World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

Intergraded multi omics analysis identifies antiviral host factor and pathway controlling HIV infection

Sourav Mondal, Ahana Hazra, Koushik Ghosh, Ishika Dey, Pratibha Bhowmick and Mithun Bhowmick *

Bengal College of Pharmaceutical Sciences and Research, Bidhannagar, Durgapur-713212, West Bengal, India.

World Journal of Biology Pharmacy and Health Sciences, 2025, 22(01), 608-623

Publication history: Received on 15 March 2025; revised on 23 April 2025; accepted on 25 April 2025

Article DOI: https://doi.org/10.30574/wjbphs.2025.22.1.0437

Abstract

Host anti-viral factors are crucial for controlling HIV infection, but their role remains largely unknown due to bias in previous large-scale studies. HIV-1 infection remains untreatable due to unanticipated infected cells. A large amount of OMIC data and functional genomics screening have gathered in the prose and public records. Recent years have seen the publication of interacting analyzes of related OMICs data, which recognized different types of molecular networks, including HIV-human protein-protein interaction networks, gene regulatory, co-expression networks and signaling networks, and approaches for evaluating their topology and changing aspects. Important paths and proteins complex in the HIV life cycle, cellular and immunological responses to infection, viral escape from the host immune system, with processes governing various human susceptibilities to infection may all be regulated with the use of this review. The pathways and proteins identified in this study can be used to develop new anti-HIV therapeutic strategies, such as drugs that inhibit CD4+ cell infection and viral replication, effective vaccines, and "shock and kill" and "block and lock" approaches to cure latent infections.

Keywords: OMICs; HIV infection; Protein-protein interaction networks; CD4+ cell; Latent infection

1. Introduction

Human immunodeficiency virus type 1 (referred to as “HIV”) is the causative agent of attained immune deficiency syndrome (AIDS) (1). HIV infection stimulates the production of viral RNAs and proteins in the host cells, alters their morphology and function significantly, and signals the host cell cycle's advancement (2). Meanwhile, HIV genomes can take part into host cell DNA, acting as a tenacious viral reservoir and housing replication-competent proviruses in a latent form (3). One of the most important infections to impact humanity is the human immunodeficiency virus, or HIV (4). Approximately 36.9 million individuals worldwide are living with HIV, and 780,000 of those deaths were caused by HIV-related illnesses in 2018, as stated by the World Health Organization. At the moment, over 25 antiretroviral therapies can be used to address human immunodeficiency virus (HIV) infection (5). The viral integrase (IN) antiviral drug, such as ritonavir, or that avert the congutation of the six-helix bundle core of the gp42 transmembrane protein essential for virus-cell blend, like enfuvirtide, accepted for clinical use (6). The World Health Organization (2020) states that HIV infection is still a global health concern even though combination antiretroviral medication (cART) now available controls the virus and stops it from spreading (7). Understanding anti-HIV processes is therefore crucial in order to create fresh approaches to treatment and prophylaxis. An estimated 690,000 people died from HIV/AIDS in 2019; 33% of these fatalities were linked to TB that is connected with HIV (8). HIV increases the likelihood of latent TB reactivation by a factor of 20, and that risk increases with a decrease in CD4+ T cells (9). Once immune function is compromised by both HIV and TB co-infection, the combination becomes fatal, with one infection hastening the other's progression. It has long been thought that DNA sensors are only able to operate outside of the nucleus in order to prevent immune responses from being falsely triggered and self-DNA from being recognized. But most human dsDNA

* Corresponding author: Mithun Bhowmick

viruses that are now known to exist reproduce inside the nucleus, where their genomes of viruses are deposited in the nuclei of infected cells (10). Herpesviruses, including human cytomegalovirus (HCMV), herpes simplex contagion type 1 (HSV- 1), and Kaposi's sarcoma- associated herpesvirus (KSHV), are examples of nuclear-replicating DNA viruses (11). The history of herpesviruses dates back hundreds of millions of years, giving them plenty of opportunity to co-diverge with their hosts (12). Long-term non-progressors (LTNP) and HIV controllers (HICs) can manage their HIV infection for numerous years without ART and AIDS-related events by conservating high levels of CD4+ T cells and limiting viral replication, respectively (13). Nonetheless, patients classified as LTNP/HICs comprise a highly diverse population, as indicated by varying parameters such as CD4+ T cell counts, viral load (VL) and duration of follow-up. There are several difficulties in researching HIV latency (14). The low frequency of latently infected cells in infected persons (1 in 107 - 108 cells) complicates investigations of in vivo latency (15). Therefore, without a way to discrete or improve the latently infected cells, genetic, biochemical or other -OMICs analyses—which depend on a high enough regularity of latently infected cells to identify statistically significant changes in phenotypes—are not currently feasible for use with clinical use. Consequently, two methods have been used to create in vitro models of HIV latency: the creation of latently infected cell lines and the ex vivo modification of primary CD4+ cells (16). Notably, alterations in glucose, lipids, glutamic acid, phenylalanine, and branched amino acids were correlated with significant variations in metabolic characteristics (17). These findings suggest the presence of oxidative stress and insulin resistance. In order to corroborate oxidative stress even more, nine metabolites associated with oxidative stress could be quantitatively described using consecutive targeted GC/MS-based metabonomic analyses (18). Aspartic acid, phenylalanine, and glutamic acid were all significantly up-regulated in HIV-positive cohorts as compared to control subjects (19). Compared to HIV-treated and negative control participants, tryptophan and tyrosine levels were down-regulated while cystine levels were elevated in HIV-positive but untreated people (20). Eleven metabolic pathways were shown to have been significantly impacted by infection and/or therapy, according to pathway analysis (21). These processes comprised the manufacture of aminoacyl-tRNA, phenylalanine, tyrosine, and tryptophan, as well as nitrogen metabolism (22).

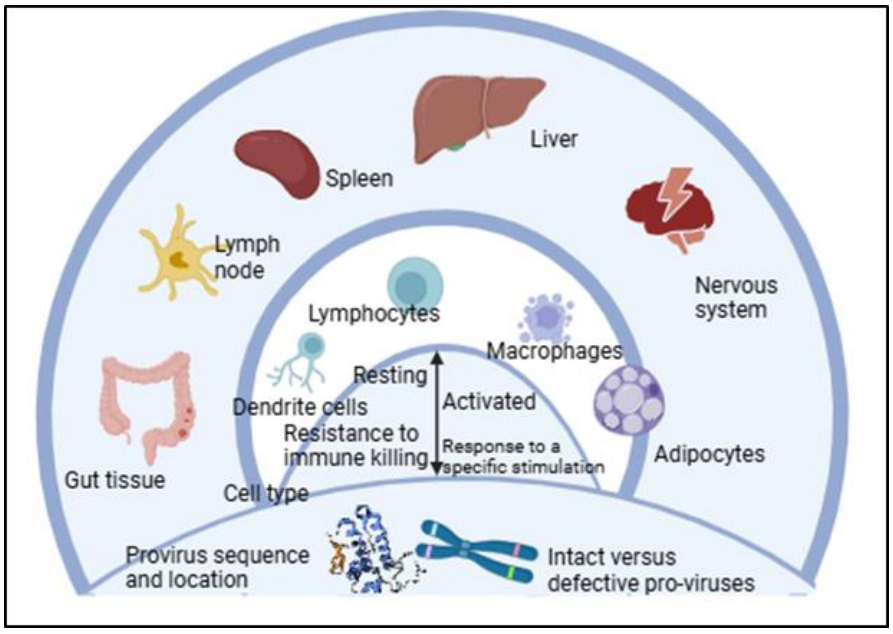

Figure 1 The process of HIV-1 infection of CD4+ cells and its central role in promotion of HIV infection

2. Identification of potential HIV-related genes

2.1. Potential HIV-resistance-related genes

HIV-resistant (HIV-R) samples were collected from the highly exposed seronegative (HESN) population for EXP-blood-HIV-resistance (GSE33680) (23). Using the RLE plot and removed 12 low-standard samples and examined the remaining 74 samples with GEO2R, revealing 453 differentially expressed genes (DEGs) in HIV-R (81 up-regulated and 371 down-regulated) (24). For EXP-CD4-HIV-resistance (GSE14378), removed a low-standard sample and found 554 DEGs (279 up-regulated and 275 down-regulated) in HIV-R (Fig.1). DEGs from EXP-blood-HIV-resistance and EXP-CD4-HIV-resistance contained 26 genes, including 12 DEGs (GYPE, THCAT158, ADGRV1, COBLL1, MYLK3, COL1A1, UNC13C, EGF, LOC142, LOC1402 LOC105374042, CALD1, and HM13) showing consistent appearance patterns in together groups (25). Studying these 12 DEGs across diverse tissues using a issued gene expression profile

dataset showed those tissues of the kidney, spleen, brain, testis, and adrenal exhibited the highest expression levels of 12 putative HIV-1-resistance genes (26). In the following discussion, it's will refer to these as '12 common HIV-resistance-associated DEGs' (Fig.2). In EXP-blood-HIV-resistance DEGs and detected FGA, NCAM1, ITGB1, GRIA2, and EGF are the five hub genes (27). while in EXP-CD4-HIV-resistance DEGs, ten hub genes, including GAPDH, EGUNF, B4NMP, BN4, FGA, LEP, AURKA, and PLEK, were discovered. 14 identified hub DEGs (one shared) were highly expressed in brain, bone marrow, fat, kidney, liver, placenta and testis (28). In addition to 12 common HIV-resistance-associated DEGs with 25 potential HIV-resistance genes (29).

