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Molecular Biology and Pathogenesis of Retroviruses

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Abstract

Retroviruses consist of a varied family of enveloped RNA viruses with positive-sense RNAs that replicate in a host cell through the process of reverse transcription. Retroviruses belong to the Retroviridae family that typically carries their genetic material in the form of ribonucleic acid, while the genetic material of their hosts is in the form of deoxyribonucleic acid. Infections with a number of retroviruses can lead to serious conditions, such as AIDS, a range of malignancies, neurological diseases, and added clinical conditions. In addition, some can even become integrated as DNA in the germ line and passed as endogenous viruses from generation to generation. Surprisingly, retroviruses do not appear to straightforwardly activate host innate defenses. On the other hand, attention in these viruses extends beyond their disease causing capabilities. For example, studies on the retroviruses led to the discovery of oncogenes, understanding of mechanisms that regulate eukaryotic gene expression, and these are proving to be valuable research tools in molecular biology and have been used successfully in gene therapy. The central goals of retrovirology today are the treatment and the prevention of human and non-human diseases and to use this virus in research.

Keywords: retrovirus, Retroviridae, reverse transcriptase, replication, immune responses, ART

1. Introduction

During the past few decades retrovirus has done an adequate amount of harm to the human life and became a big threat globally. These are the group of viruses that belong to the family Retroviridae and that typically carry their genetic material in the form of ribonucleic acid (RNA), while the genetic material of their hosts is in the form of deoxyribonucleic acid (DNA). Retroviruses are named for an enzyme known as reverse transcriptase (RT), which was discovered independently in 1971 by American virologists Howard Temin and David Baltimore for which they have received Nobel Prize in physiology and medicine in the year

1975. Retroviridae is a family of enveloped, obligate parasites with single-stranded positive-sense RNA (ssRNA) that replicate in a host cell through the process of reverse transcription. The activity of RT makes it feasible for genetic material from a retrovirus to become permanently integrated into the DNA genome (provirus) of an infected cell.

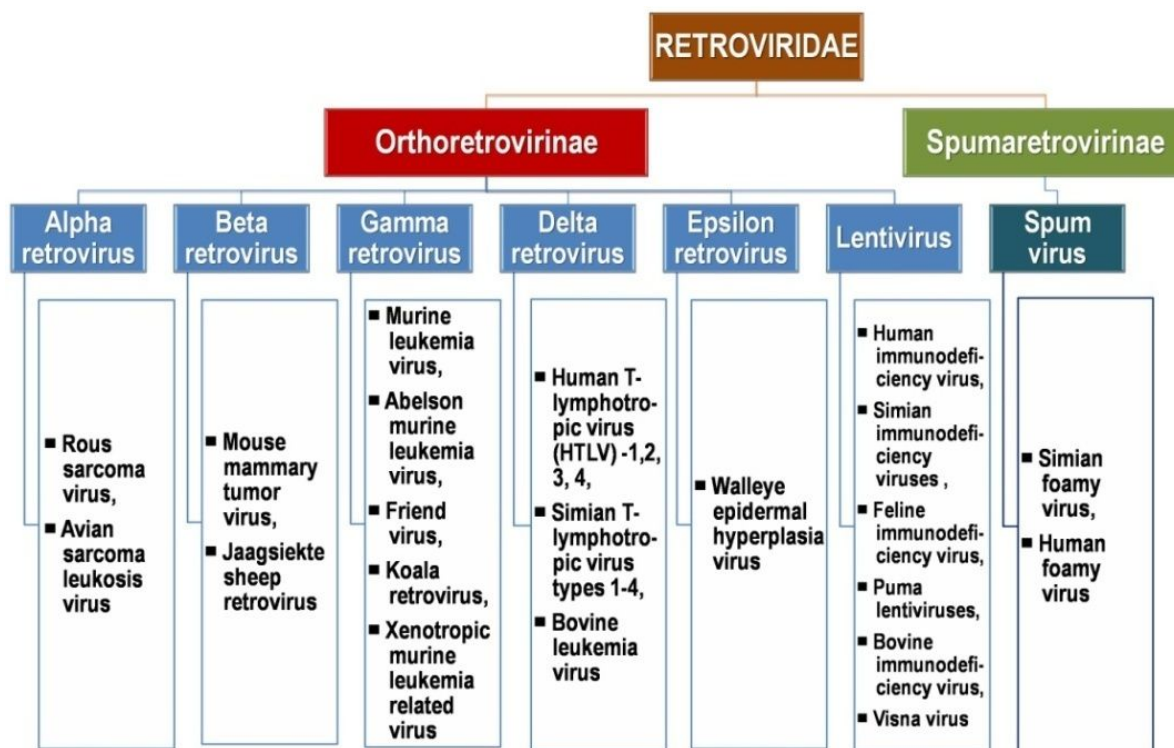


Figure 1. Classification of *Retroviridae* family of viruses.

