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Review Article

HIV Latency and Distinct Anatomical Reservoirs: A Systemic Review

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ABSTRACT

Although the HAART (Highly Active Antiretroviral Therapy) a triple form of drugs has exponentially enhanced the CD4+ T immune cell count in HIV-1 infected patients and has improved the expectancy of many HIV-1 infected patients' life. The drug results have also contributed to bringing the plasma virus load up to a clinically undetectable level in HIV-1 infected patients for several years. However, with these drug interventions, complete eradication or treatment of the virus is hard to achieve. The primary obstacle that has been raised is the persistence of ongoing viral replication inside the host CD4+ T immune cells. These infected immune cells can be transformed into the latent stage (transcriptionally silent) for many years and hardly be targeted by the current HAART-based interventions. Besides this incredible specialty of the HIV-1 virus, it can also simply hide in diverse anatomical reservoirs having immune cells at separated locations. The presence of these locations easily facilitates the virus to escape from the host immune surveillance and also contributes to low viral production in patients on antiretroviral therapy. As a result, we review our current knowledge to provide a better understanding of multifactorial mechanisms during the establishment of HIV-1 latency with numerous experimental studies that strongly uphold the ongoing viral replication and persistence at the distinct anatomical reservoirs.

Keywords: HIV-1; Latency; Reservoirs; HAART

INTRODUCTION

Acquired Immune Deficiency Syndrome (AIDS) the deadliest stage of HIV-1 infection (Human Immunodeficiency Virus) caused by two species of lentiviruses groups (HIV-1 and HIV-2) [1]. These lentiviruses (LV) are belonging to the Retroviridae family and were initially identified in the year 1981 [1]. As per UNAIDS 2020, it is one of the major and the most serious public health concern for many countries and territories all across the globe [2]. Although the majority of the common cases came from the Low Middle-Income Countries (LMIC) with a high effecting rate of more than >75 million peoples. A recent estimation by the World Health Organization (WHO) showed that during the past three decades over 32 million infected peoples have died globally and the numbers are rising very rapidly. Other findings from UNAIDS 2019 showed that more than >38 million peoples were active with HIV, and most of them were group age between (15-49) years [3]. Despite the HAART based therapy has substantially emerged to control the viremia count up to an undetectable level (<50 copies/ml) in plasma for a very long period and has seen improvement in the CD4+ T cell level which further helps the expectation of an HIV-1 infected patient to live a normal life [4]. Since the HIV-1 virus targets the immune cells especially Helper CD4+ T cells of the host residing at various tissue locations. Only a few of these CD4+ T cells revert back and become memory cells called to be transcriptionally silent for a long duration of time, which are termed to be non-permissive for viral gene expression. As per the American Journal of virology (AJI), only ~1 per million CD4+ T cells which is a very limited number of resting CD4+ T cells turned out into a latent reservoir. These viruses' highjack the host immune cells at the host molecular level and make them their reservoirs for further replication. It is key to note that the establishment of the latent stage of the virus occurs during the preliminary weeks of early infection (an acute phase) and becomes fully functional after interrupting the ART or HAART therapy within a few weeks. We undertook a review on this molecular concept in transcriptional latency and different studies from numerous clinical experiments strongly uphold the ongoing viral replication at the distinct anatomical sides.

HIV LATENCY

The latency can de well-defined as a non-reproductive stage of HIV-1 infection in individual cells. Latently infected immune cells do not yield any viral particles but have the capability to do so [5]. It is a multifactorial mechanism that involves many complex processes that restricts the host cellular environment for viral replication. Even though the process that leads to HIV-1 establishment in resting CD4+ T cells it is still a highly controversial topic in the scientific fields to understand the concept of latency. Evidence suggested that HIV-1 latency can be classified into two parts depending upon the integration of HIV-1 virus into the host cell

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genome or not. Pre-integration and post-integration latency. Pre-integration latency refers to the partial or complete blockage of the viral life cycle at steps-initial to the integration of the virus into the host cellular genome (incomplete integration and incomplete reverse transcription) [6]. These unintegrated or non-integrated linear persist in the cytoplasmic with a half-life of approximately 1-6 days [7]. However, due to the instability of the pre-integration complex, these are no further clinically important as post-integration latency which involved the major mechanisms by which HIV-1 established for latency like Transcriptional Interferences, insufficient availability of host transcriptional factors enzymes such as (NF-KappaB and NFAT), Chromatin organization and epigenetic modifications causing suppression in HIV-1 expression, insufficient Tat gene activity promoting a high level of transcription activity, Blocks to mRNA splicing or nuclear export, Post-transcriptional mechanisms, and cellular mRNAs.

MOLECULAR MECHANISM OF POSTTRANSCRIPTIONAL HIV LATENCY

Transcriptional interferences

The HIV-1 latency mostly occurs at the post-transcriptional level, where HIV-1 proviral DNA integrates into the region of host cell chromosomal region that is actively transcribed into latent resting CD4+ T cells in HIV-1 infected patients currently on HAART regimen or in infected cell line model [8]. The findings from the interaction of the viral Pre-Integration Complex (PIC) with the active gene site of the host factor suggest that the Transcriptional Interferences (TI) may help as a potential driver for the establishment of latency by maintaining the transcriptionally silencing process of integrated HIV-1 provirus [9]. Viral replication from these proviruses related to the host gene can suffer intense TI due to convergently orientation of the HIV-1 proviruses or their close proximity to a stronger host cell gene promotor [10]. Using the Jurkat cell-based *in vitro* latency models has revealed the occurrence of integration with the host cell, and ongoing transcription from a host promotor which would prevent the Pre-Initiation Complex (PIC) assembly on the 5' Long Term Repeated (LTR), thus subsequently interfering with the viral transcription mechanism [11,12]. Importantly transcriptional interferences act as the suppressive influence of one transcriptional process that occurs in most of the genomes and has the best possibility to be evolved during the time and persistence in regulating gene expression [13]. This mechanism of transcriptional interferences may suggest as one of the important factors to enforce the HIV-1 latency in the primary cell line model, even though orientation preference was not observed persistently in acutely infected cells of the host gene [14].

