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Tissue Reservoirs of HIV

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Abstract

Purpose—Tissue reservoirs of HIV may promote the persistent immunopathology responsible for non-AIDS morbidity and data support multifocal reactivation from tissues as the source of viral rebound during ART interruption. The heterogeneity of tissue reservoirs and incomplete knowledge about their composition are obstacles to an HIV cure.

Recent findings—In addition to the higher concentration of infected CD4+ T cells found in both central lymphoid tissues and gut, specific subsets of CD4+ T cells appear to play a disproportionate role in HIV persistence. Recently, a subset of central memory T cells enriched in lymphnode germinal centers called T-follicular helper cells have been identified that express more viral RNA and occupy an anatomic niche inaccessible to CTL killing. Additional observations suggest that ARV concentrations may be lower in some tissues raising the possibility for localized, low-level viral replication. Finally, some recent data implicate the persistence of infected, non-CD4+ T cell types in tissues during ART.

Summary—The retention of infected cells in a wide variety of tissues, often with distinct viral and cellular characteristics, underscores the importance of studying tissue reservoirs in the development and assessment of cure strategies. Both inhibitory ARVs and latency reversing drugs must reach these sites and novel strategies may be needed to attack virus in cells as variable as Tfh and macrophages.

Keywords

HIV; anatomic reservoirs; viral persistence

Introduction

Where and how much HIV persists in the body are central questions when developing strategies to eradicate HIV and for understanding the factors contributing to the persistent immune dysfunction thought to be responsible for non-AIDS clinical morbidities despite combination antiretroviral therapy (ART)[1]. While cells from the peripheral blood are easily accessed for study and have provided many basic insights into HIV pathogenesis with and without ART, it is important to consider that the circulating CD4+ T cells comprise <2% of total-body CD4+ T cell numbers[2,3]. Whether residual viral replication persists in the

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setting of combination ART that suppresses plasma virus levels to <20-50copies/ml remains controversial but if occurring is likely to involve tissue reservoirs[4,5]. Tissue sanctuaries of low ARV penetration might permit limited viral propagation at levels insufficient to allow the emergence of drug resistance or other detectable sequence change[6,7]. In addition, some tissues act as immune privileged sites that could theoretically prevent effective immune recognition, resulting in delayed immune clearance of infected cells[8,9]. Finally, although many if not all tissues harbor some CD4+ T cells, the distribution of T cell subsets and other infectable cell types including macrophages and possibly other cell types will vary among tissues[10-12]. Each of these factors may contribute to the complexity of HIV reservoirs across organs and tissues in HIV infected persons on ART.

We use the definition of HIV tissue reservoir as a tissue or organ containing cells that continue to harbor HIV in the setting of combination ART, regardless of the mechanism maintaining them (cell quiescence and stability, cell proliferation, low-level viral replication). Most studies of HIV persistence in tissues rely on the detection of viral nucleic acids and occasionally viral antigen but don't distinguish between replication competent and defective virus or viral remnants incapable of producing viral rebound. The presence of a large excess of genetically defective proviruses has been observed in cells in blood[13,14] and in brain[15] but likely applies to all tissues. Nevertheless, “replication incompetent” viral reservoirs might still contribute to pathogenesis if they were able to support abortive viral expression (either viral RNA or antigen) that could elicit inflammatory or immune responses as encountered with other viral infections[16,17]. We review observations concerning tissue reservoirs by organ system with particular attention to the nature of the infected cell types, evidence for viral compartmentalization if any, and evidence for differences in ARV concentrations. We conclude with a discussion of some implications and unanswered questions in the field.

Lymph Nodes and Spleen

Central lymphoid tissues are a primary site for viral replication and contain massive numbers of infected cells and free virions captured on the follicular dendritic cell network[18,19]. Although potent ART results in an exponential 3-log decrease in HIV-RNA in lymph node (LN), with a clearance half-life only slightly longer than the blood (6 vs. 1.9 days)[20,21], HIV-RNA and DNA can still be detected in the LN after years of ART[22-24].