Retroviridae is subdivided into *Orthoretrovirinae* and *Spumaretrovirinae* (Figure 1). Under *Orthoretrovirinae* the various genus are *Alpharetrovirus* (Rous sarcoma virus, avian sarcoma leukosis virus), *Betaretrovirus* (Mouse mammary tumor virus, Jaagsiekte sheep retrovirus), *Gammaretrovirus* (murine leukemia virus, Abelson murine leukemia virus, Friend virus, koala retrovirus, xenotropic murine leukemia-related virus), *Deltaretrovirus* (Human T-lymphotropic virus (HTLV) types 1–4, simian T-lymphotropic virus types 1–4, Bovine leukemia virus), *Epsilonretrovirus* (Walleye epidermal hyperplasia virus), and *Lentivirus* (human immunodeficiency virus (HIV), simian immunodeficiency viruses (SIV), feline immunodeficiency virus, puma lentiviruses, bovine immunodeficiency virus, caprine arthritis encephalitis virus, visna virus) are present, whereas under *Spumaretrovirinae* only one genus is present *spumavirus* (simian foamy virus, human foamy virus) [1]. The retroviruses host range include human, murine, feline (cat), avian (birds), and bovine (pig), and it is dependent upon the viral envelope, glycoproteins and structural proteins, involved in integration. Infections with a number of retroviruses can lead to serious conditions, such as AIDS, a range of malignancies, neurological diseases, and added clinical conditions [2]. In addition, some retroviruses can even become integrated as DNA in the germ line and passed as endogenous viruses from generation to generation. Using retrovirus in research has built up the need to advance the investigation in detail regarding the viral particles and genomes, their modes of replication, integration, and

host immune evasion. The basic replication of retroviruses includes that (Figure 2) the ssRNA become double-stranded DNA (dsDNA) and gets into the host genetic material and employs host machinery for the synthesis of new virions.