Limited availability of transcriptional activators level (NF-kappaB and NFAT) factors

The importance of insufficient availability of host transcriptional activators factors such as NF-KappaB (Nuclear Factor Kappa Light Enhancer) or NFAT (Nuclear Factor of Activated T Cell) can strongly influence the cause of HIV-1 latency. Both the factors NF-KappaB (p50 and p65 heterodimer) and NFAT are sequestered in the cytoplasmic region with lacking the initial unstimulated signals, partially because of protein Murr1 on account of NF-kappaB1 [15]. The presence of Murr1 protein here in HIV-infected T cells inhibits the HIV-1 viral replication up to a certain level in resting CD4+ lymphocytes [16]. The 5′ LTR promotor of the HIV-1 region has multiple DNA binding sites to activate the various host cells transcriptional factor such as (SP1, AP-1, NF-kappaB, and NFAT) via binding sites to an array of DNA cis-regulatory elements which further initiates the binding of RNA pol II for enhancing transcriptional process [17]. The absence or below the threshold level of NF-kappaB factor strongly repeal the latency establishment, one hypothesis study on Jurkat cell treated with PMA (Phorbol Myristate Acetate) or prostratin (known to activates HIV expression by the host factor activity NF-KappaB) strongly repealed the establishment of latency in the infected cell [18]. Although the Sp1 and kB sites (NF-kappaB) also increase the viral replication to a distinct variation while having mutations at the binding site of Sp1 and kB of the 5' LTR can reduce the gene expression of HIV-1 by causing viral latency [19]. Other evidence suggests that the Activator Protein 1 (AP-1) binding site has the potential in regulating the establishment of HIV-1 latency. Deletion of this AP-1 site could deprive the latency in HIV-1 infection, additionally, the extension of this region from 4 nucleotide to 7 nucleotide of AP-1 has also increased the establishment of latency event, suggesting that the minimal mutations at the AP-1 binding site could possibly alter the establishment of HIV-1 latency via promoter [20].

Chromatin organization and epigenetic modifications

One significant mechanism for continuing the latent stage is the involvement of the epigenetic modification in the chromatin which suppresses the HIV-1 gene expression [21]. The chromatin structure is dynamic and has extreme control over regulating the gene expression of the host transcriptional process inside the cell [22]. The infected J-Lat cell model revealed the HIV-1 integrating sites of heterochromatin impairs the expression factor as a consequence results in latent infection [23]. The function of chromatin Histone Acetyltransferase (HAT) and hypoacetylation of Histone Deacetylase (HDACs) has also significant regulation towards the HIV-1 gene expression. However, HDACs can also competent to repressing the undergoing activity of transcriptional factors by signaling pathways [24]. The transcriptional factor protein CTIP2 recruits the HDAC1 and HDAC2 additionally plays an important role in the repression of chromatin at the HIV-1 LTR region site leads to induced HIV-1 latency, further, the removal of HDAC1 or HDAC2 enzymes had no impact on HIV-1 transcription [25]. Other findings on the expression of YY1 (ubiquitous transcription factor Yin Yang 1) and LSF (Late SV40 factor) found that histone acetylation may be causing an inhibition effect on HIV-1 transcription and induces viral production [26]. Another *in vitro* study found that HDACs may play a role in enforcing the HIV-1 latency, although treating with an inhibitor like Valproic Acid (VPA) has seen less effecting in HIV-1 expression [27]. *In vivo* prolong treatment with VPA showed no effect on HIV latency [28]. Similarly, DNA methylation is likewise also one of several key epigenetic mechanisms which mostly help in suppressing the gene expression of HIV-1 associated with transcriptional repression. However, DNA CpG methylation showed alterations and triggering dysregulation at the binding site of the HIV promoter region [29]. Meanwhile other evidence also strongly suggested that DNA methylation may be tempted away from evaluation, considering it to play no more importance in transcriptional control over HIV-1 expression and promoting latency [30].

Insufficient TAT expression

Tat an important factor for inducing a high level of transcription activity at the 5' LTR promoter region when available in sufficient quantities. The TAT gene expression cooperates with NFAT protein additionally with AP-1 protein to transactivate the HIV-1 expression

in the Jurkat cell line [31]. Also, insufficient or absence of TAT transactivation activity can easily suppress the viral transcription contributes to the establishment of latency inside the CD4+ T cell model [32]. One finding suggested that naturally occurring TAT mutations can influence the transactivation property by almost 40% during the course of HIV-1 infection in the Jurkat cell model [32,33]. Furthermore, strong stochastic fluctuation in TAT may also influence the viral latency [34]. Although treating with TAT inhibitor like didehydro-cortistatin A (dCA) combined with ART can block the transcriptional reactivation by lowering down the viral replication in latently infected CD4+ T cells *in vivo* resulted in the replenishment of the latent reservoir [35]. Based on these results context the TAT inhibitor (dCA) reduces the viral residual size and contributes to a state of persistent latency.