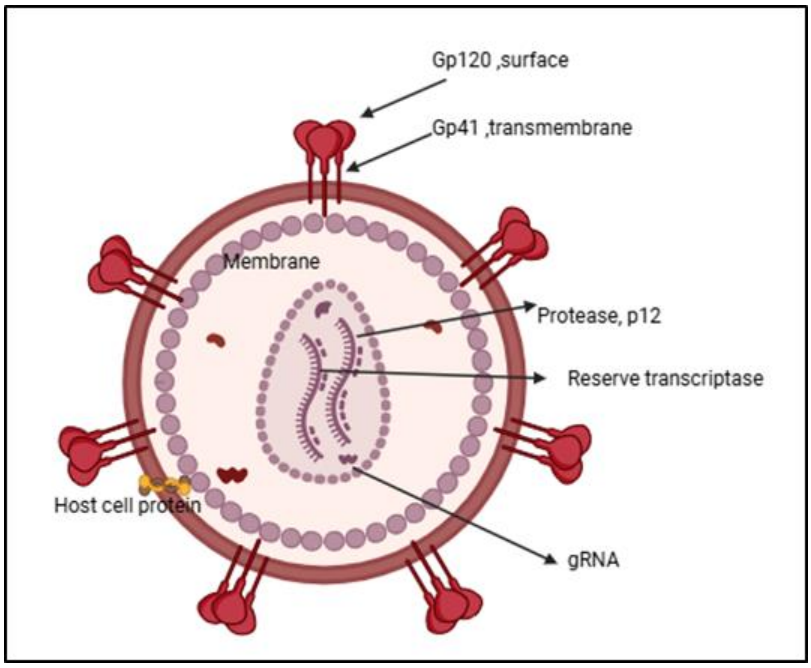

Figure 2 The manifestation and operation of potential genes linked to HIV resistance

2.2. Genes possibly related to HIV infection

To study the part of these possible Gene, die mit HIV-1-Resistenz in Verb in dung stehen in reaction to HIV disclosure, they estimated EXP- Blood-HIV-Infection (GSE29329) and EXP-CD4-HIV-Infection (GSE73978) are two datasets after carrying out quality assurance (Fig.2) (30). Researchers discovered 1458 DEGs, of which 533 are down-regulated and 925 are up-regulated associated with EXP: HIV infection in the blood (31). In central memory CD4+ T cell samples, EXP-CD4+ HIV infection they linked 152 DEGs (33 down-regulated and 119 over-regulated), while in naïve CD4+ T cell samples, they setup 274 DEGs (82 down-regulated and 192 over-regulated) (32). Using the same strategy as for HIV- R mecca DEGs, set of connections for HIV mecca DEGs and set up 16 mecca genes(PLEK, JUN, CXCL8, TYROBP, MYC, CCL5, IL1B, MPO, CYBB, CCL4, GZMB, CD68, CDPTG62, CD682, CD68, CD68, GZMB) in EXP- CD4- HIV- infection (Fig.3) and 9 mecca genes (JUN, RRM1, BUB1B, RAD51, GATA2, ERAB2, UBA5, IRF4 and FBXO7) among DEGs of EXP- blood- HIV-infection (S13) (33). In all, there are 36 hub genes associated with HIV, 36 hub genes were assembled into a PPI network and their expression in different tissues was examined (34). According to the findings, JUN and PLEK are hub genes shared by HIV infection and HIV resistance (35). In the bone marrow, hub genes associated with HIV infection showed preferentially higher expression than genes associated with HIV resistance (p-value < 0.044, Wilcoxon test) (36).

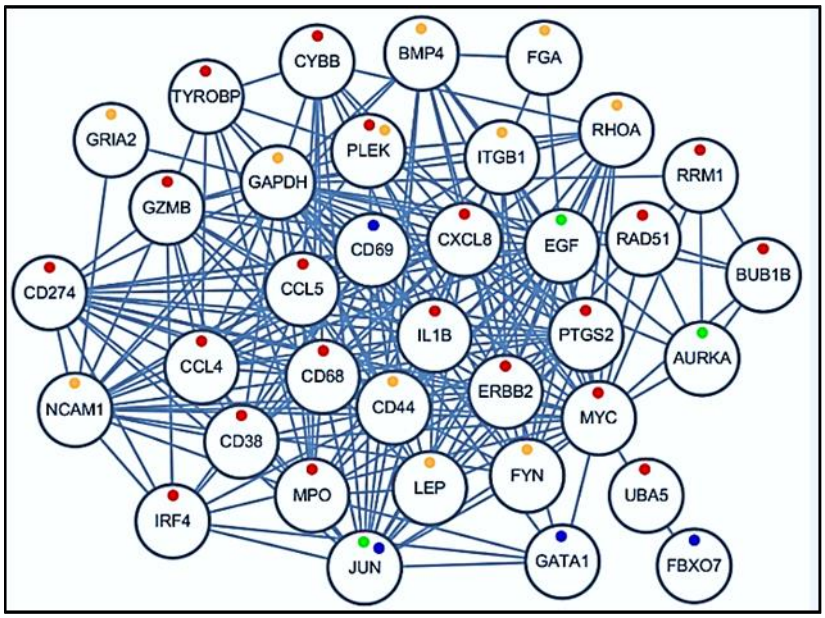

Figure 3 The 36 hub genes associated with HIV are shown in the PPI network diagram. Red dots indicate genes associated with HIV infection that are increased, blue dots indicate genes associated with HIV infection that are inhibited, Dark yellow dots indicate genes associated with HIV resistance that are downregulated, and green dots indicate genes associated with HIV resistance that are upregulated

3. Host factors targeted by antiretroviral therapy

3.1. Targeting viral entry

Viruses lack an independent metabolism and are obligate intracellular parasites, and only reproduce within their hosts (37). The primary CD4 cellular receptor for the virus was identified more than 20 years ago and confirmed as a biological requirement for HIV-1 replication, mediating viral tropism to CD4+ T cells and tissue macrophages (38). It's considered a number of approaches to inhibit binding between the host cell CD4 and gp120 on the external viral envelope (39). Examples of each are soluble CD4 or CD 4 mimetics that appear to trigger more a non-functional than inactive gp 120 conformation, small molecule inhibitors designed for the conserved binding site between Cd4-gp 120 as well as very strong antibodies from patients against CDS (40). Among these, one CD4 antibody (TNX-355) has reached clinical properties with certain existing advantages (41). Synergizes with enfuvirtide (T20) targeting a sequence within gp41 which disrupts viral entry at in a further stage of the procedure still, TNX-355 is hampered by optimal oral bioavailability and to date no CD4 inhibitor has been developed for clinical applications (42). Ten years after the identification of CD4 as the major HIV receptor, the seven-transmembrane G protein-coupled chemokine receptors, CCR5 and CXCR4, were found to serve as crucial coreceptors for HIV-1 entry (43). A short time later, multiple organizations disclosed which involves a homozygous exclusion in the CCR4 phenotype (Δ31/Δ32), which occurs naturally within approximately 2% of Caucasians, defendants regarding HIV-1 infection and does not significantly reduce immunity (44). It has been noted that heterozygous CCR5 deletion is associated with a delayed course of the disease (45). These outcomes indicate that CCR5 is a useful target for anti-HIV treatment, as its inhibition ought to be safe and efficient against HIV-1 strains that are CCR5-tropic (R5) (46). At first, a number of adjusted versions of the inorganic CCL5/RANTES (which is governed due to trigger, manifestation and exercised by normal T cells) ligand for CCR5 were developed (47). Despite their failure in clinical studies, PSC-RANTES is then undergoing investigation as potential HIV microbicides (48). Maraviroc, one of these inhibitors, has received approval from the European Medicines Agency and the US Food and Drug Administration (FDA) with multidrug-resistant HIV-1 strains (49). To make siRNA-mediated CCR5 knock-down clinically applicable, work is being done to reduce the resulting cytotoxicity (50). The use of small inhibitory transfer protocols for molecules or gene therapy aimed at inhibiting or downregulating CCR5 demonstrates potential but also has drawbacks (51). A concern is that CCR5 might be involved in immunity against certain pathogens (52). Another drawback is its lack of efficacy against X4 HIV-1 strains (53). It would clearly be best to combine inhibitors of CCR5 and CXCR4 (54). Therefore, effective and milder CXCR4 inhibitors could be made accessible in the future to support CCR5-targeting antiretroviral treatments (55). Fig.4 described the protein host factors effect of HIV-1 replication.

