Review Article

DRUG RESISTANCE IN ANTI-VIRAL MEDICATIONS: A CASE STUDY OF HUMAN IMMUNODEFICIENCY VIRUS

Abstract

HIV drug resistance (HIVDR) is a growing challenge in the management of HIV, with global prevalence rising significantly since the widespread adoption of antiretroviral therapy (ART). Resistance mutations compromise treatment effectiveness, leading to virological failure and transmission of resistant strains to others, including newly infected individuals. Pregnant women face added risks, as resistant strains complicate treatment options and increase the likelihood of vertical transmission. Addressing this issue is critical to sustaining the success of ART and advancing global HIV control efforts. Therefore, this review aims to explore the drug resistance in anti-viral medications: a case study of HIV.This review was conducted using PubMed, Google Scholar, and reports from WHO and UNAIDS, focusing on peer-reviewed publications from the past 20 years. Search terms included “HIV drug resistance,” “antiretroviral resistance,” and “mother-to-child transmission.” Articles were selected based on relevance to resistance mechanisms, prevalence, and management, ensuring a comprehensive and rigorous analysis of the topic.HIV drug resistance is a critical challenge to effective HIV treatment, driven by the virus's high mutation rate and genetic diversity. Resistance occurs across all major antiretroviral drug classes, particularly in low- and middle-income countries, where factors like limited access to testing and poor adherence exacerbate the problem. Combating resistance requires enhanced monitoring, innovative therapies, and strategies to improve adherence and reduce selective pressure. Integrating resistance data into treatment guidelines and utilizing technologies like AI can optimize treatment outcomes and support global efforts to control HIV/AIDS.

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1. Introduction

The prevalence of drug resistance has become a significant challenge to the effective management of HIV infection globally(1–3). Data from the World Health Organization (WHO), the Global Fund to Fight AIDS, Tuberculosis, and Malaria, and the Centers for Disease Control and Prevention (CDC) reveal a significant rise in the prevalence of HIV drug resistance, which has increased from 11% to 29% since the global rollout of antiretroviral therapy (ART) in 2001(4). In response, international health agencies, including the Joint United Nations Program on HIV/AIDS (UNAIDS) and WHO, have prioritized addressing this issue as part of their commitment to ending AIDS as a public health threat by 2030. Central to this effort is the "90-90-90" framework introduced in 2020, which aimed to ensure that 90% of individuals living with HIV know their status, 90% of those diagnosed receive ART, and 90% of those on ART achieve sustained viral suppression(4). Attaining viral suppression is not only crucial for improving individual health and survival but is also important for controlling the HIV epidemic(3).

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Human Immunodeficiency Virus (HIV) is a virus that progressively weakens the immune system. It is an RNA that depends on the reverse transcriptase enzyme to convert its RNA genome into DNA. This DNA is then integrated into the host's genome, enabling the virus to replicate and persist within the body(5,6). The genetic material of HIV is in the form of two positive single-strand RNAs which encode 10 types of genes (gag, pol, env, tat, rev, nef, vif, vpr, vpu, and tev) which collectively result in 19 proteins(6,7). The major genes usually used as a foundation for classifying HIV genotypes and subtypes are the gag, pol, and env genes. The regulation of the process of viral replication and encoding structural proteins is done by the gag gene, and also by the pol gene which produces enzymes needed for virus replication (transcriptase, integrase, and protease), Meanwhile, the env gene is responsible for forming the viral envelope (membrane glycoprotein) of the HIV(8). Other genes also play a significant role in regulating HIV transcription(9).