Posttranscriptional mechanisms and cellular miRNAs

The posttranscriptional mechanism of HIV-1 replication is precisely controlled by both the viral and host factors level. The establishment of latency at the post-transcriptional stage is due to the blockage of viral mRNAs export or by inhibiting the HIV-1 translational initiation. These cellular miRNAs are single standard non-coding oligoribonucleotides are approximately (19-25) nucleotides long in size derived from the RNA polymerase II (pol II) transcript assist in the progression of transcriptional regulation in viral infection [36]. Furthermore, these cellular microRNAs like miR-28, miR-125b, miR-150, miR-223, and miR-382 also contribute and are equally involved in maintaining the latency inside the primary resting CD4+ T cells [37]. Importantly in these primary resting CD4+ T cells, the overall expression of miR-225 and miR-150 is much higher than the activated CD+4 T cells, with the help of these expressions they target the multiply spliced or unspliced viral RNA excluding the Nef encoding mRNA may promote the key factor to post-integrated latency of primary resting CD4+ T cells [38]. *In vitro*, the repressive effect of both Dicer and Drosha in infected U1 cells has also been observed with a high threshold to regulate the silencing miRNAs machinery which resulted in effectively lowering the expression of HIV-1 replication [39]. Since Dicer and Drosha complexes are also very much important necessities for the miRNAs biogenesis machinery, knockdown of these two complexes enhances the production of HIV-1 infection [40]. Together these significant findings strongly uphold the cellular miRNAs may promoting to posttranscriptional blockage and has contributed to viral latency [41].

The central nervous system

The Central Nervous System (CNS) is the best-hidden place for the HIV-1 virus, passage occurs through the brain perivascular residing macrophages, microglial cells, and astrocyte cells [42-44]. Although astrocyte is the major targeted cell type for infection in the CNS recorded the most noticeably infected cell type with having 10%(-20% of HIV-1 DNA inside the cell genome [45]. The cells are hidden inside the CNS by two special boundaries: the Blood-Brain Barrier (BBB) and blood-Cerebrospinal Fluid (CSF), the BBB is relatively similar to blood-Cerebrospinal Fluid barriers [46]. These barriers are highly semipermeable to avoid unnecessary solutes particles or molecules, with having a tight junction of endothelial cells in the brain capillaries restricting the passage of undesirable solutes [47]. The HIV-1 virus infects the brain in the acute stage of infection and became adapted to the brain condition further contributing to contaminate the brain cells and cause-specific mutation in almost all genes of the virus resulting in a High Group of Neurocognitive Disorders (HAND) which comprises of several opportunistic infections like Mild Neurocognitive Impairment (MNI) and Mild Neurocognitive Disorder (MND) to a high group of HIV-1 Associated Dementia (HAD) [48,49]. A recent study was done by Fluorescence In Situ Hybridization (FISH) technique to detect HIV-1 virus in the anatomical area simply found the host-specific mRNAs by amplifying the viral mRNA from the infected cell [50]. Another *in vitro* finding showed that this HIV-1 initially arrives in the CNS system via infected monocyte, or by infected lymphocyte cells by the "Trojan horse hypothesis" model [51,52]. Due to these two barriers, it is impossible to target the highly evolved retrovirus with HAART drugs also the complete eradication is hard to achieve when it comes to latent HIV inside the brain residing cells, still slow rate of viral replication can be easily noticed in the latent stage [53,54]. Particularly these brain-living cells only permit a limited number of hydrophobic molecules by passive diffusion, even to cross these barriers special transport proteins are required while checking in [55]. The current therapeutic intervention like HAART has poor penetration capability to diffuse inside these anatomical compartments, importantly new researches and studies are underway based on nanoparticle encapsulate drugs having the capabilities to penetrate these special barriers. Also, these barriers are selectively permeable just for those molecules which are essential for neural function. Targeting these infected regions with Proteases Inhibitor (PI) drugs potentially results in a high increase of proteases concentration outside the BBB barrier.

Peripheral Lymphoid Tissue Reservoir (LTR)

Lymphoid Tissue (LT) a special reservoir like other different tissue reservoirs for HIV infection [56]. These viruses efficiently infect the Dendritic cell, monocyte, or macrophages, and further lymph nodes through afferent lymphatics results in infected CD4+ T lymphocytes [57]. Even the Follicular Dendritic Cells (FDCs) inside lymph nodes have seen likely to retain HIV-1 for a long course of duration [58]. The ability to serves as classical Antigen Presenting Cells (APCs), these cells easily bind with antigen on their cell surface throw Pattern Recognition Molecular Pattern (PAMP) getting inside the LT allowing the activation of T cell interaction through CD28 and B7 which led the stimulation of T cell activation [59]. Many cells here like (T-lymphocyte, Follicular dendritic cells, macrophages) can transmit viral fusion throw cell to cell interaction via viral transmission possibly can infect its large cell population, *in vitro* study on the cell-to-cell transmission on HIV-1 showed that T lymphocyte has the enormous ability for the infection that could be 100-1000 overlays higher than the normal cell-free viral particle [60]. Additionally, FDCs cells have been also seen very much affected by the HIV-1 viral pool during the acute stage of progression since primarily HIV-1 targets the Helper CD4+ T cell these infected cells further migrate from lymphoreticular tissue and likely to affect FDCs cells functions ahead [61,62]. Other findings done by PCR in situ methods showed the presence of HIV DNA in 25% CD4 lymphocyte present inside interstitial spaces of the germinal center in lymph nodes, however, the greatest number of these CD4+ cells can acquire latent stage during the acute phase of infection [61-64]. During the latent stage, there is still ongoing progressing viral replication that can be observed in peripheral tissues and peripheral blood. In contrast, the current ongoing drugs like Nucleotide Reverse Transcriptase Inhibitors (NRTIs), Protease Inhibitors (PI), or Non-Nucleotide Reverse Transcriptase Inhibitors (NNRTIs), results in bringing a reduction of HIV viral replication in the majority of patients in these peripheral lymphoid tissue regions [65].