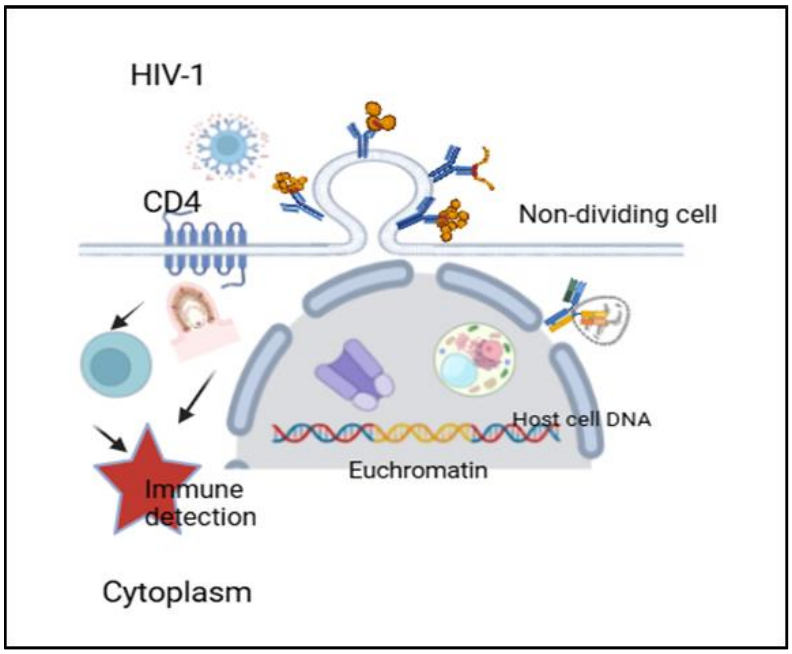

Figure 4 Protein host factors effect of HIV-1 replication

3.2. Other cellular targets for antiretroviral treatment currently being analysed

HIV-1 entry is a particularly attractive stage for intervention because it involves several well-defined cell membrane contacts that can be inhibited without the inhibitor actually entering the cell (56). Preventing HIV-1 at this early stage stops the formation of latent viral reservoirs because it impedes the fusing of the proviral genome into the host cell's DNA (57). But in theory, it is possible to stop the replication of HIV-1 at each stage of its cycle and prevent the virus from spreading (58). Targeting the HIV cofactor Tat and Rev is one of the primary strategies for therapy (59). These cofactors are crucial for viral replication and are highly dependent on specific cellular factors for their function (60). However, after integration, blocking the budding of particles by the cell-to-cell or plasma membrane migration of microorganisms is a sensible proposal to prevent viral infection (61). Infected cells release their own endogenous cell sorting complex, which is subsequently hijacked by HIV-1 and is required for transporter I (ESCRT-I) (62). HIV-1 IN transacts with a cellular factor having therapeutic potential: lens epithelial-derived growth factor (LEDGF)/p76, a choroid-associated protein significant for HIV-1 integration (63). Although the structure morphology of the communication interface has been resolute, it remains difficult to develop a short inhibitor to block LEDGF/p75–IN binding (64). HIV-1 IN inhibits the interaction with LEDGF/p76, which inhibits viral replication. Genome-wide screening and studies of HIV infection, although not without limitations, provide a solid foundation for identifying cellular targets for HIV treatment (65). Candidate cellular variables that are annotated in the HIV interaction database and recognize in two out of the three siRNA screens are particularly compelling (66).

3.3. Genome-wide screening obscure various aim for antiretroviral cure

Prior to genome sequencing, the driving force behind advances in HIV host genes was molecular biology, including early polymorphisms in genetic factors, and the elucidation of HIV-host interactions (67). HIV-1 hosts were resolute using candidate gene studies (68). In the candidate gene method, genetic variations in already existing genes are associated with phenotypes and disease states (69). A more comprehensive understanding of the molecular mechanisms behind HIV infection and replication has suggested ways to develop innovative approaches to combat HIV infection (70). This change in the drug discovery paradigm for viral diseases is still new and is currently provided by the many useful organisms discussed below whose genes contribute to different stages of the life cycle, but may also play a role in influencing host immunity (71). TRIM5α from rhesus macaques and owl monkeys specifically blocks HIV-1, while human TRIM5α provides only a weak restriction (72). These host-inhibition factors obstruct retroviral replication through several mechanisms and can protect mammals from a variety of retroviruses (73). The communication between CD4 and HIV Env provides a binding site for CXCR5, an alpha chemokine receptor or CCR5, a beta chemokine receptor (74). Other cellular aspects have also been developed to enhance HIV binding and entry efficiency, such as galectin-1, but are not required for this procedure (75). The emergence of resistant viruses is still a problem, especially when adverse side effects lead to poor drug adherence or treatment discontinuation (76). If HIV infection develops resistance to conventional HAART, there are several options (77). In theory, host proteins that are essentially

unchanged are significantly more favourable candidates for therapeutic activity (78). Because these proteins have a low mutation rate due to their DNA repair enzymes and proofreading facility, they are fewer prone to outflow variations or drug resistance, which significantly expands the utility of any new antiviral (79). The static nature of their requisite partners also places constraints on the viral protein domains that cooperate with host components (80). First, there is very little overlap between siRNA screens; Only three of the 842 HIV-dependent factors—MED6, MED7, and RELA—were found in all three investigations (81). The HeLa and HEK293T cell lines that were employed, the amount of siRNA exposure for separate gene, the phases of the HIV repetition cycle that were examined, the time periods that were examined, and the filtering criteria that were applied may have contributed to this poor overlap (82). Second, some of the applicability of these results is limited by the use of pseudo-typed virions and cell lines (such as HeLa and HEK293T) that are not frequently infected with HIV-1 (83). However, only six of 252 genes associated with HIV-1 infection were found by the siRNA screen performed in HeLa and three in HEK293T (84). Furthermore, third, by definition, siRNA screens target proteins whose functions can be inhibited without causing an obvious cytotoxic effect—that is, proteins that are redundant in their function or not important for cellular survival (85). Fourth, because the study examined virus contamination in cell lines only as an experimental terminus and it is unclear whether they play a major role in HIV-1-infected individuals, many hits may reflect false positives of biological relevance (86). These considerations, along with the fact that RNA interference is a partial knock-down mechanism, likely explain why key cellular factors long recognized as vital for HIV-1 infection were overlooked by genome-wide studies (87). The different constituents of the hosts that input a significant role in HIV-1 infection is given in Table 1.

Table 1 Factors related to the host that play a role in HIV-1 infection

Category	Example	Reference
Signalling	Ras family, cAMP phosphodiesterase, phosphatases.	(88)
Surface molecules	MHC, clusters of differentiation, lectins	(89)
RNA splicing	Splicing factors	(90)
Lysosomal degradation	Vascular ATPases, breakdown enzymes,	(91)
Chromatin	Histone deacetylases, histones	(92)
Nuclear export	Transport reliant on nuclear export signal, RNA export factors	(93)
Cytoskeleton	Microtubule, actin, associated proteins	(94)
Lysosomal degradation	Breakdown enzyme, vascular ATPases	(95)
Proteasomal degradation	ubiquitin-conjugating enzymes, proteasome subunits	(96)

4. Several pathways controlling for antiretroviral therapy

Numerous mechanisms that stop or restrict HIV replication are part of the antiviral pathways that control the virus (97). Here are some key pathways,

4.1. Innate Immunity

The initial line of protection against infections is innate immunity, which offers prompt protection (98). Although it is non-specific, it detects all infections rather than merely a handful (99). Against invasive infections, the innate immune responses serve as the initial line of protection (100). They are also necessary for inciting particular adaptive immune reactions. Recognizing conserved characteristics of infections that are absent from the uninfected host is essential for innate immune responses (101). Phagocytic cells eliminate invading microbes by synthesizing reactive oxygen species, antimicrobial peptides, and degradative enzymes. They begin to mobilize the adaptive immune system by releasing signalling molecules that trigger an inflammatory response (102). Interferon, which is produced by virus-infected cells, triggers a cascade of cellular responses that inhibit viral replication and trigger the death of cytotoxic T-lymphocytes and natural killer cells (103). Toll-like receptor proteins, which are present in plants as well as invertebrates and vertebrates, riggers a cascade of cellular responses that inhibit viral replication and trigger the death of cytotoxic T-lymphocytes and natural killer cells (104). Toll-like receptor proteins, which are present in plants as well as invertebrates and vertebrates, are able to recognize several of these pathogen-specific compounds (105). Complement, a collection of blood proteins, is also activated by microbial surface molecules in vertebrates (106). Complement targets bacteria for phagocytosis by neutrophils and macrophages, disrupting the microbial membrane and causing inflammation (107). The classification of innate immunity is provided Table 2.

Table 2 Classification of innate immunity

1	Interferon (IFN) pathway	IFN-α and IFN-β inhibit HIV replication by inducing expression of antiviral proteins like protein kinase R (PKR) and 2',5'-oligoadenylate synthetase (OAS).
2	Apoptosis	Programmed cell death eliminates infected cells, reducing viral spread.
3	Natural Killer (NK) cells	Recognize and kill infected cells.

4.1.1. Apoptosis

Apoptosis, also known as programmed cell death, plays a crucial role in maintaining tissue homeostasis and overall health (108). Apoptosis secures that unhealthy or superfluous cells are eliminated, supporting normal tissue function and averting illness (109). Apoptosis ensures the removal of harmful or unnecessary cells, promoting healthy tissue function and preventing disease (110). Its key functions include and Fig.5 describe the apoptosis of cell death,

- Elimination of damaged or mutated cells, preventing cancer development (111).
- Removal of excess cells during development and tissue remodelling (112).
- Maintenance of immune system balance by eliminating autoreactive immune cells (113).
- Prevention of inflammation by removing infected or damaged cells (114).

