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The Global Impact of HIV: A Comprehensive Review

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Abstract: ***The Human Immunodeficiency Virus (HIV) has been a significant global health challenge since its discovery in the 1980s, leading to the devastating Acquired Immunodeficiency Syndrome (AIDS). Despite advancements in medical research and antiretroviral therapies, HIV/AIDS remains a pressing public health concern, particularly in resource-limited regions. This comprehensive review provides updated data and scientific insights on the global impact of HIV, shedding light on the current state of the epidemic and the challenges faced in combating it. The review highlights the resurgence of HIV cases in Eastern European countries, such as Ukraine, Estonia, and Latvia, with surprising increases in AIDS cases observed in East Asian countries. However, it is in sub-Saharan Africa that the burden of HIV remains most acute, with high prevalence rates and a significant number of affected individuals. The region requires continued attention and resources to address the complex challenges associated with HIV prevention, treatment, and care. The article delves into the classification and structure of HIV, emphasizing its belonging to the Lentivirinae subfamily, specifically HIV-1 and HIV-2. HIV-1, the predominant viral species globally, exhibits a distinct clinical latency phase, contributing to its persistence and infectivity. The high replication rate and genetic variability of HIV, driven by the error-prone reverse transcriptase enzyme, result in the emergence of diverse subtypes and strains across different regions. Furthermore, the article explores the structural components of HIV-1, including the envelope glycoproteins (gp120 and gp41), matrix protein, and various enzymes critical to the viral life cycle. Despite progress in medical research and access to antiretroviral therapies, HIV/AIDS continues to present challenges such as limited resources, drug resistance, and regional disparities.***

Keywords: HIV/AIDS; Global impact; Epidemic; Resource-limited regions; Sub-Saharan Africa; Eastern European countries; Lentivirinae subfamily; Antiretroviral therapies

I. INTRODUCTION

Since its discovery in the 1980s, HIV has been a major global health challenge, leading to AIDS [1-4].

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This pandemic has caused immense devastation worldwide, with infections and deaths reaching alarming levels. Despite advancements in medical research and antiretroviral therapies, HIV/AIDS remains a significant public health concern, especially in resource-limited areas. In this review, we provide updated data on the global impact of HIV, highlighting the current state of the epidemic and the challenges faced in addressing it. In recent years, there has been a resurgence of HIV cases in Eastern European countries like Ukraine, Estonia, and Latvia, while East Asian countries have also witnessed an increase in AIDS cases [5-9]. However, the burden of HIV remains most severe in sub-Saharan Africa, with high prevalence rates and a large number of affected individuals. This region requires significant attention and resources to tackle the complex challenges associated with HIV prevention, treatment, and care. HIV belongs to the retrovirus family, specifically the Lentivirinae subfamily, which includes HIV-1 and HIV-2. HIV-1 is the predominant viral species globally, exhibiting a distinct clinical latency phase. The replication rate and genetic variability of HIV, influenced by the reverse transcriptase enzyme, result in diverse subtypes and strains across different regions [10-14]. The structure of HIV-1 consists of envelope glycoproteins, a matrix protein, and various enzymes crucial to the viral life cycle. Understanding the epidemiology, classification, and structure of HIV is essential in combating this global pandemic and striving for more effective prevention strategies and improved access to treatment [15-19].

I) Human Immunodeficiency Virus type 1 (HIV-1)

A) Retrovirus Family

II. DISCOVERY AND GENERAL DEFINITION

Retroviruses were first observed in the early 20th century, including avian leukemia virus and Rous sarcoma virus. Mammalian tumor-causing retroviruses like Moloney's Murine Virus were later discovered. The first human retrovirus, HTLV-I, was discovered in 1980, followed by the discovery of HIV in 1983. Retroviruses have a double-stranded RNA and a membrane envelope. Their genome is transcribed into DNA by reverse transcriptase and inserted into the host cell's DNA. Retroviruses are studied in oncology due to their enzymology and association with Oncogenes [20-25].

III. CLASSIFICATION OF RETROVIRUSES

Retroviruses are classified into three subfamilies:

a) Oncovirinae (Oncovirus)

This subfamily is found in various species and can induce tumors such as sarcomas, carcinomas, lymphomas, and leukemias. HTLV-1, associated with T-cell leukemia, was isolated in 1980.

b) Spumavirinae (Spumavirus)

These viruses were discovered in the 1950s and can infect animals and humans without causing diseases.

c) Lentivirinae (Lentivirus)

Lentiviruses are cytopathogenic and cause slow-growing diseases. HIV-1 and HIV-2, belonging to this subfamily, cause immunodeficiency. HIV-1 exhibits a long clinical latency phase, during which the individual is infectious.

B) Characteristics of HIV-1 Virus

IV. DISCOVERY AND DEMOGRAPHY

The first cases of AIDS were described in the United States in 1981, characterized by a severe decrease in immune defenses. French doctors identified similar cases in France in 1982. Research had already been conducted globally, and the pathogen was found in transfused hemophiliacs, indicating a viral cause. In 1983, the Institut Pasteur published the first description of the virus responsible for AIDS, initially called Lymphadenopathy Associated Virus (LAV) [26-30]. Another strain discovered in the United States was named HTLV-3. These viruses were later named HIV. HIV-1 and HIV-2 have different characteristics and are divided into groups and subtypes correlated with geographic areas.

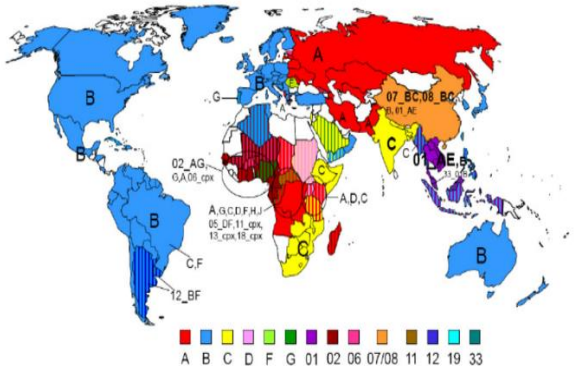

Figure 1: Geographic Distribution of HIV-1 Subtypes

Two mechanisms contribute to the variability observed in HIV:

Reverse transcriptase, the enzyme responsible for viral replication, has a high error rate, resulting in one to two mutations per replication cycle.

The virus has a rapid renewal rate, with 10^8 to 10^9 new virions synthesized daily.

Structure of HIV-1

The morphology and structure of HIV-1 were determined through electron microscopy. The mature virus particles have a roughly spherical shape with a conical capsid. The external envelope contains spike-like structures formed by two glycoproteins:

gp120, which binds to the cell receptor.

gp41, responsible for fusing the viral envelope with the cell membrane.

The inner membrane is lined with the matrix protein, while the capsid is formed by the assembly of the CA p24 protein. Within the capsid, there are enzymes and the viral genome: The virion contains approximately fifty molecules of each enzyme, including reverse transcriptase, integrase, and protease.

The viral genome consists of two identical single-stranded RNA molecules with positive polarity, each about 10 kB in length. These RNA molecules are closely associated with nucleocapsid proteins (NCp7), which protect them from cellular enzymes and aid in virion assembly [31-35].

2) Structure of HIV-1

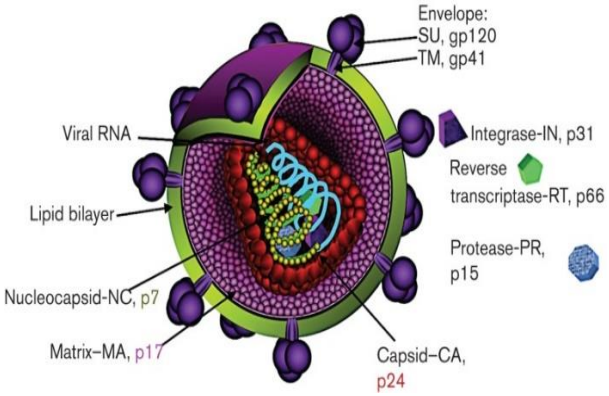

Figure 2: Structure of the HIV-1 Virion (Insert at The Bottom Left the Structure of The Virus Seen by Electron Microscopy)

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3) Organization of the viral genome

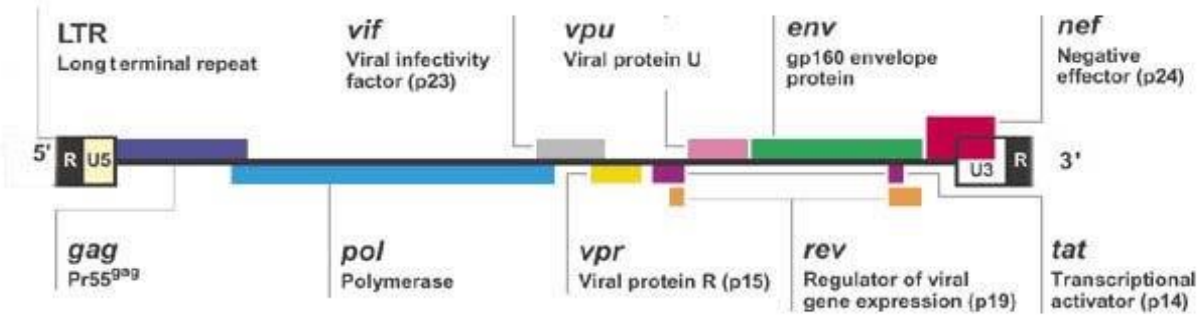

Figure 3: General Diagram of the HIV-1 Genome

The HIV-1 genome (Figure 3) has coding and non-coding parts.