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HIV drug resistance (HIVDR) as defined by WHO is: "HIV drug resistance (HIVDR) is caused by one or more changes (mutation/s) in the genetic structure of HIV that affects the ability of a specific drug or combination of drugs to block replication of the virus. All current antiretroviral (ARV) drugs, including newer classes, are at risk of becoming partly or fully inactive because of the emergence of drug-resistant virus. People receiving ART can acquire HIVDR, and people can also be infected with HIV that is already drug resistant"(1). WHO categorizes HIVDR into three main categories(1): "1. Acquired HIV drug resistance (ADR) develops because of viral replication in the presence of ARV drugs. 2. Transmitted HIV drug resistance (TDR) is detected among ARV drug–naive people with no history of ARV drug exposure. TDR occurs when previously uninfected individuals are infected with virus that has drug resistance mutations. 3. Pretreatment HIV drug resistance (PDR) refers to resistance that is detected among ARV drug–naive people initiating ART or people with previous ARV drug exposure initiating or reinitiating first-line ART. PDR is either TDR or ADR or both. PDR may have been transmitted at the time of infection (TDR) or may be acquired through previous ARV drug exposure (such as among women exposed to ARV drugs for preventing mother-to-child transmission of HIV, among people who have received pre-exposure prophylaxis or among individuals reinitiating first-line ART after a period of treatment interruption). ARV drug–naive applies to people with no history of ARV drug exposure"(1).

Kommentiert [A.Y.6]: Replace "and" with "while"

Kommentiert [A.Y.7]: Add "strains"

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Drug resistance mutations (DRMs) arise through viral replication and selective pressure in individuals receiving antiretroviral therapy (ART). These mutations not only result in treatment failure but can also be passed on to drug-naïve individuals, including those newly infected with HIV(2,10,11). In pregnant women, the transmission of DRM strains poses additional problems, as it increases the risk of passing resistant strains to the infant, complicating treatment options and infant HIV care(2,12). Therefore, this review aims to explore the drug resistance in anti-viral medications: a case study of HIV.

Search Methods

This narrative review was conducted using the following:

1. **Databases**
    - PubMed
    - Google Scholar
    - WHO and UNAIDS publications for global statistics and reports.
    - ResearchGate

2. Search Terms

These keywords were used during the literature search

- *"*HIV drug resistance" AND "antiviral therapy"
- "HIV resistance mutations" OR "antiretroviral resistance"
- "Mother-to-child transmission" AND "HIV resistance", and etc.

3. **Inclusion Criteria**:
   - *Articles published in peer-reviewed journals.*
   - *Studies and reports published in the last 20 years (with exceptions for seminal work and highly relevant articles).*
   - *Research focusing on resistance mechanisms, prevalence, clinical outcomes, and management strategies.*

4. **Exclusion Criteria**:
   - Non-peer-reviewed sources unless from reputable organizations (e.g., WHO).
   - Studies without clear relevance to HIV drug resistance or antiviral treatments.

5. Search Strategy:

- Performed initial searches using broad terms to capture a wide range of literature.
- Used filters for publication date, study type, and full-text availability.
- Hand-selected and reviewed reference lists of relevant articles to identify additional sources.

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2. Pathogenesis of Viruses and Mechanism of Action of Antiviral Drugs

2.1 Pathogenesis of Viruses

Kommentiert [A.Y.10]: Instead of focusing on the pathogenesis of viruses, it is recommended that you rather focus on the replication of HIV and what pathways are targeted by ART

Viral pathogenesis is the complex process by which viruses enter, replicate within, and spread across host cells, ultimately leading to illness. Viral entry is usually the first stage of infection where viruses bind to specific receptors on host cells. They use receptor-mediated endocytosis, membrane fusion, or direct penetration, helped by viral envelope proteins like spikes or glycoproteins that aid membrane fusion or endocytosis(13,14). Once inside, viruses replicate by hijacking the host cell's machinery. This process involves the synthesis of viral RNA or DNA, the production of viral proteins, and the assembly of new virus particles. RNA viruses replicate in the cytoplasm, while DNA viruses typically replicate in the nucleus. After replication, viruses spread from the initial site of infection to other tissues or organs via pathways such as local cell-to-cell spread, lymphatic or blood circulation, or neural routes. This dissemination results in the development of systemic illnesses(13,15).Viral proteins play a significant role in pathogenesis by interacting with host proteins to manipulate cellular pathways, evade immune responses, and improve viral replication. To counteract infections, the host immune system launches innate responses, including the production of antiviral cytokines, activation of pattern recognition receptors, and recruitment of immune cells. This is followed by adaptive immune responses, where B cells and T cells produce antigen-specific defences to eliminate the virus and provide immunity. Together, these

mechanisms highlight the dynamic interplay between viruses and the host during infection(13–16).

