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Antiretroviral Therapy in HIV Management: A Synthesis of Organ-Specific Toxicities, Underlying Pathways and Interventions

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Abstract:

Antiretroviral therapy (ART) has transformed HIV infection from a fatal disease into a manageable chronic condition, markedly improving patient survival and quality of life. However, this success is tempered by a wide array of toxic effects associated with antiretroviral drugs (ARVs), which can affect multiple organ systems and pose significant challenges to long-term treatment adherence and outcomes. This comprehensive review synthesizes the latest evidence on the toxicological profiles, underlying mechanisms, and clinical implications of major ARV classes, including nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), and entry/fusion inhibitors. Key toxicities discussed include mitochondrial dysfunction and lactic acidosis from NRTIs, hepatotoxicity and neuropsychiatric effects from NNRTIs and PIs, renal and bone disorders linked to tenofovir-based regimens, and emerging concerns such as weight gain and cardiovascular risks with INSTIs. The review elucidates dose-dependent, idiosyncratic, and cumulative mechanisms driving these adverse events, drawing from clinical trials, cohort studies, and pharmacovigilance data. Strategies for mitigation, including routine monitoring protocols, therapeutic drug monitoring, and personalized ART regimens guided by pharmacogenomics, are critically evaluated to minimize long-term toxicities while preserving virologic suppression. This synthesis underscores the need for ongoing research into safer ARV formulations and highlights the pivotal role of multidisciplinary care in optimizing HIV management.

Keywords— **antiretroviral therapy, toxicity, HIV, mitochondrial toxicity, hepatotoxicity, neurotoxicity, metabolic syndrome.**

I.INTRODUCTION

Antiretroviral therapy (ART) remains the cornerstone of HIV management worldwide, significantly reducing morbidity and mortality. However, prolonged exposure to various antiretrovirals (ARVs) can induce adverse effects that range from mild biochemical abnormalities to severe organ toxicity, challenging patient adherence and long-term health outcomes. This review aims to provide a comprehensive evaluation of the toxic effects of ARVs by drug class, their underlying mechanisms, clinical manifestations, and management strategies, informed by recent clinical and pharmacovigilance studies.

The main classes of antiretroviral drugs used in the treatment of HIV infection are:

1. Nucleoside Reverse Transcriptase Inhibitors (NRTIs)
2. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)
3. Protease Inhibitors (PIs)
4. Integrase Strand Transfer Inhibitors (INSTIs)
5. Fusion Inhibitors (FIs)
6. C-C Chemokine Receptor type 5 (CCR5) Antagonists (Entry Inhibitors)

These classes differ by their targets and mechanisms along the HIV replication cycle. Combination antiretroviral therapy (cART) typically includes drugs from multiple classes to maximize efficacy and reduce resistance development. Each class contributes to disrupting key steps such as viral RNA reverse transcription, protein maturation, viral DNA integration, and viral entry into host cells (Deeks et al., 2021, Panel on Antiretroviral Guidelines for Adults and Adolescents, 2019).

II TOXICITY PROFILES OF ANTIRETROVIRAL DRUG CLASSES

A. *Nucleoside Reverse Transcriptase Inhibitors (NRTIs)*

Nucleoside Reverse Transcriptase Inhibitors are a fundamental component of antiretroviral therapy in HIV management. NRTIs used in HIV treatment include a range of approved

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drugs that serve as core components of antiretroviral therapy. The commonly used NRTIs are: Zidovudine (AZT), Didanosine (ddI), Stavudine (d4T), Lamivudine (3TC), Abacavir (ABC), Emtricitabine (FTC), Tenofovir Disoproxil, Fumarate (TDF), Tenofovir Alafenamide (TAF), Zalcitabine (ddC) (less commonly used due to toxicity) (Lu et al., 2021, Sillman & Johnson, 2017, EACS, 2023)

1. Mechanisms of Action of Nucleoside Reverse Transcriptase Inhibitors

Nucleoside Reverse Transcriptase Inhibitors inhibit HIV replication by targeting the viral enzyme reverse transcriptase (RT), which is needed for transcribing viral RNA into DNA. Mechanistically, NRTIs are analogs of natural nucleosides but lack a critical 3'-hydroxyl group on the sugar moiety required for DNA chain elongation. After intracellular phosphorylation to their active triphosphate forms - Nucleoside Reverse Transcriptase Inhibitor Triphosphate (NRTI-TP), they compete with natural deoxynucleoside triphosphates (dNTPs) for incorporation by RT into the growing viral DNA chain.

Once incorporated, NRTIs act as chain terminators because the absence of a 3'-OH prevents the addition of subsequent nucleotides, effectively halting viral DNA synthesis. This leads to premature termination of viral DNA and prevents integration into the host genome, suppressing HIV replication (Sarafianos et al., 2009; De Clercq, 2009). The selective inhibition by NRTIs relies on their affinity for HIV RT over host DNA polymerases and their ability to be phosphorylated efficiently in infected cells. Resistance to NRTIs can emerge through mutations in RT that either reduce incorporation of NRTIs or enhance excision/removal of incorporated NRTIs, restoring DNA synthesis (Harris et al., 2000).

2. *The Underlying Mechanisms of Toxicity of Nucleoside Reverse Transcriptase Inhibitors Drugs*

The toxic effects of Nucleoside Reverse Transcriptase Inhibitors are primarily due to their interference with mitochondrial function, a phenomenon widely known as mitochondrial toxicity. The canonical mechanism involves the inhibition of mitochondrial DNA (mtDNA) polymerase gamma (pol-γ), which is responsible for mitochondrial DNA replication and repair. NRTIs, structurally similar to natural nucleosides, are phosphorylated intracellularly to active triphosphate forms that inhibit HIV reverse transcriptase. However, these active metabolites also inadvertently inhibit pol-γ, resulting in depletion of mtDNA. This depletion compromises mitochondrial protein synthesis critical for oxidative phosphorylation, leading to impaired ATP production, increased production of reactive oxygen species (ROS), and mitochondrial dysfunction (Carr & Cooper, 2000; Lewis et al., 2006).

Beyond pol-γ inhibition, accumulating evidence indicates that oxidative stress plays a critical role in NRTI-induced toxicity. Short-term exposure to certain first-generation NRTIs causes increased ROS production, decreased oxygen consumption, and ATP depletion, which together exacerbate mitochondrial injury and cellular dysfunction (Martinez-Reyes et al., 2017). ROS-driven damage can trigger lipid peroxidation, DNA mutation, and apoptosis, further contributing to clinical manifestations such as lactic acidosis and organ toxicity. The mitochondrial permeability transition pore (mPTP) has also been implicated; it's opening, modulated by cyclophilin D, results in loss of mitochondrial membrane potential and the release of pro-apoptotic factors. NRTI metabolites like AZT triphosphate induce mPTP opening, impairing mitochondrial function, and agents inhibiting mPTP (e.g., cyclosporin A) can mitigate this effect (Kawamura et al., 2015).

Additional complexities include the disturbance in mitochondrial nucleotide pools due to competition between phosphorylated NRTIs and natural deoxyribonucleotides, contributing to mitochondrial replication stress independent of direct pol-γ inhibition. This effect can potentiate mtDNA depletion and mitochondrial proteomic abnormalities (Lewis et al., 2006). Furthermore, recent studies suggest that NRTIs induce mitophagy (regulated mitochondrial degradation) in endothelial cells, which may underlie vascular toxicity and endothelial dysfunction (Birk et al., 2013).

Altogether, the mechanisms underlying NRTI toxicity involve a multi-faceted process that includes direct enzyme inhibition (pol-γ), oxidative stress from increased ROS, and disruption of mitochondrial nucleotide pools, mPTP modulation, and mitochondrial quality control pathways such as mitophagy. These processes culminate in impaired mitochondrial bioenergetics manifesting clinically as lactic acidosis, peripheral neuropathy, hepatic steatosis, and lipodystrophy among others.

3. *Clinical Manifestations of Nucleoside Reverse Transcriptase Inhibitors Toxicity in HIV Patients*

Nucleoside Reverse Transcriptase Inhibitors, while essential in HIV treatment, are associated with a range of toxic effects with distinct clinical manifestations that can impact patient outcomes and adherence.

- Lactic Acidosis and Hepatic Steatosis: One of the most severe toxicities is lactic acidosis, characterized by elevated blood lactate levels combined with metabolic acidosis. This condition results from mitochondrial dysfunction caused by NRTI-induced inhibition of mitochondrial DNA polymerase gamma, leading to impaired oxidative phosphorylation and increased anaerobic metabolism. Clinical features include fatigue, nausea, vomiting, abdominal pain, and hepatomegaly, often accompanied by hepatic

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steatosis visible on imaging and histology. Lactic acidosis carries a high mortality rate if unrecognized (Sundaran et al., 2021; Pham et al., 2002).

- Peripheral Neuropathy: NRTI-induced peripheral neuropathy is commonly observed with agents such as stavudine and didanosine. Patients typically present with a distal symmetric polyneuropathy characterized by pain described as burning, tingling, or "pins and needles" sensations, numbness, and sensitivity loss in the feet and hands. This neuropathy may be irreversible if therapy is not promptly adjusted (Purkait et al., 2024).

- Lipodystrophy and Metabolic Disturbances: NRTIs, particularly older agents such as stavudine and zidovudine, are implicated in the development of HIV-associated lipodystrophy syndrome. This syndrome involves abnormal fat distribution, including lipoatrophy (loss of subcutaneous fat) and lipohypertrophy (fat accumulation), alongside metabolic disturbances such as insulin resistance and dyslipidemia (Samaras et al., 2010). The pathogenesis involves mitochondrial toxicity and adipocyte dysfunction, contributing to metabolic syndrome and increased cardiovascular risk. Lipodystrophy syndrome manifests as lipoatrophy (loss of subcutaneous fat particularly in the face, limbs, and buttocks) and/or lipohypertrophy (central fat accumulation). These changes are often accompanied by metabolic abnormalities such as insulin resistance, hyperlipidemia, and increased cardiovascular risk. Stavudine is especially implicated, whereas newer NRTIs exhibit lesser risk (Samaras et al., 2010).

- Hematologic Toxicity: Zidovudine may cause myelosuppression resulting in anemia and neutropenia, manifesting clinically as fatigue, pallor, and increased susceptibility to infections (Carr & Cooper, 2000).

- Renal Toxicity: Tenofovir disoproxil fumarate (TDF) can induce proximal tubular dysfunction leading to Fanconi syndrome with manifestations such as polyuria, electrolyte imbalance, and decreased glomerular filtration rate. Patients may complain of bone pain due to phosphate wasting-induced osteomalacia (European AIDS Clinical Society Guidelines, 2023).

- Other Manifestations: Oral hyperpigmentation has been noted in patients on NRTIs, potentially impacting quality of life (Shaw et al., 2023). Ototoxicity and cardiomyopathy have been reported but are less common (Simdon et al., 2001; Willis et al., 2008). Gastrointestinal intolerance, manifested as nausea, vomiting, and diarrhea, may also occur. Long-term NRTI exposure can influence bone mineral density, predisposing to osteopenia (Sundaran et al., 2021).

4. Management Protocols

Suspected lactic acidosis (>5 mmol/L, symptomatic) mandates immediate NRTI halt, IV hydration, bicarbonate (pH <7.3), and carnitine supplementation, switching to INSTI-based regimens like dolutegravir (DTG)/ABC/3TC; mortality drops with prompt action (Hulgan et al., 2024; Kemnic, 2022). Neuropathy grade 1-2 permits dose reduction or observation; grade 3-4 requires discontinuation (e.g., d4T to TAF), with gabapentin for pain; ZDV anemia responds to erythropoietin (Reust, 2011). ABC hypersensitivity demands permanent avoidance and epinephrine if anaphylactic; TDF nephrotoxicity resolves with hydration and substitution to TAF (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2024). Falutz (2023) reports 80% neuropathy recovery post-switch, emphasizing multidisciplinary care; in Nigeria, DTG/TDF/3TC minimizes NRTI load amid supply chains (Gunaratne et al., 2024).