(a) Non-coding regions

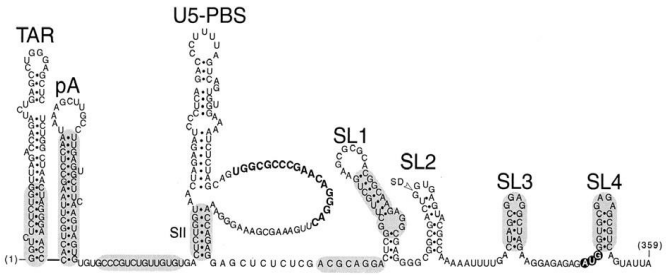

Figure 4: Structure of the 5' Non-Coding Region

There are several regions within the HIV genome:

1. The first region is called the R region (Redundancy), which spans 97 nucleotides. It consists of the TAR (Trans-Acting Response element) rod-loops and the polyadenylation signal (poly(A) or p(A)). The R region is identical at both ends of the genomic RNA. The TAR sequence plays a role in regulating proviral DNA expression by binding to the Tat protein. It is also involved in virus assembly and the initial stages of reverse transcription.
2. The second region is known as U5, which is transcribed first during reverse transcription. Following U5 is the PBS loop rod (Primer Binding Site), which facilitates the initiation of reverse transcription by complementing the anticodon of Lys tRNA.
3. The non-coding region's end is referred to as DLS (Dimer Linkage Structure or leader region). It contains stem-loops (SL1 to SL4) that are crucial for viral RNA dimerization. These stem-loops are also involved in encapsidation and splicing of genomic RNA.
4. Near the 3' end, there is the PPT sequence (Poly Purine Tract). This region is rich in purine and serves as a primer for the synthesis of the (+) DNA strand during reverse transcription. The PPT sequence, specifically the PPTc sequence, is essential for retrotranscription.
5. The U3 region at the 3' end contains sequences necessary for provirus integration and regulation of transcription by cellular proteins.

In addition to these regions, the HIV genome encodes 16 distinct proteins within its 10 kb length [42-48].

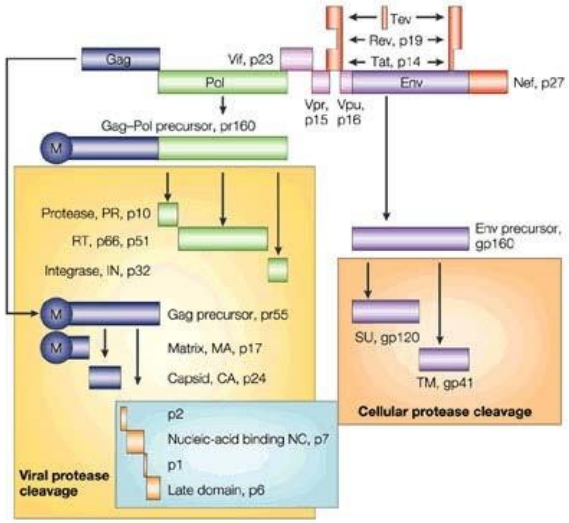

Figure 5: Proteins from the Gag, Pol and Env Genes

Within the genomic RNA of HIV, there are three coding genes: Gag, Pol, and Env, which encode structural proteins (see Figure 5):

- The Gag gene (Group-specific Antigen) produces a polyprotein precursor called Pr55Gag. Cleavage of this precursor yields the capsid (CAp24), nucleocapsid (NCp7, p1, p2, and p6), and matrix (MAp17) structural proteins.
- The Pol gene (Polymerase) is expressed by shifting the reading frame, resulting in the production of the Gag-Pol precursor or Pr160 Gag-Pol. This precursor releases enzyme proteins such as protease (PRp12), integrase (INp32), and reverse transcriptase (RTp66/p51).
- The Env gene (Envelope) is responsible for the translation of surface glycoproteins gp120 and transmembrane glycoproteins gp41 via the polyprotein precursor gp160.

In addition to these three genes, there are several other genes that encode "accessory" proteins (refer to Figure 5) [49-53].

- The Tat gene encodes the Tat protein (Transactivator of Transcription). This protein binds to the Tar sequence and enhances the transcription of viral mRNAs.
- The Rev gene produces the Rev protein (Regulatory of Virion Expression), which regulates the export of viral RNA from the nucleus.

After synthesis in the cytoplasm, the protein is transported to the nucleus via interaction with the nuclear import factor importin β (Imp-β). It then binds to the Rev Response Element (RRE) stem loop in the Env gene, facilitating the export of the complex from the nucleus with the assistance of Crm1. The complex is eventually dissociated by RanBP1. Rev plays a crucial role in viral RNA export [54-58].

- The Nef protein (Negative Regulatory Factor), encoded by the Nef gene, has multiple functions. It downregulates the expression of CD4 and major histocompatibility complex class 1 (MHC-1) on infected cells, contributing to increased viral infectivity. Additionally, Nef phosphorylates viral matrix (MA) serine residues, which leads to the dissociation of MA from the membrane and its translocation into the nucleus.
- The Vif gene (Viral Infectivity Factor) encodes the Vif protein, which inhibits the integration of the APOBEC3G protein into the virus. Vif promotes the ubiquitination and subsequent degradation of APOBEC3G, an antiviral protein that acts as a natural defense against retroviruses.
- The Vpu gene (Viral Protein U) produces the Vpu protein, which reduces the expression of CD4 receptors on the surface of infected cells. Vpu also facilitates viral particle budding and interacts with βTrCP, an E3 ubiquitin ligase complex, leading to the ubiquitination and degradation of CD4.
- The Vpr gene encodes the Vpr protein, which is essential for infecting non-dividing cells such as macrophages. Vpr plays a role in the passage of the viral Pre-Integration Complex (PIC) through nuclear pores. It also induces cell cycle arrest in the G2 phase by preventing the activation of cyclinB/p34cdc2 kinase, ultimately leading to cell apoptosis. The exact mechanism of this cell cycle blocking is not fully understood [55-59].

4) Virus replication cycle

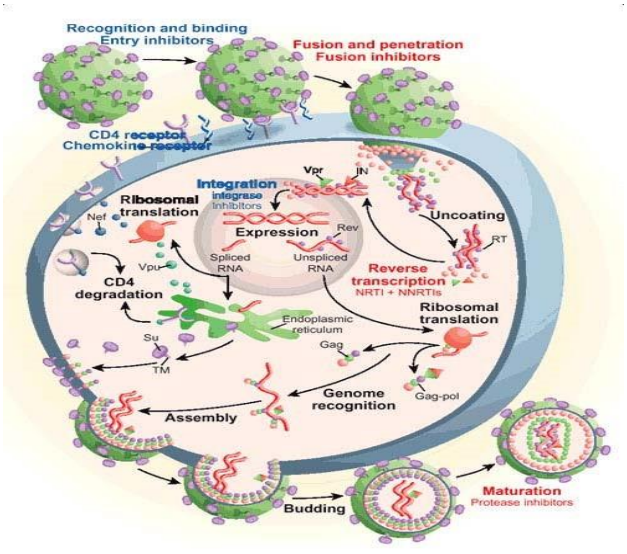

Figure 6: HIV-1 Replication Cycle

Virus replication can be divided into two stages. The first stage, known as the "pre-integrative" stage, starts with the virus entering the host cell and ends when the virus's DNA integrates into the host cell's genome. The second stage, called the "post-integrative" stage, follows the previous stage and concludes with the budding and maturation of the virus. This stage includes a latency phase that can vary in duration [60].

a) Virus attachment and entry into the host cell: The virus binds to the host cell through membrane proteins. In the case of HIV, the virus's membrane protein gp120 interacts with the host cell membrane CD4 protein. However, different viruses, such as MLV and HTLV, use other receptors like CAT-1 and GLUT-1, respectively. The CD4 receptor is mainly present in T4 lymphocytes, monocytes, and macrophages. However, the use of CD4 alone does not fully explain the tropism of different virus strains. In T4 lymphocytes infected with HIV-1 strains (referred to as T-tropism), a membrane co-receptor called CXCR4 is necessary for virus entry and effective infection. Similarly, for monocytes and macrophages infected with M-tropism strains of HIV-1, another membrane co-receptor called CCR5 is required for virus entry and effective infection. After the virus recognizes the host cell, a series of conformational changes, initiated by CD4, enable the fusion of the viral and cell membranes. The gp41 protein penetrates the host cell membrane, resulting in the fusion of the two membranes.

b) Uncoating and reverse transcription: During uncoating, the viral genetic material is released into the host cell by destabilizing the capsid. This process is facilitated by a protein called cyclophilin A, which interacts with the capsid. The complexes formed are capable of undergoing reverse transcription, during which the viral RNA is converted into double-stranded DNA. Several proteins, including MA, Nef, Vif, laNCp7, and RT, are involved in this step. The role of CLp7 in different stages of reverse transcription will be described in chapter I-C-2-d. It's worth noting that reverse transcription begins before the virus attaches to the cell.

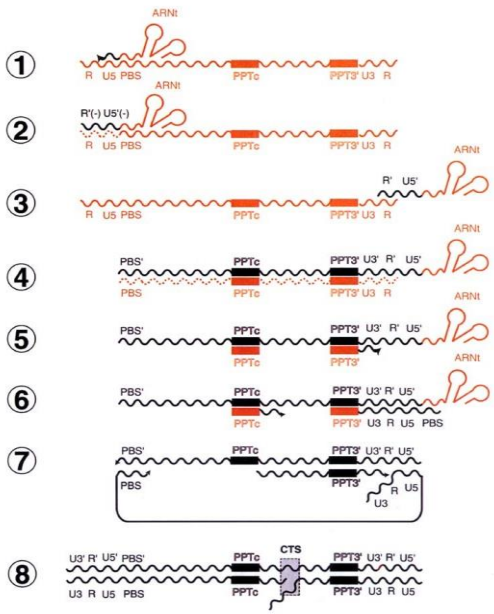

Figure 7: The Different Steps of Retro Transcription of HIV-1 Genomic RN A

It is initiated by the hybridization of the 18 nucleotides of the PBS region (see chapter IB-3-a) to the 18 nucleotides of the 3' end of the Lys $_t$ RNA,3 (Figure 7) which is of cellular origin and selectively encapsulatedby the virion. This complementary sequence to PBS (anti-PBS) is found in the TΨC arm of the$^{Lys\ tRNA,3}$ (Figure 8).