2.2 Mechanism of Action of Antiviral Drugs

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Antiviral medications are designed to specifically target the methodology of viral replication or entry, aiming to inhibit viral reproduction and decrease viral load in infected individuals. Various types of antiviral drugs have been developed to target specific viral enzymes or proteins crucial to the viral life cycle. For example, nucleoside analogues interfere with the synthesis of viral RNA or DNA, protease inhibitors block the processing of viral proteins, and entry inhibitors prevent viruses from attaching to or binding with host cells. Table 1 outlines key antiviral drugs and their mechanisms of action(13,17,18).

Table 1: Important antiviral drugs and their mechanism of action(13).

Antiviral drugs	Working against	Mechanism of action	Reference
Acyclovir	herpes simplex virus types 1 (HSV-1), 2 (HSV-2)	Inhibit DNA polymerase inhibitor	(19)
Zidovudine and Lamivudine	HIV-1	nucleoside analog-reverse transcriptase inhibitors	(17)
Raltegravir	HIV-1	Viral integrase inhibitors	(20)
Lopinavir/Ritonavir, Darunivir	HIV-1	HIV protease inhibitor	(21)
Remdesivir	SARS CoV-2	Inhibits viral RNA polymerase by inhibiting RdRp, Nucleoside analogue	(18)
Nitazoxanide	Parainfluenza virus, Coronavirus (CoV), Rotavirus, HBV, HCV, dengue virus	Antipolymerase action against hepatitis virus, blocks entry of influenza virus	(22)
Pocapavir (v-073)	Polio virus and neonatal enteroviral sepsis	Inhibit the entry of virus by inhibiting Viral capsid	(23)
Oseltamivir and Zanamivir	Influenza virus	Neuraminidase inhibitor	(24)

3. Overview of HIV and Emergence of Drug Resistance

3.1 Overview of HIV

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The HIV/AIDS pandemic has been one of the most crucial global medical challenges for more than 30 years. Human Immunodeficiency Viruses (HIV) are retroviruses of simian origin, that replicate by transcribing their RNA into DNA and integrating their genome into the human host. Two primary types of HIV are responsible for human disease: HIV-1 and

HIV-2(25). HIV is classified into two genotypes: HIV-1 and HIV-2. HIV-1 is further divided into 11 subtypes and circulating recombinant forms (CRFs). The HIV-1 group consists of three major groups: M (major), N (non-M, non-O), and O (outlier). Group M, the most common group, is divided into nine subtypes: A, B, C, D, F, G, H, J, and K(6).In some cases, viruses from different subtypes can co-infect the same host cell, leading to genetic recombination and the formation of hybrid viruses. While many of these hybrids do not persist, some can infect multiple individuals and are classified as Circulating Recombinant Forms (CRFs). To date, 34 CRFs have been identified. For example, CRF01_AE, a hybrid of subtypes A and E, is predominantly found in Southeast Asia(6).Different subtypes exhibit patterns of distribution based on transmission routes. Subtype B is more frequently associated with individuals engaging in homosexual contact and injecting drug use, while subtypes C and CRF01_AE are commonly linked to heterosexual transmission. This suggests a possible relationship between the mode of transmission and the infecting HIV subtype(6).