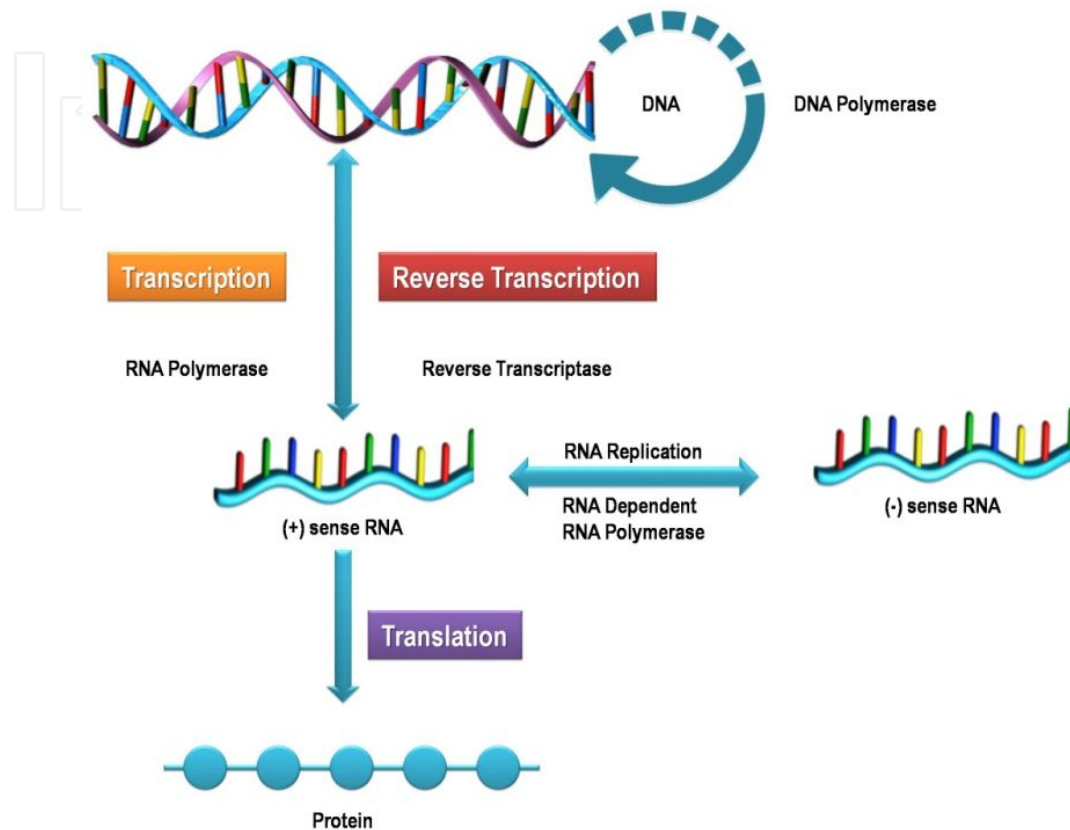


Figure 2. The reverse of Crick's central dogma that occurs in retroviruses. RNA genome is converted by reverse transcriptase into double-stranded DNA, followed by integration into the host genome, transcription and translation of viral proteins occurs along with the host.

Interesting Points about Retroviruses

- Retroviruses contain RNA as genetic material but have DNA-dependent steps in their replication.
- Replicates via reverse transcription because of the presence of reverse transcriptase enzyme.
- Integrase transfers the viral DNA into the cell nucleus and viral dsDNA is covalently and randomly integrated into the cell's genome.
- Retroviruses that can transform host cells at high rates contain gene sequences such as viral oncogenes and proto-oncogenes.
- Human retroviruses can cause immune deficiencies, cancer, and neurological diseases.

2. Retrovirus structure, genome, and proteins

The typical retrovirus structure is enveloped, spherical to pleomorphic in shape, and they have diameter of 80–100 nm. The different genres of retrovirus virions (Figure 3) have diverse morphology, but they have their same virion component, which includes the outer envelope coat, two copies of the genetic material, and the viral proteins. Envelope consists of lipids that are obtained from the host plasma membrane during budding process and the glycoprotein such as gp120 and gp41 in case of HIV [3]. The retroviral envelope serves three separate functions that includes the outer lipid bilayer protects from the extracellular environment, it also aids in the entry and way out of host cells through endosomal membrane trafficking, and the facility to straightforwardly enter cells by fusing with their membranes.

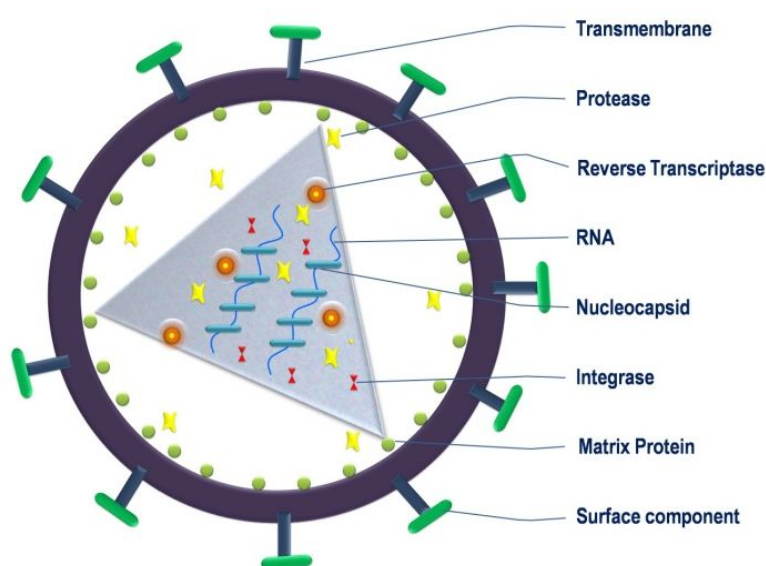


Figure 3. Schematic cross section through a retroviral particle: Showing retrovirus components.

The genome of retrovirus is monopartite, linear, dimeric, ssRNA (+) of about 8–10 kb, with a 5'-cap and a 3' poly-A tail (Figure 4). The group-specific gene (*gag*), *pol*, *pro*, envelope (*env*) genes are flanked between the R regions. The 5'-long terminal repeats (LTRs) consist of U3 (unique sequence), R primer binding site (PBS), and U5 regions. The 3' end consists of a polypurine tract (PPT), U3, and R regions. The R region is a short repeated sequence at each end of the genome used during the reverse transcription to ensure correct end-to-end transfer in the growing chain. U5, on the other hand, is a short exceptional arrangement in the middle of R and PBS [4]. PBS consists of 18 bases corresponding to 3' end of tRNA primer. L region is an untranslated leader region that gives the sign for packaging of the genome RNA. The retroviral protein includes *gag*, protease, *pol*, and *env* proteins. *Gag* is the primary retroviral structural protein responsible for orchestrating the majority of steps in viral assembly. Most of these assembly steps occur through interactions with three *gag* subdomains—matrix (MA), capsid (CA), and nucleocapsid (NC). The *gag* subdomains are structurally discrete but have functionally overlapping roles in the viral assembly process [5, 6].

