Review

Liver Damage During Treatment with Reverse-Transcriptase Inhibitors in HIV Patients

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ABSTRACT: The advent of highly active antiretroviral therapy (HAART) in 1996 has markedly enhanced the life expectancy of people living with HIV (PLWH), largely due to the effectiveness of reverse transcriptase inhibitors (RTIs). These drugs target the reverse transcriptase enzyme, crucial for the HIV virus to convert its RNA into DNA within host cells, effectively disrupting the viral replication process. This action reduces the patient's viral load, helping preserve immune function and prevent progression to AIDS. Consequently, the predominant causes of mortality among individuals living with HIV have transitioned from opportunistic infections and AIDS-related cancers to liver disease and cardiovascular complications. Liver damage in PLWH could arise from multiple sources including co-infections, chronic substance use, and notably, antiretroviral therapy itself, which can be hepatotoxic. This review highlights the risks of hepatic damage associated with nucleoside and non-nucleoside RTIs and underscores the variability in hepatotoxicity risks among different drugs. It emphasizes the necessity for regular monitoring of liver health in PLWH and adjusting antiretroviral regimens to minimize liver fibrosis risk. This risk is particularly pronounced in patients who associate the infection with hepatitis B or C virus, where the potential for hepatotoxicity significantly increases.

KEYWORDS: *HIV, hepatotoxicity, mitochondrial dysfunction, reverse transcriptase inhibitors.*

Introduction

Antiretroviral therapy and liver health

Following the advent of highly active antiretroviral therapy (HAART) back in 1996, introduced in the treatment for people living with HIV(PLWH) the lifespan of them had substantially increased and it became similar with that of the general population and the tendency of deaths have shifted away from opportunistic infections and malignancies associated with acquired immunodeficiency syndrome (AIDS) to liver diseases and cardiovascular events [1].

Liver damage can be caused by several factors like: HIV itself through multiple mechanisms, hepatitis viruses, other co-infections, chronic alcohol consumption, non-alcoholic fatty liver disease [2].

Apart from these, antiretroviral therapy is a well-known cause of hepatoxicity, fact that represents a challenge in the treatment of PLWH and can escalate the morbidity and mortality of these patients [3].

This fact raises questions about the possibility of determining the appearance of liver fibrosis in long term exposure. Various mechanisms were reported to be the cause of ARV related hepatotoxicity like: drug induced liver injury (DILI), various reactions caused by the immune system, hypersensitivity answers, mitochondrial toxicity and several other pathogenic pathways [4].

There are some antiretrovirals drugs that seem to carry the greatest risk for liver fibrosis development, like the nucleoside reverse transcriptase inhibitors representants, while others have minimal risk, like entry inhibitors [5].

Concurrent infection with hepatitis B virus (HBV) is encountered up to 7,6% (IQR 5,6-12,1%) of PLWH that means 1 from 100 persons infected with hepatitis B virus have also HIV infection [6].

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In PLWH the incidence of hepatitis C virus (HCV) co-infection varies between 6-30% with differences that depends with the route of transmission, prevalence much higher in people who inject drugs [7].

Individuals with HBV or HCV co-infection are more likely to have alredy liver damage before starting antiretroviral therapy (ART) fact that increases their susceptibility to hepatotoxicity from ART and also ART can interact with drugs active against hepatitis B or C and to exacerbate liver damage [8].

Most of the antiretroviral drugs that are part of the HIV therapy have also hepatotoxicity, which was identified in 23% of patients receiving combined ART [9,10].

ART drugs are classified in six classes (Table 1): revers-transcriptase inhibitors (nucleosidic, NRTIs and non-nucleosidic, NNRTIs), fusion inhibitors, integrase inhibitors (known as integrase nuclear strand transfer inhibitors or INSTIs), protease inhibitors (PIs), and adjunct therapy, for example immunomodulation. Usually, these drugs are administered in combinations.

Common regimens utilized in antiretroviral therapy often constitute a dual-core composition of nucleoside reverse-transcriptase inhibitors.

This dual-core composition functions as the foundational framework or 'backbone,' providing a consistent, robust substrate upon which additional antiretroviral mechanisms of action can be scaffolded. An auxiliary layer of this therapeutic regimen comprises one NNRT, PI or INSTI. This layer serves as the 'base,' supplementing the backbone component with additional modes of HIV inhibition. These multidimensional antiretroviral regimens incorporate multiple therapeutic targets, intending to inhibit the HIV replication process at various stages. NRTIs obstruct viral replication by impairing the generation of new viral DNA, whereas NNRTIs perform a similar function through distinct enzymatic inhibition pathways.