HIV infection is transmitted through sexual contact, blood transfusions, organ transplants, contaminated needles in healthcare settings, injecting drug use (IDU), and from mother to child. Once the host is infected, HIV targets CD4+ T-lymphocytes and uses the reverse transcriptase enzyme to convert its RNA into DNA(25). The host cell is then exploited to produce new HIV particles, perpetuating the infection cycle.As the disease progresses, the number and functionality of CD4+ cells decline, while the viral load increases. This immunosuppression renders the individual more vulnerable to opportunistic infections, rare tumours, and metabolic disorders. The advanced stage of HIV infection is referred to as acquired immunodeficiency syndrome (AIDS). Without targeted treatment, AIDS is fatal, although the time to progression varies between individuals(25).The burden of new HIV infections is unevenly distributed across the globe, with central Asia, Sub-Saharan Africa, and Eastern Europe being disproportionately affected. Africa remains the region most impacted, while infection rates continue to rise in parts of Asia. HIV/AIDS significantly influences individual patients' social lives, economic stability, and overall well-being, while also exerting profound social and economic pressures on heavily affected countries. Ongoing efforts to combat HIV/AIDS must be sustained and strategically directed to address this global challenge effectively(25,26).

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3.2 HIV DRUG RESISTANCE

Wild-type HIV has progressed to be the major genetically fit version of the virus. However, the inherent characteristics of HIV make it highly prone to mutations, allowing it to evade drug inhibition. Its rapid replication, error-prone reverse transcription, and high recombination rates result to a genetically diverse, heterogeneous virus population referred to as quasispecies(27–29). The in vivo mutation rate of HIV is estimated at 4.1×10^{-3} per base per cell(30).Mutations that increase or decrease viral replication capacity during viral replication are produced(29,31). Drug-resistant mutations (DRMs) are mutations that counteract ART-mediated inhibition of viral replication. These can develop under selective drug pressure (treatment-emergent) or be acquired during initial infection (transmitted resistance)(27,32). Factors resulting in the emergence of HIV drug resistance include specific HIV-1 genetic traits, patient-related factors, and the choice of ART regimen(31).

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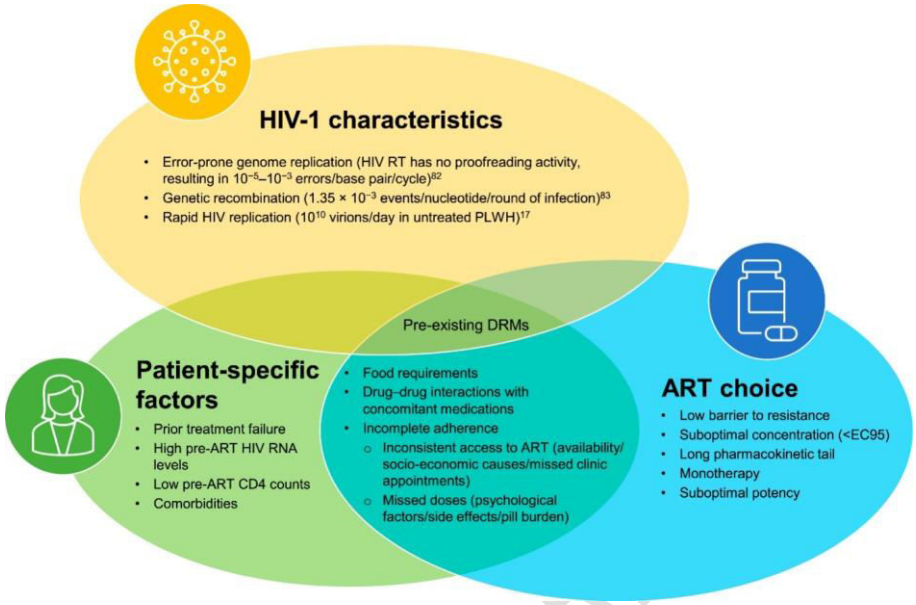