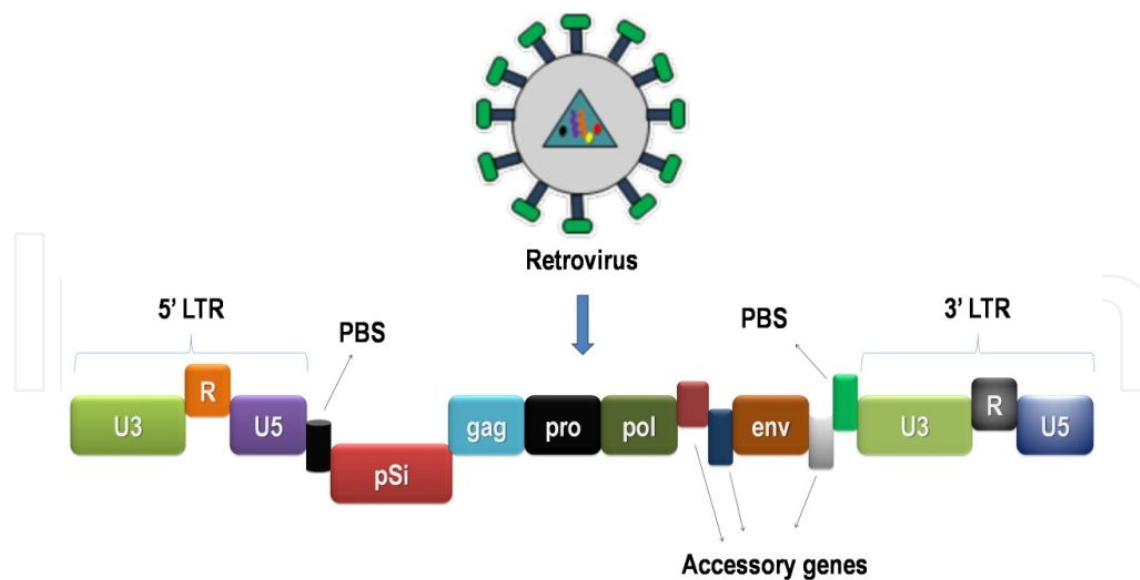


Figure 4. Retrovirus structure and genome: The three significant protein coding genes include group-specific gene (gag), pol, envelope (env) genes, which are flanked between the R regions and codes for capsid, reverse transcriptase, integrase, protease, and envelope proteins, respectively. Retroviruses are characterized by the 5' and 3' long terminal repeat (LTR) sequences, which are thought to control and gene expression. The LTRs each contain two unique non-protein-coding sequences, called U5 at the 5' end and U3 at the 3' end, which encodes controlling elements. PBS consists of 18 bases corresponding to 3' end of tRNA primer. The R region is a short repeated sequence at each end of the genome used during the reverse transcription to ensure correct end-to-end transfer in the growing chain.

3. Genetic variations and retroviruses

Retroviruses, similar to all RNA viruses, show a high mutation rate. The real component for creating genetic variation within retroviral populations is because of the polymerization error during DNA synthesis by RT, which does not have a proofreading activity [7]. The reason for this high genetic variation is because of viral mutation rate, recombination rate, rate of replication, size of the viral population, and selective forces [8, 9]. Genetic variation has been documented extensively in populations of HIV type 1. This genetic adaptability has significant consequences for the evolution of HIV-1 and other retroviruses and their impact on human health [8]. Because of the genetic variations, retroviruses are expanding its host range; for example, HIV-1 can switch from using the CCR5 co-receptor to using the CXCR4 co-receptor [10]. This difference in retroviral populations provides a mechanism for retroviruses to escape host immune responses and expand resistance to all known antiretroviral drugs [7, 11].

4. Replication of retroviruses

Replication is a multistep process; each step is crucial for the virus entry and multiplies itself in the host cell. The study of retroviruses particle assembly, budding, and release has been