To become active, NRTIs undergo a series of phosphorylation steps, guided by cellular enzymes called “kinases.” NRTIs are typically nucleoside analogs that mimic natural nucleosides, but have some modifications that block their recognition by cellular DNA or RNA polymerase. It takes three processes of phosphorylation to get to it’s active formula, that interacts with the innate nucleotides to incorporate into the viral DNA by the reverse transcriptase enzyme. NNRTIs cross with a specific spot on the reverse transcriptase enzyme, fact that produces modifications in its shape and inhibits its function [11] (Figure 1).

The role of PIs is to prohibit the proteolytic cleavage of virus-encoded polyproteins, thus thwarting the maturation of new virus particles. Ultimately, INSTIs inhibit the integration of viral DNA into the host genome, thereby reducing the spread of virus-infected cells.

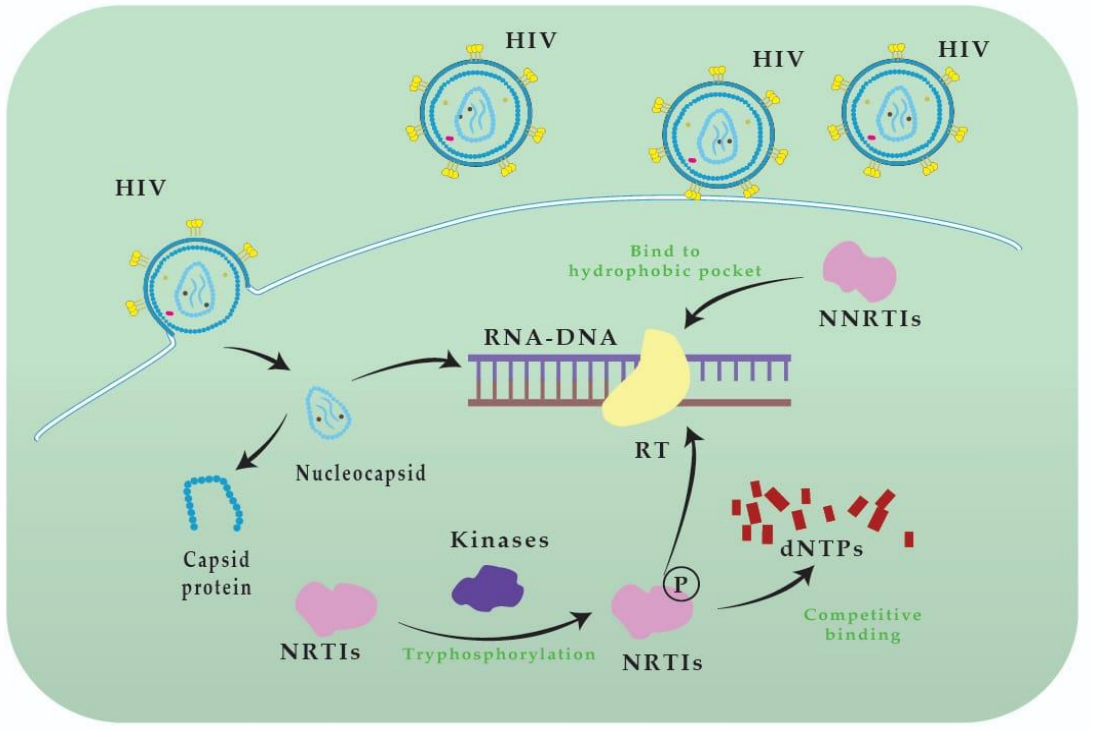

Figure 1. Action mechanisms of nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse-transcriptase inhibitors (NNRTIs).

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Table 1. Antiretroviral compounds active on human immunodeficiency virus.

Pharmaceutical class	ART drug	Mechanisms of action in HIV infection
Nucleoside reverse transcriptase inhibitors	abacavir zidovudine lamivudine emtricitabine tenofovir disoproxil fumarate	Inhibition of the human immunodeficiency virus (HIV) reverse transcriptase enzyme, thereby impeding viral replication and propagation.
Non-nucleoside reverse transcriptase inhibitors	efavirenz etravirine nevirapine rilpivirine doravirine	Inhibition of the human immunodeficiency virus (HIV) reverse transcriptase enzyme, thereby impeding viral replication and propagation.
Protease inhibitors	atazanavir darunavir fosamprenavir ritonavir tipranavir	Inhibition of HIV protease, that is required for viral replication.
Fusion inhibitors	enfuvirtide maraviroc	Prevention of HIV from entering targeted cells.
Integrase inhibitors	dolutegravir raltegravir	Blockage of HIV integrase that integrates the HIV genetic material into the cells' DNA.