Figure 1. Factors leading to the development of drug resistance, ART: antiretroviral therapy; DRM: drug-resistant mutation; EC95: effective concentrations to cause 95% inhibition; PLWH: people living with HIV; RT: reverse transcriptase (Source:31**).**

3.3 HIV Drug Classes

Kommentiert [A.Y.15]: This should be discussed before discussing HIV resistance mechanisms

HIV medications are categorized into six classes, each targeting specific viral proteins or host cell attachment mechanisms. These drug classes include(33):

1. Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs) – first approved in 1987, these drugs block the reverse transcription of viral RNA into DNA.
2. Protease Inhibitors (PIs) – introduced in 1995, these inhibit the protease enzyme, preventing the processing of viral proteins.
3. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) – approved in 1996, these bind to reverse transcriptase and disrupt its function.
4. Entry Inhibitors – launched in 2003, these target the virus's ability to attach and enter host cells. This class is further divided into:
    - Pre-attachment inhibitors
    - Post-attachment inhibitors
    - CCR5 antagonists
    - Fusion inhibitors
5. Integrase Strand Transfer Inhibitors (INSTIs) – introduced in 2007, these prevent viral DNA integration into the host genome.

6. Capsid Inhibitors – the most recent addition in 2022, targeting the viral capsid to inhibit replication.

These drug classes represent a comprehensive approach to interrupting various stages of the HIV life cycle(31).

3.4 Mechanism of HIV Drug Resistance

HIV drug resistance mechanisms are specific to each drug class or individual drug and primarily involve mutations that hinder the interaction between the antiretroviral drug and its binding site. For nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), resistance mutations occur in the *reverse transcriptase (RT)* gene. NRTI resistance mutations either reduce drug binding efficiency at the RT active site or facilitate the removal of NRTI-terminated primers. NNRTI resistance mutations disrupt drug binding or reduce access to the NNRTI binding pocket in RT(28,29,34).
For protease inhibitors (PIs), resistance results from mutations in the *HIV protease active site*, which can be influenced by additional mutations in the *gag polyprotein cleavage sites*(35). In integrase strand transfer inhibitors (INSTIs), most resistance mutations alter the *catalytic pocket* of the HIV integrase enzyme, causing conformational changes. Additional resistance mutations can occur in the *C-terminal domain* of integrase or other viral regions, such as the *3' polypurine tract* and the *envelope glycoprotein gene (Env)*. These mutations may explain rare instances of virologic failure in patients receiving second-generation INSTIs despite the absence of detectable resistance mutations in the integrase gene(31,36).

Resistance to entry inhibitors arises from mutations in *HIV envelope proteins*, which vary by drug subclass. For fusion inhibitors, mutations occur in *gp41*(37), while resistance to pre-attachment inhibitors, post-attachment inhibitors, and CCR5 antagonists involves mutations in *gp120*. These mutations are site-specific, meaning resistance to one entry inhibitor subclass does not typically confer cross-resistance to others(38–40).In capsid inhibitors, resistance mutations lead to structural changes in the *capsid hexamers*, creating steric hindrance that prevents drug binding. This disruption hinders the capsid inhibitor's ability to stabilize the viral core and block viral integration(41,42). These mechanisms illustrate the adaptability of HIV, emphasizing the importance of tailored antiretroviral regimens and strict adherence to therapy to limit the development of resistance.

3.5 Antiretroviral Therapy (ART)

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3.5.1 The Introduction of Antiretroviral Therapy (ART)

The introduction of antiretroviral therapy (ART) has revolutionized the clinical management of HIV/AIDS, significantly improving patient outcomes. Early studies following the implementation of Highly Active Antiretroviral Therapy (HAART) in 1996, which combines three classes of antiretroviral drugs (ARVs), demonstrated a dramatic reduction in HIV-related mortality and morbidity, with declines of up to 85% among treated patients(25,43,44).Individuals with HIV require antiretroviral therapy (ART) to lower viral levels and prevent progression to AIDS, while those with AIDS need treatment to manage and prevent opportunistic infections. According to WHO guidelines, universal ART should be initiated within 14 days of diagnosis, regardless of the clinical stage or CD4 count(6,45).