One study also detected abundant amounts of HIV p24, p17, and gp120/gp41 in the germinal centers of LN after 5-13 months of suppressive ART, although HIV-RNA was not detected in this study[25]. Several studies of ART-treated macaques have demonstrated that viral DNA and/or RNA levels are highest in LN and spleen[26-28]. In one study, SIV-RNA levels in LN and spleen decreased much less than in plasma and gut, which was attributed to lower drug levels in these secondary lymphoid tissues[7]. Studies from humans also suggest that levels of some ARVs may be lower in LN[6,29].

There are conflicting data on whether virus found in LN is compartmentalized and genetically separate from that in blood. Some studies report differences between LN and blood in viral sequences and drug resistance mutational patterns[24,30], while other studies

have shown that HIV sequences in lymphoid tissues are similar to blood[31,32]. Additional, unanswered questions concern whether regional differences exist among LN for infected cell content, infected cell viral expression or likelihood of compartmentalized virus with distinct genetic attributes.

Of note, while the subset of CD4+ T cells bearing markers of central and transitional memory maturation phenotypes comprise the largest proportion of the reservoir of infected CD4+ T cells in peripheral blood from patients on ART[10,33], some surveys suggest a greater contribution of CD4+ T cells with an effector memory phenotype in lymph nodes compared to blood[34]. Furthermore, several recent studies in SIV/macaques and patients on ART identify a memory subset, the CD4+ T-follicular helper cells (T_{fh}) in LN follicles bearing CXCR5 and PD-1 as highly enriched for replication competent virus and viral RNA[35,36]. The survival of infected T_{fh} has been attributed to the paucity of virus-specific CTL in LN follicles and to the expression of anti-apoptotic BCL2 by T_{fh} in the setting of chronic HIV/SIV infection [37-39]. Recently, preferential retention of HIV in cells in peripheral blood with T_{fh} markers has also been described[40].

Bone Marrow

HIV can infect various cell types in bone marrow, and HIV-DNA can be detected in bone marrow obtained from on-ART individuals. It remains unresolved whether hematopoietic progenitor cells constitute a reservoir in vivo[41]. In ART-suppressed individuals, two studies did not detect HIV-DNA in CD34+ progenitor cells[42,43], while a third found HIV-DNA in CD133+ bone marrow progenitor cells from 6/11 patients[44]. Bone marrow mast cell progenitors can be latently infected with HIV, and one study detected infected mast cells in some tissues of treated patients[45], although another study found no evidence of infected mast cells in multiple organs[46].

Thymus

A variety of cell types found in thymus of humans and non-human primates (NHP) support HIV and SIV infection and can be demonstrated in vivo in the absence of treatment. However, little evidence is available demonstrating persistence of HIV or SIV infection in the thymus of individuals on suppressive ART. In one study of ARV treated macaques, neither SIV-DNA nor replication-competent virus was detected in the thymus, while SIV-DNA was detected in spleen and LN, and infectious virus was isolated from LN[47]. In another study of SHIV-infected macaques on suppressive ART, Gag RNA was detected in the thymus in only 1 of 6 animals, and multiply-spliced HIV-RNA was not detected in the thymus[48].

Liver

Studies in untreated individuals have shown that HIV can infect Kupffer cells and T cells in the liver. In humans, one study detected HIV in the liver of some patients who died of AIDS[32], while a second detected HIV-RNA in 9/16 HIV+ participants[49]; the latter study also found evidence of compartmentalization between plasma and liver. In rhesus monkeys

infected with SHIV or SIVmac251, SHIV-RNA can be detected in liver macrophages[50] and SIV protein as well as lentiviral particles can be detected in hepatic Kupffer cells and lymphocytes. A recent study of two patients on suppressive ART, observed ex vivo viral production from highly purified liver Kupffer cells that could be passaged to lymphoblasts[51].

Gastrointestinal Tract

The gut is among the earliest targets of HIV infection and one of the organs with highest numbers of infected cells, even in on-ART individuals. The gut contains a large proportion of the lymphoid tissue (up to 85%) and lymphocytes (up to 90%) in the body[52,53]. Primary gut mucosal CD4+T cells show increased susceptibility to in vitro infection with HIV[54,55] and support higher levels of viral replication[55,56] attributed to greater CCR5 expression[54,56] and T cell activation[54].