especially rich in terms of the exchange of concepts and techniques with related areas of cell biology [12]. There are seven steps in the replication cycle of the retrovirus (Figure 5). The initial step is attachment, in which the retrovirus utilizes one of its glycoproteins to attach to one or more particular cell-surface receptors on the host cell. Some retroviruses likewise utilize an optional receptor, referred to as the co-receptor. The second and third steps are penetration and uncoating, individually. Retroviruses infiltrate the host cell by direct fusion of the virion envelope with the plasma membrane of the host. The fourth step is replication, which happens after the retrovirus undergoes partial uncoating thereby releasing its genome and three essential enzymes (RT, integrase, and pol gene coding enzymes). At this stage, the RNA genome is converted by RT into double-stranded DNA, followed by integration into the host genome, transcription and translation of viral proteins along with the host. The fifth step is assembly, in which retrovirus capsids are assembled in an immature form. The sixth step is budding, in which the immature viral particle acquires the host plasma membrane, and the final step is maturation and release, in which the gag and pol proteins of the retrovirus are cleaved by the retroviral protease, thus forming the mature and infectious form of the virus [13]. The retrovirus replication is well studied in case of HIV virus. HIV replicates million of time per day, destroying the host immune cells and eventually causing disease progression. During HIV replication the virus recognizes host cell such as CD4⁺ T- lymphocyte. Entry of HIV into the cells requires certain substances on the cell surface such as CD4 receptor and co-receptors such as CCR5 and CXCR4 [14]. These receptors interact with protein complexes that are embedded in the viral envelope. The viral proteins consist of extracellular gp120 and trans-membrane gp41 proteins. When HIV approaches the target cell, the gp120 binds with the cell surface receptor, this process is termed as attachment. Following co-receptor binding results in a conformational change in gp120, this allows gp41 to unfold and extend its hydrophobic terminal into the cell membrane. gp41 then folds back on itself, this causes the virus to move close toward the cell and facilitates the fusion of their membranes. The viral nucleocapsid then enters the cell and releasing two viral RNA strands and three essential replication enzymes; integrase, protease, and RT. HIV RT is a heterodimer composed of two subunits (p66 and p51). At first, RT begins the reverse transcription of viral RNA; it consists of two catalytic domains — ribonuclease H active site and polymerase active site. In the polymerase active site, single-stranded viral RNA is transcribed into an RNA-DNA double helix. These RNA-DNA hybrids are cleaved into individual stands by ribonuclease H. The polymerase then completes the remaining strand into DNA double helix (dsDNA). After the formation of dsDNA, integrase moves into action, it cleaves each dinucleotide from 3' end of the DNA creating two sticky ends. Integrase then transfers the viral DNA into the cell nucleus and viral dsDNA is covalently and randomly integrated into the cell's genome [15]. The host cell genome now contains the genetic information of HIV virus. Activation of the host cell induces the transcription of proviral DNA by Pol II produces viral spliced and unspliced messenger RNAs. This messenger RNA now migrates into the cytoplasm, where building blocks for a new virus were synthesized. Some of the building blocks have to be processed by the viral protease where longer proteins are cleaved into small core proteins. The processing of viral proteins is crucial to create an infectious virus. Translation of unspliced viral RNAs produces env, gag, and gag-pol polyproteins. The two viral RNA strands with three enzymes come together and core proteins

assemble around them forming a capsid, which is an immature virus particle. Capsid leaves the host cell by acquiring new envelope of host and viral proteins (mature virus) such as gp120 and gp41; this process is known as budding. Recent reports suggest that during this process of budding, clathrin is recruited into the HIV particle with high specificity [16]. These matured virus become ready to infect the other cells [15]. A critical aspect of viral replication is the assembly of virus particles, which are subsequently released as progeny virus. While a great deal of attention has been focused on better understanding this phase of the viral lifecycle, many aspects of the molecular details remain poorly understood.