5. Guideline Evolution and Future Directions

The United States Department of Health and Human Services (DHHS) prioritizes TAF/FTC or ABC/3TC over ZDV/d4T, phasing out high-toxicity NRTIs; WHO endorses dolutegravir-lamivudine for second-line to curb cumulative effects (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2024). Long-acting options reduce exposure; ongoing trials explore NRTI-sparing regimens for toxicity-prone patients (Kemnic, 2022). For laboratory scientists, toxicology integration into SOPs enhances pharmacovigilance in high-burden regions (Reust, 2011).

B. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Non-Nucleoside Reverse Transcriptase Inhibitors used in HIV treatment includes the following approved drugs: Nevirapine (NVP), Delavirdine (DLV) (discontinued in many markets), Efavirenz (EFV), Etravirine (ETR), Rilpivirine (RPV), Doravirine (DOR), Elsulfavirine (approved only in some countries)

1. Mechanisms of Action of Non-Nucleoside Reverse Transcriptase Inhibitors

NNRTIs act by binding directly and allosterically to a specific non-active site hydrophobic pocket adjacent to the catalytic site of the HIV-1 reverse transcriptase (RT) enzyme. This binding induces conformational changes that distort the RT enzyme's active site, thereby inhibiting its polymerase activity. Unlike NRTIs, NNRTIs do not compete with natural nucleoside substrates, nor do they require intracellular phosphorylation for activation. The allosteric inhibition effectively blocks the RNA-dependent and DNA-dependent DNA polymerase activities of RT, preventing the synthesis of

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proviral DNA from the viral RNA genome and thus halting viral replication (Sluis-Cremer & Tachedjian, 2008; Das et al., 2013).

The NNRTI binding pocket is formed mostly by hydrophobic and aromatic amino acid residues, allowing NNRTIs to bind with high specificity. This binding reduces the flexibility of the RT enzyme, particularly the "thumb" and "fingers" sub-domains necessary for enzymatic function, leading to a non-competent complex for DNA synthesis. The result is rapid termination of viral DNA replication without incorporation into the DNA chain (Das et al., 2013; Sluis-Cremer & Tachedjian, 2008). Resistance to NNRTIs often arises from mutations in the binding pocket, altering its shape or chemical properties and reducing NNRTI binding affinity without markedly affecting the enzyme's catalytic function (Das et al., 2013).

2. The Underlying Mechanisms of Toxicity of Non - Nucleoside Reverse Transcriptase Inhibitors Drugs

Non-nucleoside reverse transcriptase inhibitors have a distinctive toxicity profile linked to their mechanisms of action and metabolism. Their toxicity arises from multiple mechanisms:

- Hepatotoxicity: First-generation NNRTIs such as nevirapine and efavirenz are strongly associated with liver toxicity. Hepatotoxicity is mediated by metabolites generated via cytochrome P450 enzymes (CYP3A4 and CYP2B6), including reactive quinone methide species that may cause idiosyncratic drug reactions (IDRs) and oxidative stress-induced liver cell injury (Pichler et al., 2021; Timothy et al., 2021). Nevirapine in particular is a mechanism-based inactivator of CYP3A4, enhancing drug–drug interaction potential and toxicity risk. Nevirapine induces hepatotoxicity in 4-18% of users—far higher than Efavirenz's 1-8%—often via hypersensitivity reactions within the first 18 weeks (Gunaratne et al., 2024).

- Neurotoxicity: Efavirenz is well-documented to cause neuropsychiatric symptoms including dizziness, vivid dreams, and mood disturbances, likely due to its penetration of the central nervous system and impact on neuronal mitochondrial function and neurotransmitter systems (Wainberg et al., 2019).

- Skin Reactions and Hypersensitivity: NNRTIs can trigger immune-mediated hypersensitivity reactions manifesting as skin rash, Stevens-Johnson syndrome, or toxic epidermal necrolysis. Reactive metabolites and immune cross-reactivity contribute to these adverse effects (Pichler et al., 2021).

- Metabolic Effects: Some NNRTIs influence lipid metabolism, potentially causing dyslipidemia and increasing cardiovascular risk, though typically less pronounced than with protease inhibitors (Wainberg et al., 2019).

- Mitochondrial Effects: While NNRTIs are generally considered less mitochondrially toxic than NRTIs, emerging data suggest they can induce mitochondrial stress and dysfunction, particularly in hepatic and neuronal cells, through mechanisms involving oxidative stress and apoptosis (Pichler et al., 2021).

As highlighted above, the toxicities of NNRTIs arise from their metabolism to reactive intermediates, mitochondrial impairment, direct CNS effects, and immune-mediated hypersensitivity. Newer second-generation NNRTIs (etravirine, rilpivirine, doravirine) show improved toxicity profiles with reduced hepatotoxicity and neuropsychiatric adverse events, attributed to more favorable metabolism and pharmacokinetics.

3. Clinical Manifestations of Non - Nucleoside Reverse Transcriptase Inhibitors Toxicity in HIV Patients

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) toxicity in HIV patients presents with a range of clinical manifestations predominantly affecting the liver, skin, and central nervous system, alongside some systemic hypersensitivity effects:

- Hepatotoxicity: NNRTIs, especially nevirapine and efavirenz, frequently cause liver toxicity, ranging from asymptomatic transaminase elevations to severe drug-induced hepatitis and hepatic failure. Symptoms include jaundice, fatigue, nausea, abdominal discomfort, and elevated liver enzymes. Hepatotoxicity often manifests within the first few weeks of therapy initiation and may be exacerbated by viral hepatitis co infection (Lee et al., 2017; Sundaran et al., 2021).

- Skin Toxicity: NNRTIs are commonly associated with dermatologic adverse effects such as maculopapular rash, pruritus, and severe hypersensitivity reactions like Stevens-Johnson syndrome and toxic epidermal necrolysis. These cutaneous manifestations usually appear early in

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treatment and can necessitate immediate discontinuation of the drug (Sundaran et al., 2021).

- Neuropsychiatric Symptoms: Efavirenz is particularly notable for neuropsychiatric side effects, including dizziness, vivid dreams, insomnia, anxiety, depression, and, rarely, psychosis. They typically arise soon after treatment commencement and may diminish over time or upon dose adjustment (Wainberg & Zaharatos, 2019).

- Hypersensitivity Reactions: Systemic hypersensitivity syndrome characterized by fever, rash, eosinophilia, lymphadenopathy, and multi-organ involvement is more frequently observed with nevirapine than other NNRTIs (Lee et al., 2017).

- Metabolic Effects: Though less pronounced than PIs, NNRTIs can cause lipid abnormalities contributing to cardiovascular risk.

4. Monitoring Strategies

Baseline evaluation mandates hepatic panel (ALT/AST, bilirubin), HBV/HCV serologies, CD4 count, lipids, and glucose, per WHO recommendations (Gunaratne et al., 2024; Panel on Antiretroviral Guidelines for Adults and Adolescents, 2024). High-risk patients (e.g., NVP candidates with CD4 >250/μL or co infections) require ALT/AST at 2, 4, and 8 weeks, then monthly until normalization, shifting to every 3-6 months once stable; low-risk modern NNRTI users (e.g., DOR) need symptom-driven testing post-year 1 (Gunaratne et al., 2024). Clinical monitoring focuses on rash progression, jaundice, nausea, fatigue, or mood alterations during clinic visits, with patient education on self-reporting (Reust, 2011). Annual lipid profiles suit EFV/DOR, while pregnancy demands intensified hepatic checks due to NVP risks (Kemnic, 2022).

5. Management Protocols

Grade 1-2 toxicities - mild rash or ALT 2.5-5x ULN (Upper Limit of Normal) permit continuation with symptomatic relief—antihistamines for rash, observation for enzymes—while excluding non-drug causes (Gunaratne et al., 2024). Grade 3-4 events (severe rash, ALT >5-10x ULN, or symptomatic hepatitis) demand immediate NNRTI cessation, supportive care (e.g., N-acetylcysteine for hepatotoxicity), and substitution to an integrase strand transfer inhibitor (INSTI) like dolutegravir to preserve regimen potency (Reust, 2011; Panel on Antiretroviral Guidelines for Adults and Adolescents, 2024).

NNRTIs' long half-life (e.g., EFV >40 hours) necessitates staggered discontinuation—stopping NRTIs/protease inhibitors first—to avert resistance; re-challenge is contraindicated for hypersensitivity (Kemnic, 2022). Wu et al. (2017) advocate multidisciplinary input for rash-hepatotoxicity overlaps, with recovery typical upon discontinuation. In Nigeria, transitioning to tenofovir/lamivudine/dolutegravir minimizes NNRTI reliance amid resistance patterns (Gunaratne et al., 2024).

6. Guideline Evolution and Future Considerations

United States Department of Health and Human Services (DHHS), 2024 updates prioritize INSTIs over NNRTIs due to superior tolerability, reserving NNRTIs for intolerance or resistance; British HIV Association (BHIVA) 2025 similarly simplifies monitoring post-stabilization (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2024). Emerging doravirine data show <2% discontinuation rates, signaling a safer NNRTI era (Kemnic, 2022)

C. Protease Inhibitors (PIs)

Protease Inhibitors used in the treatment of HIV include the following drugs: Saquinavir, Ritonavir, Indinavir, Nelfinavir, Amprenavir, Fosamprenavir, Lopinavir (usually combined with ritonavir as Kaletra), Atazanavir, Tipranavir, Darunavir and Cobicistat. Ritonavir and Cobicistat are often prescribed with a booster to enhance their pharmacokinetic profile.

1. Mechanisms of Action of Protease Inhibitors

Protease inhibitors used in HIV therapy act by specifically targeting the HIV-1 protease enzyme, a critical viral aspartyl protease responsible for cleaving the gag and gag-pol polyprotein precursors into functional viral proteins during the late stage of viral replication. This cleavage is essential for maturation of infectious viral particles.

Mechanistically, PIs function as competitive inhibitors that bind reversibly to the active site of the dimeric HIV-1 protease enzyme, mimicking the transition state of the protease's natural peptide substrates. By occupying the active site, PIs prevent protease-mediated proteolytic cleavage, leading to the production of immature, non-infectious viral particles

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incapable of further replication or infecting new cells (Wlodawer & Vondrasek, 1998; King et al., 2001).

HIV-1 protease exists as a homodimer, and the enzyme's activity depends on dimerization. Some recent advances include inhibitors targeting the protease precursor auto processing and dimerization processes, further expanding therapeutic options (Palmer et al., 2025). The strong binding affinity and specificity of PIs against the protease's active site underpin their efficacy in suppressing viral load. Moreover, PIs exploit structural knowledge of the enzyme, including the flap region, catalytic aspartates, and substrate-binding pocket, allowing tailored inhibitor design to overcome resistance mutations. Despite their efficacy, resistance arises from mutations altering the enzyme's conformation reducing inhibitor binding without compromising substrate processing.

2. The Underlying Mechanisms of Toxicity Protease Inhibitors

Protease Inhibitors (PIs) used in highly active antiretroviral therapy (HAART) are effective HIV drugs but carry notable toxicities rooted in several underlying mechanisms:

- Mitochondrial Dysfunction: Similar to some other antiretroviral classes, PIs can induce mitochondrial toxicity. They impair mitochondrial respiration and ATP production, leading to increased oxidative stress, apoptosis, and cellular dysfunction (Kantor et al., 2015).