The ART regimens are usually daily-administered combinations of at least three different compounds from at least two drug classes. The mechanism by which ART produces hepatotoxicity is unclear [1-8].

In Table 2 we described the underlying mechanisms of liver toxicity in PLWH under treatment with reverse transcriptase inhibitors.

The literature points out that [9] a considerable number of patients exposed to antiretroviral regimens, showed symptomatic drug-induced liver injury (DILI). DILI is defined as idiosyncratic (unpredictable) is by far one of the most difficult liver disarrays to manage because of the extensive are of medications used in clinical practice, the different clinical and pathophysiological manifestations with it can present, and the lack of specific biomarkers. This makes diagnosing drug-induced liver injury a challenging and difficult task that requires a large level of attention and careful consideration of alternative causes of liver disease [10].

According to Aithal et al the principles for diagnosing drug-induced liver injury (DILI) based on liver enzyme values are: alanine aminotransferase (ALT) and aspartate aminotransferase (AST) serum values more than 5 times the upper limit of normal(ULN), alkaline phosphatase (ALP) blood levels more than 2 times the ULN in particularly with elevation of gamma-glutamyltransferase (GGT) or conjugated bilirubin and at least elevation of total bilirubin serum levels more than twice the ULN when associated with elevated ALT or AST [11].

Patterns of liver injury are usually hepatocellular, manifested from mild liver enzymes elevations to an acute form of hepatitis and potentially leading to acute liver failure. We face a growing body of evidence towards a mitochondrial mechanism, because ART long-term use leads to mitochondria depletion and compound-specific myotoxicity [7].

The liver's profoundly bioenergetic characteristics render it particularly vulnerable to toxicity stemming from drug-induced mitochondrial dysfunction. The structure called Electron Transport Chain (ETC), who is responsible for creating a proton difference across the internal mitochondrial membrane and synthesizing adenosine triphosphate through oxidative phosphorylation, can become uncoupled from ATP synthase due to some drug toxicities. Chronic mitochondrial uncoupling can lead to a process called 'thermogenesis,' causing a depletion in ATP, which can result in cell death [2,3].

Liver biopsies from patients who have manifested liver injuries have demonstrated a pronounced influx of mixed inflammatory cells including significant numbers of eosinophils.

This suggests the induction of an immune-conducted hypersensitivity process-a particular immune answer which prompts immune cells to initiate an attack on hepatocytes, the primary cells of the liver.

An immune-mediated hypersensitivity reaction often manifests as an exaggerated response by the immune system, mistakenly identifying normal liver cells as foreign or harmful agents. This can lead to a range of potentially harmful pathologies, including inflammatory liver damage.

With respect to eosinophils, which are a significant component of leukocytes and they

represent a primordial part in the human's immune armor mechanisms, it is imperative to acknowledge their essential role in maintaining optimal health. Generally, they can be protective against certain infections and parasites.

However, in situations of hypersensitivity, their numbers can significantly increase, resulting in tissue infiltration. This can lead to localized inflammation and damage, as observed in liver injuries. The degree of eosinophil infiltration and the ensuing damage is usually a clear indicator of the severity of hypersensitivity reactions. In severe cases, significant liver damage can occur, leading to cell death and, potentially, even liver failure.

Mechanistically, eosinophils and other immune cells release pro-inflammatory compounds such as cytokines and reactive oxygen species (ROS), which conduct towards hepatocyte injury. NRTIs inhibit a certain enzyme named polymerase gamma, that fulfils a decisive act in repairing mitochondrial DNA, so causing mitochondrial dysfunction.

Another mechanism for liver damage is the generation of reactive oxygen species that may produce deterioration to different cellular components, such as proteins, fats, mitochondrial DNA, but also nuclear DNA. Excess ROS cause oxidative damage, which intensifies mitochondrial dysfunction and cellular damage.

Oxidative phosphorylation decreases and causes adenosine triphosphate (ATP) production to decrease, compromising cellular function [12], especially in the liver (Figure 2).