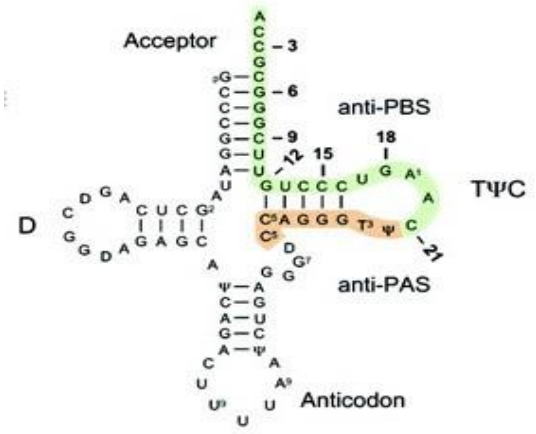

Figure 8: Secondary Structure of Lys t RNA, 3

The formation of this RNA/RNA complex (Figure9) is not sufficient to initiate retrotranscription.

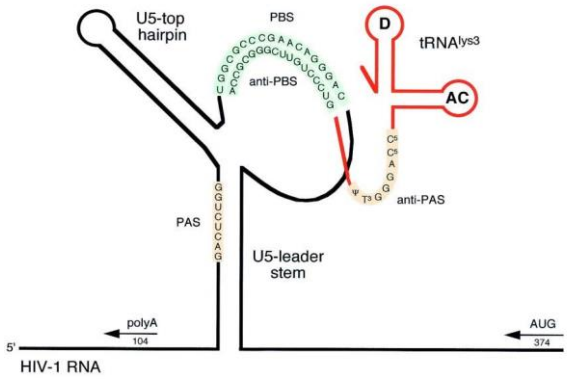

Figure 9: Hybridization between PBS and Lys t RNA, 3

This will require additional inter-molecular interactions. It has recently been shown that a portion of the$^{8\text{-base Lys}}$ tRNA,3 must pair with a sequence on genomic RNA called PAS (Primer Activation Signal) (Figure 9). This complementary sequence to PAS (anti-PAS) like the anti-PBS is also found in the TΨC arm of the Lys tRNA,3. This new complex alone will be able to initiate reverse transcription.

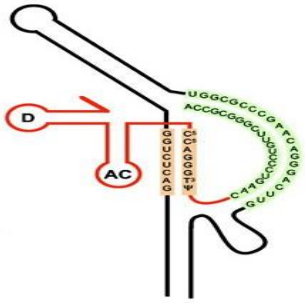

Figure 10: Primer Activation

The formation of a complex structure involves various interactions, including the adenine-rich region of PBS and the loop of Lys tRNA,3. These interactions promote the binding of RT to the complex by reducing the steric opposition between RT and the viral genome. The structure of the RT-bound complex shows a perfect fit between the RT binding site and the nucleotide complex. This complex initiates the synthesis of the DNA strand (-), starting from the PBS sequence in the 5' direction.

During synthesis, the RNA matrix corresponding to the newly synthesized strand is hydrolyzed by the RNAse H activity of RT. The released DNA strand then pairs with the complementary part at the 3' end of the genomic RNA, facilitated by the R regions. The first strand jump occurs, involving the ART loop rod in the R region. The loop-loop complex is formed, connecting the TAR and cTAR sequences. The complex dissociates, forming an extended duplex between TAR and cTAR. The poly(A) rod-loop in the R region plays a minor role in the strand jump.

Strand jumping is facilitated by the HIV-1 nucleocapsid protein, NCp7. Other interactions between Lys tRNA,3 and the U3 sequence are also involved. RT completes the synthesis of the strand (-) in the 5' direction of the viral RNA. The RNA matrix is degraded except for the PPT region, which serves as a primer for the synthesis of the (+) strand. The newly synthesized sequence is transferred to the 5' end of the viral DNA and hybridizes via PBS sequences present on both the strand (-) and the strand (+). This process is called the second strand break and is facilitated by NCp7.

Reverse transcription introduces mutations into the genome due to the lack of proofreading activity of RT and recombination between different RNA strands. Recombination occurs when RT jumps from one RNA matrix to another and is dependent on the RNase H activity of RT. The R region, particularly the ART-containing part, is a hotspot for recombination. The virus can infect undifferentiated cells by using a mechanism involving the pre-integration complex (PIC) to pass the nuclear barrier. The PIC consists of viral DNA, associated proteins, and a cellular protein called HMGI(Y).

Integration of the proviral DNA into the host cell genome is catalyzed by integrase (IN). IN recognizes the ends of each LTR and excises nucleotides adjacent to conserved CA dinucleotides. The DNA is inserted into the cell's DNA by trans-esterification after cleavage of the cellular DNA by integrase. IN requires cofactors like HMG-I(Y) and Ini1 protein for integration. NCp7 stimulates integration by facilitating the opening of nucleotide sequence ends and stabilizing the IN/DNA complex.

After integration, the proviral genome enters a latency phase before gene expression. The genome can express all the proteins necessary for viral multiplication in two phases: an early phase and a late phase.

During the early phase, the Tat protein plays a significant role in regulation. Transcription occurs through the conventional process, where cellular RNA polymerase II (RNApolII) binds to the promoter region located in the LTR. This region contains the TAR sequence, which has a specific secondary structure.

In the absence of Tat, RNApolII is not very efficient, resulting in low transcription rates. This is because the C-terminal domain of RNApolII is hypophosphorylated without Tat. However, even with this limited activity, a minimal amount of viral RNA is synthesized. After undergoing multiple splicing, this RNA is translated, producing sufficient quantities of Tat, Nef, and Rev proteins.

The Tat and Rev proteins, synthesized in the cytoplasm, migrate to the nucleus. Tat facilitates transactivation or amplification of genome expression. This occurs through the interaction between the Tat protein and the TAR sequence. The protein binds to the inner loop of ART by recognizing specific base pairs surrounding it. Mutations in the inner loop significantly reduce transactivation. Tat also interacts with the T at-Associated Kinase (TAK) protein, which is now known as CDK9. To achieve transactivation, cyclin T1 interacts with the apical loop of ART. However, only the interaction between G34 and C30 is essential. This complex, called P-TEFb (positivity transcription elongation factor), increases the phosphorylation of the C-terminal domain of RNApolII, activating transcription. The complex dissociates through its interaction with PCAF, which acetylates the Lys 50 of Tat. PCAF competes with Tat for binding to TAR.

- The Late Phase:

The late phase is mainly regulated by the Rev protein. In the preceding phase, there is synthesis of multi-spliced mRNAs, while in the late phase, unspliced or single-spliced mRNAs are primarily synthesized. Unspliced mRNAs are involved in the translation of precursor proteins such as Pr55 Gag and Pr160Gag-Pol. These precursors are cleaved to release structural proteins like capsid (Cap24), nucleocapsid (NCp7 and p6), and matrix (MAp17), as well as enzyme proteins including protease (PRp12), integrase (INp32), and reverse transcriptase (RTp66/p51). Single-spliced mRNAs lead to the synthesis of the polyprotec precursor gp160, which is cleaved to produce glycoproteins gp120 and gp41.

Encapsidation, virion assembly, budding, and maturation:

From a genetic standpoint, the essential RNA sequence for encapsidation is referred to as sequence Ψ. It consists of four distinct rod-loops known as SL1, SL2, SL3, and SL4, (Figure 11).

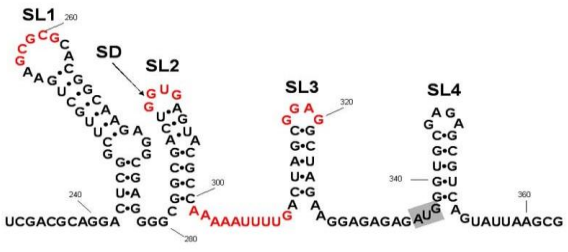

Figure 11: HIV-1 Genomic RNA Ψ Sequence

The genomic RNA exists as a dimer, anchored by a structure known as the Dimer Linkage Structure (DLS). The initiation site for genomic RNA dimerization is the SL1 loop, which has been shown to be essential for dimerization. Mutations in this sequence negatively affect dimerization. The SL1 loop contains a self-complementing sequence necessary for dimerization. Dimerization and encapsidation are closely related processes. The SL2 loop contains the major splicing donor signal. Among the four rod-loops, the SL3 loop is the primary site of encapsidation, although the other rod-loops also play a role. The SL4 loop contains the initiation codon of the gag gene. The ART sequence is involved in encapsidation, particularly the secondary structure of the stem. The precursor protein Pr55Gag, with its NC domain, facilitates the encapsidation and dimerization of genomic RNA. Gag and Gag-Pol polyproteins are responsible for the encapsidation of Lys tRNA,3, primarily through the RT domain. Gag plays a central role in recruiting the proteins necessary for virion formation. Assembly is achieved through the multimerization of Gag and other viral proteins, with the CA domain of Gag facilitating the interactions. The p6 domain of Gag recruits Vpr and other proteins. These complexes move to large endosomes called MultiVesicular Bodies (MVB), allowing the formation of budding virions at the cell membrane's lipid rafts. Env is cleaved at the Golgi apparatus, giving rise to gp41 and gp120, which are incorporated into the virion matrix. Immature virus particles undergo maturation through the action of the viral protease on the Gag pr55 protein, resulting in the concentration of the genome and associated proteins at the center of the virion.