In ART-suppressed patients, HIV-DNA and RNA have been detected in gut CD4+T cells and non-CD4+T cells[10,57,58], including CD13+ myeloid cells[11]; HIV-DNA and p24 have also been detected in duodenal macrophages[59]. Another study found that early initiation of ART resulted in comparable reduction in HIV-RNA in blood and rectum at 6 months[60]. Poles et al showed that HIV-RNA and DNA levels in rectal biopsies appeared stable over one year of ART with gut HIV-DNA+ cells twice that in blood[61]. Chun et al reported that HIV-DNA levels per million CD4+T cells were on average 5-6 times higher in the ileum compared to blood in patients on up to 10 years of ART[62]. A subsequent study of four different regions of the gastrointestinal tract determined that levels of HIV-DNA and unspliced HIV-RNA per infected CD4+ T cell were higher (up to 12 fold) in all four gut sites compared to blood (Figure 1); differences in average transcription and the relation to immune activation suggested that different mechanisms control HIV persistence in blood and gut[63]. Based on the average level of HIV-DNA across the four gut sites, this study estimated that the gut harbors 1.2×10^9 infected CD4+ T cells reflecting 83-95% of all HIV-infected cells in the body. Another study of 1-2 drug ART intensification suggested that the ileum, but not blood or other gut sites, might be a site of ongoing replication in some patients on ART[4]. Finally, a recent study of RT-SHIV-infected, ART-suppressed macaques showed that gut tissues had the highest levels of multiply-spliced HIV-RNA and the ratio of multiply-spliced to Gag RNA, while Gag RNA tended to be highest in the mesenteric lymph nodes[48]. Some investigators have reported decreased penetration of certain antiretrovirals into some sites in gut[29], and both evidence for[64-66] and against[62,67,68] compartmentalization between virus in the gut and blood have been described.

Nervous System

Neurologic impairment is a long-recognized complication of HIV infection[69] and infectious HIV can be cultured from cerebrospinal fluid (CSF) and brains of HIV +persons[70,71]. HIV infects several cell types in the brain and nervous system, and multiple studies also suggest compartmentalized CNS virus[72-79]. In vitro infection of astrocytes[80,81] and fetal neural cells[82] and productive infection of fetal glial cells[83], human brain microglia[84], and human brain capillary endothelial cells[85] have each been

demonstrated. Both nonproductive[86], and (transiently) productive infection of astrocytes and astroglial cells have been described including transient productive infection followed by viral latency that is reversible[81]. ARVs penetrate the CNS to different degrees and efforts have been made to categorize ARVs according to CNS activity[87].

HIV-DNA and RNA have also been detected in the brain of ART-treated individuals primarily localized to perivascular macrophages and microglial cells and occasionally to astrocytes. Several studies found that ART reduces CSF HIV-RNA to or near the limit of detection for most patients, although viral decay in CSF was slower than that in plasma in some cases[88,89]. However, HIV-RNA has been detected in the CSF of patients on suppressive ART[90-92], and both HIV-DNA[93] and HIV-RNA[91,94] have been detected in brain tissue obtained at autopsy from individuals on ART although whether these individuals remained on ARVs at the time of death cannot always be confirmed. In two of these studies, viruses from brain[93] and CSF[92] contained drug resistance mutations not found in the blood, further suggesting compartmentalization in the nervous system. Finally, HIV persistence in the brain is suggested by several small case series of patients presenting with new neurologic symptoms (including encephalitis) associated with rebound of CSF virus despite up to 8 years of suppressive ART[95,96].

Lung

HIV-DNA and RNA have been detected in lung cells from both untreated and on-ART individuals, and limited evidence suggests compartmentalization from blood. In untreated individuals, HIV has been detected in lung CD8+T cells[97] and macrophages obtained by bronchoalveolar lavage [98], and infection of alveolar macrophages is associated with impaired phagocytic function[12,99]. In one autopsy study of AIDS patients, HIV-DNA was detected in the lung tissues and Env sequences showed compartmentalization from blood[32]. HIV-DNA and RNA have also been detected in alveolar macrophages from some ART-treated patients[12].