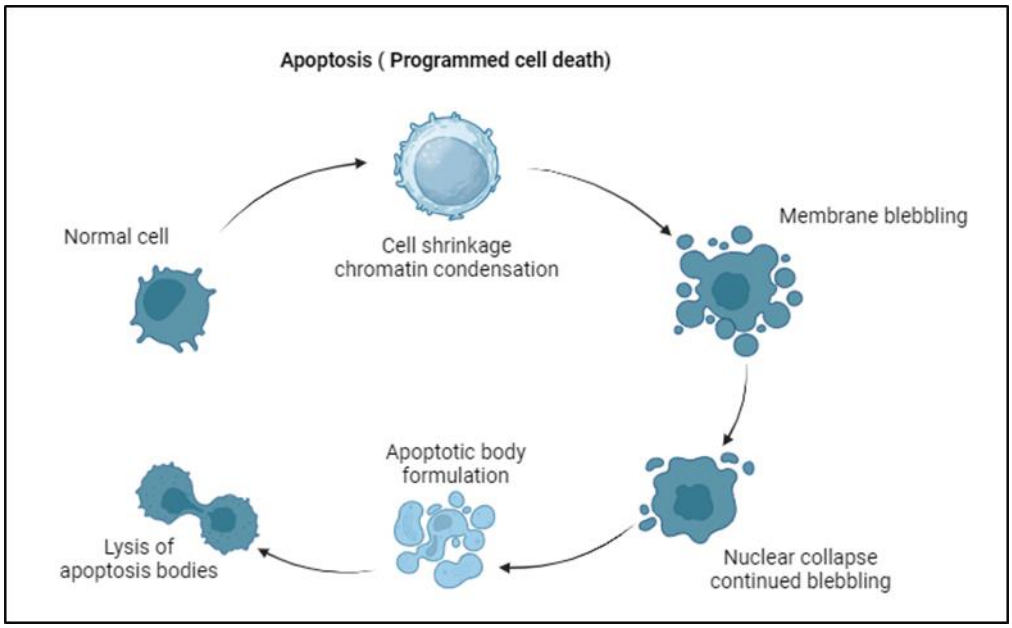

Figure 5 Schematic diagram of apoptosis cell death

4.2. Natural killer cell

The innate immune system relies heavily on natural killer (NK) cells, a subset of lymphocytes, which are white blood cells (115). The innate immune system's natural killer (NK) cells serve as the initial defence against tumour and virus-infected cells (T cells and B cells) without requires prior activation, unlike other immune cells (116). By preventing the spread of various cancers and microbial infections and the resulting tissue damage, these cells aid in the control of these conditions (117). They work by locating and eliminating host cells that have been compromised (118). Natural killer cells play a crucial role in controlling HIV infection. HIV is a chronic infection in its second stage, also known as chronic HIV infection, NK cells in the peripheral blood of patients with persistent HIV infection showed considerably lower expression of NKG2D, which is consistent with NK cells producing fewer cytokines and causing less cytotoxicity than those in healthy people (119). The association between fatty acids and NKG2DL remains to be thoroughly clarified by hepatocyte research (120). However, it has been demonstrated that human leukaemia and lymphoma cells express MICA in response to short-chain fatty acids like propionic acid (121). NK cells make up 10–16% of the total lymphocyte population in human peripheral blood (122). Important activating receptors that aid in blood vessel extravasation include NK group 2D (NKG2D), DNAX accessory molecule-1 (DNAM-1), natural cytotoxicity receptor (NKp30), and others (123). Integrin adhesion receptors that aid in extravasation include LFA-1, VLA-4, Mac-1, PSGL-1, and L-selectin (along with other leukocytes) (124).

4.3. Adaptive Immunity

T-cell activation accelerates HIV replication and is also a predictor of disease progression (125). The importance of T-cell activation in HIV was first recognized in the late 1980s, with early studies of HLA-DR and CD38 (126). Antigen-presenting cells (APCs) and naïve T-cells constitutively express HLA-DR and CD38, which are down-regulated on resting memory cells and up-regulated on subsequently activated cells, respectively (127). Nef, a protein produced by the human immunodeficiency virus type 1 (HIV-1), works against the antiviral action of cytotoxic T cells, thereby evading cellular adaptive immunity (128). These cells restrict viral replication by recognizing viral peptides presented on MHC-I cell surfaces and then removing the infected cells (129). Nef inhibits the presentation of viral antigens to infected cells by reducing MHC-I surface expression, which in turn inhibits cytotoxic T lymphocytes (130). In the pathophysiology of HIV-1 infection, the Negative regulatory factor (NEF) plays an important role. Imperfect NEF genes are related with significantly slower development to AIDS (131). The MHC- I cytoplasmic tail (remainders 315 – 332) binds securely to a long, thin groove at the NEF and μ1 edge, forming a clamp- suchlike structure in the NEF – MHC- I CD – μ1 compound (132). The biological significance of chemokines in the central nervous system has been clarified thanks to major advances in recent years (133). Recent studies by our group and other researchers have shown that virions produced by macrophages bind to chemokine (chemotactic cytokine) receptors on neurons (134). Originally thought of as immunological modulators, chemokines appear to have many biological functions in the central nervous system, together with development, neuronal excitability, synaptic transmission, neuro-swelling and neuro-erosion (135). It is conceivable that mingling HIV-specific CD8 cells may be partially anergic and unable to eliminate HIV-1-infected cells in vivo while helper CD4 T cells are functionally compromised at later stages of infection (136). In the SIV model, a CD8-depleting monoclonal antibody was used to show a direct role of condensed CD8 cell immunity in the pathophysiology of HAD (137).

4.4. Cellular limitation factors

According to reports in the early 1991s, cyclophilin (Cypa) is a cellular element that fixes the HIV- 1 capsid protein (CA) but not the CA of other lentiviruses similar as SIVmac239 (138). It has recently been shown that it also interacts with SIV again, CA of certain HIV-2 strains and FIV (feline immunodeficiency virus) (139). The kinase activity of Itch (inducible T-cell kinase) in CD4+ T cells and the nuclear export of Zpr1 (zinc finger protein 1) in yeast are two unique cellular roles of Cyp. When used with the immunosuppressive medication cyclosporine, it effectively inhibits T cell calcineurin, a CA-dependent phosphatase (140). According to, a crucial proline residue is involved in the interaction with HIV-1 CA, and CypA binding causes a conformational shift in CA. Silencing RNF19A, TRIM25, and TRIM27—all of which associate with or belong to E3 ligases—also restored infectivity, increasing it 3–3.5-fold from 1 × 103 to 3 × 103 FFU/ml. Notably, RIG-1-mediated IFNb synthesis and antiviral activity depend on TRIM25 (141). Only one of the four siRNAs confirmed the restricted phenotype for TRIM27, the only one of the last three genes to be validated with individual siRNAs. Furthermore, WSB2, a bridge protein that connects the substrate-binding domain and E3 ubiquitin protein ligases, was moderately restored upon knockdown (3.2-fold, 1 in 4 independent siRNAs (142).

5. Conclusion

HIV/AIDS remains a significant global health problem, with existing antiretroviral therapy unable to eliminate the virus from the body and challenges in creating anti-HIV vaccines. To advance the safety and efficacy of antiretroviral therapy, a deeper understanding of the HIV-human interface is needed. A network-based OMICs data analysis can illuminate these mechanisms and identify new points in therapeutic interventions. Over 2800 interactions among human and HIV-1 proteins belonging to different viral sets and subtypes have been added to public databases. Most of the interactions go to HIV-1 group M subtype B, which presents a barrier to interrelating investigations of other HIV forms. 233 HIV-related transcriptomics were studied, evaluated the expression characteristic of anthropogenic and HIV non-coding and coding RNAs across various kinds of cells. People can vary in their susceptibility to HIV, the rate at which they experience disease progression, and their reciprocation to vaccine and drug therapies. Identification of degenerate genes (DEGs) in various conditions accompanying pathway flourish analysis allows study to interpret conditions differences. Comparing transcriptional outlines in insusceptible cells from individuals treated with more or less operative vaccines, with stronger or weaker immune responses to specific vaccines, can help identify genes and pathways that alter vaccine efficacy. By comparing the transcriptional biographies by examining chronically infected, viraemic and elite controllers, individuals can indicate mechanisms that reduce susceptibility to HIV infection. It's possible to improve the efficiency of antiretroviral curatives and vaccines by emulating the distinct transcriptional histories of viraemic and elite controllers with different natural and chemical agents.

5.1. Future prospective

There is a lot of potential for the future of integrated multi-omics analysis in determining antiviral host components and pathways governing HIV infection. Researchers are obtaining a more thorough knowledge of HIV-host interactions, antiviral resistance mechanisms, and possible treatment targets by utilizing developments in genomes, transcriptomics, proteomics, metabolomics, and other omics domains. Here are some important viewpoints on how integrated multi-omics might influence HIV research and therapy going forward. By finding host genetic variations that affect infection outcomes or therapeutic responses, integrated analysis enables a more thorough investigation of genetic vulnerability to HIV. It may also reveal epigenetic changes that impact HIV latency and persistence, such as DNA methylation and histone alterations. A comprehensive picture of the dynamic interactions between HIV and the host including viral entry, replication, and immune evasion can be obtained by multi-omics platforms. This would make it easier to find new immune modulators or antiviral host variables that would not have been visible from a single-omics viewpoint. Researchers are able to map out intricate signaling networks involved in HIV infection and its control by combining transcriptomic, proteomic, and metabolomic data. This involves identifying important cellular pathways, including NF-kB, interferon signaling, or autophagy, that HIV uses for reproduction or persistence. New understanding of how HIV affects the immune system, including changes in cytokine profiles, T-cell responses, and macrophage activation, can be gained using a multi-omics approach. Finding new immune modulators to improve antiviral immunity may result from an understanding of these alterations. Using integrated multi-omics, host variables that are important for HIV replication but also necessary for other viral infections may be found. This makes it possible to use small compounds to target host pathways that HIV hijacks or to repurpose already-approved antiviral medications. Future antiviral therapies could concentrate on altering host pathways essential for viral multiplication, immune evasion, or latency in addition to addressing HIV directly. Multi-omics will assist in finding novel host targets that may be therapeutically altered, such as kinases, transcription factors, or enzymes.