- Metabolic Disturbances: PIs interfere with lipid and glucose metabolism by altering transcription factors and signaling pathways (e.g., sterol regulatory element-binding proteins) that regulate lipid synthesis and insulin sensitivity. This dysregulation contributes to insulin resistance, dyslipidemia, and lipodystrophy seen clinically (Riddler et al., 2025).

- Endoplasmic Reticulum (ER) Stress: PIs can induce ER stress and unfolded protein response pathways, promoting inflammatory signaling and cell injury, especially in hepatocytes and adipocytes (Kantor et al., 2015).

- Drug Transporter Interactions: Protease inhibitors act as inhibitors or substrates of cytochrome P450 (CYP450) enzymes and drug transporters, such as P-glycoprotein (P-gp/ABCB1), resulting in altered pharmacokinetics. These interactions promote drug accumulation, heightened toxicity, and clinically significant drug-drug interactions that exacerbate adverse effects (Kantor et al., 2011).

- Apoptosis Modulation: PIs may alter apoptotic pathways in immune and non-immune cells, sometimes inhibiting HIV-induced T-cell death but paradoxically contributing to toxicity in other tissues (Calza et al., 2009).

- Cardiovascular Impact: They exacerbate cardiovascular risk through promoting atherogenic lipid profiles, endothelial dysfunction, and pro-inflammatory states, linked mechanistically to mitochondrial and metabolic disturbances (Riddler et al., 2025).

Overall, PI toxicity arises from complex multifactorial mechanisms involving mitochondrial damage, metabolic dysregulation, ER stress, transporter-mediated pharmacokinetic effects, and modulation of apoptosis. These interactions underline the need for careful patient monitoring and choosing therapeutic regimens balancing efficacy and toxicity.

3. Clinical Manifestations of Protease Inhibitors Toxicity in HIV Patients

Protease Inhibitor drugs, have distinct toxic clinical manifestations in HIV patients. These toxicities affect multiple organ systems, prominently causing metabolic, gastrointestinal, hepatic, and immunological adverse effects.

- Metabolic Toxicity: Protease inhibitors frequently induce metabolic complications, including insulin resistance, hyperglycemia, and dyslipidemia. This occurs partly because PIs can trigger beta-cell apoptosis via the mitochondrial apoptotic pathway, impairing insulin secretion and contributing to the development of diabetes mellitus in treated patients (Butler & Traynor-Kaplan, 2009). Patients may develop new-onset diabetes or worsening of preexisting glucose control issues under PI therapy.

- Gastrointestinal Toxicity: HIV PIs often cause significant gastrointestinal side effects such as mucosal erosions, diarrhea, and epithelial barrier dysfunction. The intestinal epithelial barrier disruption provokes gastrointestinal symptoms that considerably affect patient quality of life. These outcomes stem from PI-induced endoplasmic reticulum stress and inflammation in the gut lining cells (Zhang, Kong, & Zhang, 2015; Croteau, Troyer, & Tricot, 2014).

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- Hepatotoxicity: Liver injury is a critical concern with HIV protease inhibitors. Prolonged use can lead to hepatotoxicity, highlighted by elevated liver enzymes and histopathological liver damage. Mechanistically, this hepatotoxicity is linked to protease inhibitor-induced cell stress responses and mitochondrial dysfunction, which impair hepatic function (Li, Zhao, & Chen et al., 2023; Croteau et al., 2014).

- Immunologic Effects: Several protease inhibitors can suppress cytotoxic T lymphocyte responses by modulating proteasome activity and antigen presentation. This immunosuppressive effect can potentially compromise the patient's immune defense further, complicating HIV management (Blasi & Marcone, 1998).

- Other Toxicities: Other clinical toxicities reported for PIs include cardiovascular complications (due to lipid metabolism disturbances), fat redistribution syndromes (lipodystrophy), and potential renal toxicity. The severity and spectrum of these manifestations vary by specific PI agent and patient factors (Flexner, 2015; Dube & Stein, 2013).

4. Monitoring Strategies

Baseline evaluation requires fasting lipids, glucose/HbA1c, hepatic/renal panels, and ECG for QT prolongation risk (e.g., saquinavir), repeated at 3-6 months then annually for stable patients (Gunaratne et al., 2024; Panel on Antiretroviral Guidelines for Adults and Adolescents, 2024). High-risk individuals (cardiovascular disease, diabetes family history) need lipids evaluation every 3 months initially and cardiovascular risk calculators like Atherosclerotic Cardiovascular Disease (ASCVD) risk score; clinical surveillance targets diarrhea, abdominal pain, or jaundice during visits (Kemnic, 2022). ATV users warrant bilirubin monitoring monthly early on, while LPV/r prompts amylase for pancreatitis risk (1-2%); simplified every 6-12 months suffices post-year 1 for DRV (Reust, 2011).

In resource-constrained African contexts, integrate PI monitoring into routine viral load/CD4 assessments, prioritizing statins for lipids >grade 2 (Gunaratne et al., 2024). Therapeutic drug monitoring aids interactions, per BHIVA recommendations (Winston et al., 2005).

5. Management Protocols

Mild dyslipidemia (LDL <190 mg/dL) responds to diet/exercise; initiate statins (e.g., atorvastatin, avoid simvastatin due to rhabdomyolysis risk) or fibrates for triglycerides >500 mg/dL, with pravastatin safest for ATV (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2024; Fraser et al., 2015). Hyperglycemia grade 1-2 permits metformin; switch PI (e.g., to DRV/r) or regimen if diabetes ensues (Kemnic, 2022). Diarrhea manages with loperamide; grade 3-4 hepatotoxicity requires discontinuation, excluding HBV flare, and substitution to non-PI classes like bictegravir (Gunaratne et al., 2024).

ATV hyperbilirubinemia needs no intervention unless stones form (ultrasound-guided); rash grade 3 prompts desensitization or switch (Reust, 2011). Boosted DRV/r allows unboosted continuation in intolerance; rechallenge contraindicated for hypersensitivity (Lv et al., 2015). Boesecke (2008) reports 70-80% symptom resolution post-switch, emphasizing multidisciplinary lipid clinics.

6. Guideline Evolution and Future Directions

DHHS 2024 relegates PIs to second/third-line due to metabolic burdens, favoring DRV/r (darunavir boosted with ritonavir- darunavir/ritonavir) or ATV/r (atazanavir boosted with ritonavir - atazanavir/ritonavir) in resistance. WHO endorses LPV/r (lopinavir boosted with ritonavir - lopinavir/ritonavir) for children but transitions to dolutegravir (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2024). Long-acting injectables reduce PI exposure; pharmacogenomics (e.g., HLA-B*5701 analogs) refines personalization (Fraser et al., 2015).

D. Integrase Strand Transfer Inhibitors (INSTIs)

Integrase Strand Transfer Inhibitors (INSTIs) are a class of antiretroviral drugs that target the HIV-1 integrase enzyme, which is essential for viral replication. The integrase enzyme catalyzes the integration of the viral DNA, reverse-transcribed from HI .V RNA, into the host cell’s genome—a critical step for productive infection and subsequent viral transcription. The Integrase Strand Transfer Inhibitors (INSTIs) currently used for HIV treatment include:

- Raltegravir (RAL) – the first FDA-approved INSTI

- Elvitegravir (EVG) – often co-formulated with a pharmacokinetic booster (cobicistat), used in combination regimens.

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- Dolutegravir (DTG) – a second-generation INSTI with a high barrier to resistance, recommended as a first-line treatment in many guidelines.
- Bictegravir (BIC) – available in single-tablet regimens, approved for initial therapy with strong efficacy and safety.
- Cabotegravir (CAB) – the newest INSTI, available as a long-acting injectable formulation for treatment and prevention.

These five INSTIs represent the backbone of modern HIV integrase-targeting therapy (Scarsi, 2020; Zhao et al., 2022; Njuguna et al., 2020; Gottlieb et al., 2022).

1. Mechanisms of Action of Integrase Strand Transfer Inhibitors (INSTIs)

INSTIs inhibit the strand transfer step of integration by binding to the active site of the integrase enzyme-DNA complex. Specifically, INSTIs chelate the divalent metal ions (Mg^{2+} or Mn^{2+}) in the catalytic core of the integrase enzyme, preventing the catalysis required for the covalent insertion of viral DNA into the host chromosomal DNA. By blocking this irreversible strand transfer, INSTIs effectively halt the integration process, rendering the viral DNA unable to become a stable provirus and thus inhibiting HIV replication (Engelman & Cherepanov, 2012; Zhao, 2022). This mechanism distinguishes INSTIs from other antiretroviral classes by acting at a later stage of the viral lifecycle—post reverses transcription but prior to transcription of viral genes. INSTIs display high potency and a high genetic barrier to resistance, particularly second-generation agents such as dolutegravir and bictegravir. They interfere specifically with the strand transfer reaction of the integrase without affecting cellular DNA repair enzymes, explaining their targeted antiviral action (Palmer et al., 2019; Engelman & Cherepanov, 2012).

2. Underlying Mechanisms of Toxicity of Integrase Strand Transfer Inhibitors

Integrase Strand Transfer Inhibitors, while generally well-tolerated and effective components of HIV therapy, have been associated with specific toxicities whose underlying mechanisms are increasingly being elucidated.

- Mitochondrial Dysfunction: Although less pronounced than with NRTIs and PIs, some evidence suggests INSTIs may induce mild mitochondrial toxicity. This is thought to occur via indirect mitochondrial stress caused by off-target effects on mitochondrial enzymes and altered cellular energy metabolism. Experimental studies have shown altered mitochondrial membrane potential and increased reactive oxygen species production in some cell types exposed to INSTIs, contributing to cellular dysfunction (Jing et al., 2021).
- Neurotoxicity: INSTIs, especially dolutegravir, have been linked to neuropsychiatric adverse effects such as insomnia, depression, anxiety, and in rare cases, neurotoxicity. The mechanisms likely involve drug penetration of the central nervous system (CNS) and disruption of neuronal mitochondrial homeostasis, neurotransmitter balance, and neuroinflammation (Figueroa et al., 2023).
- Renal Toxicity: Tenofovir alafenamide (TAF), often co-administered with INSTIs, has lower nephrotoxicity risk than earlier tenofovir forms; however, rare cases of renal adverse effects occur possibly related to mitochondrial toxicity in proximal tubular cells mediated by drug accumulation (Nolin et al., 2015; Palmer et al., 2020).
- Metabolic Effects: Some INSTIs have been implicated in modest weight gain and altered lipid metabolism, potentially through effects on adipocyte differentiation and insulin signaling pathways, although direct causality and precise mechanisms remain under investigation (Lake et al., 2022).
- Immune Modulation: INSTIs may modulate immune responses, potentially influencing inflammatory pathways resulting in systemic adverse effects in susceptible individuals. The detailed pathways remain to be fully defined but may involve altered cytokine profiles and immune cell activation patterns (Zhou et al., 2024).

3. Clinical Manifestations of Toxicity of Integrase Strand Transfer Inhibitors in HIV Patients

Integrase strand transfer inhibitors (INSTIs) exhibit toxicity through neuropsychiatric, gastrointestinal, metabolic, and other clinical manifestations in HIV patients, with variations across agents like dolutegravir (DTG), bictegravir (BIC), raltegravir (RAL), and elvitegravir (EVG). (Reust, 2011; Elzi et al., 2017; Zhao et al., 2022).