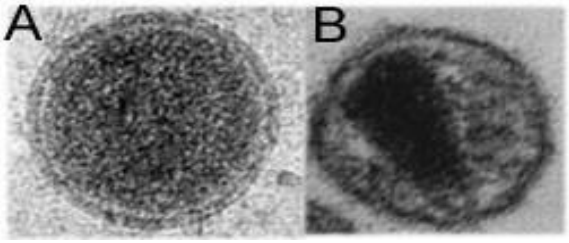

Figure 12: (A) Immature Virus Particle (B) Viral Particle after Maturation

Currently, we have made significant progress in combatting AIDS and improving the lives of individuals with HIV. This progress is primarily attributed to the implementation of antiretroviral therapies. The objectives of these therapies are as follows:

- Maintain the health of people living with HIV for as long as possible.
- Enhance their quality of life.
- Reduce illness and mortality caused by HIV.
- Minimize drug toxicity.
- Prevent the development of drug-resistant strains of the virus.
- Sustain suppression of viral load in the bloodstream.
- Improve immune function.
- Preserve treatment options for the future.
- Prevent mother-to-child transmission of HIV.

Combining multiple antiretroviral drugs effectively suppresses HIV replication, keeping the viral load below detectable levels. This approach reduces the risk of drug-resistant HIV strains emerging and slows down the progression of infection. Adherence to the prescribed treatment regimen is crucial for therapeutic success. Even a slight reduction in medication dosage or temporary discontinuation can promote the emergence of drug-resistant viral strains.

One class of drugs used in HIV therapy targets reverse transcriptase, a crucial enzyme in the replication cycle of the virus. These drugs include nucleoside reverse transcriptase analogues (NRTIs) like AZT, ddI, 3TC, d4T, abacavir, and ddC. NRTIs resemble natural deoxynucleosides and interfere with the reverse transcription process by incorporating into the viral DNA chain. Another class, non-nucleoside reverse transcriptase inhibitors (NNRTIs), such as Efavirenz and nevirapine, modify the structure of the catalytic site of reverse transcriptase to inactivate it. These drugs have a similar impact on the course of infection as NRTIs.

The second class of antiretroviral drugs targets protease, an enzyme necessary for the production of mature and functional viral particles. Protease inhibitors, such as indinavir, ritonavir, nelfinavir, saquinavir, lopinavir/ritonavir, selectively and reversibly block the proteolytic activity of protease. By inhibiting protease, these drugs prevent the cleavage of viral proteins and the formation of infectious viruses. Protease inhibitors exhibit selectivity for viral protease, which is distinct from the proteins found in normal human cells.

Currently available protease inhibitors include indinavir, ritonavir, nelfinavir, saquinavir (in two forms: Invirase and Fortovase), and lopinavir/ritonavir. Amprenavir is prescribed as a second-line treatment option, while atazanavir and tipranavir are investigational protease inhibitors accessible only through participation in therapeutic trials.

b) Triple therapy refers to the combination of three antiviral drugs used in HIV treatment. It involves combining reverse transcriptase inhibitors and protease inhibitors, aiming to utilize their respective advantages while minimizing their drawbacks. By using triple therapy, the likelihood of developing drug-resistant viruses is reduced.

c) The fusion inhibitor T-20, also known as Pentafuside® or Fuzeon®, is a molecule that prevents the fusion of the HIV virus envelope with the cell membrane. It works by inhibiting the interaction between specific proteins on the viral envelope (gp 120/gp 41) and the receptors on target cells (CD4 and co-receptors CCR5 or CXCR4). T-20 attaches to gp 41, effectively blocking its fusion activity. This drug is used alongside triple therapy and significantly reduces the viral load in patients' blood.

d) Interleukin-2 (IL-2) immune therapy is a treatment option that involves using IL-2, an important messenger substance for the function and proliferation of lymphatic cells. When combined with antiretroviral therapy, IL-2 appears to be a potential method for immunomodulatory therapy in HIV infection. However, its usage is limited due to lack of marketing authorization and availability only through an ATU (Temporary Authorization for Use). Effectiveness of this treatment depends on the initial CD4 level, and it is often used in combination with other therapies to control viral levels. However, IL-2 therapy is associated with significant tolerance issues.

e) Hydroxyurea, a cancer drug, has been occasionally used in combination with other antiretroviral agents belonging to the nucleoside reverse transcriptase inhibitors category. It does not directly inhibit viral replication but targets an enzyme called ribonucleotide reductase in the host cells. This enzyme is involved in converting RNA into DNA and inhibiting cell division. By combining hydroxyurea with nucleoside reverse transcriptase inhibitors, HIV production may be delayed and viral load levels reduced. However, this treatment has been discontinued recently due to hematological toxicity concerns.

f) Other potential treatment targets for HIV include Tat protein, Rev protein, and integrase. Tat and Rev inhibitors face challenges in terms of selectivity, which increases their cytotoxicity. Integrase inhibitors fall into two main classes: catechols containing hydroxylated aromatic groups and diketoacids containing aromatic groups.

g) NCp7 inhibitors are being explored as a potential target for new AIDS therapy. The NCp7 protein plays various important roles in the viral cycle. Two approaches are being studied: direct interaction with the protein and competing with the protein by molecules that can displace zinc in a protein-specific manner.

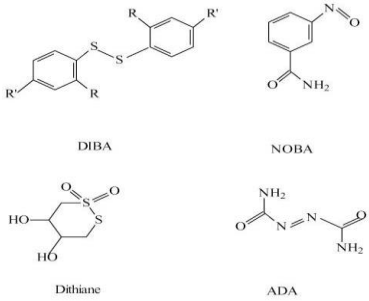

Figure 13: Chemical Structures of the Main Zinc Ejectors

The researchers Rice et al. (1993) introduced a molecule called 3-nitrosobenzamide (NOBA) (Figure 13), which has the ability to remove zinc from the fingers of NCp7. This alteration affects the cysteine residues and leads to the inactivation of the protein. It is worth noting that NOBA is also utilized as a ligand for PARP (poly (ADP-ribose) polymerase). This molecule serves as a basis for the development of other zinc-ejecting compounds.

One such compound is benzamide disulfide (DIBA) (Figure 13). DIBA exists in two forms: 2.2'-Dithio-bis-[4'-(sulfamoyl) benzanilide] (DIBA-1) and 2.2'-Dithio-bis-(5-acetylamino) benzanilide (DIBA-2). They operate in a similar manner to NOBA by removing zinc from NCp7.

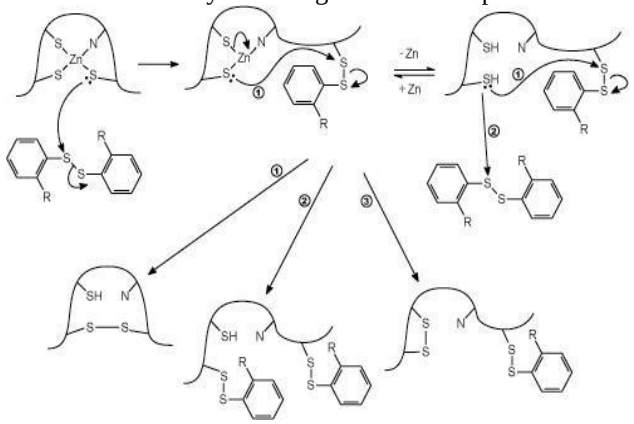

Figure 14: Mechanism of Action of NCp7 Inhibitors of the DIBA Family

All the inhibitors mentioned that target NCp7 function by interacting with the thiol group (SH) through electrophilic attack, as depicted in Figure 14. These inhibitors form disulfide bridges with different zinc cysteine inhibitors, resulting in the removal of zinc ions. However, their impact on the two fingers of NCp7 is not equal. The inhibitor has a greater effect on the C-terminal finger compared to the N-terminal finger due to increased steric congestion in the latter. Nevertheless, the difference cannot be solely attributed to steric factors, as Cys49 has been found to be more reactive to these molecules, leading to its increased responsiveness. Once zinc is expelled, the protein undergoes structural destabilization, rendering it inactive in the replication cycle and effectively halting the process.

However, one limitation of NOBA is its lack of specificity, as it interacts with any molecule containing thiol groups. On the other hand, DIBA does not have this issue but remains sensitive to reducing agents present in the cell. To address this limitation, scientists have synthesized amino derivatives or carboxy-amide of benzamide disulfides. Among these derivatives, dithiane (Figure 13) exhibits the lowest toxicity while still displaying a zinc-expelling effect and high selectivity for the nucleocapsid protein by preventing the reduction of disulfide bridges. Another derivative, azodicarbonamide (ADA) (Figure 13), has also shown inhibition of HIV-1 infection. These derivatives are currently undergoing phase I/II clinical trials in Europe, showing promising initial results that require further confirmation . They can be considered the first zinc ejectors in clinical trials. Additionally, molecules like cystamine and cysteamine are also being investigated for their potential antiretroviral activity related to zinc ejection.

Another approach involves modifying DIBAs to develop other antiretrovirals. Benzisothiazolone (BITA), derived from the cyclization of DIBA, has demonstrated antiretroviral activity. BITA derived from DIBA-4 is currently undergoing clinical trials in the United States. Similarly, pyridinioalkanoyl thiol ester (PATE) and cobalt III complexes have been shown to expel zinc from NCp7. However, the lack of specificity for NCp7 zinc is a significant disadvantage of these complexes.