Gastrointestinal tract

The Gastrointestinal (GI) tract mucosa is a unique anatomical reservoir site for HIV-1 infection where the virus can easily reside for prolong duration in GI mucosal cells and can be undetectable from mucosal immune response [66]. The (GI) tract mucosa tissues are not the only primary target for HIV but also for Simian Immunodeficiency Virus (SIV) (in Rhesus macaques) and a prominent site for viral transmission and viral replication, regardless of parenteral route transmission [67]. Due to the high susceptibility of (GI) mucosa, it shows phenotypic contrasts and expression of chemokines receptors like CCR5 (CD195) on mucosal mononuclear cells (MMCs) and CXCR4 (CD184) on Peripheral Blood Mononuclear Cells (PBMCs) can efficiently allow the infection in the freshly CD4 T cell for viral replication and dissemination [68]. Numerous studies were done on mucosal and peripheral CD4 T cell to understand the compartmental differences in co-receptor expression of CD4 lymphocyte showed the similar CXCR4 expression on both CD4 T cells (Mucosal and peripheral) compartments, yet the expression of CCR5 on intestinal mucosa is much higher than the PMNCs cells, follow-on intensified viral replication by both R5 and X4 tropic viruses [69]. It has been estimated that both SIV/acute HIV dramatic loss for mucosal CD4 T memory cell for up to 60% all over the body and can be seen in the initial phase of infection [70]. Although excluding CD4 T lymphocyte, gut-associated macrophages (lamina propria) also can persist as a reservoir unlike the other differential tissues macrophages, other experimental findings showed a detectable level of HIV DNA not HIV RNA during HAART therapy [71]. Further, with significantly less expression of CD4/CDR5 on gut macrophages as like in other cells (MMCs and PBMCs), it is possible that the virus enters by a process called endocytosis or blood-derived monocyte migrates into macrophage residing in the mucosal region of the GI tract, in contrast, these tissues residing macrophages are extremely durable and can be easily persisted as a latent reservoir for HIV type-1 infection [72]. Furthermore, to these guts residing macrophages can easily help the virus to resist the cytopathic process for many years. Nonetheless, it is still very debatable in scientists that how these residing macrophages got infected and persist as HIV latency.

Reproductive tract (male reproductive system)

Both men and women locate a wide range for transmission and potential reservoirs for HIV-1 expression because of Sexually Transmitted Diseases (STDs) [73]. However, the primary route of HIV transmission is through (genital fluids, hormone secretion, and genital mucosa), the presence of both activated immune cells (CD4+ T and CD8+ T cells) in the urethral submucosal epithelium zone which increases the possibility of infection [74,75]. Studies *in vivo* had confirmed the establishment of HIV-1 infection in numerous areas of testicular interstitial tissue due to having receptors CD4 on the T-lymphocytes cells and macrophages during the progression of HIV [76]. Another differential study on Seminal Mononuclear Cells (SMC) and sperm has shown the detectable level of HIV viral DNA [77]. Likewise, other possible cells spermatogonia, spermatocytes, and few spermatids could be most likely to be targeted [78]. In contrast, the susceptibility of these cells and regions of mucosal epithelium layers and the cell linings inside the epididymal lumen could also act as a potential reservoir for HIV-1 infection [79-81]. In terms of carrying the viral particles, these infected reservoirs can efficiently be disseminating their viral particle into another area through the blood circulation possibly may contribute to making other anatomical reservoir compartments.

Female reproductive tract

HIV-1 virus can be easily detected in mucosal-associated lymphoid tissue in the female reproductive tract, both the lower and upper reproductive tract regions are abundant in presence of CD4 T cells and the memory cell subsets having co-receptors for HIV-1 just as similar to monocyte and the macrophages are the very susceptible and primarily active site for HIV replication [82,83]. HIV-1 can be also found in genital secretion of infected women during ART therapy HIV-1 shedding is found in most women with a viral count of less than 500 copies/ml of plasma, these findings showed the separated repository of HIV-1 replication might exist in certain women [84]. Other findings have confirmed the poor drug penetration inside these cells or lower dose concentration at the infected regions possibly may help the female reproductive tract as an HIV reservoir and contribute to viral persistence [85].

Lungs

The reservoir can be observed in both infected patient lungs as well untreated which is on antiviral therapy [86]. Due to the presence of massive CD8+ T cells and Alveolar Macrophages (AM) and lymphocytes, it is to believed that the virus can simply highjack these liver immune cells as a viral carrier for HIV-1 infection [87]. During the acute and the latent stage of HIV-1 (AM) has expressed a high expression of cytokine inflammation like TNF-alpha, IL-1, and IL-6 may assist in the viral reservoirs [88]. Nonetheless, the acceptable level of HIV viral load can be easily monitored in Bronchoalveolar Lavage Fluid (BALF) in the lungs [89]. Overall high to low viral count HIV-DNA/RNA can be seen in lungs immune cells which may act as distinct possible reservoirs [90]. Due to these infected immune cells, it is not only making a favorable prolonged environment for the viral persistence but also can lead to damage to the other neighboring healthy immune cells, making it very difficult to function and may cause other opportunistic infections.