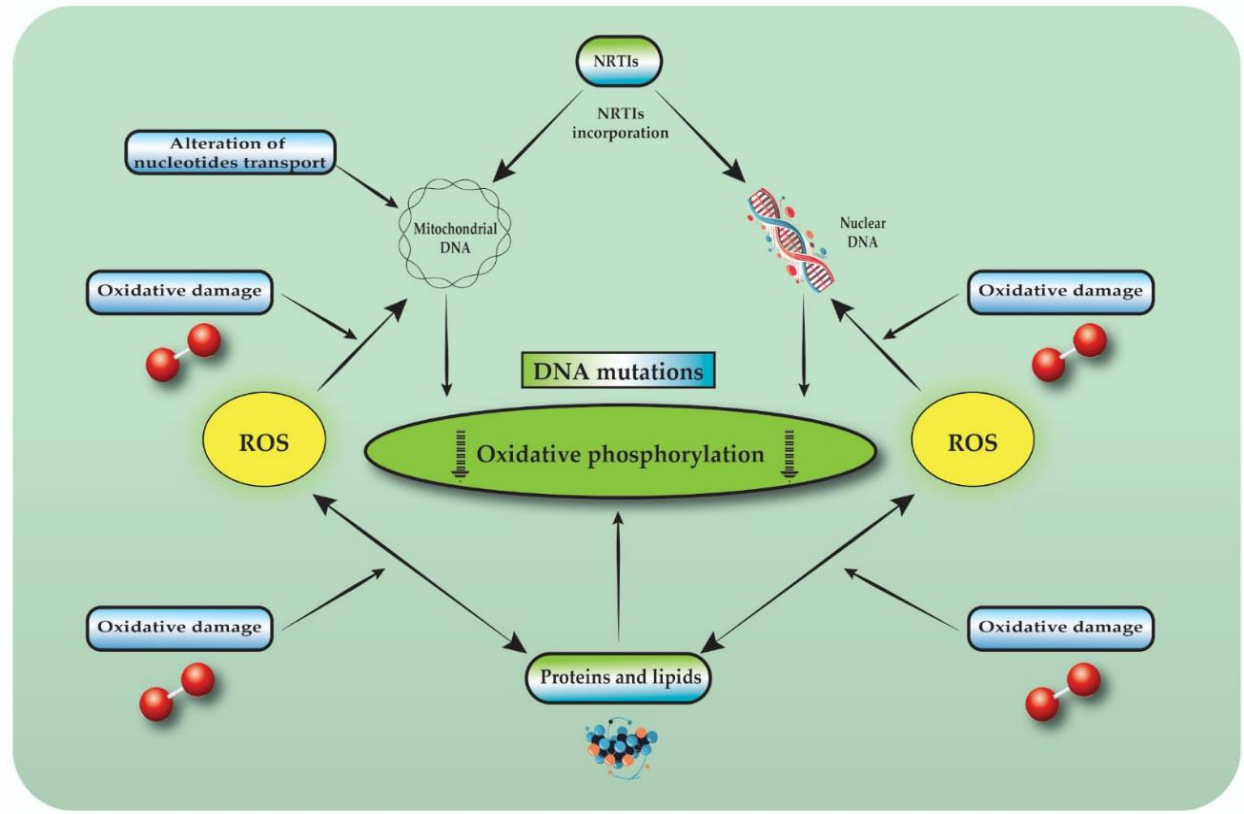

Figure 2. The mechanisms of liver damage of the HIV reverse-transcriptase inhibitors.

There are several antiretrovirals from the reverse transcriptase inhibitors category that are known to produce liver fibrosis.

Didanosine and stavudine are the oldest nucleoside reverse transcriptase inhibitors that were connected with mitochondrial disfunction, heading towards hepatic steatosis, plus, in some cases, progressive liver fibrosis [13].

Merchante et al. analyzed information about 258 people living with HIV who had no history of hepatitis B or C co-infections, and found that the period of DDI use, age, chronic alcohol consumption, anterior exhibition to abacavir (ABC), and a serum level of CD4+cell count bellow 200 cells/mL were independently connected with important liver fibrosis (LF) [14].

Not all compounds that fits in the class of non-nucleoside reverse transcriptase inhibitors present the same risk for liver damage.

Of these, patients receiving nevirapine were associated with an 18% risk and those receiving nevirapine with an 8% risk [15].