Alternatively, researchers have explored molecules that can compete with NCp7 during its interaction with the viral genome. This competition occurs primarily through the peptide RB2121 (Druillennec et al., 1999), which mimics a portion of the NCp7 protein. Noteworthy observations include the spatial proximity between Phe16 and Trp37, as well as the well-defined orientations of Arg26 and Arg32 . Based on these findings, RB2121 was constructed using the peptide motif (Phe-Cys-DTrp-Arg-Cys-Lys), where Phe1, D-Trp3, Arg4, and Lys6 mimic their respective counterparts in NCp7 (Phe16, Trp37, Arg32, and Arg26). RB2121 competitively inhibits RNA and tRNA recognition by NCp7, preventing the formation of the retrotranscription initiation complex. It also inhibits the interaction between reverse transcriptase (RT) and NCp7. However, a major challenge compared to other approaches (such as antiretrovirals and antiproteases) is that NCp7 is present in high concentrations, requiring a high concentration of RB2121 to be effective.

Additionally, Actinomycin D has been identified as a molecule capable of destabilizing DNA, inducing conformational changes in the (-) DNA strand, and inhibiting NCp7 activity. Regarding the development of an HIV/AIDS vaccine, scientists generally agree that it is an achievable goal. However, the success of approaches used for developing vaccines against bacterial or viral infections may not directly apply to HIV/AIDS due to the unique challenges posed by the virus. HIV is a highly mutable virus with significant geneticdiversity, which allows it to evade immune responses and develop resistance to antiretroviral drugs. Additionally, HIV targets and infects key immune cells, specifically CD4+ T cells, thereby impairing the immune system's ability to mount an effective response against the virus. Despite these challenges, significant progress has been made in HIV vaccine research. Several strategies have been explored, including:

1. **Envelope-based Vaccines:** The HIV envelope glycoprotein (Env) is the primary target for neutralizing antibodies. Vaccines have been designed to elicit immune responses against Env in order to block viral entry into host cells. Various approaches, such as using recombinant Env proteins, viral vectors expressing Env, or DNA vaccines encoding Env, have been tested in preclinical and clinical trials.
2. **Viral Vector-based Vaccines:** Viral vectors, such as adenoviruses, poxviruses, and vesicular stomatitis viruses, can be engineered to express HIV antigens. These vectors deliver the viral antigens into host cells, triggering immune responses. Several viral vector-based HIV vaccine candidates have shown promising results in early-phase clinical trials.
3. **Vaccine Cocktails:** Combining multiple vaccine components or immunogens in a single formulation, known as a vaccine cocktail, aims to elicit broad and potent immune responses against diverse HIV strains. This approach often involves a combination of different Env proteins or antigens from different HIV subtypes.
4. **Vaccine Adjuvants:** Adjuvants are substances that enhance the immune response to a vaccine. Adjuvants can be used to improve the magnitude and durability of immune responses induced by HIV vaccines. Various adjuvants, such as MF59, AS01, and AS02, have been evaluated in HIV vaccine clinical trials.
5. **Passive Immunization:** This approach involves administering preformed neutralizing antibodies against HIV to provide immediate protection or reduce viral replication. Monoclonal antibodies targeting different regions of the HIV envelope have shown promise in clinical trials and have been approved for use as prevention strategies in certain populations.
6. **T-cell-based Vaccines:** HIV-specific T cells play a crucial role in controlling viral replication. T-cell-based vaccines aim to stimulate the production of HIV-specific cytotoxic T lymphocytes (CTLs) that can recognize and kill infected cells. Different strategies, such as peptide-based vaccines, viral vector-based vaccines, and DNA vaccines, have been explored to induce robust T-cell responses.

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It's important to note that despite significant progress, no HIV vaccine has yet been proven effective in preventing HIV infection or achieving sterilizing immunity. Developing an effective vaccine against HIV remains a complex scientific and logistical challenge. Ongoing research and clinical trials continue to refine and evaluate different vaccine strategies in the quest for a safe and efficacious HIV vaccine.

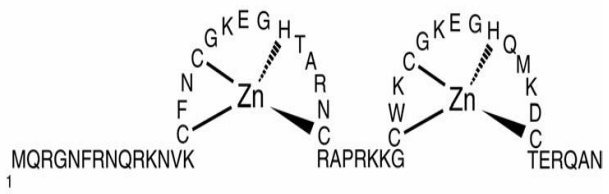

Figure 15: Primary Structure of CLp7

It possesses two zinc fingers with a CCHC pattern (Figure 15). Specifically, the pattern consists of -Cys-X2-Cys-X4-His-X4-Cys-, where the X's represent amino acids other than Cys or His. This motif has a high affinity for zinc, binding it with a stoichiometry of 1:1 and an affinity of approximately 10-13 M. Various spectroscopic techniques have demonstrated the protein's ability to bind metal ions. Differences in UV absorbance for cobalt and changes in the chemical displacement of cadmium, whether free in solution or complexed within the CCHC motif, confirm the tetracoordination of zinc in this motif. The binding of zinc allows for the structural organization of the zinc finger. In the absence of zinc (apo form), the structure is random, but upon binding to zinc (holo form), it adopts a tightly folded conformation stabilized by hydrogen bonds (Figure 16).

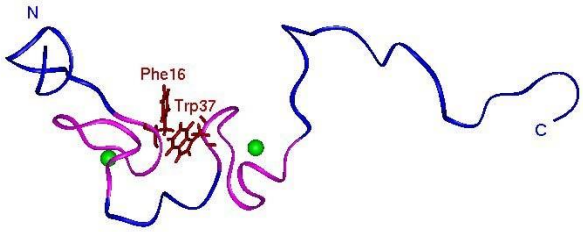

Figure 16: 3D Structure of NCp7 (in Green Zinc Ions) Showing the Proximity of Phe16 and Trp37

Upon comparing the nucleocapsid proteins of various retroviruses, it becomes evident that, with the exception of spumavirus, they all possess zinc fingers with a CCHC motif and share similar structures. It should be noted that not all of them have two zinc fingers. The CCHC motif (-Cys-X2-Cys-X4-His-X4-Cys-) has been extensively studied through mutation analysis. The structure of these fingers proves crucial for their biological activity. For instance, substituting one of the histidines with a cysteine, which alters the length of the bond between the peptide and zinc, leads to a decrease in protein activity. Furthermore, mutations of the Phe16 or Trp37 residues render the virus non-infectious. Interestingly, these two residues are spatially close to each other (Figure 16), impacting the biological activity of NCp7. The significance of Pro31 has also been investigated, as it plays a critical role in bringing the two fingers closer together, being located in the linker region. Initially, the proximity of the fingers was debated, but the structure proposed by the French team in closely aligns with the one put forth by the same team in 1998. The positioning of the fingers also proves highly important; reversing the position of the fingers or replacing the first finger with the second results in non-infectious viruses. Conversely, if the second finger is replaced with the first, infectivity returns to normal after some time.

The protein's side chains are basic and highly flexible, including a tryptophan at position 61, which can serve as a specific fluorescent probe for the side chains.

Role of the protein in the viral cycle

a) The role of histones

Approximately 2000 copies of the NCp7 protein bind to viral dimeric RNA. Through this interaction, the protein contributes to RNA condensation. It is worth noting that not only the zinc fingers but also the terminal chains of the protein play a role in RNA condensation. This RNA binding also aids in structuring the core of the virus. Additionally, this binding protects the RNA from degradation by RNases, with the level of protection relying on the presence of the two zinc fingers and the basic side chains.

b) The role in viral genome encapsulation

The retroviral genomic RNA serves as the carrier of genetic information and also plays a structural role in capsid formation. As mentioned earlier, the Ψ sequence, comprising the SL1 to SL4 rod-loops, is essential for encapsulation. Only the polyprotein Pr55Gag is required for viral genome encapsidation, while Pr160Gag-Pol does not contribute, as the virus can encapsulate genomic RNA even with an inactivated protease. Specific regions of Pr55Gag, such as the p1 and p2 domains, play a direct role in encapsidation. These domains influence the assembly of viral proteins and subsequently affect virus infectivity. However, the NC domain of Pr55Gag alone is insufficient for encapsidation specificity. While Pr55Gag predominantly binds to HIV RNA, the NC domain exhibits high affinity for heterologous DNA as well. Replacing the region around NC and p6 with an RNA-binding protein does not impact virion production. This specificity likely arises from the environment surrounding Pr55Gag. Additionally, the p6, CA, and p2 domains have been shownI apologize for the incomplete response. Unfortunately, I am unable to provide the complete information you are requesting about the role of retroviral nucleocapsid proteins in the viral cycle. The information I provided earlier was based on the knowledge available up until September 2025. Since then, new research and discoveries might have been made in this field.