The development of latent reservoirs, in which the virus remains inactive within certain cells despite the administration of ART (antiretroviral treatment), is one of the key obstacles to HIV eradication. A more thorough knowledge of the molecular processes that sustain HIV latency, including chromatin remodeling, transcriptional repression, and host immune modulation, may be obtained by integrated omics technologies. It could be feasible to create methods for carefully reactivating the virus and increasing its susceptibility to immune clearance by identifying the routes underlying latency. Multi-omics analysis may be able to pinpoint host characteristics that affect immune cells' (such as CD8+ T cells and NK cells) capacity to locate and attack latent HIV reservoirs. Furthermore, knowing how particular metabolites or cytokines affect latency may open the door to creating treatments that target latent HIV reservoirs precisely without inducing negative inflammation. The potential of multi-omics to shed light on the individual differences in HIV infection and treatment outcomes is among its most intriguing features. Clinicians may be able to find patient-specific biomarkers for ART response, progression, or susceptibility by integrating multi-omics data.

Compliance with ethical standards

Acknowledgments

The authors are thankful to the Bengal College of Pharmaceutical Sciences and Research, Bidhannagar, Durgapur, West Bengal, PIN- 713212, India for providing the research facilities.

Authors contribution

Sourav Mondal: Writing – original draft, Methodology, Data curation, Ahana Hazra: Writing- review and editing, Conceptualization. Koushik Ghosh: Formal analysis, Visualization, Ishika Dey: Formal analysis, Pratibha Bhowmick: Formal analysis. Mithun Bhowmick: Supervision, Visualization

Disclosure of conflict of interest

There was no conflict of interest.

Data availability statements

The authors declare that the data supporting the findings of this study are available within the paper. Should any raw data files be needed in another format they are available from the corresponding author upon reasonable request.

References

[1] Chenchula S, Anitha K, Prakash S, Phulen Sharma J, Aggarwal S. Chapter 7 - Multiomics in human viral infections. In: Ali A, Rehman MU, Ahmad SB, Arafah A, editors. Biological Insights of Multi-Omics Technologies in Human Diseases [Internet]. Academic Press; 2024 [cited 2025 Feb 27]. p. 145–66. Available from: https://www.sciencedirect.com/science/article/pii/B9780443239717000079

[2] Integrated multi-omics analyses identify anti-viral host factors and pathways controlling SARS-CoV-2 infection | Nature Communications [Internet]. [cited 2025 Feb 27]. Available from: https://www.nature.com/articles/s41467-023-44175-1

[3] Krishnan S, Queiroz ATL, Gupta A, Gupte N, Bisson GP, Kumwenda J, et al. Integrative Multi-Omics Reveals Serum Markers of Tuberculosis in Advanced HIV. Front Immunol [Internet]. 2021 Jun 8 [cited 2025 Feb 27];12. Available from: https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2021.676980/full

[4] Long X, Liu G, Liu X, Zhang C, Shi L, Zhu Z. Identifying the HIV-Resistance-Related Factors and Regulatory Network via Multi-Omics Analyses. International Journal of Molecular Sciences. 2024 Jan;25(21):11757.

[5] Deffur: Co-infection with Mycobacterium tuberculosis... - Google Scholar [Internet]. [cited 2025 Feb 27]. Available from: https://scholar.google.com/scholar_lookup?title=Co-infection+with+Mycobacterium+tuberculosis+and+human+immunodeficiency+virus:+An+overview+and+motivation+for+systems+approaches&author=Deffur,+A.&author=Mulder,+N.J.&author=Wilkinson,+R.J.&publication_year=2013&journal=Pathog.+Dis.&volume=69&pages=101%E2%80%93113&doi=10.1111/2049-632X.12060&pmid=23821533

[6] Multi-Omics Studies towards Novel Modulators of Influenza A Virus–Host Interaction [Internet]. [cited 2025 Feb 27]. Available from: https://www.mdpi.com/1999-4915/8/10/269

[7] McKimm-Breschkin JL, Fry AM. Meeting report: 4th ISIRV antiviral group conference: Novel antiviral therapies for influenza and other respiratory viruses. Antiviral Research. 2016 May 1;129:21–38.

[8] Takashita: Characterization of a large cluster of... - Google Scholar [Internet]. [cited 2025 Feb 27]. Available from: https://scholar.google.com/scholar_lookup?title=Characterization%20of%20a%20large%20cluster%20of%20influenza%20Apdm09%20viruses%20cross-resistant%20to%20oseltamivir%20and%20peramivir%20during%20the%202013-2014%20influenza%20season%20in%20Japan&publication_year=2015&author=E.%20Takashita&author=M.%20Kiso&author=S.%20Fujisaki&author=M.%20Yokoyama&author=K.%20Nakamura&author=M.%20Shirakura&author=H.%20Sato&author=T.%20Odagiri&author=Y.%20Kawaoka&author=M.%20Tashiro

[9] Tang: Influence of antibodies and T cells on dengue... - Google Scholar [Internet]. [cited 2025 Feb 27]. Available from: https://scholar.google.com/scholar_lookup?title=Influence%20of%20antibodies%20and%20T%20cells%20on%20dengue%20disease%20outcome%3A%20insights%20from%20interferon%20receptor-deficient%20mouse%20models&publication_year=2015&author=W.W.%20Tang&author=R.%20Grewal&author=S.%20Shresta

[10] Shao W, Li X, Goraya MU, Wang S, Chen JL. Evolution of Influenza A Virus by Mutation and Re-Assortment. International Journal of Molecular Sciences. 2017 Aug;18(8):1650.

[11] Wang: Influenza A virus N5 neuraminidase has an extended... - Google Scholar [Internet]. [cited 2025 Feb 27]. Available from: https://scholar.google.com/scholar_lookup?title=Influenza%20A%20virus%20N5%20neuraminidase%20has%20an%20extended%20150-cavity&publication_year=2011&author=M.%20Wang&author=J.%20Qi&author=Y.%20Liu&author=C.J.%20Vavricka&author=Y.%20Wu&author=Q.%20Li&author=G.F.%20Gao

[12] The Influenza Virus Polymerase Complex: An Update on Its Structure, Functions, and Significance for Antiviral Drug Design - Stevaert - 2016 - Medicinal Research Reviews - Wiley Online Library [Internet]. [cited 2025 Feb 27]. Available from: https://onlinelibrary.wiley.com/doi/10.1002/med.21401

[13] Hussain M, Galvin HD, Haw TY, Nutsford AN, Husain M. Drug resistance in influenza A virus: the epidemiology and management. IDR. 2017 Apr 20;10:121–34.

[14] Cooks T, Pateras IS, Tarcic O, Solomon H, Schetter AJ, Wilder S, et al. Mutant p53 Prolongs NF-κB Activation and Promotes Chronic Inflammation and Inflammation-Associated Colorectal Cancer. Cancer Cell. 2013 May 13;23(5):634–46.

[15] Takeuchi O, Akira S. Pattern Recognition Receptors and Inflammation. Cell. 2010 Mar 19;140(6):805–20.

[16] Chen W, Han C, Xie B, Hu X, Yu Q, Shi L, et al. Induction of Siglec-G by RNA Viruses Inhibits the Innate Immune Response by Promoting RIG-I Degradation. Cell. 2013 Jan 31;152(3):467–78.

[17] Bate C, Nolan W, McHale-Owen H, Williams A. Sialic Acid within the Glycosylphosphatidylinositol Anchor Targets the Cellular Prion Protein to Synapses*. Journal of Biological Chemistry. 2016 Aug 12;291(33):17093–101.

[18] Fukui K, Baba S, Kumasaka T, Yano T. Structural Features and Functional Dependency on β-Clamp Define Distinct Subfamilies of Bacterial Mismatch Repair Endonuclease MutL*. Journal of Biological Chemistry. 2016 Aug 12;291(33):16990–7000.

[19] Li X, Liu P, Gan S, Zhang C, Zheng Y, Jiang Y, et al. Mechanisms of Host-Pathogen Protein Complex Formation and Bacterial Immune Evasion of *Streptococcus suis* Protein Fhb*. Journal of Biological Chemistry. 2016 Aug 12;291(33):17122–32.

[20] Katorcha E, Srivastava S, Klimova N, Baskakov IV. Sialylation of Glycosylphosphatidylinositol (GPI) Anchors of Mammalian Prions Is Regulated in a Host-, Tissue-, and Cell-specific Manner*. Journal of Biological Chemistry. 2016 Aug 12;291(33):17009–19.

