

69. Asada M, Yamada T, Ichijo H, Delia D, Miyazono K, Fukumuro K, Mizutani S. 1999. Apoptosis inhibitory activity of cytoplasmic p21(Cip1/WAF1) in monocytic differentiation. EMBO J 18:1223-1234.

70. Xiong Y, Hannon GJ, Zhang H, Casso D, Kobayashi R, Beach D. 1993. p21 is a universal inhibitor of cyclin kinases. Nature 366:701-704.

71. Bergamaschi A, David A, Le Rouzic E, Nisole S, Barre-Sinoussi F, Pancino G. 2009. The CDK inhibitor p21Cip1/WAF1 is induced by FcgammaR activation and restricts the replication of human immunodeficiency virus type 1 and related primate lentiviruses in human macrophages. J Virol 83:12253-12265.

72. Allouch A, David A, Amie SM, 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.

73. Allouch A, David A, Amie SM, Lahouassa H, Chartier L, Margottin-Goguet F, Barre-Sinoussi F, Kim B, Saez-Cirion A, Pancino G. 2014. Reply to Pauls et al.: p21 is a master regulator of HIV replication in macrophages through dNTP synthesis block. Proc Natl Acad Sci U S A 111:E1325-1326.
64. Pauls E, Ruiz A, Riveira-Munoz E, Permanyer M, Badia R, Clotet B, Keppler OT, Ballana E, Este JA. 2014. p21 regulates the HIV-1 restriction factor SAMHD1. Proc Natl Acad Sci U S A 111:E1322-1324.

65. Zhang J, Scadden DT, Crumpacker CS. 2007. Primitive hematopoietic cells resist HIV-1 infection via p21. J Clin Invest 117:473-481.

66. Chen H, Li C, Huang J, Cung T, Seiss K, Beamon J, Carrington MF, Porter LC, Burke PS, Yang Y, Ryan BJ, Liu R, Weiss RH, Pereyra F, Cress WD, Brass AL, Rosenberg ES, Walker BD, Yu XG, Lichterfeld M. 2011. CD4+ T cells from elite controllers resist HIV-1 infection by selective upregulation of p21. J Clin Invest 121:1549-1560.

67. Han Y, Lassen K, Monie D, Sedaghat AR, Shimoji S, Liu X, Pierson TC, Margolick JB, Siliciano RF, Siliciano JD. 2004. Resting CD4+ T cells from human immunodeficiency virus type 1 (HIV-1)-infected individuals carry integrated HIV-1 genomes within actively transcribed host genes. J Virol 78:6122-6133.

68. Schroder AR, Shinn P, Chen H, Berry C, Ecker JR, Bushman F. 2002. HIV-1 integration in the human genome favors active genes and local hotspots. Cell 110:521-529.

69. Van Lint C, Bouchat S, Marcello A. 2013. HIV-1 transcription and latency: an update. Retrovirology 10:67.

70. Macian F. 2005. NFAT proteins: key regulators of T-cell development and function. Nat Rev Immunol 5:472-484.

71. Oh H, Ghosh S. 2013. NF-kappaB: roles and regulation in different CD4(+) T-cell subsets. Immunol Rev 252:41-51.

72. Chavez L, Calvanese V, Verdin E. 2015. HIV Latency Is Established Directly and Early in Both Resting and Activated Primary CD4 T Cells. PLoS Pathog 11:e1004955.

73. Chi H. 2012. Regulation and function of mTOR signalling in T cell fate decisions. Nat Rev Immunol 12:325-338.

74. Besnard E, Hakre S, Kampmann M, Lim HW, Hosmane NN, Martin A, Bassik MC, Verschueren E, Battivelli E, Chan J, Svensson JP, Gramatica A, Conrad RJ, Ott M, Greene WC, Krogan NJ, Siliciano RF, Weissman JS, Verdin E. 2016. The mTOR Complex Controls HIV Latency. Cell Host Microbe 20:785-797.

75. Powell JD, Delgoffe GM. 2010. The mammalian target of rapamycin: linking T cell differentiation, function, and metabolism. Immunity 33:301-311.

76. Loisel-Meyer S, Swainson L, Craveiro M, Oburoglu L, Mongellaz C, Costa C, Martinez M, Cosset FL, Battini JL, Herzenberg LA, Herzenberg LA, Atkuri KR, Sitbon M, Kinet S, Verhoeven E, Taylor N. 2012. Glut1-mediated glucose transport regulates HIV-1 infection. Proc Natl Acad Sci U S A 109:2549-2554.

77. Brown A, Zhang H, Lopez P, Pardo CA, Gartner S. 2006. In vitro modeling of the HIV-macrophage reservoir. J Leukoc Biol 80:1127-1135.

78. Saez-Cirion A, Nicola MA, Pancino G, Shorte SL. 2006. Quantitative real-time analysis of HIV-1 gene expression dynamics in single living primary cells. Biotechnol J 1:682-689.

79. Le Douce V, Herbein G, Rohr O, Schwartz C. 2010. Molecular mechanisms of HIV-1 persistence in the monocyte-macrophage lineage. Retrovirology 7:32.

80. Vetter ML, Johnson ME, Antons AK, Unutmaz D, D'Aquila RT. 2009. Differences in APOBEC3G expression in CD4+ T helper lymphocyte subtypes modulate HIV-1 infectivity. PLoS Pathog 5:e1000292.

81. Manches O, Frleta D, Bhardwaj N. 2014. Dendritic cells in progression and pathology of HIV infection. Trends Immunol 35:114-122.
82. Heesters BA, Lindqvist M, Vagefi PA, Scully EP, Schildberg FA, Altfeld M, Walker BD, Kaufmann DE, Carroll MC. 2015. Follicular Dendritic Cells Retain Infectious HIV in Cycling Endosomes. PLoS Pathog 11:e1005285.

83. Doitsh G, Cavrois M, Lassen KG, Zepeda O, Yang Z, Santiago ML, Hebbeler AM, Greene WC. 2010. Abortive HIV Infection Mediates CD4 T Cell Depletion and Inflammation in Human Lymphoid Tissue. Cell 143:789-801.

84. Doitsh G, Galloway NLK, Geng X, Yang Z, Monroe KM, Zepeda O, Hunt PW, Hatano H, Sowinski S, Muñoz-Arias I, Greene WC. 2014. Cell death by pyroptosis drives CD4 T-cell depletion in HIV-1 infection. Nature 505:509-514.