Antiretroviral (ARV) therapy has been shown to improve the quality of life for people living with HIV/AIDS (PLWHA). However, it can also drive the emergence of mutations in the HIV-1 virus, contributing to drug resistance. Resistance is often associated with high viral loads, low CD4 counts, and poor adherence to HIV/AIDS therapy. PLWHA who develop ARV resistance face greater challenges in suppressing viral replication(6).HIV-1 naturally exhibits a high mutation rate, with one nucleotide change per replication cycle. Studies have shown that exposure to ARV drugs can amplify this mutation rate. For instance, zidovudine (AZT) increases mutations by 7.6 times per replication cycle, while lamivudine (3TC) increases them by 3.4 times. While the underlying mechanisms of drug resistance are consistent globally, differences in therapy management between low- and middle-income countries contribute to variations in resistance patterns(6).

3.5.2 HIV *ART* Drug Resistance

ARV resistance can be categorized into two types: primary resistance, which occurs in treatment-naïve patients who have not yet received therapy, and secondary resistance, which develops in patients currently undergoing ARV therapy. The most commonly utilized method for detecting resistance is genotypic testing. This involves comparing gene sequences isolated from patient samples with wild-type HIV-1 sequences that are sensitive to ARVs. Resistance mutations refer to genetic variations from the wild-type consensus subtype B, which can lead to either major or minor resistance(6). Major resistance mutations significantly reduce the effectiveness of ARVs, while minor mutations enhance the replication capacity of viruses that have already developed major mutations. Studies frequently report the detection of genotypic mutations conferring ARV resistance. For pregnant individuals with low CD4+ counts (≤ 50 cells/µL), or for people living with HIV/AIDS (PLWHA) who have neurocognitive disorders, chronic kidney disease, cardiovascular conditions, or chronic hepatitis, alternative antiretroviral therapy (ART) regimens may be recommended(6,46).

Initiating ARV treatment should occur within 14 days of diagnosis, adhering to WHO recommendations. First-line treatment typically involves combination ART, although alternative regimens may be used when the preferred components are unsuitable for the individual. These adjustments aim to optimize outcomes and manage specific patient conditions effectively(6).Resistance to antiretroviral therapy (ARVs), particularly within the nucleoside reverse transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), and protease inhibitor groups, arises from the persistent inhibition of the HIV-1 protease (PR) and reverse transcriptase (RT) enzymes. To counteract this inhibition, mutations develop in the *pol* region of the HIV-1 genome, specifically in the PR and RT genes responsible for encoding these enzymes. These mutations enable the virus to preserve its capacity to produce the enzymatic proteins essential for its replication and survival(27).

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4. Impact of HIV Drug Resistance on Treatment Outcomes

The impact of HIV drug resistance on treatment outcomes is significant, affecting the effectiveness of antiretroviral therapy (ART) and the probability of virological failure. Various studies highlight the role of specific mutations, such as K103N and M184V, in exacerbating treatment challenges. Understanding these mutations and their frequencies can guide clinicians in optimizing ART regimens.

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4.1 Key Mutations and Their Effects

- K103N Mutation: Associated with increased treatment failure risk, especially in patients starting NNRTI-based regimens. The hazard ratios indicate a 3.12 and 2.38 times higher risk for ART-naïve and ART-discontinued patients, respectively(47)
- M184V Mutation: Found to increase the probability of virological failure by 1.87 times and viral blips by 2.26 times compared to those without the mutation(48).