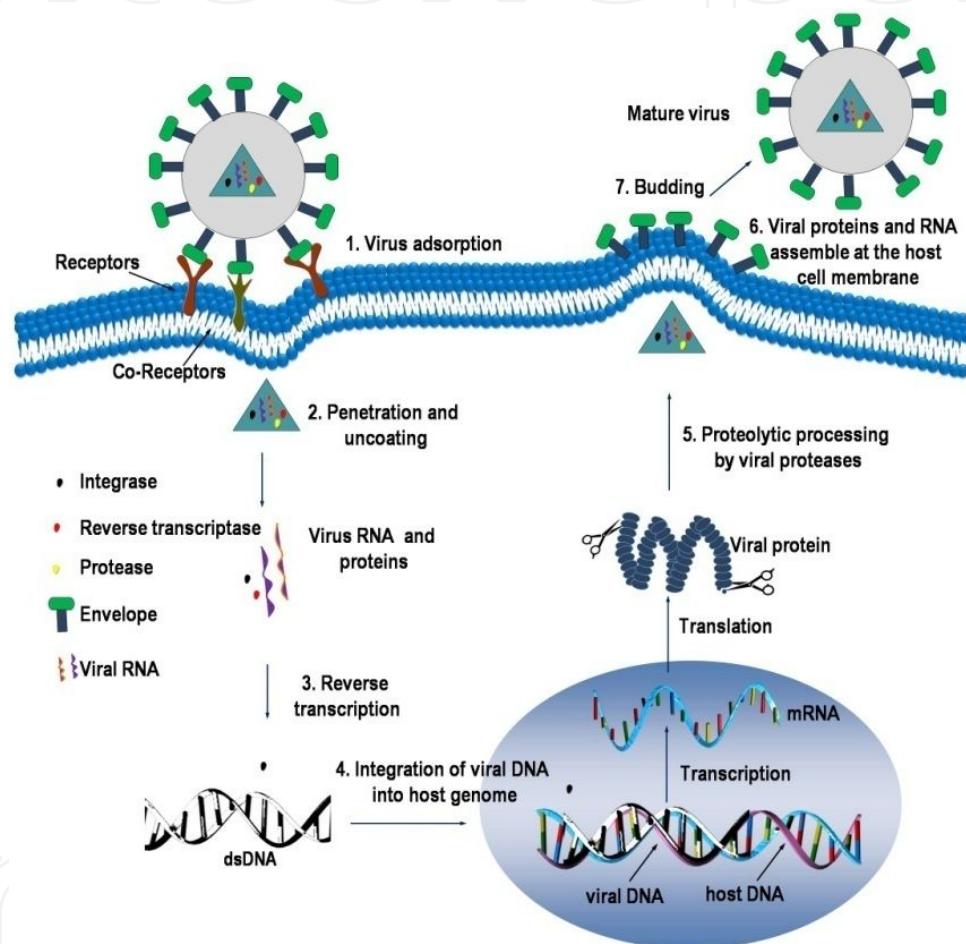


Figure 5. Replication of retroviruses: There are seven steps in the replication cycle of the retrovirus. The initial step is attachment, in which the retrovirus utilizes one of its glycoproteins to attach to one or more particular cell-surface receptors on the host cell. Some retroviruses likewise utilize an optional receptor, referred to as the co-receptor. The second step is penetration and uncoating, individually. Retroviruses infiltrate the host cell by direct fusion of the virion envelope with the plasma membrane of the host. The third step is replication, which happens after the retrovirus undergoes partial uncoating thereby releasing its genome and three essential enzymes. At this stage, the RNA genome is converted by reverse transcriptase into double-stranded DNA (dsDNA). The fourth step is integration, in which retrovirus dsDNA integrates into the host genome followed by transcription and translation of the viral proteins occurs. The fifth step includes proteolytic processing of viral proteins. The sixth step includes assembly of viral proteins and RNA. The seventh step is budding, in which the immature viral particle acquires the host plasma membrane and final step is maturation and release, in which the gag and pol proteins of the retrovirus are cleaved by the retroviral protease, thus forming the mature and infectious form of the virus.

A provirus can be transmitted through the germ line from parents to offspring as an endogenous retrovirus [17, 18]. Human endogenous retroviruses (HERVs) account for about 8% of the human genome [19]. Exogenous retroviruses seem to have arisen from endogenous retrotransposons by acquisition of a cellular envelope gene [20]. The existence of HERVs has been identified for many years, but their abundance in the genome was not predicted by earlier studies [21]. Retroviral genome gets into human genome and by *de novo* insertion followed by activation of downstream proto-oncogenes, or by gene disruption [22]. Retrovirus integration does not occur in resting (Go phase) cells yet rather requires that cells be in the S phase (DNA synthesis) of their mitotic cycle. Since the mitotic phase is induced by a binary recognition event, integration and virus reproduction perhaps require that the invaded target T-cell interact with the appropriate B-cell-processed antigen complex. Once the viral cDNA integrates, transcription to mRNA proceeds at some rate that depends on the details of the infecting virus and the invaded cell [23]. It is also reported that enhancer and promoter elements in retroviral LTRs can influence the transcription of next genes that can result in transcriptional activation or gene silencing and which may result in abnormal expression of tissue-specific proteins [24]. The human genome contains many endogenous retroviral sequences, and these have been suggested to play important roles in a number of physiological and pathological processes. Researchers also found that ERVs also take part in the body's immune defense against regular bacterial and viral pathogens. HERVs are classified into three broad classes (I, II, III). Analysis of the draft human genome has so far found only three HERV proviruses with complete open reading frames for *gag*, *pol*, and *env*, which are considered as essential viral genes, and at least one of these HERVs is mutated at a critical residue in the reverse transcriptase domain of *pol* [25]. HERVs have frequently been reported as etiological cofactors in chronic diseases such as cancer, autoimmunity, and neurological disease.