85. Finkel TH, Tudor-Williams G, Banda NK, Cotton MF, Curiel T, Monks C, Baba TW, Ruprecht RM, Kupfer A. 1995. Apoptosis occurs predominantly in bystander cells and not in productively infected cells of HIV- and SIV-infected lymph nodes. Nat Med 1:129-134.

86. Li CI, Friedman DJ, Wang C, Metelev V, Pardee AB. 1995. Induction of apoptosis in uninfected lymphocytes by HIV-1 Tat protein. Science 268:429-431.

87. Westendorp MO, Frank R, Ochsenbauer C, Stricker K, Dhein J, Walczak H, Debating K-M, Krammer PH. 1995. Sensitization of T cells to CD95-mediated apoptosis by HIV-1 Tat and gp120. Nature 375:497-500.

88. Cicala C, Arthos J, Rubbert A, Selig S, Wildt K, Cohen OJ, Fauci AS. 2000. HIV-1 envelope induces activation of caspase-3 and cleavage of focal adhesion kinase in primary human CD4(+) T cells. Proceedings of the National Academy of Sciences of the United States of America 97:1178-1183.

89. Muthumani K, Hwang DS, Desai BM, Zhang D, Dayes N, Green DR, Weiner DB. 2002. HIV-1 Vpr induces apoptosis through Caspase 9 in T Cells and Peripheral Blood Mononuclear Cells. Journal of Biological Chemistry 277:37820-37831.

90. Muthumani K, Choo AY, Hwang DS, Premkumar A, Dayes NS, Harris C, Green DR, Wadsworth SA, Siekierka JJ, Weiner DB. 2005. HIV-1 Nef-induced FasL induction and bystander killing requires p38 MAPK activation. Blood 106:2059-2068.

91. Xu XN, Laffert B, Sceatgon GR, Kraft M, Wolf D, Kolanus W, Mongkolsapay J, McMichael AJ, Baur AS. 1999. Induction of Fas ligand expression by HIV involves the interaction of Nef with the T cell receptor zeta chain. The Journal of Experimental Medicine 189:1489-1496.

92. Ohnimus H, Heinkelein M, Jassoy C. 1997. Apoptotic cell death upon contact of CD4+ T lymphocytes with HIV glycoprotein-expressing cells is mediated by caspsases but bypasses CD95 (Fas/Apo-1) and TNF receptor 1. The Journal of Immunology 159:5246-5252.

93. Gelezniunas R, Xu W, Takeda K, Ichijo H, Greene WC. 2001. HIV-1 Nef inhibits ASK1-dependent death signalling providing a potential mechanism for protecting the infected host cell. Nature 410:834-838.

94. Wolf D, Witte V, Laffert B, Blume K, Stromer E, Trapp S, d’Aloja P, Schürmann A, Baur AS. 2001. HIV-1 Nef associated PAK and PI3-kinases stimulate Akt-independent Bad-phosphorylation to induce anti-apoptotic signals. Nature Medicine 7:1217-1224.

95. Ojeda D, Lopez-Costa JJ, Sede M, Lopez EM, Berria MI, Quarleri J. 2014. Increased in vitro glial fibrillary acidic protein expression, telomerase activity, and telomere length after productive human immunodeficiency virus-1 infection in murine astrocytes. J Neurosci Res 92:267-274.

96. Swingler S, Mann AM, Zhou J, Swingler C, Stevenson M. 2007. Apoptotic Killing of HIV-1–Infected Macrophages Is Subverted by the Viral Envelope Glycoprotein. PLOS Pathogens 3:e134.

97. Olivetta E, Federico M. 2006. HIV-1 Nef protects human-macroncyte-derived macrophages from HIV-1-induced apoptosis. Experimental Cell Research 312:890-900.

98. Cooper A, García M, Petrovas C, Yamamoto T, Koup RA, Nabel GJ. 2013. HIV-1 causes CD4 cell death through DNA-dependent protein kinase during viral integration. Nature 498:376-379.
99. Nettles RE, Kieffer TL, Kwon P, Monie D, Han Y, Parsons T, Cofrancesco J, Gallant JE, Quinn TC, Jackson B, Flexner C, Carson K, Ray S, Persaud D, Siliciano RF. 2005. Intermittent HIV-1 viremia (Blips) and drug resistance in patients receiving HAART. JAMA 293:817-829.

100. Graf EH, Pace MJ, Peterson BA, Lynch LJ, Chukwulebe SB, Mexas AM, Shaheen F, Martin JN, Deeks SG, Connors M, Migueles SA, O'Doherty U. 2013. Gag-positive reservoir cells are susceptible to HIV-specific cytotoxic T lymphocyte mediated clearance in vitro and can be detected in vivo [corrected]. PloS One 8:e71879.

101. Lehrman G, Hogue IB, Palmer S, Jennings C, Spina CA, Wiegand A, Landay AL, Coombs RW, Richman DD, Mellors JW, Coffin JM, Bosch RJ, Margolis DM. 2005. Depletion of latent HIV-1 infection in vivo: a proof-of-concept study. The Lancet 366:549-555.

102. Rasmussen TA, Lewin SR. 2016. Shocking HIV out of hiding: where are we with clinical trials of latency reversing agents? Current opinion in HIV and AIDS 11:394-401.

103. Rasmussen TA, Tolstrup M, Brinkmann CR, Olesen R, Erikstrup C, Solomon A, Winckelmann A, Palmer S, Dinarello C, Buzon M, Lichterfeld M, Lewin SR, Østergaard L, Søgaard OS. 2014. Panobinostat, a histone deacetylase inhibitor, for latent-virus reactivation in HIV-infected patients on suppressive antiretroviral therapy: a phase 1/2, single group, clinical trial. The lancet HIV 1:e13-21.

104. Routy J, Tremblay C, Angel J, Trottier B, Rouleau D, Baril J, Harris M, Trottier S, Singer J, Chomont N, Sékaly R, Boulassel M. 2012. Valproic acid in association with highly active antiretroviral therapy for reducing systemic HIV-1 reservoirs: results from a multicentre randomized clinical study. Medicine 13:291-296.

105. Shan L, Deng K, Shroff NS, Durand CM, Rabi SA, Yang HC, Zhang H, Margolick JB, Blankson JN, Siliciano RF. 2012. Stimulation of HIV-1-specific cytolytic T lymphocytes facilitates elimination of latent viral reservoir after virus reactivation. Immunity 36:491-501.