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4.2 Low-Frequency Drug Resistance

- Low-frequency drug resistance mutations can negatively affect treatment outcomes. A study showed that pre-treatment low-frequency variants were linked to a higher risk of virological failure over 24 months(49). Low-frequency drug-resistant variants, often undetected by standard sequencing, can also contribute to treatment failure. Ultra-deep sequencing methods have revealed that these minor variants significantly increase the risk of virological failure, underscoring the importance of sensitive detection methods(47,50).

4.3 Resistance Testing

- The presence of drug resistance mutations necessitates careful selection of ART regimens. Resistance testing before treatment initiation can guide the choice of more effective drug combinations, potentially improving outcomes(27,51). The integration of artificial intelligence in predicting drug resistance can enhance personalized treatment strategies, potentially improving outcomes by tailoring ART to individual patient profiles(52).

Kommentiert [A.Y.22]: Discuss some of the resistance testing available

5. Case Study of HIV Drug Resistance Transmission within a Family

The study(2) concentrates on a family case involving transmitted and acquired HIV-1 drug resistance, highlighting the significance of understanding how drug-resistant strains can spread within families. The family consists of three members: the father (Patient F), the mother (Patient M), and their infant (Patient I). The father was confirmed HIV-positive after the mother was diagnosed shortly before childbirth. Patient M was initially HIV-negative during her pregnancy however she tested positive just before delivery. She had no former history of high-risk behaviors that could lead to HIV infection. The father transmitted the HIV-1 virus to the mother during late pregnancy, and subsequently, the mother transmitted it to the infant. A common mutation, V106I, was identified in all three family members. Patient M started antiretroviral therapy (ART) but discontinued it after only eight days due to a

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severe allergic reaction. This led to the acquisition of additional drug resistance mutations, including K101E and K103N, which increased her resistance to several non-nucleoside reverse transcriptase inhibitors (NNRTIs). The study employed both Sanger-based sequencing (SBS) and next-generation sequencing (NGS) to analyze drug resistance mutations. NGS proved more effective in detecting minor mutations that SBS missed, such as a minor V106M mutation in Patient M. The findings emphasize the need for simultaneous screening for sexually transmitted diseases (STDs) in both partners during pregnancy, as well as the importance of monitoring for minor mutations in complex cases of HIV infection. Overall, this case study illustrates the challenges posed by drug-resistant HIV strains and the critical need for improved screening and treatment strategies to manage HIV effectively within families.

6. Challenges and Way Forward

6.1 Challenges

Kommentiert [A.Y.24]: Why bullet points? Discuss in sentences

Challenges posed by HIV drug resistance includes butnot limited to:

- **Rapid Mutation Rates**: HIV's ability to mutate quickly leads to the development of drug-resistant strains, complicating treatment efforts(53).
- **Data Management**: The integration of next-generation sequencing (NGS) for monitoring drug resistance generates complex data, posing challenges in bioinformatics analysis and patient data security(54).
- **Treatment Gaps**: A significant percentage of individuals with HIV do not achieve viral suppression, highlighting ongoing gaps in care exacerbated by the COVID-19 pandemic(55).
- **Regional Variations**: Different regions face unique challenges due to systematic cultural, and economic factors. Resource-limited settings often struggle with access to high genetic barrier regimens, which are crucial for preventing resistance(56,57).
- **Adherence and Access**: Non-adherence to ART and limited access to potent drugs, especially in low- and middle-income countries, exacerbate the problem of drug resistance(58).

6.2Future Directions in Managing HIV Drug Resistance

- **Development of Innovative Therapies**

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The introduction of novel therapeutics, such as attachment inhibitors and capsid inhibitors, results in a promising approach to addressing drug-resistant HIV strains. These drugs are designed for broad-spectrum efficacy and enhanced resistance resilience(59,60).

- **Optimized Treatment Approaches**

Advancements in treatment strategies emphasize combination therapies to improve adherence and simplify regimens, such as reduced dosing frequencies(59,60). Integrating machine

learning and artificial intelligence (AI) enhances the prediction of drug resistance, facilitating the development of more tailored and effective treatment plans(53).