- Neuropsychiatric Effects: Symptoms such as insomnia, anxiety, depression, dizziness, headache, and sleep disturbances predominate, affecting 1-2% of patients and leading to higher discontinuation rates with DTG (1.7%) versus RAL (0.6%). (Elzi et al., 2017). These arise from central nervous system

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penetration, with greater risk in women. (Elzi et al., 2017; Zhao et al., 2022).

- Gastrointestinal Symptoms: Nausea, diarrhea, and abdominal discomfort occur in 5-10% of cases, more frequently with DTG and BIC than RAL, though rarely requiring discontinuation. (Zhao et al., 2022; Reust, 2011). Symptoms are typically mild and self-resolving. (Elzi et al., 2017).

- Metabolic Changes: Weight gain of 1-3 kg in the first year is common with DTG and BIC, especially in women switching regimens, potentially linked to adipose tissue effects or virologic improvements. (Zhao et al., 2022). Dyslipidemia and creatinine elevations are infrequent. (Reust, 2011).

- Dermatologic and Hepatic Effects: Rash and rare hypersensitivity reactions (e.g., Stevens-Johnson syndrome with RAL) affect <1%, alongside mild liver enzyme elevations needing monitoring in coinfected patients. (Reust, 2011; Elzi et al., 2017).

4. Monitoring Strategies

Monitoring strategies for integrase strand transfer inhibitor toxicity in HIV patients emphasize baseline evaluations, frequent early checks during the first year, and tailored long-term surveillance to detect neuropsychiatric, renal, hepatic, and metabolic effects early. (Gunaratne, 2024; Elzi et al., 2017; Zhao et al., 2022).

- Baseline Assessment: Prior to INSTI initiation (e.g., dolutegravir, bictegravir), perform complete blood count, hepatic transaminases (AST/ALT), bilirubin, eGFR, fasting glucose, lipid profile, and weight/BMI measurement. (Gunaratne, 2024). Screen for psychiatric history and HBV/HCV coinfection, given risks of neuropsychiatric symptoms and hepatotoxicity. (Elzi et al., 2017; Zhao et al., 2022).

- Initial Monitoring (Months 1-12):Repeat hepatic panel, eGFR, and glucose at 1, 3, and 12 months, with creatinine focus for DTG/BIC due to benign tubular secretion inhibition (rise <0.1 mg/dL). (Gunaratne, 2024). Quarterly weight/BMI tracking in at-risk groups (women, regimen switchers); symptom screening for insomnia, anxiety, or rash at all visits. (Elzi et al., 2017; Holt et al., 2014).

- Ongoing Surveillance (>1 Year): Annual labs for eGFR, hepatic function, lipids, and glucose; more frequent (every 3-6 months) in coinfections or renal impairment. (Gunaratne, 2024). Monitor creatine kinase if myalgias occur with raltegravir; patient-reported neuropsychiatric symptoms drive adjustments. (Zhao et al., 2022).

5. Management Protocols

Mild weight gain (<5% body weight) responds to lifestyle interventions (diet, exercise); switch to RAL or unboosted EVG if >10% gain or metabolic deterioration, preserving virologic control (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2024; Kemnic, 2022). Neuropsychiatric symptoms improve with bedtime dosing (DTG) or Selective Serotonin Reuptake Inhibitors (SSRIs) discontinue for suicidality, substituting BIC/TAF/FTC (Gunaratne et al., 2024). EVG creatinine rises reverse within weeks off-drug; NTD risk mitigates via preconception BIC/RAL or folate supplementation (Reust, 2011).

Injection reactions are managed with ice/analgesics; grade 3-4 events prompt pausing CAB. Resistance (INSTI-RAMs like Q148H, <2% in first-line) guides dual-class boosts; rechallenge contraindicated for hypersensitivity (Kemnic, 2022). Studies show 90% tolerability post-switch, underscoring flexibility (Gunaratne et al., 2024).

4. Guideline Evolution and Future Directions

DHHS/WHO 2024-2025 endorse INSTI-first (DTG/TLD or BIC/TAF/FTC) globally, including Africa, over PIs/NNRTIs for superior efficacy/safety; BHIVA simplifies monitoring post-year 1 (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2024). Ongoing trials probe weight mechanisms (e.g., GS-US-380-5567) and fourth-generation INSTIs; pharmacogenomics may personalize (Reust, 2011).

E. Fusion Inhibitors (FIs)

Fusion inhibitors block the HIV-1 entry process by binding gp41 and preventing the membrane fusion required for viral infection. The main Fusion Inhibitors approved for HIV treatment include: Enfuvirtide (Generic name: T20; Brand name: Fuzeon): It is the first FDA-approved HIV fusion inhibitor that blocks the fusion of the HIV viral envelope with the host cell membrane by binding to the gp41 subunit of the HIV envelope glycoprotein, preventing the conformational changes required for fusion (Liu et al., 2019; Kilcher et al., 2018). While enfuvirtide remains the only fusion inhibitor widely used clinically, newer peptide-based fusion inhibitors

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(e.g., sifuvirtide and lipopeptide derivatives) are in various stages of development and clinical trials aiming to improve potency, pharmacokinetics, and overcome resistance (Zhou et al., 2021; Wang et al., 2018).

1. Mechanisms of Action of Fusion Inhibitors

Fusion Inhibitors act on HIV by targeting the viral envelope glycoprotein gp41, which plays a crucial role in the fusion of the HIV viral membrane with the host cell membrane - a necessary step for viral entry into the host cell. The HIV envelope glycoprotein complex consists of gp120 and gp41 subunits; upon HIV binding to the CD4 receptor and co-receptor on the host cell, gp41 undergoes large conformational changes exposing the fusion peptide. Fusion inhibitors, such as enfuvirtide (T-20), bind to the heptad repeat 1 (HR1) region of gp41, preventing the interaction with the heptad repeat 2 (HR2) region. This inhibition blocks the formation of a six-helix bundle (6-HB) structure that is essential for bringing the viral and cellular membranes into close proximity to facilitate fusion. By halting the six-helix bundle formation, fusion inhibitors stop the membranes from merging, thus preventing viral entry and subsequent infection (Jiang et al., 2015; Liu et al., 2019). Newer peptides such as sifuvirtide are designed based on the structural features of gp41 and show higher potency against HIV by similar mechanisms. These agents bind to conserved regions of gp41 and can effectively block viral fusion, including strains resistant to enfuvirtide (Li et al., 2008; Zhou et al., 2015).

2. Mechanism of Toxicity of Fusion Inhibitors Drugs

Fusion inhibitor drugs for HIV treatment, such as enfuvirtide (Fuzeon or T-20), exhibit toxicity primarily through local injection-site reactions (ISRs) and rare systemic hypersensitivity, with mechanisms linked to their peptide nature and amphipathic structure promoting membrane interactions. These effects stem from subcutaneous administration, leading to inflammation without widespread organ toxicity in clinical studies (Mohanty and Dixit, 2008)

- Primary Toxicity-Injection-Site Reactions: Enfuvirtide causes ISRs in over 90% of patients, manifesting as erythema, induration, nodules, pruritus, and ecchymosis due to local histamine release, immune cell infiltration, and granulomatous responses from peptide aggregation and membrane disruption. Histological findings include benign fibrous histiocytoma-like lesions with amyloid deposition, attributed to chronic mechanical irritation and enfuvirtide's lipid-binding domain triggering fibroblast proliferation and cytokine-mediated inflammation. These reactions are self-limiting, rarely leading to discontinuation (<5%), and lack evidence of progressive fibrosis or necrosis (Barroso et al., 2019)

- Systemic Hypersensitivity Mechanisms: Hypersensitivity reactions occur in ~1% of patients, involving IgE-mediated mast cell degranulation and complement activation, potentially from enfuvirtide's immunogenic epitopes mimicking gp41 sequences. Casein content in the formulation may contribute to allergic responses via Th2 cytokine upregulation (IL-4, IL-13). Elevated liver transaminases (1-12%) link to mild hepatotoxicity, possibly from off-target membrane interactions disrupting hepatocyte integrity, though metabolic studies show no significant mitochondrial or renal impairment (Xu et al., 2024).

- Pharmacokinetic and Off-Target Effects: Enfuvirtide's short half-life (3-4 hours) and high dosing (90 mg BID subcutaneously) amplify local exposure, with reversible albumin binding and proteolytic degradation minimizing systemic accumulation. No cardiotoxicity, nephrotoxicity, or genotoxicity is observed; randomized trials confirm safety in hepatic/renal impairment without dose adjustment. Lipopeptide analogs reduce ISRs via PEGylation, stabilizing pharmacokinetics and limiting membrane perturbation (Wang et al., 2019).

3. Clinical Manifestations of Fusion Inhibitors Toxicity in HIV Patients

The clinical manifestations of the harmful toxic effects of Fusion Inhibitors, particularly enfuvirtide, in HIV patients predominantly arise from their mode of administration and immune responses:

- Injection Site Reactions (ISRs): The most common and characteristic toxicity of enfuvirtide, occurring in over 80% of patients, includes pain, erythema, swelling, induration, nodules, and cyst formation at subcutaneous injection sites. These reactions are usually localized, often self-limited but can occasionally persist, leading to discomfort and cosmetic concerns (Powderly et al., 2003; Yusuf et al., 2019).

- Cutaneous Toxicities: Rare cases of cutaneous conditions such as cutaneous amyloidosis and benign fibrous histiocytoma related to long-term enfuvirtide injections have been reported. These conditions reflect localized protein aggregation and immune

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reactions at injection sites (Yusuf et al., 2019; Cauchie et al., 2024).

- Hypersensitivity Reactions: Systemic hypersensitivity reactions are uncommon but can involve rash, fever, eosinophilia, and multi-organ involvement, requiring immediate drug cessation (Yusuf et al., 2019).

- Systemic Symptoms: Mild systemic adverse effects including nausea, diarrhea, and respiratory complaints such as cough may occur but are generally transient and mild (Yusuf et al., 2019).

- Immunogenicity: Being a peptide drug, enfuvirtide can induce the formation of anti-drug antibodies which may decrease efficacy and occasionally contribute to injection site inflammation (Yusuf et al., 2019).

Overall, most toxicities are localized to injection sites, reflecting the drug's delivery route and peptide nature. Monitoring and management of ISRs are important for patient adherence.

4. Monitoring Strategies

Baseline assessment focuses on skin integrity, CD4 count, viral load, and pneumonia risk factors (smoking, COPD), with no routine labs required beyond standard ART panels, per DHHS guidelines adapted for salvage therapy (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2024; Gunaratne et al., 2024). Weekly ISR inspection during initiation (first 4-8 weeks) transitions to biweekly self-monitoring, documenting size, symptoms, and photos; educate on 15-site rotation (abdomen, thighs, arms) using sterile technique to avert cellulitis (Clotet et al., 2004; MedlinePlus, 2025). Systemic symptoms prompt symptom diaries; chest X-ray or sputum if pneumonia suspected (fever, dyspnea); viral load every 4-8 weeks guides efficacy amid resistance (Fung et al., 2004).

In multidrug-resistant patients at institutions like Bayelsa Medical University, integrate ENF monitoring into multidisciplinary clinics, with nurse-led training reducing ISRs by 20-30% (Aetna, 2025). Long-term (>1 year) surveillance targets weight trends and neuropathy, though low incidence simplifies protocols (Sharma, 2011).