Kidney and Urine

HIV-infected cells can be found in the kidney, and limited evidence suggests compartmentalization as well as persistence on ART. HIV-DNA Env sequences from infected renal epithelial cells showed clustering from viral sequences in the blood[100], and in one case, HIV-RNA was detected in tubular epithelial cells and glomerular podocytes after 3 months of suppressive ART[101]. In another study, HIV-DNA was detected in the urine of 23% of aviremic on-ART patients[102]. Finally, HIV nucleic acids and viral particles were detected in podocytes and tubular cells of renal biopsies of 19 post-renal transplant ARV-treated patients, and HIV-DNA and RNA were detected in the urine[103].

Male Reproductive Tract

HIV has been reported to infect a variety of cell-types in the male reproductive tract[104-112], and some but not all studies suggest viral compartmentalization. HIV antibody levels are lower in semen compared to blood[113], and testicular SIV-specific

CD8+ T cells have reduced cytokine responses to mitogens[114], compatible with testis as an immune-privileged site.

In humans and primates on suppressive ART, several studies have demonstrated that HIV and/or SIV can occasionally be detected in genital tissues and secretions. HIV-RNA can be detected in the semen in 2-48% of on-ART, aviremic men[115-119], sometimes in association with drug resistance mutations[115]. Similarly, a subset of ART-treated, SIV-infected macaques continued to shed SIV in semen despite suppression in the plasma[120] with greater reduction of SIV-RNA in prostate and vas deferens, smaller decreases in epididymis and seminal vesicle but no change in urethra due to SIV+ macrophages. Multiple studies implicate a local source of seminal plasma virus showing compartmentalization from blood[32,121-123], suggesting a distinct reservoir. In contrast, one study in macaques showed that SIV-RNA sequences were evenly distributed among blood, LN, and genital tract[124].

Female Reproductive Tract

HIV can be detected in female cervical cells[125] and genital secretions[126] of most untreated patients. In addition, HIV can be detected in genital secretions of 8-87.5%women on suppressive ART[126-130], suggesting that some women may have a separate reservoir of HIV in the genital tract, perhaps due to reduced penetration of some antiretrovirals[131,132]. Compartmentalization of viral populations between blood and female genital organs has also been reported[133-137].

Skin and Adipose Tissue

In untreated HIV+ individuals, spliced HIV-RNA[138], HIV antigens, and viral particles[139] have been detected in epidermal Langerhans cells, though one study found equivocal evidence for HIV in these cells[140]. HIV-DNA has been detected in the epidermis[141] and dermis, and virus has been cultured from skin[139]. Recent studies also detected HIV/SIV-DNA/RNA in CD4+T cells from adipose tissue of ART-treated individuals and[142,143] with consequences for inflammation.

Conclusions

The persistence of virus or viral remnants in nearly all tissues studied (Table 1)[144] has important implications for viral pathogenesis and for cure. Given the diversity of cell types and anatomic environments where HIV reservoirs simultaneously persist, it is questionable whether single interventions and modalities will suffice to eliminate all possible viral reservoirs. Available data still support attempts to target latently-infected, resting memory CD4+ T cells but additional strategies may be needed to address specific cell types such as T_{fh} and macrophages found in tissues. Key too for the accurate assessment of curative interventions are better approaches to sample accessible tissue reservoirs complemented by NHP and other animal studies that permit more comprehensive analyses. The availability of biomarkers, for example measures of virus-specific antibody titers, as an indirect measure of whole body levels of residual virus [145,146] or novel in vivo imaging to assess anatomic

reservoirs deserve continued development [2,147]. Consideration of both ARV and latency reversing drug delivery to different anatomic sites should be a priority. Finally, we remain ignorant about how specific tissue reservoirs in the body contribute to immunopathology and non-AIDS morbidity. Better ways to assess the activity (intermittent production of RNA, antigen or virus; low level residual replication) and the local immune and inflammatory responses to the presence of viral products are needed so that measures to reduce residual viral burden and virus activity [148,149] can be pursued in parallel with strategies aimed at eradication.