In terms of mitigation, the early detection of hypersensitivity reactions and prompt therapeutic

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intervention are crucial for minimizing hepatic damage. This might involve the abandonment of the assumed agent, if identifiable, also starting specific treatments to manage the inflammatory response and protect liver function.

In summary, this underscores the importance of understanding how immune-mediated hypersensitivity reactions can result in liver injury and emphasizes the need for innovative approaches to the diagnosis and management of these pathogenic conditions.

There are genetic factors that seem to increase the susceptibility for a clinically significant hypersensitivity syndrome, an example of this is the treatment with abacavir. The likelihood to develop severe drug hypersensitivity reaction due to abacavir use appears to be influenced significantly by genetic factors.

It has been established that the existence of a specific human leukocyte antigen (HLA-B*57-01) represents an important predictor of abacavir hypersensitivity, also a potential susceptibility locus has been identified inside a 300-kilobase domain among the MEGT1 and C4A6 loci located in the center of the major histocompatibility complex class I [16].

Currently, the U.S. Food and Drug Administration (FDA) demands pharmacogenomic testing for the presence of HLA-B*57-01 allele previously prescribing abacavir due to it's significant danger of hypersensitivity answers, which can include DILI [17].

For more reverse transcriptase inhibitors (RTIs), there is no similar FDA-mandated pharmacogenomic testing for HLA-B*57-01.

However, there are some considerations for other RTIs that healthcare providers should keep in mind: CYP2B6 genetic variations can influence the metabolism of efavirenz, conducting towards much raised drug levels and elevated risk for adverse effects that implicates the central nervous system and probable hepatotoxicity that certain patients may experience.

In some clinical situations, genetic testing for CYP2B6 variants may be recommended to personalize dosing [18].

Genetic elements, including the presence of particular HLA alleles (e.g. HLA-DRB101: 01 and HLA-B35:05), have been connected to a heightened risk of hypersensitivity and hepatotoxicity resulting from nevirapine use [19].

For medications such as emtricitabine, lamivudine, tenofovir, doravirine, etravirine, and rilpivirine, there are no specific pharmacogenetic tests that are mandatory before prescription. The monitoring of adverse effects is contingent on clinical observation and patient history instead of genetic testing.

In certain patients who experience HIV infection, starting antiretroviral treatment can lead to a paradoxical worsening of their condition due to a restored immune response to a preexisting infection or antigen, phenomena that have been designated as Immune Reconstitution Inflammatory Syndrome (IRIS).

This immune response can sometimes target the liver, causing inflammation and potential injury.

An underlying condition such as chronic viral hepatitis and heavy alcohol intake is identified as a contributing factor to develop important liver toxicity with antiretroviral agents [20].

The risk of hepatotoxic effects in PLWH that are under HAART increases due to host factors related like age, alcohol consumption, concomitant medication use, diabetes mellitus but also, non-alcoholic fatty liver disease (NAFLD) [21,22].

All of these promote through various mechanisms a chronic inflammation of the liver and through their long-term action represent the promoters of liver fibrosis development.

Alcohol consumption increases gut permeability and represents a non-specific activator for the innate immune response, activates the synthesis for pro-inflammatory cytokine [23], and finally promotes liver inflammation and fibrosis development. In PLWH, there is a prevalence for NAFLD that is about 30-40% [24].

The accumulation of free fatty acids characteristic in NAFLD will determine insulin resistance, higher body mass index, and dyslipidemia, facts that will promote inflammation and liver fibrosis development [25].

Table 2. Mechanisms of liver toxicity in HIV reverse-transcriptase inhibitors (RTIs).