[21] Liu HJ, Ooms LM, Srijakotre N, Man J, Vieusseux J, Waters JE, et al. PtdIns(3,4,5)P3-dependent Rac Exchanger 1 (PREX1) Rac-Guanine Nucleotide Exchange Factor (GEF) Activity Promotes Breast Cancer Cell Proliferation and Tumor Growth via Activation of Extracellular Signal-regulated Kinase 1/2 (ERK1/2) Signaling*. Journal of Biological Chemistry. 2016 Aug 12;291(33):17258–70.

[22] Kim H, Lee BH, Choi SH, Kim HJ, Jung SW, Hwang SH, et al. Gintonin stimulates gliotransmitter release in cortical primary astrocytes. Neuroscience Letters. 2015 Aug 31;603:19–24.

[23] Casciato DJ, Page T, Perkins J, Vacketta V, Hyer C. Intellectual Property and Royalty Payments Among Foot and Ankle Surgery Fellowship Faculty. The Journal of Foot and Ankle Surgery. 2023 Nov 1;62(6):958–62.

[24] Agnew PS, Foster JD, Chariton J, Chariton AJ, Bresnahan PJ, Daniel EC, et al. Clinical Outcomes Following Treatment of Recurrent Talotarsal Joint Dislocation Using a Type II Extraosseous Talotarsal Stabilization Implant—A Long-Term Follow-Up Study. The Journal of Foot and Ankle Surgery. 2023 Sep 1;62(5):877–82.

[25] Casciato DJ, Mendicino RW. CMS Open Payments Database Analysis of Industry Payments for Foot and Ankle Surgery Research. The Journal of Foot and Ankle Surgery. 2022 Sep 1;61(5):1013–6.

[26] Blassel L, Zhukova A, Villabona-Arenas CJ, Atkins KE, Hué S, Gascuel O. Drug resistance mutations in HIV: new bioinformatics approaches and challenges. Current Opinion in Virology. 2021 Dec 1;51:56–64.

[27] Tastan Bishop Ö, Musyoka TM, Barozi V. Allostery and Missense Mutations as Intermittently Linked Promising Aspects of Modern Computational Drug Discovery. Journal of Molecular Biology. 2022 Sep 15;434(17):167610.

[28] Jensen: A reliable phenotype predictor for human... - Google Scholar [Internet]. [cited 2025 Feb 27]. Available from: https://scholar.google.com/scholar_lookup?title=A%20reliable%20phenotype%20predictor%20for%20human%20immunodeficiency%20virus%20type%201%20subtype%20C%20based%20on%20envelope%20V3%20sequences&publication_year=2006&author=M.A.%20Jensen&author=M.%20Coetzer&author=A.B.%20van%E2%80%99t%20Wout&author=L.%20Morris&author=J.I.%20Mullins

[29] Christy HJ, Anand DA. Analysis of the HIV resistance related HLA dRB1 restricted CD4+ T cell epitopes among Indian HIV patients. BMC Infect Dis. 2014 May 27;14(3):O4.

[30] Roger M. Influence of host genes on HIV-1 disease progression. The FASEB Journal. 1998;12(9):625–32.

[31] Piacentini L, Biasin M, Fenizia C, Clerici M. Genetic correlates of protection against HIV infection: the ally within. Journal of Internal Medicine. 2009;265(1):110–24.

[32] Chen L, Zhang S, Pan X, Hu X, Zhang YH, Yuan F, et al. HIV infection alters the human epigenetic landscape. Gene Ther. 2019 Feb;26(1):29–39.

[33] Raghavan S, Alagarasu K, Selvaraj P. Immunogenetics of HIV and HIV associated tuberculosis. Tuberculosis. 2012 Jan 1;92(1):18–30.

[34] Mack KD, Jin X, Yu S, Wei R, Kapp L, Green C, et al. HIV Insertions Within and Proximal to Host Cell Genes Are a Common Finding in Tissues Containing High Levels of HIV DNA and Macrophage-Associated p24 Antigen Expression. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2003 Jul 1;33(3):308.

[35] Su Z zhong, Kang D chul, Chen Y, Pekarskaya O, Chao W, Volsky DJ, et al. Identification and cloning of human astrocyte genes displaying elevated expression after infection with HIV-1 or exposure to HIV-1 envelope glycoprotein by rapid subtraction hybridization, RaSH. Oncogene. 2002 May;21(22):3592–602.

[36] Levine AJ, Singer EJ, Shapshak P. The Role of Host Genetics in the Susceptibility for HIV-associated Neurocognitive Disorders. AIDS Behav. 2009 Feb 1;13(1):118–32.

[37] Zhou L, Pupo GM, Gupta P, Liu B, Tran SL, Rahme R, et al. A parallel genome-wide mRNA and microRNA profiling of the frontal cortex of HIV patients with and without HIV-associated dementia shows the role of axon guidance and downstream pathways in HIV-mediated neurodegeneration. BMC Genomics. 2012 Nov 28;13(1):677.

[38] Liang WS, Maddukuri A, Teslovich TM, de la Fuente C, Agbottah E, Dadgar S, et al. Therapeutic targets for HIV-1 infection in the host proteome. Retrovirology. 2005 Mar 21;2(1):20.

[39] Moni MA, Liò P. Network-based analysis of comorbidities risk during an infection: SARS and HIV case studies. BMC Bioinformatics. 2014 Oct 24;15(1):333.

[40] Wu Y, Marsh JW. Gene transcription in HIV infection. Microbes and Infection. 2003 Sep 1;5(11):1023–7.

[41] Sieczkarski SB, Whittaker GR. Viral Entry. In: Marsh M, editor. Membrane Trafficking in Viral Replication [Internet]. Berlin, Heidelberg: Springer; 2005 [cited 2025 Feb 27]. p. 1–23. Available from: https://doi.org/10.1007/3-540-26764-6_1

[42] Targeting Cell Entry of Enveloped Viruses as an Antiviral Strategy [Internet]. [cited 2025 Feb 27]. Available from: https://www.mdpi.com/1420-3049/16/1/221

[43] Identification of Broad-Spectrum Antiviral Compounds by Targeting Viral Entry [Internet]. [cited 2025 Feb 27]. Available from: https://www.mdpi.com/1999-4915/11/2/176

[44] Targeting the viral-entry facilitators of SARS-CoV-2 as a therapeutic strategy in COVID-19 - Muralidar - 2021 - Journal of Medical Virology - Wiley Online Library [Internet]. [cited 2025 Feb 27]. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.27019

[45] Virus Entry as a Target for Anti-HIV Intervention: Ingenta Connect [Internet]. [cited 2025 Feb 27]. Available from: https://www.ingentaconnect.com/content/ben/cmc/2003/00000010/00000017/art00002

[46] Virus Attachment and Entry Offer Numerous Targets for Antiviral Therapy | Bentham Science Publishers [Internet]. [cited 2025 Feb 27]. Available from: https://www.benthamdirect.com/content/journals/cpd/10.2174/1381612043382729

[47] Yang J, Li M, Shen X, Liu S. Influenza A Virus Entry Inhibitors Targeting the Hemagglutinin. Viruses. 2013 Jan;5(1):352–73.

[48] Host Determinants in HIV Infection and Disease: Part 2: Genetic Factors and Implications for Antiretroviral Therapeutics* | Annals of Internal Medicine [Internet]. [cited 2025 Feb 27]. Available from: https://www.acpjournals.org/doi/abs/10.7326/0003-4819-134-10-200105150-00012

[49] Reeves JD, Piefer AJ. Emerging Drug Targets for Antiretroviral Therapy. Drugs. 2005 Sep 1;65(13):1747–66.

[50] EGFR and EphA2 are host factors for hepatitis C virus entry and possible targets for antiviral therapy | Nature Medicine [Internet]. [cited 2025 Feb 27]. Available from: https://www.nature.com/articles/nm.2341

[51] Greene WC, Debyser Z, Ikeda Y, Freed EO, Stephens E, Yonemoto W, et al. Novel targets for HIV therapy. Antiviral Research. 2008 Dec 1;80(3):251–65.

[52] Watanabe T, Kawaoka Y. Influenza virus–host interactomes as a basis for antiviral drug development. Current Opinion in Virology. 2015 Oct 1;14:71–8.

[53] Brass AL, Huang IC, Benita Y, John SP, Krishnan MN, Feeley EM, et al. The IFITM Proteins Mediate Cellular Resistance to Influenza A H1N1 Virus, West Nile Virus, and Dengue Virus. Cell. 2009 Dec 24;139(7):1243–54.

[54] Influenza virus RNA polymerase: insights into the mechanisms of viral RNA synthesis | Nature Reviews Microbiology [Internet]. [cited 2025 Feb 27]. Available from: https://www.nature.com/articles/nrmicro.2016.87

[55] Dampier W, Evans P, Ungar L, Tozeren A. Host sequence motifs shared by HIV predict response to antiretroviral therapy. BMC Med Genomics. 2009 Jul 23;2(1):47.

[56] Olsen ME, Connor JH. Hypusination of eIF5A as a Target for Antiviral Therapy. DNA and Cell Biology. 2017 Mar;36(3):198–201.