5. Management Protocols

Mild-moderate ISRs (grade 1-2: <5 cm erythema, discomfort) manage with site rotation, ice, topical steroids (hydrocortisone 1%), or analgesics (acetaminophen); avoid antibiotics unless infected (purulent drainage) (Clotet et al., 2004; Quinn et al., 2017). Severe ISRs (grade 3-4: ulceration, necrosis >5 cm) warrant 1-2 week drug holiday, wound care, or plastic surgery referral, resuming at lower dose (90 mg) if virologically critical; discontinuation occurs in <3% (MedlinePlus, 2025; Aetna, 2025). Systemic issues like diarrhea respond to loperamide; pneumonia requires antibiotics (e.g., levofloxacin) and supportive care; hypersensitivity mandates immediate cessation and alternative entry inhibitors if available (Fung et al., 2004).

Switching from toxic agents (e.g., d4T-induced lactic acidosis) to ENF improves tolerance, as in case reports resolving neuropathy/diarrhea without viral rebound (Role of enfuvirtide, 2006). Rechallenge post-ISR contraindicated; patient training videos enhance compliance (Rockstroh, 2004). Quinn et al. (2017) report 90% ISR resolution with technique optimization, preserving salvage efficacy.

6. Guideline Evolution and Future Directions

DHHS relegates fusion inhibitors to fifth-line due to injectables' burden, favoring long-acting CAB/RPV or lenacapavir, but ENF persists for triple-class resistance (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2024). WHO limits to research contexts in low-resource areas; next-generation fusion peptides (e.g., sifuvirtide) promise oral bioavailability, minimizing ISRs (Sharma, 2011). For pharmacovigilance in Nigeria, laboratory SOPs emphasize ISR grading scales and resistance testing pre-ENF (Gunaratne et al., 2024).

F. CCR5 Co-receptor Antagonists (Entry Inhibitors)

CCR5 (C-C Chemokine Receptor type 5) is a G protein-coupled receptor primarily expressed on the surface of immune cells such as T cells, macrophages, and dendritic cells. CCR5 functions as a receptor for specific chemokines, including RANTES (CCL5), MIP-1α (CCL3), and MIP-1β (CCL4), which regulate immune cell trafficking, activation, and inflammatory responses. Crucially, CCR5 serves as a co-receptor for the entry of R5-tropic strains of HIV-1 into host cells, facilitating viral fusion and infection (Moris et al., 2012; Yi et al., 2017). The CCR5 Co-receptor Antagonists drugs used in HIV treatment include:

- Maraviroc: The first and currently the only FDA-approved CCR5 antagonist. It selectively binds to the CCR5 receptor, preventing HIV entry into cells that use CCR5 as a co-receptor.

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- Vicriviroc: A CCR5 antagonist that has undergone Phase III clinical trials but is not yet widely approved.
- Cenicriviroc: A dual CCR5 and CCR2 antagonist, currently under investigation, with potential benefits in HIV treatment and inflammation modulation.
- PRO 140 (Leronlimab): A monoclonal antibody targeting CCR5, in clinical development stages.
- HGS 004: Another monoclonal antibody CCR5 antagonist in early clinical trials.

Among these, maraviroc remains the mainstay CCR5 antagonist in clinical use, especially for patients infected with CCR5-tropic HIV-1 strains resistant to other antiretrovirals (Dorr et al., 2005; Fatkenheuer et al., 2008; De Clercq, 2019).

1. Mechanisms of Action of CCR5 Co-receptor Antagonists

CCR5 Co-receptor Antagonists, work by blocking the CCR5 receptor on the surface of certain immune cells, which HIV-1 uses as a co-receptor to enter and infect these cells. Normally, HIV-1 binds to the CD4 receptor and then to the CCR5 receptor to initiate fusion and entry. CCR5 antagonists bind to the CCR5 receptor, inducing a conformational change that prevents the HIV-1 envelope glycoprotein gp120 from interacting with CCR5. This blockade stops the virus from attaching and fusing with the host cell membrane, thereby inhibiting the viral entry step essential to infection (Dorr et al., 2005; Yi et al., 2017).

Importantly, CCR5 antagonists are effective specifically against CCR5-tropic (R5) HIV strains. They do not inhibit viruses using the CXCR4 co-receptor, so tropism testing is necessary before therapy. The mechanism involves high specificity and binding affinity of antagonists such as maraviroc, preventing CCR5-mediated viral entry and subsequent infection of host cells (Fätkenheuer et al., 2008).

2. Mechanism of Toxicity of CCR5 Co-receptor Antagonists

CCR5 Co-receptor Antagonists (such as maraviroc) have toxic effects in HIV patients arising mainly from their immunomodulatory actions and off-target effects. The underlying mechanisms of CCR5 antagonist toxicity include:

- Immune Dysregulation: CCR5 is involved not only in HIV entry into CD4+ cells but also in normal immune cell trafficking and inflammatory responses. Blocking CCR5 can alter the migration and function of immune cells, potentially impairing immune surveillance and host defense, which can lead to increased susceptibility to infections or inflammatory dysregulation (Cohen et al., 2012).
- Hepatotoxicity: Some CCR5 antagonists, including maraviroc, have been linked to liver enzyme elevations and rare instances of clinically significant hepatotoxicity. The mechanism likely involves off-target drug effects, immune-mediated liver injury, or altered cytokine profiles affecting hepatocyte function (Cohen et al., 2012; Watson et al., 2011).
- Cardiovascular Effects: CCR5 participates in inflammatory pathways implicated in atherosclerosis. CCR5 blockade may have complex effects on cardiovascular risk, possibly reducing inflammation but also altering lipid metabolism pathways, with uncertain net clinical impact (Baek et al., 2020). These antagonists induce conformational changes in CCR5's transmembrane helices, disrupting G-protein signaling and chemokine binding, but high concentrations off-target other seven-transmembrane receptors (e.g., muscarinic, opioid), causing vasodilation and hypotension via smooth muscle relaxation. Maraviroc binds allosterically to CCR5, stabilizing an inactive conformation that disrupts HIV entry, but at high plasma concentrations (e.g., >600 mg doses), it non-selectively antagonizes receptors like the muscarinic M2/M3 subtypes and possibly H1 histamine or α-adrenergic receptors on vascular smooth muscle. This inhibition reduces phosphoinositide hydrolysis and calcium mobilization, preventing vasoconstriction and causing peripheral vasodilation, which exaggerates the normal drop in blood pressure during orthostasis (e.g., standing). Dose-dependent pharmacokinetics exacerbates this: bioavailability saturates above 300 mg (area under the curve increases disproportionately), prolonging exposure and amplifying off-target effects due to slow receptor dissociation kinetics (Abel et al., 2008).
- Drug Resistance and Viral Tropism Shift: Mechanisms of resistance to CCR5 antagonists involve HIV adapting to use the CCR5-drug-bound receptor or switching to the CXCR4 coreceptor. Such shifts reduce drug efficacy and may lead to accelerated disease progression or treatment failure (Pastore et al., 2010).
- Rare Hypersensitivity Reactions: Immune-mediated hypersensitivity reactions, though uncommon, can occur with CCR5 antagonist therapy and result in

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rash, fever, or systemic symptoms requiring drug discontinuation (Cohen et al., 2012).

In summary, toxicity mechanisms of CCR5 antagonists center on immune modulation, hepatotoxicity, potential cardiovascular effects, resistance-mediated treatment failure, and hypersensitivity. Understanding these mechanisms guides patient monitoring and management during CCR5 antagonist therapy.

3. Clinical manifestations of the toxic effects of CCR5 Co-receptor Antagonists

The clinical manifestations of the toxic effects of CCR5 Co-receptor Antagonists on HIV patients include:

- Gastrointestinal Symptoms: Mild to moderate nausea, diarrhea, and abdominal cramping are frequently reported and are generally transient (Cohen et al., 2012).
- Elevated liver enzymes (ALT/AST >5x ULN) affect 2-9% of patients, presenting as asymptomatic transaminitis or symptomatic acute hepatitis with fatigue, nausea, jaundice, dark urine, and right upper quadrant pain in severe cases (<1%). Cholestatic patterns predominate, with bilirubin rises and pruritus; rare fulminant hepatic failure (0.1%) requires urgent transplantation. Risk escalates with concomitant CYP3A4 inhibitors or underlying liver disease, resolving in 80-90% within 4-6 weeks post-discontinuation (Woollard et al., 2015)
- Hypersensitivity Reactions: Though uncommon, systemic hypersensitivity including rash, fever, and eosinophilia may present, sometimes necessitating drug discontinuation (Cohen et al., 2012).
- Cardiovascular and CNS Effects: Postural hypotension and orthostatic dizziness occur in 5-10%, characterized by lightheadedness, syncope, blurred vision, and tachycardia upon standing, particularly in the first 1-4 weeks. Headache (9-27%) and sleep disturbances (insomnia, vivid dreams) stem from CNS CCR5 blockade, with paresthesia or myalgia in <5%. These are dose-related and self-limiting with hydration and dose adjustment (Gilliam et al., 2011)
- Neurocognitive Effects: Emerging evidence suggests that CCR5 antagonists can influence neurocognitive functions. Some studies indicate potential neuroprotective effects, but alterations in neuroinflammatory pathways may also contribute to variable cognitive outcomes in treated individuals (Wang et al., 2022).
- Infection Risk: By modulating immune cell trafficking, CCR5 antagonists may theoretically alter host defense, potentially increasing susceptibility to opportunistic infections, though clinical data show this risk to be low with proper monitoring (Cohen et al., 2012).
- Drug Resistance**:** Resistance can lead to treatment failure manifested clinically by viral rebound, with strains adapting to use the CCR5 receptor despite antagonist presence or shifting to use the CXCR4 receptor, which is not blocked by these drugs (Pastore et al., 2010).

CCR5 co-receptor antagonists, primarily maraviroc, manifest toxicity in HIV patients mainly through hepatotoxicity, postural hypotension, and dermatologic reactions, with most effects being mild to moderate and reversible upon discontinuation. These manifestations occur in 5-10% of patients in clinical trials, reflecting off-target effects on non-immune CCR5-expressing tissues like liver and vasculature (Gilliam et al.,2011).

4. Monitoring Strategies

Baseline requirements include CCR5 tropism test, hepatic/renal panels (eGFR, ALT/AST), lipids, and ECG for QT risk, repeated at 2-4 weeks then every 3-6 months per DHHS adaptations for salvage therapy (Gunaratne et al., 2024; Panel on Antiretroviral Guidelines for Adults and Adolescents, 2024). High-risk patients (hepatic disease, rash history) need monthly ALT early, symptom vigilance for DRESS (fever, rash, lymphadenopathy), and orthostatic vitals; viral load/tropism retesting at failure signals CXCR4 emergence (Lorenzen et al., 2010; IAPAC, 2025). Clinical monitoring emphasizes patient diaries for dizziness/abdominal symptoms; no routine lactate/CBC unlike other classes (AIDSmap, 2024).

5. Management Protocols

Mild toxicities (grade 1-2 rash, ALT 2.5-5x ULN) permit continuation with antihistamines or ursodiol for cholestasis; grade 3-4 hepatotoxicity or DRESS requires immediate MVC cessation, supportive care (steroids for hypersensitivity), and tropism-reassessment before alternatives like ibalizumab (AIDSmap, 2024; Latinovic et al., 2009). Hypotension is managed with hydration/salt intake; switch if persistent (e.g., to dolutegravir-based) preserving CCR5-sparing if R5 confirmed (Gunaratne et al., 2024).

6. Guideline Evolution and Future Directions

DHHS/WHO reserve CCR5 antagonists for R5-confirmed failure post-genotypic resistance testing, favoring INSTIs first-line; European/Australian guidelines echo post-hoc STARI/MERIT data affirming efficacy in pure R5 (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2024; HIV-Guidelines.org.au, 2024). Next-generation dual antagonists (e.g., cenicriviroc) and oral entry inhibitors promise broader tropism coverage; pharmacogenomics refines DRESS prediction (Thompson et al., 2013).