- **Enhanced Monitoring and Resistance Surveillance**

Comprehensive surveillance systems, such as HIV-DRIVES, are pivotal for identifying and managing drug-resistant mutations(54). Expanded genotypic resistance testing and regular monitoring of HIV viral loads are essential to preventing virological failure. AI-driven tools further support resistance surveillance by predicting mutation trends, ensuring timely and precise intervention(27,61).

- **Guideline Updates and Preventive Measures**

Continuous updates to treatment guidelines that reflect evolving resistance patterns are essential for optimizing antiretroviral therapy(55). Preventive measures, including improved ART-regimen switching practices and the use of high-resistance-barrier therapies, help reduce the emergence and transmission of resistant mutations, safeguarding the long-term efficacy of treatment regimens(58).

7. Conclusion

HIV drug resistance depicts a significant barrier to the effective management of HIV/AIDS, particularly in the context of the global roll-out of antiretroviral therapy (ART). The continuous prevalence of drug-resistant mutations (DRMs) highlights the dynamic interplay between viral evolution and therapeutic intervention. Resistance arises mainly due to the high mutation rate of HIV, driven by its error-prone reverse transcription, high replication rates, and recombination. These mechanisms produce a genetically diverse viral population, enabling the virus to adapt rapidly under selective drug pressure. Consequently, treatment-emergent and transmitted resistance have been documented across all major classes of antiretroviral drugs, including NRTIs, NNRTIs, protease inhibitors, integrase inhibitors, and entry inhibitors.The global burden of HIV drug resistance is unequally distributed, with low- and middle-income countries (LMICs) experiencing disproportionate challenges. Limited access to resistance testing, suboptimal adherence, and inconsistent ART regimens contribute to higher resistance rates in these regions. Moreover, socioeconomic barriers and lack of healthcare infrastructure further complicate the effective management of resistance, leading to virological failure and increased transmission of resistant strains.

Efforts to combat HIV drug resistance must be multifaceted, addressing both the biological and structural determinants of resistance. Enhanced monitoring, including routine viral load testing and expanded genotypic resistance testing, is critical to detect resistance early and guide the optimization of treatment regimens. Surveillance systems, such as HIV-DRIVES, play a vital role in tracking resistance trends and informing public health strategies.Innovative therapeutics targeting different stages of the HIV life cycle, such as attachment inhibitors, capsid inhibitors, and broadly neutralizing antibodies, offer promising solutions to overcome resistance. These drugs are designed to retain efficacy against resistant strains, ensuring continued viral suppression even in the presence of DRMs. Additionally, the application of machine learning and artificial intelligence (AI) to predict resistance mutations and optimize drug design holds transformative potential for personalized HIV care.

Preventive strategies are equally important in mitigating resistance. High-resistance-barrier regimens and improved ART-switching protocols can reduce the selection pressure for resistant mutations. Adherence-enhancing interventions, including simplified regimens with infrequent dosing, can improve treatment outcomes and limit resistance development. Tailored community-based interventions addressing the unique challenges encountered by LMICs are essential to ensuring equitable access to resistance management.Finally, the integration of resistance data into clinical guidelines is critical for maintaining the relevance of treatment protocols. Regular updates based on evolving resistance patterns can optimize therapeutic decisions and enhance patient outcomes. The global fight against HIV drug resistance requires a collaborative approach, leveraging advancements in research, innovation in therapeutic development, and equitable healthcare delivery systems.

In conclusion, while HIV drug resistance poses complex challenges, the convergence of science, technology, and policy presents substantial opportunities to overcome these barriers. Sustained investment in research, capacity building, and health system strengthening is imperative to achieving the long-term goal of eradicating HIV/AIDS as a public health threat. By addressing resistance comprehensively, we can ensure the continued effectiveness of ART, improve patient outcomes, and move closer to ending the global HIV epidemic.

8. References

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