RTI	Mechanism of liver toxicity
Nucleosidic RTIs	
abacavir (Ziagen)	Drug-Induced liver injury, especially in combination with alcohol consumption due to synergistic hepatotoxic effects. Mitochondrial toxicity via inhibition of DNA polymerase-y, conducting towards defective mitochondrial DNA replication and function. Hypersensitivity reactions mediated by HLA-B*57-01 allele, involving immune-mediated liver damage. Lactic acidosis resulting from mitochondrial dysfunction and subsequent hepatic steatosis and failure.
emtricitabine (Emtriva)	Drug-Induced liver injury potentially through ROS generation and oxidative stress. Hepatitis B exacerbation following discontinuation of therapy due to immune reconstitution and viral rebound.
lamivudine (Epivir)	Drug-Induced liver injury trough mitochondrial DNA depletion and impaired oxidative phosphorylation. Mitochondrial toxicity via inhibition of DNA polymerase-y, leading to impaired mitochondrial DNA replication and function. Hepatitis B exacerbation following discontinuation of therapy due to loss of viral suppression. Immune reconstitution inflammatory syndrome (IRIS) leading to hepatic inflammation as the immune system recovers and targets infected cells.
tenofovir disoproxil fumarate (Viread)	Stabilization or regression fibrosis development in patients with active hepatitis B virus replication. Potential for DILI through mitochondrial damage and oxidative stress.
zidovudine (Retrovir)	Mitochondrial toxicity via inhibition of DNA polymerase-y, conducting towards defective mitochondrial DNA replication and function. Termination of DNA synthesis in the host hepatocytes, leading to hepatocyte dysfunction and apoptosis.
Non-nucleoside RTIs	
doravirine (Pifeltro)	Oxidative stress induction through increased production of ROS and subsequent lipid peroxidation in hepatocytes.
efavirenz (Sustiva)	Drug-Induced liver injury, especially in combination with alcohol consumption which increases CYP2B6-mediated metabolism to toxic metabolites. Inflammatory liver injury through immune system activation and cytokine release.
etravirine (Intelence)	No specific liver toxicity mechanisms detailed in current literature; potential for class-related effects such as ROS generation and immune-mediated damage.
rilpivirine (Edurant)	Drug-Induced liver injury potentially via ROS generation and oxidative stress.
nevirapine (Viramune)	Up-regulation of fatty acids, leading to intra-hepatocyte imbalances, leading to steatosis and hepatocyte injury. Up-regulation of Acyl-CoA Synthetase Long-Chain enzyme family (ACSL), conducting to fatty acid β-oxidation and further to mitochondrial dysfunction. Mitochondrial toxicity via depletion of mitochondrial DNA and impaired oxidative phosphorylation. Alteration of Antigen Presentation Pathway leading to immune-mediated hepatocyte damage.

Note: No foot note associated.

The European Association for the Study of the Liver (EASL) Clinical Practice Guideline for Drug-Induced Liver Injury provide comprehensive recommendations on the appraisal, management, and check-out of people experiencing DILI. They emphasize the importance of identifying the offending drug, monitoring liver function, and ensuring safe and effective alternative therapies [10].

Because DILI-producing antivirals are stopped as recommended, it is impossible to assess the rate of progression of liver fibrosis produced by a DILI-producing antiretroviral.

According to the literature there are numerous lines of research to address these consequences. Several innovative strategies have been suggested in the literature for controlling the progression of liver stiffness in PLWH. These include lifestyle modifications such as limiting alcohol consumption, managing metabolic conditions, and optimizing the patient's lifestyle. Additionally, the use of antifibrotic agents, stem cell therapy, and immune modulation has been explored [26].

Various antifibrotic drugs are currently under investigation for their potential to target liver fibrosis development. For instance, Farnesoid X receptor (FXR) agonists have shown promise in reducing liver fibrosis, while Peroxisome proliferator-activated receptor (PPAR) agonists are currently being tested for their antifibrotic effects. Galectin-3 inhibitors, which target the protein galectin-3 that is involved in liver fibrosis development, are also being studied [27].

A novel approach to reversing liver fibrosis is mesenchymal stem cell (MSC) therapy, which

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has the capacity to turn into hepatocytes and enhance tissue repair and regeneration through its immune-modulatory abilities, production of growth factors and cytokines, and other factors [28].

Given the connection between HIV and liver fibrosis, researchers are exploring therapies that can modify immune responses. This includes the use of anti-inflammatory medications and techniques aimed at restoring immune function in HIV patients [26].

Clinical features of ART-produced liver toxicity

These clinical features can vary according to the underlying mechanisms involved. In hypersensitivity reaction patients may experience drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, which involves fever, skin rash, swollen lymph nodes, and liver inflammation. Other systemic symptoms can involve the kidneys and lungs [29].

Hepatitis caused by hypersensitivity can be severe, and in some instances, it can progress to acute liver failure, especially for those patients who have high CD4 counts and those who possess specific genetic markers like the DRB1*0101 antigen [29].

Protease Inhibitors (PIs), like ritonavir and lopinavir, as well as specific Nucleoside Reverse Transcriptase Inhibitors (NRTIs) like zidovudine and didanosine, may result in direct liver toxicity. Clinical manifestations often include: elevated liver enzymes when patients may experience asymptomatic increases in aminotransferases (ALT and AST), with severe cases progressing to clinical hepatitis accompanied by complaints: jaundice, nausea, vomiting, and abdominal pain [30].