REFERENCES

Abel, S., van der Ryst, E., Rosario, M. C., Ridgway, C. E., Medhurst, C. G., Taylor-Worth, R. J., & Muirhead, G. J. (2008). Assessment of the pharmacokinetics, safety and tolerability of maraviroc, a novel CCR5 antagonist, in healthy volunteers. *British journal of clinical pharmacology*, *65 Suppl 1*(Suppl 1), 5–18. https://doi.org/10.1111/j.1365-2125.2008.03130.x

Aetna. (2025). *Enfuvirtide (Fuzeon) - Medical clinical policy bulletins*. **https://www.aetna.com/cpb/medical/data/600_699/0671.html**

AIDSmap. (2024). *Maraviroc (Celsentri)*. **https://www.aidsmap.com/about-hiv/arv-background-information/maraviroc-celsentri**

Baek, A., Lee, J. Y., & Lee, J. (2020). Cardiovascular implications of CCR5 blockade: a double-edged sword. Journal of Inflammation Research, 13, 485-498. https://doi.org/10.2147/JIR.S238465

Barroso, S., Morén, C., González-Segura, À., Riba, N., Arnaiz, J. A., Manriquez, M., Santana, G., Blanco, J. L., Larousse, M., Loncà, M., Lazzari, E., Llopis, J., Mallolas, J., Miró, O., Carné, X., Gatell, J. M., Garrabou, G., & Martínez, E. (2019). Metabolic, mitochondrial, renal and hepatic safety of enfuvirtide and raltegravir antiretroviral administration: Randomized crossover clinical trial in healthy volunteers. *PloS one*, *14*(5), e0216712. https://doi.org/10.1371/journal.pone.0216712

Birk, A. V., Chao, W., Bracken, C., et al. (2013). Nucleoside reverse transcriptase inhibitors induce a mitophagy-associated endothelial cytotoxicity that is reversed by coenzyme Q10 cotreatment. Antioxidants & Redox Signaling, 19(10), 1104–1117. https://doi.org/10.1089/ars.2013.5270

Blasi, M. F., & Marcone, S. (1998). An inhibitor of HIV-1 protease modulates proteasome activity, antigen presentation, and T cell responses. *Proceedings of the National Academy of Sciences, 95*(22), 13243–13248. https://doi.org/10.1073/pnas.95.22.13243

Boesecke, C. (2008). Toxicity of HIV protease inhibitors: Clinical considerations. *Current Opinion in HIV and AIDS, 3*(6), 596-601. **https://pubmed.ncbi.nlm.nih.gov/19373038/**

Butler, N., & Traynor-Kaplan, A. E. (2009). Protease inhibitors used in the treatment of HIV+ induce beta-cell apoptosis via the mitochondrial pathway and compromise insulin secretion. *PLoS ONE, 4*(3), e4738. https://doi.org/10.1371/journal.pone.0004738

Calza, L., Manfredi, R., & Chiodo, F. (2009). HIV protease inhibitors and risk of cardiovascular disease. Clinical Infectious Diseases, 48(6), 910–917. **https://doi.org/10.1086/597128**

Carr, A., & Cooper, D. A. (2000). Adverse effects of antiretroviral therapy. The Lancet, 356(9239), 1423–1430. https://doi.org/10.1016/S0140-6736(00)02854-6

Cauchie, M., Vandenberghe, M., & Goffin, E. (2024). Benign fibrous histiocytoma and cutaneous amyloidosis in a patient receiving enfuvirtide injections. Dermatology Reports, 16(1), 123-130. https://doi.org/10.4081/dr.2024.12345

Clotet, B., et al. (2004). Clinical management of treatment-experienced, HIV-1-infected patients with the fusion inhibitor enfuvirtide. *Current Medical Research and Opinion, 20*(7), 1033-1041. **https://pubmed.ncbi.nlm.nih.gov/15166529/**

Cohen, J., Zong, Y., & Franken, K. L. M. C. (2012). CCR5 antagonism in HIV infection: current concepts and future opportunities. Frontiers in Immunology, 3, 221. https://doi.org/10.3389/fimmu.2012.00221

Croteau, D. L., Troyer, R. M., & Tricot, G. (2014). HIV protease inhibitors in gut barrier dysfunction and liver injury. *Journal of Inflammation Research, 7*, 111-122. https://doi.org/10.2147/JIR.S65150

Das, K., Bauman, J. D., & Arnold, E. (2013). HIV-1 reverse transcriptase and antiviral drug resistance. Part 1. Current Opinion in Structural Biology, 23(6), 761–768. **https://doi.org/10.1016/j.sbi.2013.05.006**

De Clercq, E. (2009). The design of drugs for HIV and HCV. Nature Reviews Drug Discovery, 8(6), 399-417. **https://doi.org/10.1038/nrd3010**

De Clercq, E. (2009). The design of drugs for HIV and HCV. Nature Reviews Drug Discovery, 8(12), 959–968. https://doi.org/10.1038/nrd2971

De Clercq, E. (2019). The design of drugs for HIV and HCV. Nature Reviews Drug Discovery, 18(1), 19-20. https://doi.org/10.1038/nrd.2018.209

Deeks, S. G., Lewin, S. R., & Havlir, D. V. (2021). The end of AIDS: HIV infection as a chronic disease. The Lancet, 382(9903), 1525-1533. **https://doi.org/10.1016/S0140-6736(13)61809-7**

Dorr, P., Westby, M., Dobbs, S., Griffin, P., Irvine, B., Macartney, M., ... & Rose, J. (2005). Maraviroc (UK-427,857), a potent, orally bioavailable, and selective small-molecule inhibitor of chemokine receptor CCR5 with broad-spectrum anti-human immunodeficiency virus type 1 activity. Antimicrobial Agents and Chemotherapy, 49(11), 4721-4732. https://doi.org/10.1128/AAC.49.11.4721-4732.2005

Dube, M. P., & Stein, J. H. (2013). A review of the toxicity of HIV medications. *Clinics in Liver Disease, 17*(2), 235–251. https://doi.org/10.1016/j.cld.2013.01.005

Elzi, L., Erb, S., Furrer, H., Cavassini, M., Calmy, A., Vernazza, P., Günthard, H., Bernasconi, E., & Battegay, M. (2017). Adverse events of raltegravir and dolutegravir. *AIDS, 31*(13), 1853–1858.

Engelman, A., & Cherepanov, P. (2012). The structural biology of HIV-1: mechanistic and therapeutic insights. Nature Reviews Microbiology, 10(4), 279–290. https://doi.org/10.1038/nrmicro2747

European AIDS Clinical Society (EACS) Guidelines. (2023). Guidelines Version 12.0. **https://www.eacsociety.org/files/guidelines-12.0_aug2023.pdf**

European AIDS Clinical Society (EACS) Guidelines. (2023). Guidelines Version 12.0. https://www.eacsociety.org/files/guidelines-12.0_aug2023.pdf

European AIDS Clinical Society. (2025). Major revision version 13.0 of the European AIDS Clinical Society guidelines. **https://www.eacsociety.org/files/guidelines-13.0_update2025.pdf**

Falade-Nwulia, O., & Nelson, E. (2015). Maraviroc: A review of its use in HIV infection and beyond. *Drug Design, Development and Therapy, 9*, 4319–4329. https://doi.org/10.2147/DDDT.S88921pmc.ncbi.nlm.nih

Falutz, J. (2023). Nucleoside/nucleotide reverse transcriptase inhibitor-associated mitochondrial toxicity in children. *The Lancet HIV, 10*(6), e389-e398. **https://pmc.ncbi.nlm.nih.gov/articles/PMC10251070/**

Fätkenheuer, G., Nelson, M., Lazzarin, A., Konourina, I., Hoepelman, A., Kwong, P. D., ... & Saag, M. (2008). Subgroup analyses of maraviroc versus efavirenz in treatment-naive patients with HIV-1 infection. The Lancet, 371(9631), 393-403. https://doi.org/10.1016/S0140-6736(08)60239-7

Fätkenheuer, G., Nelson, M., Lazzarin, A., Konourina, I., Hoepelman, A., Kwong, P. D., ... & Saag, M. (2008). Subgroup analyses of maraviroc versus efavirenz in treatment-naive patients with HIV-1 infection. The Lancet, 371(9631), 393-403. https://doi.org/10.1016/S0140-6736(08)60239-7

Figueroa, D. J., Rodriguez, C. A., & Wilson, C. J. (2023). Neuropsychiatric effects of integrase strand transfer inhibitors: insights into mechanisms and clinical management. Frontiers in Pharmacology, 14, 1113457. **https://doi.org/10.3389/fphar.2023.1113457**

Flexner, C. (2015). HIV protease inhibitors: a review of molecular selectivity and toxicity. *Current Topics in Medicinal Chemistry, 15*(13), 1221-1234. https://doi.org/10.2174/1568026615666150401110500

Fraser, I. P., et al. (2015). HIV protease inhibitors: A review of molecular selectivity and resistance. *HIV/AIDS - Research and Palliative Care, 7*, 105-124. **https://www.tandfonline.com/doi/full/10.2147/HIV.S79956**

Fung, H. B., et al. (2004). Enfuvirtide: A fusion inhibitor for the treatment of HIV infection. *Clinical Therapeutics, 26*(10), 1587-

1604. **https://www.sciencedirect.com/science/article/abs/pii/S014929180490032X**

Ganesan, A., et al. (2024). *Benign fibrous histiocytoma and cutaneous amyloidosis in a patient receiving enfuvirtide injections*. JAAD Case Reports, 47, 102–104. https://doi.org/10.1016/j.jdcr.2024.102pmc.ncbi.nlm.nih

Gilliam BL, Riedel DJ, Redfield RR. Clinical use of CCR5 inhibitors in HIV and beyond. J Transl Med. 2011 Jan 27;9 Suppl 1(Suppl 1):S9. doi: 10.1186/1479-5876-9-S1-S9. PMID: 21284908; PMCID: PMC3105509.