5. Mode of transmission

Most of the retroviruses transmission occurs through cell to cell, mother to fetus transmission, and through biological fluids. Cell-to-cell transmission of retroviruses is much more efficient as compared with cell-free conditions, and as retroviruses reach through the tight cell-cell interface, they are out of reach of the immune system [26]. Retrovirus employs various mechanisms of immune evasion, however, and can destroy the immune system or subvert it to enable successful transmission [27].

6. Immune system and retroviruses

The human immune system needs to manage with various pathogens, ranging from RNA viruses to 30-foot-long tapeworms [28]. Although we have gained much understanding of innate immune recognition of many microbial pathogens, currently we have very little knowledge about innate immune responses against retroviral infections [29]. The immune system retroviruses (ISRV) are defined as a retrovirus (HIV) whose target is T4-positive T-

helper cells of the immune system that requires stimulation by antigens to reproduce. T-cells are part of the response mechanism that defends the body against attacking agents and are stimulated to reproduce by such agents [23]. Antiviral responses are characteristically marked by stimulation of type I interferon through various mechanisms that recognize viral nucleic acids. These responses restrain the viral replication by various mechanisms and activate the adaptive immune responses with the help of antigen presenting cells and also aids in developing memory and viral clearance. But, quite number of reports suggests that viruses also have developed a variety of means for circumventing innate immune responses, ensuring their survival and transmission. Surprisingly retroviruses do not appear to straightforwardly activate host innate defenses. It was observed that generalized immune activation and increased amount of cytokines and immunoglobulins along with the progressive loss of CD4⁺ T-cells was reported during HIV-1 infection [30].

Generally, viral infection triggers innate immune sensors to produce type I interferon. However, this is not the case with retroviruses; the reason is still not known. The recent reports suggest various molecules it includes: TREX1, which is a cytosolic exonuclease that degrades DNA [31] derived from HIV or endogenous retroelements, thereby preventing the accumulation of cytosolic DNA, which would otherwise trigger innate immunity. In a study on Trex1(-/-) mouse cells and human CD4⁺ T-cells and macrophages in which TREX1 was inhibited by RNA-mediated interference, cytosolic HIV-DNA accumulated and HIV infection induced type I interferon that inhibited HIV replication and spreading [32]. The recent study on innate immune sensors during retroviral infection has identified the enzyme cyclic guanosine monophosphate–adenosine monophosphate (cGAMP) synthase (cGAS) which triggers the cytosolic DNA and activates the production of type I interferons and other cytokines. The mechanism in which these sensors act by includes firstly viral DNA binds and activates cGAS, which catalyzes the synthesis of a cGAMP isomer from adenosine triphosphate (ATP) and guanosine triphosphate (GTP). This cGAMP isomer that is termed has 2'3'-cGAMP contains both 2'-5' and 3'-5' phosphodiester linkages. cGAMP then binds and activates the endoplasmic reticulum protein stimulator of IFN genes (STING) and functions as a second messenger. STING activates the NF- κ B, interferon regulatory factor 3 (IRF3) to induce interferons and other cytokines through the activation of protein kinases I κ B kinase (IKK) and TANK-binding kinase 1 (TBK1) [32–35]. In our view, there is currently insufficient understanding about how the retroviral infection, in general, is sensed by the innate immune system. If the innate immune part is traced, that will aid in understanding the activation of adaptive immunity and development of antiviral against retroviruses.

7. Antiretroviral therapy

There are about 34 million HIV-1–infected people in the world [36], and this number plainly says that there is an urgent unmet need for investigation of antiretroviral therapy (ART), and management of this worldwide risk is highly desired [37]. ART is treatment of people infected with the retroviruses using anti-retroviral drugs. The goal of antiretroviral therapy is to reduce the amount of virus in infected individual body (viral load) to a level that can no longer be

detected with ongoing treatment blood test. Considerable advances in ART have been made since the introduction of zidovudine (3'-azido-3'-deoxythymidine—AZT) in 1987 [38]. The regular treatment consists of a grouping of at least three drugs called as highly active antiretroviral therapy (HAART) that hold back the viral replication within the host cell and thereby reduces the viral load.