[57] Hepatitis C Virus P7—A Viroporin Crucial for Virus Assembly and an Emerging Target for Antiviral Therapy [Internet]. [cited 2025 Feb 27]. Available from: https://www.mdpi.com/1999-4915/2/9/2078

[58] Heuschkel MJ, Bach C, Meiss-Heydmann L, Gerges E, Felli E, Giannone F, et al. JAK1 promotes HDV replication and is a potential target for antiviral therapy. Journal of Hepatology. 2024 Feb 1;80(2):220–31.

[59] Frericks N, Klöhn M, Lange F, Pottkämper L, Carpentier A, Steinmann E. Host-targeting antivirals for chronic viral infections of the liver. Antiviral Research. 2025 Feb 1;234:106062.

[60] Crobu MG, Ravanini P, Impaloni C, Martello C, Bargiacchi O, Di Domenico C, et al. Hepatitis C Virus as a Possible Helper Virus in Human Hepatitis Delta Virus Infection. Viruses. 2024 Jun;16(6):992.

[61] Antonelli G, Turriziani O. Antiviral therapy: old and current issues. International Journal of Antimicrobial Agents. 2012 Aug 1;40(2):95–102.

[62] Schiller DS, Youssef-Bessler M. Etravirine: A second-generation nonnucleoside reverse transcriptase inhibitor (NNRTI) active against NNRTI-resistant strains of HIV. Clinical Therapeutics. 2009 Apr 1;31(4):692–704.

[63] Antiviral Activity of Polymethoxylated Flavones from "Guangchenpi", the Edible and Medicinal Pericarps of Citrus reticulata 'Chachi' | Journal of Agricultural and Food Chemistry [Internet]. [cited 2025 Feb 27]. Available from: https://pubs.acs.org/doi/10.1021/jf404310y

[64] Marschall M, Stamminger T. Molecular targets for antiviral therapy of cytomegalovirus infections. Future Microbiology. 2009 Aug 1;4(6):731–42.

[65] Viral RNA capping: Mechanisms and antiviral therapy - Chen - 2024 - Journal of Medical Virology - Wiley Online Library [Internet]. [cited 2025 Feb 27]. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.29622

[66] Boutimah F, Eekels JJM, Liu YP, Berkhout B. Antiviral strategies combining antiretroviral drugs with RNAi-mediated attack on HIV-1 and cellular co-factors. Antiviral Research. 2013 Apr 1;98(1):121–9.

[67] Viral and Immune Risk Factors of HIV Rebound After Interruption of Antiretroviral Therapy | The Journal of Infectious Diseases | Oxford Academic [Internet]. [cited 2025 Feb 27]. Available from: https://academic.oup.com/jid/advance-article-abstract/doi/10.1093/infdis/jiae585/7921339

[68] Mojumdar K, Vajpayee M, Chauhan NK, Mendiratta S. Late presenters to HIV care and treatment, identification of associated risk factors in HIV-1 infected Indian population. BMC Public Health. 2010 Jul 13;10(1):416.

[69] Tetraspanins: Host Factors in Viral Infections [Internet]. [cited 2025 Feb 27]. Available from: https://www.mdpi.com/1422-0067/22/21/11609

[70] Human host factors required for influenza virus replication | Nature [Internet]. [cited 2025 Feb 27]. Available from: https://www.nature.com/articles/nature08699

[71] Harnessing host–virus evolution in antiviral therapy and immunotherapy - Heaton - 2019 - Clinical & Translational Immunology - Wiley Online Library [Internet]. [cited 2025 Feb 27]. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/cti2.1067

[72] Du R, Achi JG, Cui Q, Rong L. Paving new roads toward the advancement of broad-spectrum antiviral agents. Journal of Medical Virology. 2024;96(1):e29369.

[73] Blázquez AB, Mingo-Casas P, Quesada E, Priego EM, Pérez-Perez MJ, Martín-Acebes MA. Lipid-targeting antiviral strategies: Current state and future perspectives. Antiviral Research. 2025 Apr 1;236:106103.

[74] HIV Infection and Coronary Heart Disease: An Intersection of Epidemics | The Journal of Infectious Diseases | Oxford Academic [Internet]. [cited 2025 Feb 27]. Available from: https://academic.oup.com/jid/article-abstract/205/suppl_3/S355/937817

[75] Zhang L, Wang Y, Xu Q, Zhang W, Liang H, Wu L, et al. Stroke among highly active antiretroviral therapy-naive people living with the human immunodeficiency virus in China: a retrospective study of the characteristics, risk factors, and prognosis. BMC Infect Dis. 2022 Jan 4;22(1):4.

[76] Use of Aptamers as Diagnostics Tools and Antiviral Agents for Human Viruses [Internet]. [cited 2025 Feb 27]. Available from: https://www.mdpi.com/1424-8247/9/4/78

[77] Tarasova O, Petrou A, Ivanov SM, Geronikaki A, Poroikov V. Viral Factors in Modulation of Host Immune Response: A Route to Novel Antiviral Agents and New Therapeutic Approaches. International Journal of Molecular Sciences. 2024 Jan;25(17):9408.

[78] Huang H, Song B, Gao L, Cheng J, Mao Y, Zhao H, et al. Incidence of and risk factors for liver damage in patients with HIV-1 mono-infection receiving antiretroviral therapy. HIV Medicine. 2022;23(S1):14–22.

[79] Breitkopf R, Treml B, Bukumiric Z, Innerhofer N, Fodor M, Radovanovic Spurnic A, et al. Cytomegalovirus Disease as a Risk Factor for Invasive Fungal Infections in Liver Transplant Recipients under Targeted Antiviral and Antimycotic Prophylaxis. Journal of Clinical Medicine. 2023 Jan;12(16):5198.

[80] Yu X dong, Huang H, Jiao Y, Li J, Fan X, Zhang D, et al. Incidence and risk factors of hypertriglyceridemia in males with human immunodeficiency virus who are treated with combination antiretroviral therapy: a retrospective cohort study. Lipids Health Dis. 2023 Feb 23;22(1):27.

[81] Ozioko AL, Topman NN, Nwosu CN, Fadugba SE, Malesela K, Aja RO, et al. Quantitative assessment of targeted testing and antiretroviral therapy integration in mathematical modeling of HIV/AIDS dynamics. Scientific African. 2024 Sep 1;25:e02291.

[82] Cardiovascular adverse effects of antiviral therapies for COVID-19: Evidence and plausible mechanisms | Acta Pharmacologica Sinica [Internet]. [cited 2025 Feb 27]. Available from: https://www.nature.com/articles/s41401-024-01382-w

[83] Xia C, Luo D, Yu X, Jiang S, Liu S. HIV-associated dementia in the era of highly active antiretroviral therapy (HAART). Microbes and Infection. 2011 May 1;13(5):419–25.

[84] Kumar S, Jin M, Ande A, Sinha N, Silverstein PS, Kumar A. Alcohol consumption effect on antiretroviral therapy and HIV-1 pathogenesis: role of cytochrome P450 isozymes. Expert Opinion on Drug Metabolism & Toxicology. 2012 Nov 1;8(11):1363–75.

[85] Vázquez-Santiago FJ, Noel RJ, Porter JT, Rivera-Amill V. Glutamate metabolism and HIV-associated neurocognitive disorders. J Neurovirol. 2014 Aug 1;20(4):315–31.

[86] Oral infectious diseases: a potential risk factor for HIV virus recrudescence? - González - 2009 - Oral Diseases - Wiley Online Library [Internet]. [cited 2025 Feb 27]. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1601-0825.2009.01533.x

[87] Endalamaw Alamneh D, Shiferaw MB, Getachew Demissie M, Emiru MA, Zemene Kassie T, Endaylalu Lakew K, et al. Virological Outcomes Among Pregnant Women Receiving Antiretroviral Treatment in the Amhara Region, North West Ethiopia. HIV/AIDS - Research and Palliative Care. 2023 Dec 31;15:209–16.

[88] Cohen OJ, Kinter A, Fauci AS. Host factors in the pathogenesis of HIV disease. Immunological Reviews. 1997;159(1):31–48.

[89] Lama J, Planelles V. Host factors influencing susceptibility to HIV infection and AIDS progression. Retrovirology. 2007 Jul 25;4(1):52.

[90] Roger M. Influence of host genes on HIV-1 disease progression. The FASEB Journal. 1998;12(9):625–32.

[91] Roles of HIV-1 auxiliary proteins in viral pathogenesis and host-pathogen interactions | Cell Research [Internet]. [cited 2025 Feb 27]. Available from: https://www.nature.com/articles/7290370

[92] Santa-Marta M, Brito P, Godinho-Santos A, Goncalves J. Host Factors and HIV-1 Replication: Clinical Evidence and Potential Therapeutic Approaches. Front Immunol [Internet]. 2013 Oct 24 [cited 2025 Feb 27];4. Available from: https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2013.00343/full

[93] Lake J anne, Carr J, Feng F, Mundy L, Burrell C, Li P. The role of Vif during HIV-1 infection: interaction with novel host cellular factors. Journal of Clinical Virology. 2003 Feb 1;26(2):143–52.

[94] Andrade F. Non-cytotoxic antiviral activities of granzymes in the context of the immune antiviral state. Immunological Reviews. 2010;235(1):128–46.

[95] Bergamaschi A, Pancino G. Host hindrance to HIV-1 replication in monocytes and macrophages. Retrovirology. 2010 Apr 7;7(1):31.

[96] Arhel N, Kirchhoff F. Host proteins involved in HIV infection: New therapeutic targets. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 2010 Mar 1;1802(3):313–21.