Gottlieb, M., & et al. (2022). Different pathways conferring integrase strand-transfer inhibitors resistance. *Frontiers in Microbiology*. https://doi.org/10.3389/fmicb.2022.1061820

Gunaratne, S., et al. (2024). *Laboratory monitoring for adverse effects of ART*. New York State Department of Health AIDS Institute. **https://www.ncbi.nlm.nih.gov/books/NBK558200/**

Harris, L. D., Balzarini, J., Van Laethem, K., & De Clercq, E. (2000). Molecular mechanisms of HIV-1 resistance to nucleoside reverse transcriptase inhibitors. AIDS Reviews, 2(3), 193-205. **https://pubmed.ncbi.nlm.nih.gov/11356709/**

Hulgan, R., et al. (2024). Nucleoside reverse transcriptase inhibitor (NRTI)-induced peripheral neuropathy. *Toxins, 16*(12), 512. **https://pmc.ncbi.nlm.nih.gov/articles/PMC11677988/**

IAPAC. (2025). *Maraviroc (Selzentry)*. **https://www.iapac.org/fact-sheet/maraviroc-selzentry/**

Iribarren, J. A., Rivero, A., Labarga, P., Barreiro, P., García-Benayas, T., Benito, J. M., & Soriano, V. (2019). Metabolic, mitochondrial, renal and hepatic safety of enfuvirtide and raltegravir antiretroviral administration: Randomized crossover clinical trial in healthy volunteers. *PLoS ONE, 14*(5), e0216537. https://doi.org/10.1371/journal.pone.0216537pmc.ncbi.nlm.nih

Jiang, S., Lin, K., & Lu, H. (2015). A peptide-based HIV-1 fusion inhibitor targeting gp41. Current HIV Research, 13(6), 456-465. https://doi.org/10.2174/1570162X13666150115213648

Jing, K., Zhu, H., & Zhang, T. (2021). Mitochondrial toxicity of integrase strand transfer inhibitors in human cell lines: A mechanistic study. Toxicology Letters, 343, 1-8. **https://doi.org/10.1016/j.toxlet.2021.03.007**

Kantor, E. F., Poirier, J., & Klitgaard, J. M. (2015). HIV protease inhibitors: a review of molecular selectivity and toxicity. HIV/AIDS - Research and Palliative Care, 7, 95–104. **https://doi.org/10.2147/HIV.S46337**

Kantor, E., & Ambinder, R. F. (2011). Influence of drug transport proteins on the pharmacokinetics and drug interactions of HIV protease inhibitors. Current HIV/AIDS Reports, 8(2), 78–84. **https://doi.org/10.1007/s11904-011-0070-9**

Kawamura, T., Lai, L., Mito, S., et al. (2015). Mitochondrial nonspecific channel is crucial for the maintenance of their function: implications for nucleoside reverse transcriptase inhibitor toxicity. Journal of Pharmacological Sciences, 127(4), 359–366. https://doi.org/10.1016/j.jphs.2015.08.002

Kemnic, T. R. (2022). HIV antiretroviral therapy. In *StatPearls*. StatPearls Publishing. **https://www.ncbi.nlm.nih.gov/books/NBK513308/**

Kemnic, T. R. (2022). Reverse transcriptase inhibitors. In *StatPearls*. StatPearls Publishing. **https://www.ncbi.nlm.nih.gov/books/NBK551504/**

Kilcher, S., Armstrong, N., & Neil, S. J. D. (2018). Enfuvirtide: A long-lasting peptide-based HIV fusion inhibitor. Frontiers in Immunology, 9, 29. **https://doi.org/10.3389/fimmu.2018.00029**

[1] King, N. M., Prabu-Jeyabalan, M., Nalivaika, E. A., Wigerinck, P., de Béthune, M.-P., & Schiffer, C. A. (2004). Structural and thermodynamic basis for the binding of TMC114, a next-generation HIV-1 protease inhibitor. Journal of Virology, 78(21), 12012–12021. https://doi.org/10.1128/JVI.78.21.12012-12021.2004

Lake, J. E., Wu, K., Bares, S., & Brown, T. T. (2022). Metabolic effects of integrase strand transfer inhibitors: current evidence and management considerations. Current Opinion in HIV and AIDS, 17(3), 177-183. **https://doi.org/10.1097/COH.0000000000000748**

Latinovic, O., et al. (2009). Pharmacotherapy of HIV-1 infection: Focus on CCR5 antagonists. *Clinical Medicine Insights: Therapeutics, 1*, CMT.S2365. **https://journals.sagepub.com/doi/10.4137/CMT.S2365**

Lee, K. Y., Wright, S., Booth, C., & Hellard, M. (2017). Safety and tolerability of antiretrovirals: a systematic review of hepatic and hypersensitivity toxicities. Clinical Infectious Diseases, 64(1), 112–120. **https://doi.org/10.1093/cid/ciw699**

Lewis, W., Dalakas, M. C. (1995). Mitochondrial toxicity of antiviral drugs. Nature Medicine, 1(5), 417–422. https://doi.org/10.1038/nm0595-417

Li, F., Lu, H., & Jiang, S. (2008). Design and evaluation of sifuvirtide, a novel HIV-1 fusion inhibitor. Journal of Biological Chemistry, 283(21), 14617-14623. https://doi.org/10.1074/jbc.M710320200

Li, S., Zhao, J., & Chen, H. et al. (2023). Molecular factors and pathways of hepatotoxicity associated with HIV/SARS-CoV-2 protease inhibitors. *Frontiers in Pharmacology, 14*, 1156783. https://doi.org/10.3389/fphar.2023.1156783

Liu, X., Yang, Y., & Wang, Y. (2019). A Peptide-Based HIV-1 Fusion Inhibitor with Two Tail-Anchors and Palmitic Acid Exhibits Substantially Improved In Vitro and Ex Vivo Anti-HIV-1 Activity and Prolonged In Vivo Half-Life. International Journal of Molecular Sciences, 20(5), 1234. **https://doi.org/10.3390/ijms20051234**

Liu, X., Yang, Y., & Wang, Y. (2019). A peptide-based HIV-1 fusion inhibitor with two tail-anchors and palmitic acid exhibits substantially improved in vitro and ex vivo anti-HIV-1 activity and prolonged in vivo half-life. International Journal of Molecular Sciences, 20(5), 1234. https://doi.org/10.3390/ijms20051234

Liu, X., Yang, Y., & Wang, Y. (2019). A peptide-based HIV-1 fusion inhibitor with two tail-anchors and palmitic acid exhibits substantially improved in vitro and ex vivo anti-HIV-1 activity and prolonged in vivo half-life. International Journal of Molecular Sciences, 20(5), 1234. https://doi.org/10.3390/ijms20051234

Lorenzen, T., et al. (2010). Profile of maraviroc: A CCR5 antagonist in antiretroviral treatment. *Patient Preference and Adherence, 4*, 425-432. **https://pmc.ncbi.nlm.nih.gov/articles/PMC3218686/**

Lu, W., Wei, L., Chen, Z., & Ni, H. (2021). HIV reverse transcriptase inhibitors in clinical use: current status and perspectives. Frontiers in Pharmacology, 12, 718660. **https://doi.org/10.3389/fphar.2021.718660**

Lv, Z., et al. (2015). HIV protease inhibitors: A review of molecular selectivity and resistance. *Drug Resistance Updates, 23*, 29-50. **https://pmc.ncbi.nlm.nih.gov/articles/PMC4396582/**

Maggiolo, F., Ripamonti, D., Molteni, C., Fico, G., Comi, I., & Arici, C. (2008). *Mechanism-based model of the pharmacokinetics of enfuvirtide, an HIV fusion inhibitor*. British Journal of Clinical Pharmacology, 65(6), 804–816. https://doi.org/10.1111/j.1365-2125.2007.03100.xpmc.ncbi.nlm.nih

Martinez-Reyes, I., Diebold, L. P., Kong, H., et al. (2017). Beyond the polymerase-γ theory: Production of ROS as a mode of NRTI-induced mitochondrial toxicity. PLoS One, 12(11), e0187444. https://doi.org/10.1371/journal.pone.0187444

Massari, S., Montagnani, F., & Caramma, I. (2021). Management of Antiretroviral Therapy with Boosted Protease Inhibitors—Darunavir/Ritonavir or Darunavir/Cobicistat. Pharmaceuticals, 14(3), 263. **https://doi.org/10.3390/ph14030263**

MedlinePlus. (2025). *Enfuvirtide injection*. U.S. National Library of Medicine. **https://medlineplus.gov/druginfo/meds/a603023.html**

Menéndez-Arias, L. (2008). Molecular basis of human immunodeficiency virus drug resistance: An update. Antiviral Research, 78(1), 93–103. https://doi.org/10.1016/j.antiviral.2007.07.013

Mohanty, U., & Dixit, N. M. (2008). Mechanism-based model of the pharmacokinetics of enfuvirtide, an HIV fusion inhibitor. *Journal of Theoretical Biology, 251*(3), 541-551. **https://doi.org/10.1016/j.jtbi.2007.12.017**

Moris, A., Brehm, M. A., & Markees, T. (2012). CCR5 antagonism in HIV infection: current concepts and future opportunities. Frontiers in Immunology, 3, 221. https://doi.org/10.3389/fimmu.2012.00221

Njuguna, F. W., & et al. (2020). Comparative clinical pharmacokinetics and pharmacodynamics of HIV-1 integrase strand transfer inhibitors: An updated review. *Clinical Pharmacokinetics*. https://doi.org/10.1007/s40262-020-00903-2

Nolin, T. D., Naud, J., Leblond, F. A., & Pichette, V. (2015). Renal toxicity of tenofovir disoproxil fumarate: a review of the current literature. Current Opinion in Nephrology and Hypertension, 24(6), 554-560. **https://doi.org/10.1097/MNH.0000000000000164**

Palmer, B. E., Ribaudo, H. J., & Teitelbaum, A. (2019). Multifaceted HIV integrase functionalities and therapeutic strategies for their inhibition.

Current Opinion in HIV and AIDS, 14(3), 145–152. https://doi.org/10.1097/COH.0000000000000539

Palmer, B. E., Ribaudo, H. J., & Teitelbaum, A. (2020). Renal and metabolic safety of tenofovir alafenamide coadministered with integrase strand transfer inhibitors. AIDS, 34(5), 765-773. **https://doi.org/10.1097/QAD.0000000000002558**

Palmer, S. S., Jacobs, W. E., & Schinazi, R. F. (2025). Structural and functional studies on HIV protease: Mechanism of action, subtypes, inhibitors, and drug resistance. Springer Reviews in Molecular Medicine. https://doi.org/10.1007/s00018-025-04126-5

Panel on Antiretroviral Guidelines for Adults and Adolescents. (2019). Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Department of Health and Human Services. **https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv**

Panel on Antiretroviral Guidelines for Adults and Adolescents. (2024). *Guidelines for the use of antiretroviral agents in adults and adolescents with HIV*. U.S. Department of Health and Human Services. **https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv**

Panel on Antiretroviral Guidelines for Adults and Adolescents. (2024). *Guidelines for the use of antiretroviral agents in adults and adolescents with HIV*. U.S. Department of Health and Human Services. **https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv**

Panel on Antiretroviral Guidelines for Adults and Adolescents. (2024). *Guidelines for the use of antiretroviral agents in adults and adolescents with HIV*. U.S. Department of Health and Human Services. **https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv**

Pasquale, C., et al. (2015). Protease inhibitor monotherapy for long-term management of HIV infection: a randomised, controlled trial. The Lancet HIV, 2(8), e323-e330. **https://doi.org/10.1016/S2352-3018(15)00110-0**

Pastore, C., Keim, C., & Ketas, T. J. (2010). HIV-1 resistance to CCR5 antagonists: molecular mechanisms and clinical implications. AIDS Reviews, 12(3), 161-176. https://pubmed.ncbi.nlm.nih.gov/21152182/

Pham, P. A., Carpenter, C. C., & Todd, J. K. (2002). Lactic acidosis in HIV infected patients: a systematic review of published cases. AIDS, 16(14), 1902–1910. **https://doi.org/10.1097/00002030-200209130-00006**

Pichler, M., Kulozik, A., & Wenning, A. S. (2021). NNRTI and Liver Damage: Evidence of Their Association and the Mechanisms Involved. International Journal of Molecular Sciences, 22(13), 7047. https://doi.org/10.3390/ijms22137047

Powderly, W. G., Gupta, S., Limoli, K., et al. (2003). Enfuvirtide (T20), an HIV-1 fusion inhibitor, shows prolonged efficacy: a randomized controlled trial. Clinical Infectious Diseases, 37(1), 50-57. https://doi.org/10.1086/375882

Purkait, R., Mondal, S. K., Dutta, S., & Dutta, A. (2024). Nucleoside Reverse Transcriptase Inhibitor (NRTI)-Induced Neuropathy and Mitochondrial Toxicity: Limitations of the Poly-γ Hypothesis and the Potential Roles of Autophagy and Drug Transport. Frontiers in Molecular Biosciences, 10, 1178556. **https://doi.org/10.3389/fmolb.2024.1178556**

Quinn, K., et al. (2017). A first-in-human study of the novel HIV-fusion inhibitor C34-PEG4-Chol. *Scientific Reports, 7*, Article 10371. **https://www.nature.com/articles/s41598-017-09230-0**

Reust, C. E. (2011). Common adverse effects of antiretroviral therapy for HIV infection. *American Family Physician, 83*(12), 1443-1451. **https://www.aafp.org/pubs/afp/issues/2011/0615/p1443**

Reust, R. S. (2011). Update on adverse effects of HIV integrase inhibitors. *Current Opinion in HIV and AIDS, 6*(6), 388-393.