106. Huang S, Jones RB. 2017. CTLs Pare Defective HIV Proviruses Without Impacting Infectious Latent Reservoirs. CROI.

107. Descours B, Petitjean G, López-Zaragoza J-L, Bruel T, Raffel R, Psomas C, Reynes J, Lacabaratz C, Levy Y, Schwartz O, Lelievre JD, Benkiran M. 2017. CD32a is a marker of a CD4 T-cell HIV reservoir harbouring replication-competent proviruses. Nature 543:564-567.

108. Aillet F, Masutani H, Elbim C, Raoul H, Chêne L, Nugeyre MT, Paya C, Barré-Sinoussi F, Gougerot-Pocidalo MA, Israël N. 1998. Human immunodeficiency virus induces a dual regulation of Bcl-2, resulting in persistent infection of CD4(+) T- or monocytic cell lines. Journal of Virology 72:9698-9705.

109. Berro R, Fuente Cdl, Klase Z, Kehn K, Parvin L, Pumfery A, Agbottah E, Vertes A, Nekhai S, Kashanchi F. 2007. Identifying the Membrane Proteome of HIV-1 Latently Infected Cells. Journal of Biological Chemistry 282:8207-8218.

110. Tan J, Wang X, Devadas K, Zhao J, Zhang P, Hewlett I. 2013. Some mechanisms of FLIP expression in inhibition of HIV-1 replication in Jurkat cells, CD4+ T cells and PBMCs. Journal of Cellular Physiology 228:2305-2313.

111. Wang X, Ragupathy V, Zhao J, Hewlett I. 2011. Molecules from apoptotic pathways modulate HIV-1 replication in Jurkat cells. Biochemical and Biophysical Research Communications 414:20-24.

112. Badley AD, Sainski A, Wightman F, Lewin SR. 2013. Altering cell death pathways as an approach to cure HIV infection. Cell Death Dis 4:e718.

113. Olvera-García G, Aguilar-García T, Gutiérrez-Jasso F, Imaz-Rosshandler I, Rangel-Escareño C, Orozco L, Aguilar-DelFín I, Vázquez-Pérez JA, Zúñiga J, Pérez-Partrigean S, Espinosa E. 2016. A transcriptome-based model of central memory CD4 T cell death in HIV infection. BMC Genomics 17:956.
114. Giri MS, Nebozyhn M, Raymond A, Gekonge B, Hancock A, Creer S, Nicols C, Yousef M, Foulkes AS, Mounzer K, Shull J, Silvestri G, Kostman J, Collman RG, Showe L, Montaner LJ. 2009. Circulating Monocytes in HIV-1-Infected Viremic Subjects Exhibit an Antiapoptosis Gene Signature and Virus- and Host-Mediated Apoptosis Resistance. The Journal of Immunology 182:4459-4470.

115. Monroe KM, Yang Z, Johnson JR, Geng X, Doitsh G, Krogan NJ, Greene WC. 2014. IFI16 DNA Sensor Is Required for Death of Lymphoid CD4 T Cells Abortively Infected with HIV. Science 343:428-432.

116. Cai R, Liu L, Luo B, Wang J, Shen J, Shen Y, Zhang R, Chen J, Lu H. 2016. Caspase-1 Activity in CD4 T Cells Is Downregulated Following Antiretroviral Therapy for HIV-1 Infection. AIDS Research and Human Retroviruses 33:164-171.

117. Herbeuval J-P, Boasso A, Grivel J-C, Hardy AW, Anderson SA, Dolan MJ, Choungnet C, Lifson JD, Shearer GM. 2005. TNF-related apoptosis-inducing ligand (TRAIL) in HIV-1–infected patients and its in vitro production by antigen-presenting cells. Blood 105:2458-2464.

118. Herbeuval J-P, Nilsson J, Boasso A, Hardy AW, Kruhlak MJ, Anderson SA, Dolan MJ, Dy M, Andersson J, Shearer GM. 2006. Differential expression of IFN-α and TRAIL/DR5 in lymphoid tissue of progressor versus nonprogressor HIV-1-infected patients. Proceedings of the National Academy of Sciences 103:7000-7005.

119. Katsikis PD, Wunderlich ES, Smith CA, Herzenberg LA, Herzenberg LA. 1995. Fas antigen stimulation induces marked apoptosis of T lymphocytes in human immunodeficiency virus-infected individuals. Journal of Experimental Medicine 181:2029-2036.

120. Sloand EM, Young NS, Kumar P, Weichold FF, Sato T, Maciejewski JP. 1997. Role of Fas Ligand and Receptor in the Mechanism of T-Cell Depletion in Acquired Immunodeficiency Syndrome: Effect on CD4+ Lymphocyte Depletion and Human Immunodeficiency Virus Replication. Blood 89:1357-1363.

121. Badley AD, Dockrell D, Simpson M, Schut R, Lynch DH, Leibson P, Paya CV. 1997. Macrophage-dependent Apoptosis of CD4+ T Lymphocytes from HIV-infected Individuals Is Mediated by FasL and Tumor Necrosis Factor. The Journal of Experimental Medicine 185:55-64.

122. Badley AD, Dockrell DH, Algeciras A, Ziesmer S, Landay A, Lederman MM, Connick E, Kessler H, Kuritzkes D, Lynch DH, Roche P, Yakita H, Paya CV. 1998. In vivo analysis of Fas/FasL interactions in HIV-infected patients. Journal of Clinical Investigation 102:79-87.

123. Badley AD, Mcelhinny JA, Leibson PJ, Lynch DH, Alderson MR, Paya CV. 1996. Upregulation of Fas ligand expression by human immunodeficiency virus in human macrophages mediates apoptosis of uninfected T lymphocytes. Journal of Virology 70:199-206.

124. Muro-Cacho CA, Pantaleo G, Fauci AS. 1995. Analysis of apoptosis in lymph nodes of HIV-infected persons. Intensity of apoptosis correlates with the general state of activation of the lymphoid tissue and not with stage of disease or viral burden. The Journal of Immunology 154:5555-5566.

125. Grossman Z, Meier-Schellersheim M, Paul WE, Picker LJ. 2006. Pathogenesis of HIV infection: what the virus spares is as important as what it destroys. Nature Medicine 12:289-295.