Certain NRTIs, like stavudine, didanosine, and zidovudine, were linked with mitochondrial toxicity, that has the possibility towards hepatic steatosis and lactic acidosis. Various clinical presentations associated with these conditions include hepatic steatosis that can develop gradually with mild symptoms or be entirely asymptomatic. Patients may experience fatigue, hepatomegaly, and mildly elevated liver enzymes, and lactic acidosis that is a severe, life-threatening condition characterized by elevated lactate levels, metabolic acidosis, and multiorgan failure. Symptoms include rapid breathing, abdominal pain, nausea, and muscle weakness [29,30].

Method for Study Selection

A thorough literature search was conducted across several databases, like PubMed, Scopus, Web of Science, and Google Scholar. This research was performed using a mix of related keywords and phrases, like "HIV," "reverse transcriptase inhibitors," "antiretroviral therapy," "liver damage," "hepatotoxicity," "mitochondrial dysfunction," and "liver fibrosis." Initially, titles and abstracts were screened to remove irrelevant studies. Subsequently, full-text articles were examined in detail, and only studies that provided data on liver damage associated with reverse transcriptase inhibitors in HIV patients and were peer-reviewed were included in this review. Non-peer-reviewed articles, conference abstracts, reviews, and studies not directly related to antiretroviral therapy-induced liver damage were excluded from the analysis. An informal assessment of study quality was performed, considering study design, sample size, and the robustness of the findings.

This approach ensures a thorough and systematic selection of relevant studies, providing an extensive overview of the actual knowledge of liver damage associated with reverse transcriptase inhibitors in HIV patients.

Nucleoside reverse transcriptase inhibitors

It's important to note that liver damage is a crucial matter in mortality amid PLWH, with drug-induced hepatotoxicity identified in a significant percentage of patients receiving combined ART. NRTIs, are important compounds in ARV therapy, and their association with serious hepatic adverse events conducted to liver-related warnings issued by regulatory agencies. Some purine analogues as abacavir and didanosine are particularly noted for their immediate and concentration-dependent effects on mitochondrial function in hepatic cells, as described in the study.

Abacavir

Abacavir is an antiretroviral medication utilized for the therapy of HIV-1 infection, typically with alternative antiretroviral substances. It achieves its antiviral effect through the formation of its intracellular metabolite, carbovir-triphosphate, which interferes with the viral RNA-dependent DNA polymerase (reverse transcriptase) of the HIV virus, ultimately resulting in the suppression of viral replication [31].

Abacavir can induce liver injury through a mechanism involving mitochondrial dysfunction

and also it was shown to enhance acetaminophen-induced hepatotoxicity[32]. Abacavir has been demonstrated to induce a prompt and concentration-dependent blockage of oxygen consumption and the activity of mitochondrial complexes I and III in hepatic cells[5,32]. This inhibition leads to increased production of reactive oxygen species (ROS), decrease in intracellular ATP levels, and a reduction in mitochondrial membrane potential, thereby undermining mitochondrial function. However, these mitochondrial interferences by abacavir did not initially compromise cell survival on their own [32].

Adverse drug reactions (ADRs), such as hypersensitivity reactions to the HIV reverse transcriptase inhibitor abacavir (ABC), have been linked to HLA alleles, particularly HLA-B*57-01. However, not all HLA-B*57-01+ patients develop ADRs, indicating that other factors may also influence the response to the drug. Researchers have used HLA-B*57-01-Tg mice to study HLA-linked ADRs in vivo. These studies revealed that although ABC activated Tg mouse CD8+ T cells in vitro in an HLA-B*57-01-dependent manner, the drug was tolerated in vivo. In immunocompetent Tg animals, ABC induced CD8+ T cells with an anergy-like phenotype that did not lead to ADRs. However, in vivo depletion of CD4+ T cells prior to ABC administration enhanced DC maturation to induce systemic ABC-reactive CD8+ T cells with an effector-like and skin-homing phenotype, along with CD8+ infiltration and inflammation in drug-sensitized skin [16,33].