Liver

Numerous studies were done on liver tissue like Kupffer Cells (KC), hepatocytes, and macrophages strongly endorse a productive HIV-1 infection and have been confirmed by numerous methods *in vivo* [91]. Findings obtained from a liver sample of 7 infected patients shortly after AIDS death found three of them have detected HIV-1 virus [92]. Another immunohistochemistry study examined on 14 HIV patients throw liver biopsy found expression of p24 antigen on the Kupffer cells, endothelial, and hepatocytes cells additionally with serious lung damage might be related to liver cell apoptosis [93]. The treatment with HAART-based drugs has been found to be mild effective particularly when it comes to parenchymal cells (hepatocytes), which could contribute to the silent reservoir as liver macrophages. Other clinical evidence of HIV-1 reveals the infection in the many cell types of the liver contributing to the production of infected cells with high viral particle release like hepatocyte and Kupffer cells could migrate via blood circulation to another reservoir [94]. During these complex periods of HIV duration, a highly productive synthesis of liver enzyme can be observed like Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), and Alkaline Aminotransferase (ALP) in 60% infected patients at HAART therapy may cause liver dysfunction and could lead to liver fibrosis [95].

Bone marrow

Many subsets of bone marrow cells can be infected and may act as a potent reservoir for HIV. A study done *in vivo* on infected patients CD34+ a cellular marker of HPCs (Hematopoietic Progenitor Cells) expresses both HIV co-receptor and shown potentially high susceptibility for HIV-1 infection [96], along with HPCs, Mast Cell progenitors (prMCs) can occur as the same, the infection in HPCs cells can be processed to either HPCs death or can act as a latent reservoir for prolonged periods HIV persistence [97]. Mast Cell progenitors (prMCs) are also sensitive to M-tropic virus and dual-tropic (R5X4) viruses, not the T-tropic virus however, these infected prMCs cells further became mature within the several tissues, which suggests that they might act latent reservoir [98]. The persistence of these HIV-1 viruses inside these several tissues could be for several months or years on HAART drugs, but still, there is much contradiction that is to be investigated.

Adipose tissues

Due to the massive availability of memory CD4 T cells and macrophages found inside the Adipose Tissue (AT) [99], these cells easily harbor as latent reservoirs. Leukocytes residing in adipose tissue have activated memory CD4+ T cells which resemble like the other tissue reservoirs, *in vivo* findings showed a detectable amount of HIV provirus in Adipose Tissue-Stromal Vascular Fraction (AT-SVF) causes a high decline in the CD4+ T cells count in five infected HIV-1 patients [100]. Importantly, receptors present on the adipocytes cell can also able to permit the HIV-1 virus inside the adipose cells [101]. These adipocytes cells interact with CD4+ T cells and macrophages to boost the immune cell activation and inflammation which might capable to support HIV-1 persistence and viral replication [102]. However, viral replication may differ according to the diverse tissue reservoirs like the peripheral lymphoid tissue where a high density of immune cells is deposited.

CONCLUSION

Overall, the current therapeutic approach HAART drugs have greatly minimized the viral replication but still, a long way of a process which gone take for complete eradication of the HIV-I infection by these current HAART based interventions especially when the virus has acquired the latent stage. The post-integration latency of HIV replication has the best complex mechanism to hide from the host immune system as well as from ART or HAART-based drugs have shown the best capability of adaption system of the HIV-1 virus. At the moment having less understanding of diverse tissue reservoirs indeed its a major obstacle while treating the disease with HAART. Importantly targeting these complex tissue reservoirs with a high dosage of ART or HAART drugs has raised numerous immunological disorders in HIV patients. Unfortunately to live a near-normal life these patients must have to rely on these drugs for a longer period of time.

REFERENCES

1. Sharp PM, Hahn BH. Origins of HIV and the AIDS pandemic. Cold Spring Harb Perspect Med. 2011;1(1):a006841.
2. UNIADS. Start Free Stay Free Aids Free. 2020 Report.
3. GHO. Number of People (All Ages) Living with HIV Estimates by Who Region Data 2020.
4. Zehnacker L, Abe E, Mathez D, Alvarez JC, Leibowitch J, Azoulay S. Plasma and intracellular antiretroviral concentrations in HIV-infected patients under short cycles of antiretroviral therapy. AIDS Res Treat. 2014.
5. Eisele E, Siliciano RF. Redefining the viral reservoirs that prevent HIV-1 eradication. Immunity. 2012; 377-388.
6. Van-Lint C, Bouchat S, Marcello A. HIV-1 transcription and latency: An update 2013. Retrovirol. 2013.
7. Vanhamel J, Bruggemans A, Debyser Z. Establishment of latent HIV-1 reservoirs: What do we really know? J Virus Erad. 2019; 5:3-9.
8. Vatakis DN, Kim S, Kim N, Chow SA, Zack JA. Human immunodeficiency virus integration efficiency and site selection in quiescent CD4+ T cells. J Virol. 2009; 83:6222-6233.
9. Battistini A, Sgarbanti M. HIV-1 latency: An update of molecular mechanisms and therapeutic strategies. Viruses. 2014; 1715-1758.
10. Abbas W, Herbein G. Molecular understanding of HIV-1 latency. Adv Virol. 2012;574967.
11. Burnett JC, Lim KI, Calafi A, Rossi JJ, Schaffer DV, Arkin AP. Combinatorial latency reactivation for HIV-1 subtypes and variants. J Virol. 2010; 5958-5974.
12. Lenasi T, Contreras X, Peterlin BM. Transcriptional interference antagonizes proviral gene expression to promote HIV latency. Cell Host Microbe. 2008;4: 123-133.
13. Shearwin KE, Callen BP, Egan JB. Transcriptional interference–a crash course. Trends Genet. 2005;21: 339-345.
14. Shan L, Yang HC, Rabi SA. Influence of host gene transcription level and orientation on HIV-1 latency in a primary-cell model. J Virol. 2011;85: 5384-5393.
15. Donahue DA, Wainberg MA. Cellular and molecular mechanisms involved in the establishment of HIV-1 latency. Retrovirol. 2013; 10-11.
16. Ganesh L, Burstein E, Guha-Niyogi A. The gene product Murr1 restricts HIV-1 replication in resting CD4+ lymphocytes. Nature. 426; 853-857.
17. Roebuck KA, Saifuddin M. Regulation of HIV-1 transcription. Gene Expr. 1999; 67-84.
18. Duverger A, Jones J, May J. Determinants of the establishment of human immunodeficiency virus type 1 latency. J Virol. 2009;83: 3078-3093.
19. Burnett JC, Miller-Jensen K, Shah PS, Arkin AP, Schaffer DV. Control of stochastic gene expression by host factors at the HIV promoter. PLoS Pathog. 2009; 5(1): e1000260.
20. Duverger A, Wolschendorf F, Zhang M. An AP-1 binding site in the enhancer/core element of the HIV-1 promoter controls the ability of HIV-1 to establish latent infection. J Virol. 2013;87: 2264-2277.
21. Siliciano RF, Greene WC. HIV latency. Cold Spring Harb Perspect Med. 2011;1(1).
22. Felsenfeld G, Groudine M. Controlling the double helix. Nature. 2003; 448-453.
23. Jordan A, Bisgrove D, Verdin E. HIV reproducibly establishes a latent infection after acute infection of T cells *in vitro*. EMBO J. 2003;22: 1868-1877.
24. Legube G, Trouche D. Regulating histone acetyltransferases and deacetylases. EMBO Rep. 2003;4: 944-947.
25. Marban C, Suzanne S, Dequiedt F. Recruitment of chromatin-modifying enzymes by CTIP2 promotes HIV-1 transcriptional silencing. EMBO J. 2007;26: 412-423.