126. Muñoz-Arias I, Doitsh G, Yang Z, Sowinski S, Ruelas D, Greene WC. 2015. Blood-Derived CD4 T Cells Naturally Resist Pyroptosis during Abortive HIV-1 Infection. Cell Host & Microbe 18:463-470.

127. Paiardini M, Muller-Trutwin M. 2013. HIV-associated chronic immune activation. Immunol Rev 254:78-101.

128. Trinité B, Chan CN, Lee CS, Levy DN. 2016. HIV-1 Vpr- and Reverse Transcription-Induced Apoptosis in Resting Peripheral Blood CD4 T Cells and Protection by Common Gamma-Chain Cytokines. Journal of Virology 90:904-916.
129. Estaquier J, Idziorek T, Zou W, Emilie D, Farber CM, Bouriez JM, Ameisen JC. 1995. T helper type 1/T helper type 2 cytokines and T cell death: preventive effect of interleukin 12 on activation-induced and CD95 (FAS/APO-1)-mediated apoptosis of CD4+ T cells from human immunodeficiency virus-infected persons. Journal of Experimental Medicine 182:1759-1767.

130. Betts MR, Nason MC, West SM, Rosa SCD, Migueles SA, Abraham J, Lederman MM, Benito JM, Goepfert PA, Connors M, Roederer M, Koup RA. 2006. HIV nonprogressors preferentially maintain highly functional HIV-specific CD8+ T cells. Blood 107:4781-4789.

131. Graf EH, Pace MJ, Peterson BA, Lynch LJ, Chukwulebe SB, Mexas AM, Shaheen F, Martin JN, Deeks SG, Connors M, Migueles SA, O'Doherty U. 2013. Gag-Positive Reservoir Cells Are Susceptible to HIV-Specific Cytotoxic T Lymphocyte Mediated Clearance In Vitro and Can Be Detected In Vivo. PLOS ONE 8:e71879.

132. Jennes W, Verheyden S, Demanet S, Adjé-Touré CA, Vuylsteke B, Nkengasong JN, Kestens L. 2006. Cutting edge: resistance to HIV-1 infection among African female sex workers is associated with inhibitory KIR in the absence of their HLA ligands. Journal of Immunology (Baltimore, Md: 1950) 177:6588-6592.

133. Martin MP, Gao X, Lee J-H, Nelson GW, Detels R, Goedert JJ, Buchbinder S, Hoots K, Vlahov D, Trowsdale J, Wilson M, O'Brien SJ, Carrington M. 2002. Epistatic interaction between KIR3DS1 and HLA-B delays the progression to AIDS. Nature Genetics 31:429-434.

134. Ravet S, Scott-Algara D, Bonnet E, Tran HK, Tran T, Nguyen N, Truong LX, Theodorou I, Barré-Sinoussi F, Pancino G, Paul P. 2007. Distinctive NK-cell receptor repertoires sustain high-level constitutive NK-cell activation in HIV-exposed uninfected individuals. Blood 109:4296-4305.

135. Sáez-Cirión A, Lacabaratz C, Lambotte O, Versmisse P, Urrutia A, Boufassa F, Barré-Sinoussi F, Delfraissy J-F, Sinet M, Pancino G, Venet A, Group ANdRslSEHCS. 2007. HIV controllers exhibit potent CD8 T cell capacity to suppress HIV infection ex vivo and peculiar cytotoxic T lymphocyte activation phenotype. Proceedings of the National Academy of Sciences of the United States of America 104:6776-6781.

136. Sáez-Cirión A, Sinet M, Shin SY, Urrutia A, Versmisse P, Lacabaratz C, Boufassa F, Avettand-Fenoël V, Rouzioux C, Delfraissy J-F, Barré-Sinoussi F, Lambotte O, Venet A, Pancino G, Group AEHCS. 2009. Heterogeneity in HIV suppression by CD8 T cells from HIV controllers: association with Gag-specific CD8 T cell responses. Journal of Immunology (Baltimore, Md: 1950) 182:7828-7837.

137. Alter G, Heckerman D, Schneidewind A, Fadda L, Kadie CM, Carlson JM, Oniangue-Ndza C, Martin M, Li B, Khakoo SI, Carrington M, Allen TM, Altfeld M. 2011. HIV-1 adaptation to NK-cell-mediated immune pressure. Nature 476:96-100.

138. Borrow P, Lewicki H, Wei X, Horwitz MS, Peffer N, Meyers H, Nelson JA, Gairin JE, Hahn BH, Oldstone MB, Shaw GM. 1997. Antiviral pressure exerted by HIV-1-specific cytotoxic T lymphocytes (CTLs) during primary infection demonstrated by rapid selection of CTL escape virus. Nature Medicine 3:205-211.

139. Deng K, Pertain M, Rongvaux A, Wang L, Durand CM, Ghiaur G, Lai J, McHugh HL, Hao H, Zhang H, Margolick JB, Gurer C, Murphy AJ, Valenzuela DM, Yancopoulos GD, Deeks SG, Strowig T, Kumar P, Siliciano JD, Salzberg SL, Flavell RA, Shan L, Siliciano RF. 2015. Broad CTL response is required to clear latent HIV-1 due to dominance of escape mutations. Nature 517:381-385.

140. Mailliard RB, Smith KN, Fecek RJ, Rappocciolo G, Nascimento EJM, Marques ET, Watkins SC, Mullins JI, Rinaldo CR. 2013. Selective induction of CTL helper rather than killer activity by natural epitope variants promotes dendritic cell-mediated HIV-1 dissemination. Journal of Immunology (Baltimore, Md: 1950) 191:2570-2580.

141. Noel N, Pena R, David A, Avettand-Fenoël V, Erkizia I, Jimenez E, Lecroux C, Rouzioux C, Boufassa F, Pancino G, Venet A, Van Lint C, Martinez-Picado J, Lambotte O, Saéz-Cirion A,
Prado JG. 2016. Long-Term Spontaneous Control of HIV-1 Is Related to Low Frequency of Infected Cells and Inefficient Viral Reactivation. J Virol 90:6148-6158.

142. Cohen GB, Gandhi RT, Davis DM, Mandelboim O, Chen BK, Strominger JL, Baltimore D. 1999. The Selective Downregulation of Class I Major Histocompatibility Complex Proteins by HIV-1 Protects HIV-Infected Cells from NK Cells. Immunity 10:661-671.