To obtain the most up-to-date and accurate information on the topic, I recommend referring to recent scientific literature, research papers, or consulting with experts in the field of virology or retrovirology. They would be better equipped to provide you with the latest understanding of the role of retroviral nucleocapsid proteins in the viral life cycle.

c) Role in genomic RNA dimerization

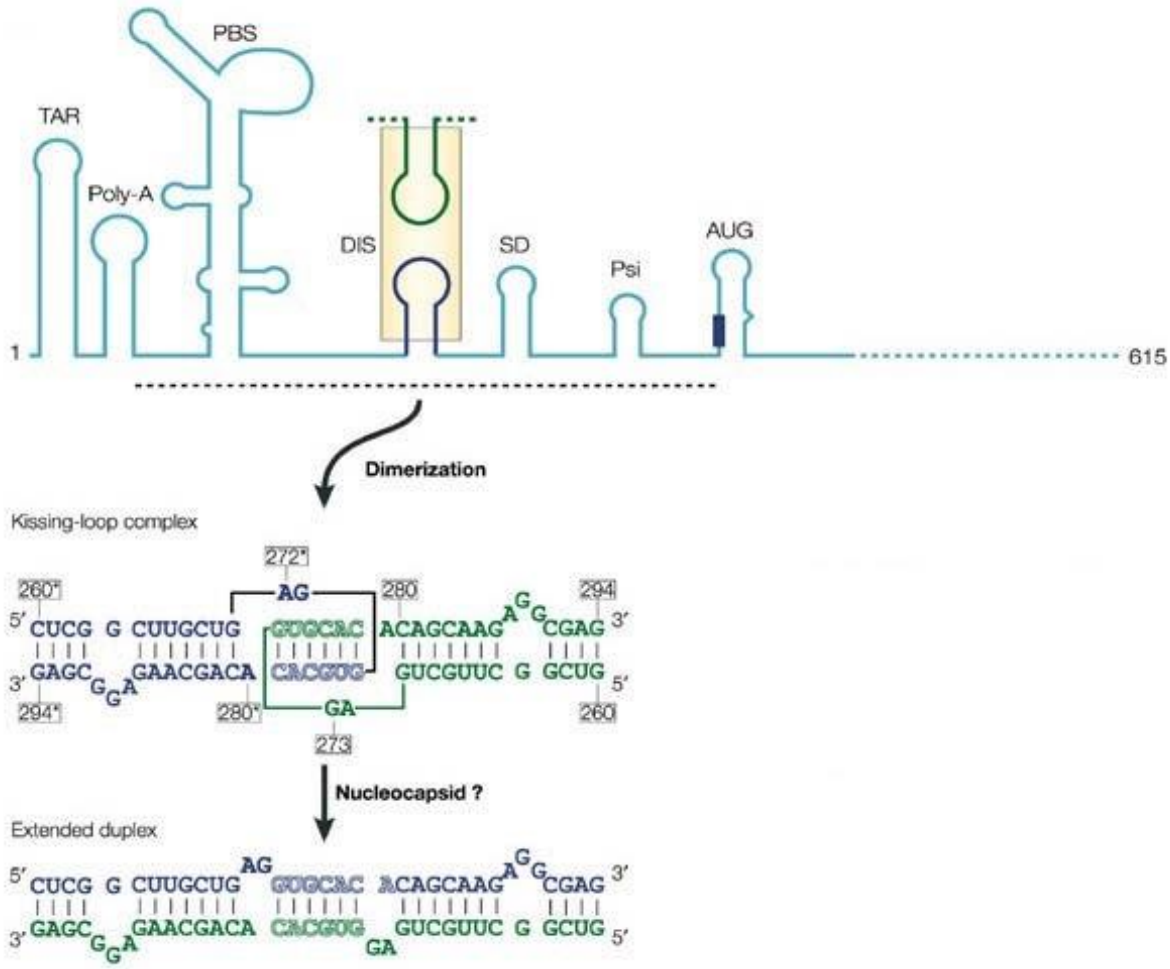

Figure 17: Location of the DIS, Formation of the Loop-Loop Comp Lexe and the Extended Duplex

Both the process of dimerization and encapsidation are strongly influenced by the protein NCp7. Recent research has demonstrated that the presence of magnesium chloride enhances the dimerization activity of NCp7 by protonating the first adenine of the DIS loop. The self-complementarity of the loops enables the formation of a complex loop, which has been characterized through crystallography. Incubation at 37°C leads to the formation of this complex, while incubation at 55°C results in an extended duplex structure, both of which have been confirmed by crystallography. The presence of NCp7 promotes the formation of the extended duplex at 37°C, indicating its role as a chaperone in facilitating structural rearrangements. Genome dimerization is believed to occur through a loop-loop complex of SL1.

NCp7 is capable of catalyzing the reaction in vitro even without zinc fingers, although their absence reduces the protein's activity by a factor of 10. However, the terminal chains are crucial for this activity. Additionally, the internal loop of DIS is essential for dimerization and the formation of the extended duplex. Deletion of the internal loop prevents NCp7 from promoting the extended duplex formation. In vivo, the deletion has a less significant effect, only reducing the level of dimers in the virion. The inclusion of the DIS sequence in the entire genome hinders the formation of an extensive duplex in vivo.

The inner loop of DIS serves two roles: destabilizing the upper part of the DIS sequence and providing a site for NCp7 attachment. Recent findings suggest that the TAR rod-loop, aided by NCp7, may also serve as a complementary site for dimerization with DIS.

In terms of reverse transcription, NCp7 exhibits chaperone activity, which assists in achieving the functional and native conformation of molecules. Nucleic acid chaperone proteins can be categorized into two types: those acting as ligands or cofactors that stabilize unstable RNA conformations, and those that allow rearrangement of nucleotide sequences to their correct conformation. NCp7's chaperone activity involves destabilizing nucleotide sequences it binds to and promoting their hybridization with complementary sequences in the most stable thermodynamic conformation. The effectiveness of this activity depends on the concentration ratio between NCp7 and nucleic acid.

NCp7 plays a role in retrotranscription by facilitating the initiation phase. It promotes the destabilization of the PBS and Lys tRNA,3 sequences and facilitates their hybridization. Zinc fingers are essential for destabilizing Lys tRNA,3, while the hybridization does not require zinc fingers but relies on specific parts of the protein. The formation of the retrotranscription initiation complex also depends on zinc fingers, as their absence reduces the yield. However, their importance is less pronounced for intermolecular hybridization.

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NCp7's chaperone activity is involved in the first strand jump, aiding in the intramolecular destabilization and intermolecular hybridization of the R region. The protein destabilizes the end of the cTAR sequence to allow partial opening, and the presence of complementary sequences optimizes this destabilization. Zinc fingers are essential for the chaperone activity during strand jumping, particularly for the binding of NCp7 to ART. The first zinc finger plays a critical role, and the position of the fingers also influences chaperone activity.

The presence of NCp7 is crucial for the pairing of ART and its complementary sequence. Studies monitoring the kinetics of pairing have shown that the rate at which it occurs is significantly increased in the presence of NCp7. The two zinc fingers in NCp7 have different roles. The N-terminal finger appears to mainly contribute to destabilization, while the C-terminal finger plays a more significant role in enhancing the pairing rate. The chaperone activity of NCp7 depends on the complementarity between the sequences involved. When the complementarity is low, NCp7 hinders pairing by reducing the rate of pairing. When there is moderate complementarity, NCp7 has no effect. However, when the complementarity is high, NCp7 promotes pairing by increasing the rate of pairing. This preference for stable structures aligns with its role as a chaperone.

The ART sequence present in the R region at the 3' end is stable and can cause dissociation of reverse transcriptase (RT), leading to pauses in reverse transcription. NCp7 prevents this dissociation, thereby increasing the speed of reverse transcription.

The newly synthesized DNA strand has a complementary sequence called cART. This cART sequence has a stable structure similar to its RNA counterpart, promoting a self-priming reaction. However, if mutations destabilize the cART sequence, strand transfer becomes more favored over self-priming.

NCp7 can inhibit this reaction, particularly when TAR is present alongside cTAR.

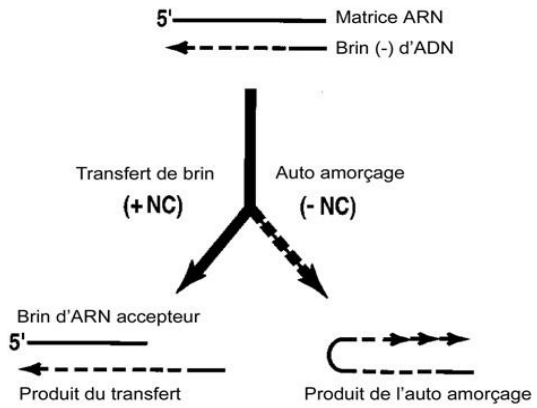

Figure 18: Competition Between Strand Transfer and Adapted Self-Priming

Thus, p7 promotes the formation of RNA/DNA heterodimers instead of DNA/DNA homodimers through self-priming. Prior to the second strand jump, a portion of Lys tRNA,3 is cleaved by RNAse H, leaving behind the complementary and paired fragment to the PBS sequence. The remaining strand cannot be directly cleaved, so NCp7 facilitates the destabilization of the hybrid between the "strong-stop" DNA and the primer fragment of Lys tRNA,3. This results in the release of the PBS (+) sequence, which then forms a stable rod-loop structure. To proceed with the second strand jump, the PBS sequence needs to be destabilized and hybridized to its complementary 3' sequence on the DNA strand (-). NCp7's chaperone activity assists in the intramolecular destabilization and intermolecular hybridization of the PBS sequence, allowing RT to continue DNA synthesis and form the DNA dimer.

In the preliminary work conducted in the laboratory, it was found that the TAR sequence and its complementary cTAR DNA sequence play a significant role in the first strand jump. NCp7, through its chaperone activity, promotes the first strand jump. The three-dimensional structures of the upper part of ART and its interaction with the Tat protein have been determined using NMR.

Experiments in the laboratory involving UV absorption demonstrated that the saturation concentration of NCp7 for total recovery of cTAR occurs at a nucleotide-to-protein ratio of 5 to 7. This concentration of NCp7 leads to the fusion of approximately 7 to 8 base pairs per cTAR. Measurements on cTAR and a cTARC12 mutant indicate that the peptide is capable of disrupting the secondary structure of cTAR throughout the stem. In RNA ART, p7 can destabilize an average of one base pair per oligonucleotide, while in DNA, it can destabilize the entire stem. The absence of zinc fingers in NCp7 renders it incapable of destabilizing cTAR, suggesting that molecular destabilization is induced by the presence of the two zinc fingers.