26. Romerio F, Gabriel MN, Margolis DM. Repression of human immunodeficiency virus type 1 through the novel cooperation of human factors YY1 and LSF. J Virol. 1997; 9375-9382.

27. Matalon S, Rasmussen TA, Dinarello CA. Histone deacetylase inhibitors for purging HIV-1 from the latent reservoir. Mol Med. 2011;17: 466-472.

28. Sagot-Lerolle N, Lamine A, Chaix ML. Prolonged valproic acid treatment does not reduce the size of latent HIV reservoir. AIDS. 2008;22: 1125-1129.

29. Zhang X, Justice AC, Hu Y. Epigenome-wide differential DNA methylation between HIV-infected and uninfected individuals. Epigenetics. 2016;11: 750-760.

30. LaMere SA, Chaillon A, Huynh C, Smith DM, Gianella S. Challenges in quantifying cytosine methylation in the hiv provirus. mBio. 2019;10(1).

31. Hidalgo-Estévez AM, González E, Punzón C, Fresno M. Human immunodeficiency virus type 1 Tat increases cooperation between AP-1 and NFAT transcription factors in T cells. J Gen Virol. 2006; 1603-1612.

32. Kamori D, Ueno T. HIV-1 tat and viral latency: What we can learn from naturally occurring sequence variations. Front Microbiol. 2017; 8:80.

33. Donahue DA, Kuhl BD, Sloan RD, Wainberg MA. The viral protein tat can inhibit the establishment of HIV-1 latency. J Virol. 2012;86: 3253-3263.

34. Weinberger LS, Burnett JC, Toettcher JE, Arkin AP, Schaffer DV. Stochastic gene expression in a lentiviral positive-feedback loop: HIV-1 Tat fluctuations drive phenotypic diversity. Cell. 2005;122: 169-182.

35. Mousseau G, Kessing CF, Fromentin R, Trautmann L, Chomont N, Valente ST. The tat inhibitor didehydro-cortistatin a prevents hiv-1 reactivation from latency. mBio. 2015;6.

36. Houzet L, Yeung ML, de Lame V, Desai D, Smith SM, Jeang KT. MicroRNA profile changes in human immunodeficiency virus type 1 (HIV-1) seropositive individuals. Retrovirol. 2008;5: 118.

37. Han Y, Siliciano RF. Keeping quiet: MicroRNAs in HIV-1 latency. Nat Med. 2007;13: 1138-1140.

38. Huang J, Wang F, Argyris E. Cellular microRNAs contribute to HIV-1 latency in resting primary CD4+ T lymphocytes. Nat Med. 2007;1241-1247.

39. Triboulet R, Mari B, Lin YL. Suppression of microRNA-silencing pathway by HIV-1 during virus replication. Sci. 2007; 1579-1582.

40. Nathans R, Chu CY, Serquina AK, Lu CC, Cao H, Rana TM. Cellular microRNA and P bodies modulate host-HIV-1 interactions. Mol Cell. 2009;34: 696-709.

41. Sarracino A, Gharu L, Kula A. Posttranscriptional regulation of HIV-1 gene expression during replication and reactivation from latency by nuclear matrix protein MATR3. mBio. 2018;9.

42. Navia BA, Jordan BD, Price RW. The AIDS dementia complex: I clinical features. Ann Neurol. 1986; 517-524.

43. Kure K, Weidenheim KM, Lyman WD, Dickson DW. Morphology and distribution of HIV-1 gp41-positive microglia in subacute AIDS encephalitis: Pattern of involvement resembling a multisystem degeneration. Acta Neuropathol. 1990;80: 393-400.

44. Li GH, Henderson L, Nath A. Astrocytes as an HIV reservoir: Mechanism of HIV infection. Curr HIV Res. 2016;14: 373-381.