Six classes of antiretroviral agents (Table 1) currently exist (specifically towards HIV); they include the following:

1. Nucleoside reverse transcriptase inhibitors (NRTIs) such as abacavir, emtricitabine, and tenofovir [39] takes action by interfering with the HIV replication cycle through competitive inhibition of reverse transcriptase enzyme a key enzyme in replication and thereby terminates the DNA formation. These can also terminate the DNA formation by incorporating into the proviral DNA; the reason is that NRTIs are structurally similar to the DNA nucleoside bases.
2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) includes niverapine, efavirenz, and etravirine, which acts by non-competitive binding of NNRTIs at the hydrophobic pocket of p66 subunit of the enzyme results in a conformational change and alters the active site and limits RT activity. The limitation of these drugs is that it has a low genetic barrier, i.e., a single mutation in RT genome induces a high-level of phenotypic resistance and prevents its use [40–42].
3. Protease inhibitors (PIs) include indinavir, atazanavir, darunavir, and tipranavir. This retrovirus protease is a 99-amino-acid, aspartic acid protein, which plays an important role in the maturation of virus particles late in the viral life cycle. During or immediately after viral budding from an infected cell, proteases systematically cleaves individual proteins from the gag and gag-pol polypeptide precursors into functional subunits for viral capsid formation. Protease inhibitors act as competitive inhibitors that directly bind to protease and put off the subsequent cleavage of polypeptides. It has recently been suggested that PIs can directly inhibit lymphocyte apoptosis and this effect may contribute to an immunologic benefit independently of an antiviral effect [43–45].
4. Integrase inhibitors (INSTIs) such as dolutegravir and raltegravir are used in combination with a protease inhibitor and target the strand transfer step of retroviral DNA integration. These are approved by FDA in 2007. Integration is essential for viral replication and is thus an attractive target for novel chemotherapy [46]. The integrase enzyme is responsible for transfer of virus-encoded DNA to the host cell chromosome, a necessary event in retrovirus replication [15] INSTIs active against a wide range, including both CCR5 co-receptor and CXCR4 coreceptor—using strains [47].
5. Fusion inhibitors (FIs) include enfuvirtide—act extracellularly to prevent the fusion. It is a peptide based on the gp41 sequence that specifically prevents membrane fusion by competitively binds to gp41 and preventing the conformational change of gp41 required to complete the final step in the fusion process [48].

6. Chemokine receptor antagonist. This small molecule such as maraviroc [49] selectively and reversibly binds the CCR5 coreceptor, blocking the V3 loop interaction and inhibiting fusion of the cellular membranes. Using these inhibitors individually or in combination the virus replication process is slowed and the retroviruses find it more difficult to overcome this combined attack. ART has the potential both to reduce mortality and morbidity rates among infected people, and to improve their quality of life [50].

	Antiretroviral agents	Examples	Mode of action
1.	Nucleoside reverse transcriptase inhibitors (NRTIs)	Abacavir, Emtricitabine	Competitive inhibition of reverse transcriptase enzyme a key enzyme in replication and there by terminates the DNA formation.
2.	Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Niverapine, Efavirenz, Etravirine	Non-competitive binding of NNRTIs at the hydrophobic pocket of p66 subunit of the reverse transcriptase enzyme results in a conformational change and alters the active site and limits enzyme activity.
3.	Protease inhibitors (PIs)	Indinavir, Atazanavir, Darunavir, Tipranavir	Act as competitive inhibitors that directly bind to protease and put off the subsequent cleavage of polypeptides which is an important step in viral maturation.
4.	Integrase inhibitors (INSTIs)	Dolutegravir, Raltegravir	Target the strand transfer step of retroviral DNA integration.
5.	Fusion inhibitors (FIs)	Enfuvirtide	Specifically prevents membrane fusion by competitively binding to gp41 and preventing the conformational change of gp41 required to complete the final step in the fusion process.
6.	Chemokine receptor antagonist	Maraviroc	It binds selectively and reversibly binds the CCR5 coreceptor, blocking the V3 loop interaction and inhibiting fusion of the cellular membranes.

Table 1. Classes of antiretroviral agents and their mode of action

8. Conclusions

The central goals of retrovirology nowadays are the treatment and the prevention of human and non-human diseases and to use this virus in research. Recent studies have shown that

retroviruses can be used in a number of ways such as model for biological research, for understanding of genes, molecular and cell biology studies. On the other hand, attention in these viruses extends beyond their disease causing capabilities, discovery of oncogenes, understanding of mechanisms that regulate eukaryotic gene expression was possible because of the study on retroviruses. The complete understanding of retrovirus could help the researchers and clinicians to use them in various fields of biology and medicine for the development of new methodologies and techniques. Ongoing investigation on application of retroviruses in gene therapy and anti-cancer agents makes these type a widely studying group. The way retroviruses enter and target the specific cells and integrate itself into the host genome was very fascinating to the scientists globally, and these can be used as models to develop new vectors that could be employed in research. Collaborative international project needs to be taken up to understand the complete life cycle of retroviruses. The reason is that this not only aids in developing antiviral, but also gives us idea where gained knowledge could be applied in other fields such as engineering and material sciences and to develop new technologies.

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