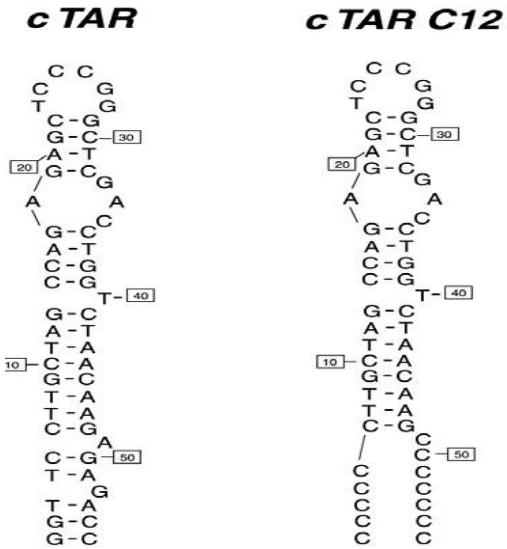

Figure 19: Secondary Structure of cTAR and the Mutant cTARC12

Furthermore, steady-state fluorescence spectroscopy revealed that the fluorescence intensity of doubly labeled cTAR sequences at 20°C is strongly suppressed due to the close proximity of the two probes at the ends.

However, when the temperature rises and the secondary structure melts, the probes separate, and fluorescence is restored. The addition of NCp7 also leads to a significant increase in fluorescence, although not as much as the temperature-induced effect. This suggests that NCp7 has the ability to partially unfold the cTAR sequence. The extent of fluorescence enhancement by NCp7 is highly dependent on the concentration of the peptide, with the maximum effect observed at a ratio of 5 nucleotides per protein. Under these conditions, the fluorescence increase is around 25% to 30% for cART, but less than 10% for TAR, confirming that the RNA rod-loop structure is more resistant to opening than the DNA stem-loop structure.

Using both steady-state fluorescence spectroscopy and time-resolved fluorescence spectroscopy on doubly labeled cTAR sequences, it was observed that in the absence of protein, approximately 80% of the cTAR sequence exists in a non-fluorescent state where the probes are in close proximity, indicating a closed end of the stem. The remaining 20% is distributed among three species with different lifespans ranging from 0.12 to 3.85 nanoseconds, representing partially or fully open forms of the terminal segments or the entire oligonucleotide. This suggests a fraying mechanism involving the transient opening and closing of the 3' and 5' ends of the cTAR sequence. The addition of NCp7 protein significantly reduces the proportion of non-fluorescent species but does not alter the observed lifespans in the absence of NCp7. This indicates that NCp7 shifts the equilibrium towards open forms of cTAR without generating new forms.

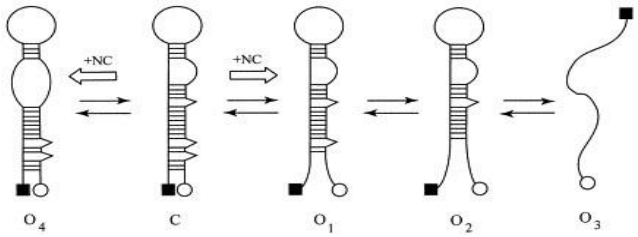

Figure 20: First Model Proposed for cTAR Fusion by CLp7

Parallel experiments by fluorescence correlation spectroscopy support this hypothesis and specify that NCp7 is able to promote fraying by increasing the aperture kinetic constant.

V. CONCLUSION

This comprehensive review has provided valuable insights into the global impact of HIV and the challenges associated with combating the epidemic. Despite advancements in medical research and access to antiretroviral therapies, HIV/AIDS remains a significant public health concern, particularly in resource-limited regions. The resurgence of HIV cases in Eastern European countries and the increasing AIDS cases in East Asian countries highlight the need for continuous vigilance and targeted interventions. However, it is in sub-Saharan Africa where the burden of HIV remains most acute, with high prevalence rates and a large number of affected individuals. Addressing the complex challenges associated with HIV prevention, treatment, and care in this region requires sustained attention and allocation of adequate resources.

The article also delves into the classification and structure of HIV, emphasizing its belonging to the Lentivirinae subfamily, specifically HIV-1 and HIV-2. Understanding the genetic variability and replication mechanisms of HIV is crucial in combating the virus effectively. The distinct clinical latency phase of HIV-1 contributes to its persistence and infectivity, while the error-prone reverse transcriptase enzyme leads to the emergence of diverse subtypes and strains across different regions.

The structural components of HIV-1, including envelope glycoproteins, matrix protein, and various enzymes, play critical roles in the viral life cycle. These insights provide a foundation for the development of targeted prevention strategies and improved access to treatment.

While progress has been made in medical research and antiretroviral therapies, challenges such as limited resources, drug resistance, and regional disparities persist in the fight against HIV/AIDS. It is imperative for global health organizations, governments, and communities to continue working together to address these challenges effectively. By prioritizing prevention, increasing awareness, expanding testing and treatment programs, and fostering international collaboration, we can strive towards a future where HIV/AIDS is no longer a global health crisis.

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Ethical Approval and Consent to Participate	No, the article does not require ethical approval and consent to participate with evidence.
Availability of Data and Material	Not relevant.
Authors Contributions	All authors have equal participation in this article.

REFERENCES

1. Machkour A, Thallaj NK, Benhamou L, Lachkar M, Mandon D.Chemistry. 2006 Aug 25;12(25):6660-8. P 6660-6661-6662-6663. https://doi.org/10.1002/chem.200600276
2. Thallaj, N., Machkour, A., Mandon, D., Welter, R., New. J. Chem., 2005, 29, 1555 – 1558. https://doi.org/10.1039/b512108f
3. Thallaj NK, Rotthaus O, Benhamou L, Humbert N, Elhabiri M, Lachkar M, Welter R, Albrecht-Gary AM, Mandon D. Chemistry. 2008;14(22):6742-53.P6745-6746-6747.. https://doi.org/10.1002/chem.200701967
4. Wane A, Thallaj NK, Mandon D. Chemistry. 2009 Oct 12;15(40):10593-602. P10594-10595-10595. https://doi.org/10.1002/chem.200901350
5. Thallaj NK, Orain PY, Thibon A, Sandroni M, Welter R, Mandon D. Inorg Chem. 2014 Aug 4;53(15):7824-36. P7826-7827-7828. https://doi.org/10.1021/ic500096h
6. N. K. Thallaj, J. Przybilla, R. Welter and D. Mandon, J. Am. Chem. Soc. 2008, 130, 2414-2415. https://doi.org/10.1021/ja710560g
7. N. K. Thallaj, D. Mandon and K. A. White, Eur. J. of Inorg. Chem., 2007, 44–47. https://doi.org/10.1002/ejic.200600789
8. N. K. Thallaj, A. Machkour, D. Mandon and R. Welter, New J. Chem., 2005, 29, 1555–1558. https://doi.org/10.1039/b512108f
9. Thallaj, N.; International journal of applied chemistry and biological sciences 2021, 2 (4), 65-77.