45. Churchill MJ, Wesselingh SL, Cowley D. Extensive astrocyte infection is prominent in human immunodeficiency virus-associated dementia. Ann Neurol. 2009;66: 253-258.

46. Redzic Z. Molecular biology of the blood-brain and the blood-cerebrospinal fluid barriers: Similarities and differences. Fluids Barriers CNS. 2011;8: 1.

47. Daneman R, Prat A. The blood-brain barrier. Cold Spring Harb Perspect Biol. 2015.

48. Churchill M, Nath A. Where does HIV hide? A focus on the central nervous system. Curr Opin HIV AIDS. 2013;8: 165-169.

49. Clifford DB, Ances BM. HIV-associated neurocognitive disorder. Lancet Infect Dis. 2013; 976-986.

50. Gray LR, Roche M, Flynn JK, Wesselingh SL, Gorry PR, Churchill MJ. Is the central nervous system a reservoir of HIV-1? Curr Opin HIV AIDS. 2014; 552-558.

51. Ene L. Human immunodeficiency virus in the brain-culprit or facilitator? Infect Dis. 2018;11: 117863371775268.

52. Kramer-Hämmerle S, Rothenaigner I, Wolff H, Bell JE, Brack-Werner R. Cells of the central nervous system as targets and reservoirs of the human immunodeficiency virus. Virus Res. 2005;11: 194-213.

53. Andrews SM, Rowland-Jones S. Recent advances in understanding HIV evolution. F1000Res. 2017;6: 597.

54. Letendre SL, Ellis RJ, Ances BM, McCutchan JA. Neurologic complications of HIV disease and their treatment. Top HIV Med. 2010; 45-55.

55. Obermeier B, Daneman R, Ransohoff RM. Development, maintenance and disruption of the blood-brain barrier. Nat Med. 2013;19: 1584-1596.

56. Leyre L, Kroon E, Vandergeeten C. Abundant HIV-infected cells in blood and tissues are rapidly cleared upon ART initiation during acute HIV infection. Sci Transl Med. 2020;12: 3491.

57. Alvarez D, Vollmann EH, von-Andrian UH. Mechanisms and consequences of dendritic cell migration. Immunity. 2008;29: 325-342.

58. Dave RS, Jain P, Byrareddy SN. Follicular dendritic cells of lymph nodes as human immunodeficiency virus/simian immunodeficiency virus reservoirs and insights on cervical lymph node. Front Immunol. 2018;9.

59. Zhang YQ, Joost RJ, van Gool SW, Coorevits L, de Boer M, Ceuppens JL. B7-CD28 interaction is a late acting co-stimulatory signal for human T cell responses. Int Immunol. 1997; 1095-1102.

60. Bracq L, Xie M, Benichou S, Bouchet J. Mechanisms for cell-to-cell transmission of HIV-1. Front Immunol. 2018; 9.

61. Embretson J, Zupancic M, Ribas JL. Massive covert infection of helper T lymphocytes and macrophages by HIV during the incubation period of AIDS. Nature. 1993;362: 359-362.

62. Spiegel H, Herbst H, Niedobitek G, Foss HD, Stein H. Follicular dendritic cells are a major reservoir for human immunodeficiency virus type 1 in lymphoid tissues facilitating infection of CD4+ T-helper cells. Am J Pathol. 1992: 15-22.

63. Cohen OJ, Pantaleo G, Lam GK, Fauci AS. Studies on lymphoid tissue from HIV-infected individuals: Implications for the design of therapeutic strategies. Springer Semin Immunopathol. 1997; 305-322.

64. Fox CH, Tenner-Rácz K, Rácz P, Firpo A, Pizzo PA, Fauci AS. Lymphoid germinal centers are reservoirs of human immunodeficiency virus type 1. J Infect Dis. 1991;164: 1051-1057.

65. van Zyl G, Bale MJ, Kearney MF. HIV evolution and diversity in ART-treated patients. Retrovirol. 2018;15.

66. Brenchley JM, Douek DC. HIV infection and the gastrointestinal immune system. Mucosal Immunol. 2008;1: 23-30.

67. Lackner AA, Mohan M, Veazey RS. The gastrointestinal tract and AIDS pathogenesis. Gastroenterol. 2009;136: 1965-1978.

68. Poles MA, Elliott J, Taing P, Anton PA, Chen IS. A preponderance of CCR5(+) CXCR4(+) mononuclear cells enhances gastrointestinal mucosal susceptibility to human immunodeficiency virus type 1 infection. J Virol. 2001;75: 8390-8399.

69. Anton PA, Elliott J, Poles MA. Enhanced levels of functional HIV-1 co-receptors on human mucosal T cells demonstrated using intestinal biopsy tissue. AIDS. 2000;14: 1761-1765.

70. Mattapallil JJ, Douek DC, Hill B, Nishimura Y, Martin M, Roederer M. Massive infection and loss of memory CD4+ T cells in multiple tissues during acute SIV infection. Nature. 2005;434: 1093-1097.

71. Shen R, Richter HE, Clements RH. Macrophages in vaginal but not intestinal mucosa are monocyte-like and permissive to human immunodeficiency virus type 1 infection. J Virol. 2009;83: 3258-3267.

72. Brown D, Mattapallil JJ. Gastrointestinal tract and the mucosal macrophage reservoir in HIV infection. Clin Vaccine Immunol. 2014;21: 1469-1473.

73. Galvin SR, Cohen MS. Genital tract reservoirs. Curr Opin HIV AIDS. 2006; 162-166.

74. Wu X, Jackson S. Plasma and salivary IgA subclasses and IgM in HIV-1-infected individuals. J Clin Immunol. 2002; 106-115.