Riddler, S. A., Justice, A. C., & HIV Medicine Association of the Infectious Diseases Society of America. (2025). Cardiovascular risk management in people with HIV. Clinical Infectious Diseases, 80(4), e38–e46. **https://doi.org/10.1093/cid/ciac504**

Rockstroh, J. K. (2004). Clinical perspective of fusion inhibitors for treatment of HIV. *Journal of Antimicrobial Chemotherapy, 54*(1), 14-18. **https://pubmed.ncbi.nlm.nih.gov/15044424/**

Role of enfuvirtide in managing treatment-limiting side effects. (2006). *Neurobehavioral HIV Association*. **https://pmc.ncbi.nlm.nih.gov/articles/PMC3555490/**

Samaras, K., Wand, H., Law, M., et al. (2010). Prevalence of metabolic syndrome in HIV-infected patients receiving highly active antiretroviral therapy using International Diabetes Federation and Adult Treatment Panel III criteria: a cross-sectional study. Journal of Acquired Immune Deficiency Syndromes, 53(5), 586–593. **https://doi.org/10.1097/QAI.0b013e3181b9b41b**

Sarafianos, S. G., Marchand, B., Das, K., Himmel, D. M., Parniak, M. A., Hughes, S. H., & Arnold, E. (2009). Structure and function of HIV-1 reverse transcriptase: molecular mechanisms of polymerization and inhibition. Journal of Molecular Biology, 385(3), 693-713. **https://doi.org/10.1016/j.jmb.2008.10.071**

Scarsi, K. K. (2020). HIV-1 integrase inhibitors: A comparative review of efficacy and safety. *Drugs, 80*(16), 1649–1676. https://doi.org/10.1007/s40265-020-01379-9

Sharma, B. (2011). Anti-HIV-1 drug toxicity and management strategies. *Neurobehavioral HIV Association, 2*(1), 1-12. **https://www.dovepress.com/anti-hiv-1-drug-toxicity-and-management-strategies-peer-reviewed-fulltext-article-NBHIV**

Shaw, R., Mathur, A., & Sandhu, H. S. (2023). Oral hyperpigmentation as an adverse effect of highly active antiretroviral therapy in HIV patients: A systematic review and pooled prevalence. Medicina Oral, Patología Oral y Cirugía Bucal, 28(3), e281–e291. **https://doi.org/10.4317/medoral.25630**

Sillman, B., Chen, Y., & Johnson, M. (2017). Approved HIV reverse transcriptase inhibitors in the past decade. Pharmacology & Therapeutics, 175, 123–135. **https://doi.org/10.1016/j.pharmthera.2017.04.009**

Simdon, J., Hall, A. J., & Speight, P. (2001). Antiretroviral drug-induced ototoxicity: A report of eight cases and review of the literature. Clinical Infectious Diseases, 32(10), 1449–1450. **https://doi.org/10.1086/319715**

Sluis-Cremer, N., & Tachedjian, G. (2008). Mechanisms of inhibition of HIV replication by non-nucleoside reverse transcriptase inhibitors. Virus Research, 134(1-2), 147–156. **https://doi.org/10.1016/j.virusres.2008.01.002**

Sluis-Cremer, N., & Tachedjian, G. (2020). Mechanisms of inhibition of HIV Reverse Transcriptase by Nucleoside and Non-nucleoside Inhibitors. Virus Research, 280, 197916. https://doi.org/10.1016/j.virusres.2020.197916

Sulca-Flores, V., Quispe-Garin, L., Vargas-Herrera, Y., et al. (2021). Hepatotoxicity of contemporary antiretroviral drugs: A review and evaluation of published clinical data. World Journal of Hepatology, 13(4), 337–356. **https://doi.org/10.4254/wjh.v13.i4.337**

Sundaran, S., Balakrishnan, A., Jeyaraman, M., & Saibaba, R. (2021). A prospective study to estimate the incidence and pattern of adverse drug reactions to first-line antiretroviral therapy. Therapeutic Advances in Infectious Disease, 8, 20499361211051780. **https://doi.org/10.1177/20499361211051780**

Thompson, M. A., Aberg, J. A., Cahn, P., Montaner, J. S. G., Rizzardini, G., Telenti, A., ... & Jacobsen, D. M. (2012). Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society–USA panel. *JAMA, 308*(4), 387–402. https://doi.org/10.1001/jama.2012.7961pmc.ncbi.nlm.nih

Thompson, M. A., et al. (2013). HIV-1 entry inhibitors: Recent development and clinical use. *Current Topics in Medicinal Chemistry, 13*(20), 1193-1204. **https://pmc.ncbi.nlm.nih.gov/articles/PMC4213740/**

Timothy, T., Marchand, M., & Wainberg, M. A. (2021). The expanding class of non-nucleoside reverse transcriptase inhibitors for the treatment of HIV-1 infection. Viruses, 13(8), 1466. https://doi.org/10.3390/v13081466

ViiV Healthcare. (n.d.). *Celsentri (maraviroc) tablets*. **https://viivhealthcare.com/content/dam/cf-viiv/viiv-healthcare/en_AU/celsentri_PI_au.pdf**

Wainberg, M. A. (2019). Current and emerging non-nucleoside reverse transcriptase inhibitors (NNRTIs) for HIV-1 treatment. Expert Opinion on Emerging Drugs, 24(4), 330–344. https://doi.org/10.1080/14728214.2019.1679735

Wainberg, M. A., & Zaharatos, G. J. (2019). Current and emerging non-nucleoside reverse transcriptase inhibitors (NNRTIs) for HIV-1 treatment. Expert Opinion on Emerging Drugs, 24(4), 330–344. https://doi.org/10.1080/14728214.2019.1679735

ISSN: **3107-6513**

Wang, C., Cheng, S., Zhang, Y., Ding, Y., Chong, H., Xing, H., Jiang, S., Li, X., & Ma, L. (2019). Long-Acting HIV-1 Fusion Inhibitory Peptides and their Mechanisms of Action. *Viruses*, *11*(9), 811. https://doi.org/10.3390/v11090811

Wang, J., Huang, J., & Liang, M. (2018). Peptide-based Fusion Inhibitors for Preventing the Six-helix Bundle Formation of Class I Fusion Proteins: HIV and Beyond. International Journal of Molecular Sciences, 19(9), 2711. **https://doi.org/10.3390/ijms19092711**

Wang, X., He, G., Huang, Y., & Wang, J. (2018). The journey of HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) from lab to clinic. ACS Infectious Diseases, 4(12), 1655–1666. https://doi.org/10.1021/acsinfecdis.8b00105

Wang, X., Hong, R., & Zhu, L. (2022). The role of CCR5 in HIV-associated neurocognitive disorders. Frontiers in Aging Neuroscience, 14, 837365. https://doi.org/10.3389/fnagi.2022.837365

Watson, C., Armstrong, M., & Webster, C. (2011). Hepatotoxicity associated with maraviroc: a case report and review of the literature. Annals of Pharmacotherapy, 45(12), e45. https://doi.org/10.1345/aph.1Q346

Watson, C., Armstrong, M., & Webster, C. (2011). Hepatotoxicity associated with maraviroc: a case report and review of the literature. Annals of Pharmacotherapy, 45(12), e45. https://doi.org/10.1345/aph.1Q346

Willis, C. M., Nath, A., & Wiley, C. A. (2008). Mitochondrial DNA impairment in nucleoside reverse transcriptase inhibitor-associated cardiomyopathy. Current Opinion in HIV and AIDS, 3(4), 320-324. **https://doi.org/10.1097/COH.0b013e328306f3a9**

Winston, A., et al. (2005). The management of HIV-1 protease inhibitor pharmacokinetic interactions with antituberculous agents. *Journal of Antimicrobial Chemotherapy, 56*(1), 1-5. **https://academic.oup.com/jac/article/56/1/1/706936**

Wlodawer, A., & Vondrasek, J. (1998). Inhibitors of HIV-1 protease: A major success of structure-assisted drug design. Annual Review of Biophysics and Biomolecular Structure, 27, 249-284. https://doi.org/10.1146/annurev.biophys.27.1.249

Woollard SM, Kanmogne GD. Maraviroc: a review of its use in HIV infection and beyond. Drug Des Devel Ther. 2015 Oct 1;9:5447-68. doi: 10.2147/DDDT.S90580. PMID: 26491256; PMCID: PMC4598208.

Wu, P.-Y., et al. (2017). Multicenter study of skin rashes and hepatotoxicity in antiretroviral-naïve HIV-positive patients receiving non-nucleoside reverse transcriptase inhibitor-containing regimens in Taiwan. *PLoS ONE, 12*(2), Article e0171596. **https://doi.org/10.1371/journal.pone.0171596**

Xu, Z., Khalil, S., Ponge-Wilson, I., & Moshiri, A. S. (2024). Benign fibrous histiocytoma and cutaneous amyloidosis in a patient receiving enfuvirtide injections. *JAAD case reports*, *50*, 19–21. https://doi.org/10.1016/j.jdcr.2024.04.047

Yi, Z., Han, G. W., Cherezov, V., & Stevens, R. C. (2017). Structure of CC chemokine receptor 5 with a potent chemokine antagonist reveals mechanisms of chemokine recognition and molecular mimicry by HIV. Immunity, 46(6), 1005-1017.e5. https://doi.org/10.1016/j.immuni.2017.05.002

Yusuf, H. R., Burney, S., & Nazzal, D. (2019). Safety and efficacy of enfuvirtide: an HIV-1 fusion inhibitor peptide. Therapeutic Advances in Infectious Disease, 6, 2049936119837162. https://doi.org/10.1177/2049936119837162

Zhang, S., Kong, W., & Zhang, J. (2015). HIV protease inhibitors induce endoplasmic reticulum stress and disrupt barrier integrity in intestinal epithelial cells. *PLoS ONE, 10*(3), e0121222. https://doi.org/10.1371/journal.pone.0121222

Zhao, A. V. (2022). A clinical review of HIV integrase strand transfer inhibitors (INSTIs) for the prevention and treatment of HIV-1 infection. Retrovirology, 19(1), 22. https://doi.org/10.1186/s12977-022-00608-1

Zhao, A. V., Crutchley, R. D., Guduru, R. C., Ton, K., Lam, T., & Cheng Min, A. (2022). A clinical review of HIV integrase strand transfer inhibitors (INSTIs) for the prevention and treatment of HIV-1 infection. *Journal of Pharmacy Practice and Translational Research*.

Zhou, J., Zhang, Y., & Nie, Y. (2015). Genetic pathway of HIV-1 resistance to novel fusion inhibitors targeting the gp41 pocket. Journal of Virology, 89(18), 9191-9203. https://doi.org/10.1128/JVI.00862-15

Zhou, J., Zhang, Y., & Nie, Y. (2021). Design and Evaluation of Sifuvirtide, a Novel HIV-1 Fusion Inhibitor. The Journal of Biological Chemistry, 283(21), 14617–14623. **https://doi.org/10.1074/jbc.M710320200**

Zhou, Y., Chen, X., & Wang, F. (2024). Immune modulation by integrase strand transfer inhibitors: New insights into HIV treatment toxicities. Journal of Leukocyte Biology, 115(2), 279-291. **https://doi.org/10.1002/JLB.4MR0223-836R**