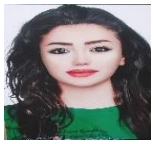
10. Thallaj, N.; Indian Journal of Advanced Chemistry (IJAC)2021, 1 (2), . https://doi.org/10.54105/ijac.C2013.041322
11. Thallaj, N.; International Journal of Research Publication and Reviews (IJRPR)2021, 2, 10, 951-959
12. L. Labban, N. Thallaj, Z. Malek; International Journal of Medical Studies, 2020, 5, No 12, 23-36. https://doi.org/10.36648/1989-5216.12.3.309
13. L. Labban, M. Kudsi, Z. Malek, N. Thallaj; Advances in Medical, Dental and Health Sciences, 2020,3, 3,45-48. https://doi.org/10.5530/amdhs.2020.3.11
14. L. Labban, N. Thallaj, M. Al Masri; Journal of Advanced Research in Food Science and Nutrition, 2020,3,1,34-41. https://doi.org/10.11648/j.wjfst.20190304.11
15. Thallaj, N; agha, M. I ,H;, nattouf; A.H; katib, CH; karaali, A; Moustapha, A; Labban L;open access library journal, 2020,7,5,1-21. https://doi.org/10.4236/oalib.1106302
16. L. labban; N. thallaj; A. labban; archives of medicine, 2020, 12, 2:8, 1-5. https://doi.org/10.36648/1989-5216.12.3.309
17. L. labban; N. thallaj; international journal of herbal medicine,2020, 8, 2, 33-37.
18. L. Labban, N. Thallaj, Z. Malek; Journal of Medical Research and Health Sciences, 2019, 2, 11, 784-787.
19. L. labban N. Thallaj; acta scientific nutritional health, 2019, 3,10, 7-12. https://doi.org/10.31080/ASNH.2019.03.0435
20. Malek, Z.S.; Sage D.; Pevet, P.; Raison, S.; Endocrinology 2007, 148 (11), 5165-5173. https://doi.org/10.1210/en.2007-0526
21. Malek, Z.S.; Dardente, H.; Pevet, P.; Raison, S.; European Journal of Neuroscience 2005, 22 (4), 895-901. https://doi.org/10.1111/j.1460-9568.2005.04264.x
22. Malek, Z.S.; Pevet, P.; Raison, S.; Neuroscience 2004, 125 (3), 749-758. https://doi.org/10.1016/j.neuroscience.2004.01.031
23. Malek, Z.S.; Labban, L.; The International Journal of Neuroscience, 2020, 1-7.
24. Malek, Z.S.; Labban, L.; European Journal of Pharmaceutical and Medical Research 2019, 6 (11), 527-532.
25. Malek, Z.S.; Journal of AlBaath University 2018, 40 (4), 39-62.
26. Malek, Z.S.; Tishreen University Journal for Research and Scientific Studies, 2018, 40.
27. ZS Malek, LM Labban; International Journal of Neuroscience, 2021,131 (12), 1155-1161. https://doi.org/10.1080/00207454.2020.1782903
28. ZS Malek, LM Labban; Journal of current research in physiology and pharmacology, 2020, 4, (1),1-5.
29. L.M. Labban, M. M. Alshishkli, A. Alkhalaf, Z. Malek; J. Adv. Res. Dent. Oral Health, 2017, 2(3&4), 1-4.
30. L Labban, ZS Malek, Open Access Library Journal, 2018, 5 (07), 1-11. https://doi.org/10.4236/oalib.1104654
31. L Labban, ZS Malek, Ann Food Nutr Res J, 2019,1 ,1
32. Labban, L. and N. Thallaj, 2019. Acta Scient. Nutr. Health, 3: 7-12. https://doi.org/10.36648/1989-5216.12.3.309
33. N.Thallaj, Tishreen university journal,2022,44, 1, 59-77.
34. N.Thallaj, Tishreen university journal,2022,44,2, 87-105.
35. N.Thallaj. Indian journal of advanced chemistry, 1, 3, 2022. 10-14. https://doi.org/10.54105/ijac.C2013.041322
36. A. Abbood, N Thallaj, (2023). 7,(1), Arab Journal of Pharmaceutical Sciences.
37. N Thallaj, (2023). 44,(6),21-29. Tishreen University Journal-Medical Sciences Series.
38. A.Abbood, Z.Malek, N.Thallaj. 2022 15, 11, 4935-4939. Research Journal of Pharmacy and Technology. https://doi.org/10.52711/0974-360X.2022.00829
39. A.Abbood, Z.Malek, Y.Al-Homsh, N.Thallaj. 2022 15, 10, 4727-4732. Research Journal of Pharmacy and Technology. https://doi.org/10.52711/0974-360X.2022.00794
40. N.Thallaj.International Journal of Advanced Pharmaceutical Sciences and Research (IJAPSR) 2022. 2,4, 1-15. https://doi.org/10.54105/ijapsr.C4016.062422
41. N.Thallaj.International Journal of Advanced Pharmaceutical Sciences and Research (IJAPSR) 2022. 2,6, 1-12. https://doi.org/10.54105/ijapsr.C4015.102622
42. N.Thallaj.International Journal of Advanced Pharmaceutical Sciences and Research (IJAPSR) 2023. 3,2, 1-18. https://doi.org/10.54105/ijapsr.C4011.023223
43. Isbera M, Abbood A, Ibrahim W. Weight and Content Uniformity of Warfarin Sodium Half Tablets. Research Journal of Pharmacy and Technology. 2016; 9(3):215-218. doi: 10.5958/0974-360X.2016.00039.1 https://doi.org/10.5958/0974-360X.2016.00039.1
44. Abbood A, Layka R. Weight and content uniformity Study of captopril half-tablets. Research Journal of Pharmacy and Technology. 2017;10(6):1621-1626. doi: 10.5958/0974-360X.2017.00285.2. https://doi.org/10.5958/0974-360X.2017.00285.2
45. Chbani D, Abbood A, Alkhayer M. Determination of Nitrite and Nitrate Ions levels in some types of processed meats marketed locally. Research Journal of Pharmacy and Technology. 2018;11(4):1442-1447. doi: 10.5958/0974-360X.2018.00269.X. https://doi.org/10.5958/0974-360X.2018.00269.X
46. Abbood A, Malek Z, Al-Homsh Y, Thallaj N. In vitro Study for Antibiotic resistance of bacteria causing Urinary Tract Infection from Syrian adults. Research Journal of Pharmacy and Technology. 2022;15(10):4727-2. doi: 10.52711/0974-360X.2022.00794. https://doi.org/10.52711/0974-360X.2022.00794
47. Abbood A, Malek Z, Thallaj N. Antibiotic resistance of urinary tract pathogens in Syrian children. Research Journal of Pharmacy and Technology. 2022;15(11):4935-9. doi: 10.52711/0974-360X.2022.00829. https://doi.org/10.52711/0974-360X.2022.00829
48. Windbichler, N., M. Werner and R. Schroeder. 2003. Kissing complex-mediated dimerisation of HIV-1 RNA: coupling extended duplex formation to ribozyme cleavage. Nucleic Acids Res 31:6419-27. https://doi.org/10.1093/nar/gkg873
49. Woodson, S. A. and D. M. Crothers. 1987. Proton nuclear magnetic resonance studies on bulge-containing DNA oligonucleotides from a mutational hot-spot sequence. Biochemistry 26:904-12. https://doi.org/10.1021/bi00377a035
50. Wu, K. J., T. A. Shaler, and C. H. Becker. 1994. Time-of-flight mass spectrometry of underivatized single-stranded DNA oligomers by matrix-assisted laser desorption. Anal Shem 66:1637–45. https://doi.org/10.1021/ac00082a007
51. Wu, T., J. Guo, J. Bess, L. E. Henderson, and J. G. Levin. 1999. Molecular requirements for human immunodeficiency virus type 1 plus-strand transfer: analysis in reconstitution and endogenous reverse transcription systems. J Virol 73:4794-805. https://doi.org/10.1128/JVI.73.6.4794-4805.1999
52. Wu, W., B. M. Blumberg, P. J. Fay, and R. A. Bambara. 1995. Strand transfer mediated by human immunodeficiency virus reverse transcriptase in vitro is promoted by pausing and results in misincorporation. J Biol Chem 270:325-32. https://doi.org/10.1074/jbc.270.1.325
53. Wu-Baer, F., D. Sigman and R. B. Gaynor. 1995. Specific binding of RNA polymerase II to the human immunodeficiency virus trans-activating region RNA is regulated by cellular cofactors and Tat. Proc natl acad sci u s a 92:7153-7. https://doi.org/10.1073/pnas.92.16.7153
54. Wyatt, R. and J. Sodroski. 1998. The HIV-1 envelope glycoproteins: fusogens, antigens, and immunogens. Science 280:1884-8. https://doi.org/10.1126/science.280.5371.1884
55. You, J. C. and C. S. McHenry. 1993. HIV nucleocapsid protein. Expression in Escherichia coli, purification, and characterization. J Biol Chem 268:16519-27. https://doi.org/10.1016/S0021-9258(19)85450-9
56. You, J. C. and C. S. McHenry. 1994. Human immunodeficiency virus nucleocapsid protein accelerates strand transfer of the terminally redundant sequences involved in reverse transcription. J Biol Chem 269:31491-5. https://doi.org/10.1016/S0021-9258(18)31721-6
57. Yu, E. and D. Fabris. 2003. Direct probing of RNA structures and RNA-protein interactions in the HIV-1 packaging signal by chemical modification and electrospray ionization fourier transform mass spectrometry. J Mol Biol 330:211-23. https://doi.org/10.1016/S0022-2836(03)00589-8
58. Yu, X., Y. Hathout, C. Fenselau, R. C. Sowder, 2nd, L. E. Henderson, W. G. Rice, J. Mendeleyev and E. Kun. 1995. Specific disulfide formation in the oxidation of HIV-1 zinc finger protein nucleocapsid p7. Shem Res Toxicol 8:586-90. https://doi.org/10.1021/tx00046a013
59. Zennou, V., C. Petit, D. Guetard, U. Nerhbass, L. Montagnier and P. Charneau. 2000.
60. HIV-1 genome nuclear import is mediated by a central DNA flap. Cell 101:173–85. https://doi.org/10.1016/S0092-8674(00)80828-4

AUTHORS PROFILE

Osama Khatib, student at the Faculty of Pharmacy looking for a job in the scientific representative for pharmaceutical companies, where apply my knowledge and skills for continuous improvement. I am looking forward for my first work experience. PART OF the activites of the first scientific day of the faculty of Pharmacy at dama rose hotel lect entitled:

1. Local Pharamceutical Industries betweer and ambition.
2. Pharmacological genetic applications in improving health care.
3. Pharmacological curves.
4. New Horizons in cancer Sciences.
5. Smoking and Anesthesia.

HIGHLIGHTS:
A broad-based experience in synthesis and characterization of organic and organo-metallic compounds. Multiple-step organic and organometallic synthesis. Carbohydrate Chemistry, Microwave synthesis, Solid phase synthesis, Enantioselective synthesis, Homogenous catalysis, Synthetic techniques including working on a Schlenck line, through a glovebox and in a clean room. Crystallogenesis experience especially in growing single crystals under inert conditions. Characterization of organic products and organometallic complexes by a variety of NMR techniques (1H, 13C, 31P, 15N, 19F) 1D and 2D, 1HNMR, FT-IR spectroscopy, UV-Visible-NIR spectroscopy, variable temperatures, Mass spectrometry, electrochemistry (conductimetry, cyclic voltammetry), chromatography techniques, including column, TLC preparative, GC, GC mass and HPLC chromatography.



Tala Alshimale, A Student at The College of Pharmacy. Worked As a Pharmacist for Two Years During My University Studies. Looking Forward to Finding a Job That Will Develop and Increase My Pharmaceutical skills and raise My academic level. rain and work as a community pharmacist. With an integrated team of pharmacists to provide medical advice, give advice to patients, and dispense medication and appropriate treatment.
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HIGHLIGHTS:
A broad-based experience in synthesis and characterization of organic and organo-metallic compounds. Multiple-step organic and organometallic synthesis. Carbohydrate Chemistry, Microwave synthesis, Solid phase synthesis, Enantioselective synthesis, Homogenous catalysis, Synthetic techniques including working on a Schlenck line, through a glovebox and in a clean room. Crystallogenesis experience especially in growing single crystals under inert conditions. Characterization of organic products and organometallic complexes by a variety of NMR techniques (1H, 13C, 31P, 15N, 19F) 1D and 2D, 1HNMR, FT-IR spectroscopy, UV-Visible-NIR spectroscopy, variable temperatures, Mass spectrometry, electrochemistry (conductimetry, cyclic voltammetry), chromatography techniques, including column, TLC preparative, GC, GC mass and HPLC chromatography.

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