143. Apps R, Del Prete GQ, Chatterjee P, Lara A, Brumme ZL, Brockman MA, Neil S, Pickering S, Schneider DK, Piechocka-Trocha A, Walker BD, Thomas R, Shaw GM, Hahn BH, Keele BF, Lifson JD, Carrington M. 2016. HIV-1 Vpu Mediates HLA-C Downregulation. Cell Host & Microbe 19:686-695.

144. Collins KL, Chen BK, Kalams SA, Walker BD, Baltimore D. 1998. HIV-1 Nef protein protects infected primary cells against killing by cytotoxic T lymphocytes. Nature 391:397-401.

145. Xu XN, Screaton GR, Gotch FM, Dong T, Tan R, Almond N, Walker B, Stebbings R, Kent K, Nagata S, Stott JE, McMichael AJ. 1997. Evasion of cytotoxic T lymphocyte (CTL) responses by nef-dependent induction of Fas ligand (CD95L) expression on simian immunodeficiency virus-infected cells. J Exp Med 186:7-16.

146. Rainho JN, Martins MA, Cunyat F, Watkins IT, Watkins DI, Stevenson M. 2015. Nef Is Dispensable for Resistance of Simian Immunodeficiency Virus-Infected Macrophages to CD8+ T Cell Killing. Journal of Virology 89:10625-10636.

147. Vojnov L, Martins MA, Bean AT, Veloso de Santana MG, Sacha JB, Wilson NA, Bonaldo MC, Galler R, Stevenson M, Watkins DI. 2012. The majority of freshly sorted simian immunodeficiency virus (SIV)-specific CD8(+) T cells cannot suppress viral replication in SIV-infected macrophages. J Virol 86:4682-4687.

148. Sacha JB, Giraldo-Vela JP, Buechler MB, Martins MA, Maness NJ, Chung C, Wallace LT, León EJ, Friedrich TC, Wilson NA, Hiraoka A, Watkins DI. 2009. Gag- and Nef-specific CD4+ T cells recognize and inhibit SIV replication in infected macrophages early after infection. Proceedings of the National Academy of Sciences of the United States of America 106:9791-9796.

149. Soghoian DZ, Jessen H, Flanders M, Sierra-Davidson K, Cutler S, Pertel T, Ranasinghe S, Lindqvist M, Davis I, Lane K, Rychert J, Rosenberg ES, Piechocka-Trocha A, Brass AL, Brenchley JM, Walker BD, Streeck H. 2012. HIV-Specific Cytolytic CD4+ T Cell Responses During Acute HIV Infection Predict Disease Outcome. Science Translational Medicine 4:123ra125-123ra125.

150. Johnson S, Eller M, Teigler JE, Maloveste SM, Schultz BT, Soghoian DZ, Lu R, Oster AF, Chenine A-L, Alter G, Dittmer U, Marovich M, Robb ML, Michael NL, Bolton D, Streeck H. 2015. Cooperativity of HIV-Specific Cytolytic CD4+ T Cells and CD8 T Cells in Control of HIV Viremia. Journal of Virology 89:7494-7505.

151. Jouve M, Sol-Foulon N, Watson S, Schwartz O, Benaroch P. 2007. HIV-1 buds and accumulates in "nonacidic" endosomes of macrophages. Cell Host Microbe 2:85-95.

152. Welsch S, Groot F, Krausslich HG, Keppeler OT, Sattentau QJ. 2011. Architecture and regulation of the HIV-1 assembly and holding compartment in macrophages. J Virol 85:7922-7927.

153. Tan J, Sattentau QJ. 2013. The HIV-1-containing macrophage compartment: a perfect cellular niche? Trends Microbiol 21:405-412.

154. Letendre S, Marquie-Beck J, Capparelli E, Best B, Clifford D, Collier AC, Gelman BB, McArthur JC, McCutchan JA, Morgello S, Simpson D, Grant I, Ellis RJ. 2008. Validation of the CNS Penetration-Effectiveness Rank for Quantifying Antiretroviral Penetration Into the Central Nervous System. Archives of Neurology 65:65-70.

155. Joseph SB, Arrildt KT, Sturdevant CB, Swanstrom R. 2015. HIV-1 target cells in the CNS. Journal of NeuroVirology 21:276-289.

156. Kivisäkk P, Mahad DJ, Callahan MK, Trebst C, Tucky B, Wei T, Wu L, Baekkevold ES, Lassmann H, Staugaitis SM, Campbell JJ, Ransohoff RM. 2003. Human cerebrospinal fluid central memory
CD4+ T cells: Evidence for trafficking through choroid plexus and meninges via P-selectin. Proceedings of the National Academy of Sciences 100:8389-8394.

157. Young KG, MacLean S, Dudani R, Krishnan L, Sad S. 2011. CD8+ T Cells Primed in the Periphery Provide Time-Bound Immune-Surveillance to the Central Nervous System. The Journal of Immunology 187:1192-1200.

158. Wakim LM, Woodward-Davis A, Bevan MJ. 2010. Memory T cells persisting within the brain after local infection show functional adaptations to their tissue of residence. Proceedings of the National Academy of Sciences 107:17872-17879.

159. Kessing CF, Spudich S, Valcour V, Cartwright P, Chalermchai T, Fletcher JLK, Nichols C, Josey BJ, Slike B, Krebs SJ, Sailsuta N, Lerdsum L, Jagodzinski L, Tipsuk S, Suttichom D, Rattanamanee S, Zetterberg H, Hellmuth J, Panuphak N, Robb ML, Michael NL, Ananworanich J, Trautmann L. 2017. High Number of Activated CD8+ T Cells Targeting HIV Antigens are Present in Cerebrospinal Fluid in Acute HIV Infection. Journal of Acquired Immune Deficiency Syndromes (1999) doi:10.1097/QAI.0000000000001301.

160. Ganesh A, Lemongello D, Lee E, Peterson J, McLaughlin BE, Ferre AL, Gillespie GM, Fuchs D, Deeks SG, Hunt PW, Price RW, Spudich SS, Shacklett BL. 2016. Immune Activation and HIV-Specific CD8(+) T Cells in Cerebrospinal Fluid of HIV Controllers and Noncontrollers. AIDS research and human retroviruses 32:791-800.

161. Sadagopal S, Lorey SL, Barnett L, Basham R, Lebo L, Erdem H, Haman K, Avison M, Waddell K, Haas DW, Kalans SA. 2008. Enhancement of Human Immunodeficiency Virus (HIV)-Specific CD8+ T Cells in Cerebrospinal Fluid Compared to Those in Blood among Antiretroviral Therapy-Naive HIV-Positive Subjects. Journal of Virology 82:10418-10428.