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Key Points

- In patients on ART without detectable plasma viremia, HIV infected cells can still be found in nearly all tissues but particularly in central and mucosal lymphoid tissues.
- CD4+ T cell subsets that comprise HIV reservoirs in persons on ART differ in their distribution at different anatomic sites with particularly high contributions of central and transitional memory cells in blood, effector memory in GALT
- While each major maturation subset of CD4+ T cells contributes to the reservoir of HIV DNA+ cells in lymph nodes, a subset of central memory cells, the T follicular helper cell expresses much higher levels of HIV RNA and may have particular importance in viral persistence
- Some tissues, including some gut sites and lymph node regions where infected cell frequencies seem to be highest, have recently been noted to be associated with limited ARV penetration
- Non-CD4+ T cell types that harbor HIV DNA including macrophages, microglial cells and astrocytes, though far fewer in number, persist in a variety of organs and tissues and are important because they may require different approaches to purge and for their potential contribution to local immunopathology.

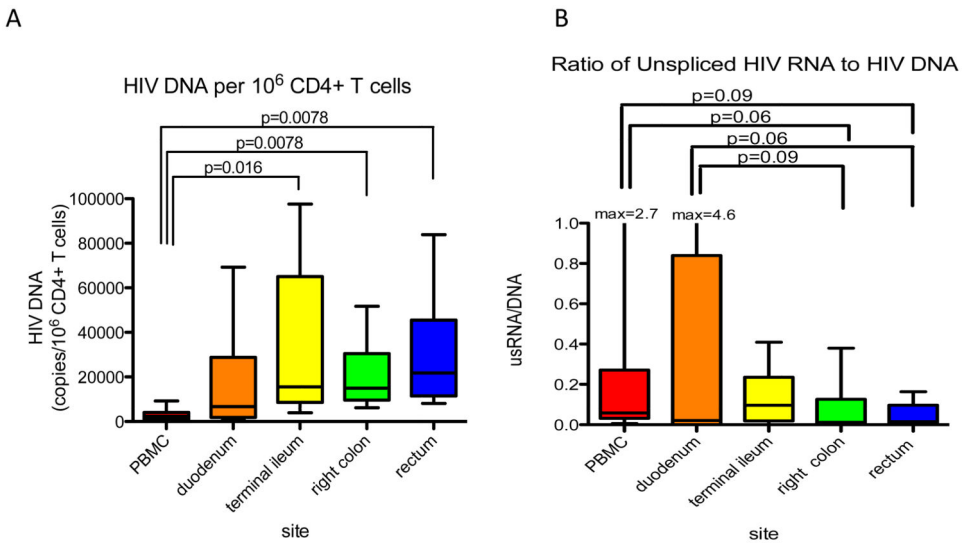

Figure 1.

A) HIV DNA copies per million CD4 cells present in blood or different gut sites from 8 patients on ART with undetectable plasma virus. B) Ratio of HIV RNA (unspliced, genomic) to HIV DNA providing measures of HIV expression per average infected cell. Horizontal bars = medians; whiskers show standard deviations. Adapted from Yukl et al JID 2010[61]

Table 1

Tissues with detectable HIV or SIV during ART with suppression of plasma virus

Tissue	HIV-DNA	HIV-RNA	Protein/Antigen	Virus (EM)	Infectious Virus	Compartmentalization from blood
Lymph nodes	X	X	X		X	Some but not all studies
Spleen	X (SHIV, SIV)	X (SHIV, SIV)				No
Bone marrow	X					
Thymus		+/- (1 of 6 SHIV-infected macaques)				Some evidence
Liver	X (macrophages)				X	Yes (one study)
Gut	X	X	X (macrophages)			Some but not other studies
Nervous system	X	X (brain, CSF)				Yes (multiple reports)
Lung	X	X				Yes (one study)
Heart						
Kidney	X	X (3mo ART)		X		Yes (one study)
Male reproductive tract	X (SIV)	X (SIV; human genital secretions)				Most but not all studies
Female reproductive tract	X (genital secretions)	X (genital secretions)				Most but not all studies
Placenta	X (mast cells)				X (mast cells)	
Breast and breast milk	X	X	X			No
Skin						
Adipose tissue	X	X				

Adapted from Yukl S and Wong J, Anatomic compartments as a barrier to HIV cure, 2015 [143]