75. Gonzalez SM, Aguilar-Jimenez W, Su RC, Rugeles MT. Mucosa: Key interactions determining sexual transmission of the HIV infection. Front Immunol. 2019; 10.

76. Le Tortorec A, Dejucq-Rainsford N. HIV infection of the male genital tract–consequences for sexual transmission and reproduction. Int J Androl. 2010;33: e98.

77. Bagasra O, Farzadegan H, Seshamma T, Oakes JW, Saah A, Pomerantz RJ. Detection of HIV-1 proviral DNA in sperm from HIV-1-infected men. AIDS. 1994;8: 1669-1674.

78. Nuovo GJ, Becker J, Simsir A, Margiotta M, Khalife G, Shevchuk M. HIV-1 nucleic acids localize to the spermatogonia and their progeny-A study by polymerase chain reaction in situ hybridization. Am J Pathol. 1994; 1142-1148.

79. Anderson D, Politch JA, Pudney J. HIV infection and immune defense of the penis. Am J Reprod Immunol. 2011;65: 220-229.

80. Politch JA, Mayer KH, Welles SL. Highly active antiretroviral therapy does not completely suppress HIV in semen of sexually active HIV-infected men who have sex with men. AIDS. 2012;26: 1535-1543.

81. Borzy MS, Connell RS, Kiessling AA. Detection of Human Immunodeficiency Virus in cell-free seminal fluid. J Acquir Immune Defic Syndr. 1988; 419-424.

82. Shacklett BL, Greenblatt RM. Immune responses to HIV in the female reproductive tract, immunologic parallels with the gastrointestinal tract, and research implications. Am J Reprod Immunol. 2011;65: 230-241.

83. Haase AT. Targeting early infection to prevent HIV-1 mucosal transmission. Nature. 2010;464: 217-223.

84. Kovacs A, Wasserman SS, Burns D. Determinants of HIV-1 shedding in the genital tract of women. Lancet. 2001;10: 1593-1601.

85. Taylor S, Davies S. Antiretroviral drug concentrations in the male and female genital tract: Implications for the sexual transmission of HIV. Curr Opin HIV AIDS. 2010;5: 335-343.

86. Wong JK, Yukl SA. Tissue reservoirs of HIV. Curr Opin HIV AIDS. 2016;11: 362-370.

87. Semenzato G, Agostini C, Ometto L. CD8+ T lymphocytes in the lung of acquired immunodeficiency syndrome patients harbor human immunodeficiency virus type 1. Blood. 1995;85: 2308-2314.

88. Sierra-Madero JG, Toossi Z, Hom DL, Finegan CK, Hoenig E, Rich EA. Relationship between load of virus in alveolar macrophages from human immunodeficiency virus type 1-infected persons, production of cytokines, and clinical status. J Infect Dis. 1994;169: 18-27.

89. Twigg HL, Soliman DM, Day RB. Lymphocytic alveolitis, bronchoalveolar lavage viral load, and outcome in human immunodeficiency virus infection. Am J Respir Crit Care Med. 1999;159: 1439-1444.

90. Cribbs SK, Lennox J, Caliendo AM, Brown LA, Guidot DM. Healthy HIV-1-infected individuals on highly active antiretroviral therapy harbor HIV-1 in their alveolar macrophages. AIDS Res Hum Retroviruses. 2015;31: 64-70.

91. Ganesan M, Poluektova LY, Kharbanda KK, Osna NA. Liver as a target of human immunodeficiency virus infection. World J Gastroenterol. 2018;24: 4728-4737.

92. Hufert FT, Schmitz J, Schreiber M, Schmitz H, Rácz P, von Laer DD. Human kupffer cells infected with HIV-1*in vivo*. J Acquir Immune Defic Syndr. 1993; 772-777.

93. Jiang TJ, Zhao M, Zhao JM. Zhonghua shi yan he lin chuang bing du xue za zhi. 2005; 152-154.

94. Blackard JT, Sherman KE. HCV/ HIV co-infection: Time to re-evaluate the role of HIV in the liver? J Viral Hepat. 2008;15: 323-330.

95. Sterling RK, Chiu S, Snider K, Nixon D. The prevalence and risk factors for abnormal liver enzymes in HIV-positive patients without hepatitis B or C coinfections. Dig Dis Sci. 2008;53: 1375-1382.

96. Carter CC, Onafuwa-Nuga A, McNamara LA. HIV-1 infects multipotent progenitor cells causing cell death and establishing latent cellular reservoirs. Nat Med. 2010;16: 446-451.

97. McNamara LA, Collins KL. Hematopoietic stem/precursor cells as HIV reservoirs. Curr Opin HIV AIDS. 2011;6: 43-48.

98. Bannert N, Farzan M, Friend DS. Human mast cell progenitors can be infected by macrophagetropic human immunodeficiency virus type 1 and retain virus with maturation *in vitro*. J Virol. 2001;75: 10808-10814.

99. Hampton T. Adipose tissue: An HIV reservoir with inflammatory potential. JAMA. 2015; 314:1788.

100. Couturier J, Suliburk JW, Brown JM. Human adipose tissue as a reservoir for memory CD4+ T cells and HIV. AIDS. 2015; 29:667-674.

101. Munier S, Borjabad A, Lemaire M, Mariot V, Hazan U. *In vitro* infection of human primary adipose cells with HIV-1: A reassessment. AIDS. 2003; 17:2537-2539.

102. Couturier J, Lewis DE. HIV persistence in adipose tissue reservoirs. Curr HIV/AIDS Rep. 2018; 15:60-71.