162. Lescure F-X, Moulignier A, Savatovsky J, Amiel C, Carcelain G, Molina J-M, Gallien S, Pacanovski J, Pialoux G, Adle-Biassette H, Gray F. 2013. CD8 Encephalitis in HIV-Infected Patients Receiving CART: A Treatable Entity. Clinical Infectious Diseases 57:101-108.

163. Miller RF, Isaacson PG, Hall-Craggs M, Lucas S, Gray F, Scaravilli F, An SF. 2004. Cerebral CD8+ lymphocytosis in HIV-1 infected patients with immune restoration induced by HAART. Acta Neuropathologica 108:17-27.

164. Marcondes MCG, Morsey B, Emanuel K, Lamberty BG, Flynn CT, Fox HS. 2015. CD8+ T Cells Maintain Suppression of Simian Immunodeficiency Virus in the Central Nervous System. The Journal of Infectious Diseases 211:40-44.

165. Banga R, Procopio FA, Noto A, Pollakis G, Cavassini M, Ohmiti K, Corpataux J-M, de Leval L, Pantaleo G, Perreau M. 2016. PD-1+ and follicular helper T cells are responsible for persistent HIV-1 transcription in treated aviremic individuals. Nature Medicine 22:754-761.

166. Perreau M, Savoye A-L, Crignis ED, Corpataux J-M, Cubas R, Haddad EK, Leval LD, Graziosi C, Pantaleo G. 2013. Follicular helper T cells serve as the major CD4 T cell compartment for HIV-1 infection, replication, and production. Journal of Experimental Medicine 210:143-156.

167. Connick E, Mattila T, Folkvord JM, Schlichtemeier R, Meditz AL, Ray MG, McCarter MD, MaWhinney S, Hage A, White C, Skinner PJ. 2007. CTL Fail to Accumulate at Sites of HIV-1 Replication in Lymphoid Tissue. The Journal of Immunology 178:6975-6983.

168. Folkvord JM, Armon C, Connick E. 2005. Lymphoid Follicles Are Sites of Heightened Human Immunodeficiency Virus Type 1 (HIV-1) Replication and Reduced Antiretroviral Effector Mechanisms. AIDS Research and Human Retroviruses 21:363-370.

169. Fukazawa Y, Lum R, Okoye AA, Park H, Matsuda K, Bae JY, Hagen SI, Shoemaker R, Deleage C, Lucero C, Morcock D, Swanson T, Legasse AW, Axthelm MK, Hesselgesser J, Geleziusnas R, Hirsch VM, Edlefson PT, Piatak M, Estes JD, Lifson JD, Picker LJ. 2015. B cell follicle sanctuary permits persistent productive simian immunodeficiency virus infection in elite controllers. Nature Medicine 21:132-139.
170. Hong JJ, Amancha PK, Rogers K, Ansari AA, Villinger F. 2012. Spatial Alterations between CD4+ T Follicular Helper, B, and CD8+ T Cells during Simian Immunodeficiency Virus Infection: T/B Cell Homeostasis, Activation, and Potential Mechanism for Viral Escape. The Journal of Immunology 188:3247-3256.

171. Leong YA, Chen Y, Ong HS, Wu D, Man K, Deleage C, Minnich M, Meckiff BJ, Wei Y, Hou Z, Zotos D, Fenix KA, Atenkar A, Preston S, Chipman JG, Beilman GJ, Allison CC, Sun L, Wang P, Xu J, Toe JG, Lu HK, Tao Y, Palendiria U, Dent AL, Landay AL, Pellegrini M, Comerford I, McColl SR, Schacker TW, Long HM, Estes JD, Busslinger M, Belz GT, Lewin SR, Kallies A, Yu D. 2016. CXCR5+ follicular cytotoxic T cells control viral infection in B cell follicles. Nature Immunology 17:1187-1196.

172. Petrovas C, Ferrando-Martinez S, Gerner MY, Casazza JP, Pegu A, Deleage C, Cooper A, Hataye J, Andrews S, Ambrozak D, Estrada PMDR, Boritz E, Paris R, Moysi E, Boswell KL, Ruiz-Mateos E, Vagios I, Leal M, Ablanedo-Terrazas Y, Rivero A, Gonzalez-Hernandez LA, McDermott AB, Moir S, Reyes-Terán G, Docobo F, Pantaleo G, Douek DC, Betts MR, Estes JD, Germain RN, Mascola JR, Koup RA. 2017. Follicular CD8 T cells accumulate in HIV infection and can kill infected cells in vitro via bispecific antibodies. Science Translational Medicine 9:eaaq2285.

173. Murphey-Corb M, Wilson LA, Trichel AM, Roberts DE, Xu K, Ohkawa S, Woodson B, Bohm R, Blanchard J. 1999. Selective Induction of Protective MHC Class I-Restricted CTL in the Intestinal Lamina Propria of Rhesus Monkeys by Transient SIV Infection of the Colonic Mucosa. The Journal of Immunology 162:540-549.

174. Lohman BL, Miller CJ, McChesney MB. 1995. Antiviral cytotoxic T lymphocytes in vaginal mucosa of simian immunodeficiency virus-infected rhesus macaques. The Journal of Immunology 155:5855-5860.

175. Damouche A, Lazure T, Avettand-Fenoël V, Huot N, Dejucq-Rainsford N, Satie A-P, Mélard A, David L, Gommet C, Ghosn J, Noel N, Poucher G, Martinez V, Benoist S, Béréziat V, Cosma A, Favier B, Vaslin B, Rouzioux C, Capeau J, Müller-Trutwin M, Dereuddre-Bosquet N, Grand RL, Lambotte O, Bourgeois C. 2015. Adipose Tissue Is a Neglected Viral Reservoir and an Inflammatory Site during Chronic HIV and SIV Infection. PLOS Pathogens 11:e1005153.

176. Finzi D, Siliciano RF. 1998. Viral Dynamics in HIV-1 Infection. Cell 93:665-671.

177. Avettand-Fenoël V, Hocqueloux L, Ghosn J, Cheret A, Frange P, Melard A, Viard JP, Rouzioux C. 2016. Total HIV-1 DNA, a Marker of Viral Reservoir Dynamics with Clinical Implications. Clin Microbiol Rev 29:859-880.