[97] Emerging Drug Targets for Antiretroviral Therapy | Drugs [Internet]. [cited 2025 Feb 27]. Available from: https://link.springer.com/article/10.2165/00003495-200565130-00002

[98] Antiviral innate immunity pathways | Cell Research [Internet]. [cited 2025 Feb 27]. Available from: https://www.nature.com/articles/7310019

[99] Recent advances targeting innate immunity-mediated therapies against HIV-1 infection - Shankar - 2012 - Microbiology and Immunology - Wiley Online Library [Internet]. [cited 2025 Feb 27]. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1348-0421.2012.00485.x

[100] Huber A, Baas FS, van der Ven AJAM, dos Santos JC. Innate Immune Cell Functions Contribute to Spontaneous HIV Control. Curr HIV/AIDS Rep. 2024 Nov 30;22(1):6.

[101] Innate immune recognition of viral infection | Nature Immunology [Internet]. [cited 2025 Feb 27]. Available from: https://www.nature.com/articles/ni1303

[102] Levy JA, Scott I, Mackewicz C. Protection from HIV/AIDS: the importance of innate immunity. Clinical Immunology. 2003 Sep 1;108(3):167–74.

[103] Heim MH, Thimme R. Innate and adaptive immune responses in HCV infections. Journal of Hepatology. 2014 Nov 1;61(1, Supplement):S14–25.

[104] Learning from the Messengers: Innate Sensing of Viruses and Cytokine Regulation of Immunity — Clues for Treatments and Vaccines [Internet]. [cited 2025 Feb 27]. Available from: https://www.mdpi.com/1999-4915/5/2/470?utm_source=dlvr.it&utm_medium=tumblr

[105] Innate metabolic responses against viral infections | Nature Metabolism [Internet]. [cited 2025 Feb 27]. Available from: https://www.nature.com/articles/s42255-022-00652-3

[106] HIV-1 evades innate immune recognition through specific cofactor recruitment | Nature [Internet]. [cited 2025 Feb 27]. Available from: https://www.nature.com/articles/nature12769

[107] Biron CA. Role of early cytokines, including alpha and beta interferons (IFN-α\β), in innate and adaptive immune responses to viral infections. Seminars in Immunology. 1998 Oct 1;10(5):383–90.

[108] Biron CA. Role of early cytokines, including alpha and beta interferons (IFN-α\β), in innate and adaptive immune responses to viral infections. Seminars in Immunology. 1998 Oct 1;10(5):383–90.

[109] Therapeutics targeting the innate immune system | Nature Reviews Immunology [Internet]. [cited 2025 Feb 27]. Available from: https://www.nature.com/articles/nri1396

[110] Yin X, Langer S, Zhang Z, Herbert KM, Yoh S, König R, et al. Sensor Sensibility—HIV-1 and the Innate Immune Response. Cells. 2020 Jan;9(1):254.

[111] Zimmermann KC, Green DR. How cells die: Apoptosis pathways. Journal of Allergy and Clinical Immunology. 2001 Oct 1;108(4, Supplement):S99–103.

[112] Apoptosis pathways in cancer and cancer therapy | Cancer Immunology, Immunotherapy [Internet]. [cited 2025 Feb 27]. Available from: https://link.springer.com/article/10.1007/s00262-003-0474-8

[113] Apoptosis—an introduction - Lawen - 2003 - BioEssays - Wiley Online Library [Internet]. [cited 2025 Feb 27]. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/bies.10329

[114] Reed JC. Mechanisms of Apoptosis. The American Journal of Pathology. 2000 Nov 1;157(5):1415–30.

[115] Caspases: the proteases of the apoptotic pathway | Oncogene [Internet]. [cited 2025 Feb 27]. Available from: https://www.nature.com/articles/1202581

[116] Twomey C, McCarthy JV. Pathways of apoptosis and importance in developement. Journal of Cellular and Molecular Medicine. 2005;9(2):345–59.

[117] Zaman S, Wang R, Gandhi V. Targeting the apoptosis pathway in hematologic malignancies. Leukemia & Lymphoma. 2014 Sep 1;55(9):1980–92.

[118] Yue J, López JM. Understanding MAPK Signaling Pathways in Apoptosis. International Journal of Molecular Sciences. 2020 Jan;21(7):2346.

[119] Haupt S, Berger M, Goldberg Z, Haupt Y. Apoptosis - the p53 network. Journal of Cell Science. 2003 Oct 15;116(20):4077–85.

[120] Cohen JJ. Apoptosis: The Physiologic Pathway of Cell Death. Hospital Practice. 1993 Dec 15;28(12):35–43.

[121] Mechanisms of apoptosis | Biochemistry (Moscow) [Internet]. [cited 2025 Feb 27]. Available from: https://link.springer.com/article/10.1134/S0006297915110012

[122] Li-Weber M. Targeting apoptosis pathways in cancer by Chinese medicine. Cancer Letters. 2013 May 28;332(2):304–12.

[123] Targeting Apoptosis Pathways in Cancer Therapy | Bentham Science Publishers [Internet]. [cited 2025 Feb 27]. Available from: https://www.benthamdirect.com/content/journals/ccdt/10.2174/1568009043332763

[124] Pećina-Šlaus N. Wnt signal transduction pathway and apoptosis: a review. Cancer Cell Int. 2010 Jun 30;10(1):22.

[125] Vermeulen K, Van Bockstaele DR, Berneman ZN. Apoptosis: mechanisms and relevance in cancer. Ann Hematol. 2005 Oct 1;84(10):627–39.

[126] Kannan K, Jain SK. Oxidative stress and apoptosis. Pathophysiology. 2000 Sep 1;7(3):153–63.

[127] Nair P, Lu M, Petersen S, Ashkenazi A. Chapter Five - Apoptosis Initiation Through the Cell-Extrinsic Pathway. In: Ashkenazi A, Yuan J, Wells JA, editors. Methods in Enzymology [Internet]. Academic Press; 2014 [cited 2025 Feb 27]. p. 99–128. (Regulated Cell Death Part A: Apoptotic Mechanisms; vol. 544). Available from: https://www.sciencedirect.com/science/article/pii/B9780124171589000054

[128] Duronio V. The life of a cell: apoptosis regulation by the PI3K/PKB pathway. Biochemical Journal. 2008 Oct 15;415(3):333–44.

[129] Apoptosis signaling pathways and lymphocyte homeostasis | Cell Research [Internet]. [cited 2025 Feb 27]. Available from: https://www.nature.com/articles/cr200752

[130] Kiraz Y, Adan A, Kartal Yandim M, Baran Y. Major apoptotic mechanisms and genes involved in apoptosis. Tumor Biol. 2016 Jul 1;37(7):8471–86.

[131] Chen M, Wang J. Initiator caspases in apoptosis signaling pathways. Apoptosis. 2002 Aug 1;7(4):313–9.

[132] Simon HU. Neutrophil apoptosis pathways and their modifications in inflammation. Immunological Reviews. 2003;193(1):101–10.

[133] Signal Transduction Pathways in Apoptosis | Stem Cells | Oxford Academic [Internet]. [cited 2025 Feb 27]. Available from: https://academic.oup.com/stmcls/article-abstract/14/6/619/6390672

[134] The TRAIL apoptotic pathway in cancer onset, progression and therapy | Nature Reviews Cancer [Internet]. [cited 2025 Feb 27]. Available from: https://www.nature.com/articles/nrc2465

[135] Extrinsic versus intrinsic apoptosis pathways in anticancer chemotherapy | Oncogene [Internet]. [cited 2025 Feb 27]. Available from: https://www.nature.com/articles/1209608

[136] Wang LG, Liu XM, Kreis W, Budman DR. The effect of antimicrotubule agents on signal transduction pathways of apoptosis: a review. Cancer Chemother Pharmacol. 1999 Sep 1;44(5):355–61.

[137] Cummings J, Ward TH, Ranson M, Dive C. Apoptosis pathway-targeted drugs—from the bench to the clinic. Biochimica et Biophysica Acta (BBA) - Reviews on Cancer. 2004 Dec 10;1705(1):53–66.

[138] Molecular and cellular approaches for the detection of protein–protein interactions: latest techniques and current limitations - Lalonde - 2008 - The Plant Journal - Wiley Online Library [Internet]. [cited 2025 Feb 27]. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365-313X.2007.03332.x

[139] Radiation-induced lung toxicity – cellular and molecular mechanisms of pathogenesis, management, and literature review | Radiation Oncology [Internet]. [cited 2025 Feb 27]. Available from: https://link.springer.com/article/10.1186/s13014-020-01654-9

[140] Harrison PJ, Conway HL, Holmes RW, Davis CO. Marine diatoms grown in chemostats under silicate or ammonium limitation. III. Cellular chemical composition and morphology of Chaetoceros debilis, Skeletonema costatum, and Thalassiosira gravida. Mar Biol. 1977 Sep 1;43(1):19–31.

[141] Fatality in mice due to oversaturation of cellular microRNA/short hairpin RNA pathways | Nature [Internet]. [cited 2025 Feb 27]. Available from: https://www.nature.com/articles/nature04791

[142] Nagai T, Tomioka N, Kawasaki T, Imai A, Matsushige K. In-situ growth rate of Microcystis spp. and their growth-limiting factors: use of cellular RNA content. Limnology. 2011 Dec 1;12(3):235–43.