178. Perelson AS. 2002. Modelling viral and immune system dynamics. Nat Rev Immunol 2:28-36.

179. Lugli E, Dominguez MH, Gattinoni L, Chattopadhyay PK, Bolton DL, Song K, Klatt NR, Brenchley JM, Vaccari M, Gostick E, Price DA, Waldmann TA, Restifo NP, Franchini G, Roederer M. 2013. Superior T memory stem cell persistence supports long-lived T cell memory. The Journal of Clinical Investigation 123:594-599.

180. Macallan DC, Wallace D, Zhang Y, De Lara C, Worth AT, Ghatts H, Griffin GE, Beverley PC, Tough DF. 2004. Rapid turnover of effector-memory CD4(+) T cells in healthy humans. J Exp Med 200:255-260.

181. Vrisekoop N, den Braber I, de Boer AB, Ruiter AF, Ackermans MT, van der Crabben SN, Schrijver EH, Spiereburg G, Sauerwein HP, Hazenberg MD, de Boer RJ, Miedema F, Borghans JA, Tessaelaar K. 2008. Sparse production but preferential incorporation of recently produced naive T cells in the human peripheral pool. Proc Natl Acad Sci U S A 105:6115-6120.

182. Gattinoni L, Lugli E, Ji Y, Pos Z, Paulos CM, Quigley MF, Almeida JR, Gostick E, Yu Z, Carpenito C, Wang E, Douek DC, Price DA, June CH, Marincola FM, Roederer M, Restifo NP. 2011. A human memory T cell subset with stem cell-like properties. Nat Med 17:1290-1297.
183. Clark RA. 2015. Resident memory T cells in human health and disease. Science translational medicine 7:269rv261.

184. DiNapoli SR, Ortiz AM, Wu F, Matsuda K, Twigg HL, Hirsch VM, Knox K, Brenchley JM. 2017. Tissue-resident macrophages can contain replication-competent virus in antiretroviral-naive, SIV-infected Asian macaques. JCI Insight 2.

185. Crowe S, Zhu T, Muller WA. 2003. The contribution of monocyte infection and trafficking to viral persistence, and maintenance of the viral reservoir in HIV infection. Journal of Leukocyte Biology 74:635-641.

186. Stevenson M. 2003. HIV-1 pathogenesis. Nat Med 9:853-860.

187. Jambo KC, Banda DH, Kankwawita AM, Sukumar N, Allain TJ, Heyderman RS, Russell DG, Mwandumba HC. 2014. Small alveolar macrophages are infected preferentially by HIV and exhibit impaired phagocytic function. Mucosal Immunol 7:1116-1126.

188. Eguiluz-Gracia I, Schultz HH, Sikkeland LI, Danilova E, Holm AM, Pronk CJ, Agace WW, Iversen M, Andersen C, Jahnsen FL, Baekkevold ES. 2016. Long-term persistence of human donor alveolar macrophages in lung transplant recipients. Thorax 71:1006-1011.

189. Nayak DK, Zhou F, Xu M, Huang J, Tsuji M, Hachem R, Mohanakumar T. 2016. Long-Term Persistence of Donor Alveolar Macrophages in Human Lung Transplant Recipients That Influences Donor-Specific Immune Responses. Am J Transplant 16:2300-2311.

190. Tay TL, Savage JC, Hui CW, Bisht K, Tremblay ME. 2017. Microglia across the lifespan: from origin to function in brain development, plasticity and cognition. Journal of Physiology-London 595:1929-1945.

191. Carter CA, Ehrlich LS. 2008. Cell biology of HIV-1 infection of macrophages. Annu Rev Microbiol 62:425-443.

192. Jones G, Power C. 2006. Regulation of neural cell survival by HIV-1 infection. Neurobiol Dis 21:1-17.

193. McNelis JC, Olefsky JM. 2014. Macrophages, immunity, and metabolic disease. Immunity 41:36-48.

194. Cohn LB, Silva IT, Oliveira TY, Rosales RA, Parrish EH, Learn GH, Hahn BH, Czartoski JL, McElrath MJ, Lehmann C, Klein F, Caskey M, Walker BD, Siliciano JD, Siliciano RF, Jankovic M, Nussenzweig MC. 2015. HIV-1 integration landscape during latent and active infection. Cell 160:420-432.

195. Maldarelli F, Wu X, Su L, Simonetti FR, Shao W, Hill S, Spindler J, Ferris AL, Mellors JW, Kearney MF, Coffin JM, Hughes SH. 2014. Specific HIV integration sites are linked to clonal expansion and persistence of infected cells. Science 345:179-183.

196. Simonetti FR, Sobolewski MD, Fyne E, Shao W, Spindler J, Hattori J, Anderson EM, Watters SA, Hill S, Wu X, Wells D, Su L, Luke BT, Halvas EK, Besson G, Penrose KJ, Yang Z, Kwan RW, Waes CV, Uldrick T, Citrin DE, Kovacs J, Polis MA, Rehm CA, Gorelick R, Piatak M, Keele BF, Kearney MF, Coffin JM, Hughes SH, Mellors JW, Maldarelli F. 2016. Clonally expanded CD4+ T cells can produce infectious HIV-1 in vivo. Proceedings of the National Academy of Sciences 113:1883-1888.

197. Wagner TA, McLaughlin S, Garg K, Cheung CYK, Larsen BB, Styrchak S, Huang HC, Edlefsen PT, Mullins JI, Frenkel LM. 2014. Proliferation of cells with HIV integrated into cancer genes contributes to persistent infection. Science 345:570-573.

198. Boritz EA, Darko S, Swaszek L, Wolf G, Wells D, Wu X, Henry AR, Laboune F, Hu J, Ambrozak D, Hughes MS, Hoh R, Casazza JP, Vostal A, Bunis D, Nganou-Makamdop K, Lee JS, Migueles SA, Koup RA, Connors M, Moir S, Schacker T, Maldarelli F, Hughes SH, Deeks SG, Douek DC. 2016. Multiple Origins of Virus Persistence during Natural Control of HIV Infection. Cell 166:1004-1015.
199. Hosmane NN, Kwon KJ, Bruner KM, Capoferri AA, Beg S, Rosenbloom DIS, Keele BF, Ho Y-C, Siliciano JD, Siliciano RF. 2017. Proliferation of latently infected CD4+ T cells carrying replication-competent HIV-1: Potential role in latent reservoir dynamics. Journal of Experimental Medicine doi:10.1084/jem.20170193:jem.20170193.

200. Berard M, Tough DF. 2002. Qualitative differences between naive and memory T cells. Immunology 106:127-138.

201. Bosque A, Famiglietti M, Weyrich AS, Goulston C, Planelles V. 2011. Homeostatic Proliferation Fails to Efficiently Reactivate HIV-1 Latently Infected Central Memory CD4+ T Cells. PLOS Pathogens 7:e1002288.

202. Boyman O, Purton JF, Surh CD, Sprent J. 2007. Cytokines and T-cell homeostasis. Current Opinion in Immunology 19:320-326.

203. Seddon B, Tomlinson P, Zamoyska R. 2003. Interleukin 7 and T cell receptor signals regulate homeostasis of CD4 memory cells. Nature Immunology 4:680-686.

204. Surh CD, Sprent J. 2008. Homeostasis of Naive and Memory T Cells. Immunity 29:848-862.

205. Pennock ND, White JT, Cross EW, Cheney EE, Tamburini BA, Kedl RM. 2013. T cell responses: naive to memory and everything in between. Advances in Physiology Education 37:273-283.

206. Hammarlund E, Lewis MW, Hansen SG, Strelow LI, Nelson JA, Sexton GJ, Hanifin JM, Slifka MK. 2003. Duration of antiviral immunity after smallpox vaccination. Nature Medicine 9:1131-1137.

207. Badia R, Pujantell M, Riveira-Munoz E, Puig T, Torres-Torronteras J, Marti R, Clotet B, Ampudia RM, Vives-Pi M, Este JA, Ballana E. 2016. The G1/S Specific Cyclin D2 Is a Regulator of HIV-1 Restriction in Non-proliferating Cells. Plos Pathogens 12.

208. Pauls E, Ruiz A, Badia R, Pernmaner M, Gubern A, Riveira-Muñoz E, Torres-Torronteras J, Álvarez M, Mothe B, Brander C, Crespo M, Menéndez-Arias L, Clotet B, Keppeler OT, Martí R, Posas F, Ballana E, Esté JA. 2014. Cell Cycle Control and HIV-1 Susceptibility Are Linked by CDK6-Dependent CDK2 Phosphorylation of SAMHD1 in Myeloid and Lymphoid Cells. The Journal of Immunology 193:1998-1997.

209. Jenkins SJ, Ruckerl D, Cook PC, Jones LH, Finkelman FD, Rooijen NV, MacDonald AS, Allen JE. 2011. Local Macrophage Proliferation, Rather than Recruitment from the Blood, Is a Signature of TH2 Inflammation. Science 332:1284-1288.

210. Robbins CS, Hilgendorf I, Weber GF, Theurl I, Iwamoto Y, Figueiredo J-L, Gorbatov R, Sukhova GK, Gerhardt LMS, Smyth D, Zavitz CCJ, Shikatani EA, Parsons M, van Rooijen N, Lin HY, Huang M, Libby P, Nahrendorf M, Weissleder R, Swirski FK. 2013. Local proliferation dominates lesional macrophage accumulation in atherosclerosis. Nature Medicine 19:1166-1172.

211. Zamarro BF, Mergian TA, Cho KW, Martinez-Santibanez G, Luau D, Singer K, DelProposto JL, Geletka LM, Muir LA, Lumeng CN. 2016. Macrophage Proliferation Sustains Adipose Tissue Inflammation in Formerly Obese Mice. Diabetes doi:10.2337/db16-0500:db160500.

212. Douek DC, Brenchley JM, Betts MR, Ambrozak DR, Hill BJ, Okamoto Y, Casazza JP, Kuruppu J, Kunzman K, Wolinsky S, Grossman Z, Dybul M, Oxenius A, Price DA, Connors M, Koup RA. 2002. HIV preferentially infects HIV-specific CD4+ T cells. Nature 417:95-98.

213. Gosselin A, Wiche Salinas TR, Planas D, Wacleche VS, Zhang Y, Fromentin R, Chomont N, Cohen EA, Shacklett B, Mehraj V, Ghali MP, Routy JP, Ancuta P. 2017. HIV persists in CCR6+CD4+ T cells from colon and blood during antiretroviral therapy. AIDS 31:35-48.

214. Kryczek I, Zhao E, Liu Y, Wang Y, Vatan L, Szelig W, Moyer J, Klimeczak A, Lange A, Zou W. 2011. Human TH17 Cells Are Long-Lived Effector Memory Cells. Science Translational Medicine 3:104ra100-104ra100.

215. Muranski P, Borman Zachary A, Kerkar Sid P, Klebanoff Christopher A, Ji Y, Sanchez-Perez L, Sukumar M, Reger Robert N, Yu Z, Kern Steven J, Roychoudhuri R, Ferreyra Gabriela A, Shen W, Durum Scott K, Feigenbaum L, Palmer Douglas C, Antony Paul A, Chan C-C, Laurence A,
Danner Robert L, Gattinoni L, Restifo Nicholas P. 2011. Th17 Cells Are Long Lived and Retain a Stem Cell-like Molecular Signature. Immunity 35:972-985.
Figure 1. **Cellular determinants for the establishment and persistence of HIV reservoirs.** The establishment of viral reservoirs is first determined by the susceptibility of cells to infection (i), which is regulated by the balance of HIV host dependency factors and viral restriction factors present in the cells. In order to persist, infected cells need first to resist apoptotic signals induced by viral infection and avoid immune surveillance (ii). These resistant infected cells will persist for variable periods of time depending on their specific life span and capacity to proliferate without enhancing HIV dependent cell death signals (iii).
Figure 2. Estimation of potential of different cell subsets to HIV persistence. Among lymphoid cell subsets, naïve, central memory and stem-cell like memory T cells are thought of as major contributors to long-term HIV cellular reservoir, while effector memory and terminally differentiated helper T cell subsets are depleted first during infection and have limited turnover.
potential. Myeloid cells, despite their relatively low susceptibility to infection, are now increasingly recognized as important contributors to the reservoir in both lymphoid and non-lymphoid tissues due to their long half-life and resistance to apoptosis and immune-mediated killing. Although not reflected here, tissue localization and activation status influences various parameters of persistence, with actively producing cells being more susceptible to cell death thus reducing their contribution to long term reservoir.