The association of abacavir with acetaminophen, even at concentrations under the concentrations believed to be hepatotoxic, the combination exacerbates the harmful effects on mitochondrial activity and compromises cellular growth, demonstrating a connection with low glutathione levels, which is crucial for detoxifying reactive oxygen species, in the context of increased oxidative stress encountered in HIV infection. Therefore, the interaction between abacavir and acetaminophen substantially potentiates mitochondrial damage, boosting the risk of liver damage [32].

Approximately 5-8% of patients taking abacavir can develop a hypersensitivity reaction. This reaction can occur at any time but is most common in the first six weeks of therapy. In other situations, this hypersensitivity reaction can involve the liver, manifesting as hepatitis with elevations in serum aminotransferase levels. If abacavir is discontinued and then restarted (known as rechallenge), the hypersensitivity reaction can recur and can be severe or even fatal. Additionally, Abacavir treatment was associated with IRIS, that can impact the liver structure on the long-term leading to fibrosis.

Following the serum levels of liver enzymes, therefore, recommended in patients on abacavir particularly in the first few months of therapy, and the drug should be discontinued if a hypersensitivity reaction is suspected.

Severe cholestatic hepatitis can be induced after switching to an antiretroviral treatment consisting of abacavir, lamivudine, and dolutegravir. In one case report, it was noted a remarkable elevation in AST and ALT levels, which are indicative of liver damage [9].

Another defined mechanism for hepatotoxicity is lactic acidosis, which occurs when there's an accumulation of lactate in the body beyond the liver’s capability to metabolize it. This can result in liver cell damage and even liver failure.

Zidovudine

Zidovudine is a medication that has demonstrated effectiveness as an antiretroviral agent. Intracellular, after is phosphorylated to zidovudine triphosphate, it inhibits the reverse transcriptase activity of HIV-1, ultimately terminating the proviral DNA. Additionally, it was demonstrated that can significantly cut down the vertical transmission of HIV infection when is prescribed to neonates for a period of six weeks, provided that breastfeeding is not allowed [34].

The process by which hepatic lipid accumulates in individuals treated with AZT remains unclear. The authors propose that AZT-induced oxidative stress and endoplasmic reticulum (ER) stress may contribute to the accumulation of hepatic lipid in AZT-treated individuals. In a study involving C57BL/6J female mice that were administered 400 mg/day/kg body weight of AZT via intraperitoneal injection for 10 consecutive days, the authors observed an important rise in hepatic triglyceride levels, but also inflammation. Furthermore, the researchers determined that oxidative stress indicators, including protein oxidation, nitration, glycation, and lipid peroxidation, were noticeably higher in the mice that received AZT in comparison with the control group that received a vehicle. The study also revealed that the levels of ER stress marker proteins, such as GRP78, p-PERK, and p-eIF2α, were significantly increased in the AZT-treated mice. Collectively, these results imply that

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increased oxidative and ER stress may be a significant contributing factor, at least in part, to the fats accumulation, inflammation, and hepatotoxicity that occur in mice treated with AZT [35].

Additionally, some studies documenting ultrastructural damage to liver mitochondria of rats treated with AZT [36].

The incidence of important adverse consequences of AZT, attributed to damage to mitochondria and mtDNA depletion, has been considerable obstruction for the use of AZT. The integration of AZT monophosphate into viral DNA leads to the precipitate cessation of DNA replication, affecting not only viral replication but also host cellular functions, particularly those involving mitochondria [36].

The mechanisms through which zidovudine induces liver injury involves oxidative deterioration to mitochondrial DNA and increased peroxide production by liver mitochondria, conducting to mitochondrial damage and hepatotoxicity. This oxidative damage and its prevention by antioxidant vitamins highlight the impact of oxidative stress in the side effects of AZT on the liver.

Zidovudine, a drug that can cause hepatic steatosis and contribute to liver fibrosis, has been shown to progress towards LF in a group of individuals diagnosed with HIV plus HBV co-infection [37].

Lamivudine

Lamivudine is a medication that treats both HIV-1 infection and HBV infection. It works by being activated within cells to form lamivudine triphosphate, which then inhibits the elongation of viral DNA[38].

It is generally considered to possess a reliable security profile with small risk for hepatotoxicity. However, like any medication, it can in rare cases cause adverse reactions, including potential liver injury. The liver injury mechanism is not well known although is believed to be connected to a hypersensitivity reaction. Additionally, lamivudine can induce mitochondrial toxicity by inhibition of DNA polymerase gamma, which may result in liver damage.

If this agent is being used in the treatment of chronic hepatitis B associated with HIV infection, there is a possibility that when the medication is stopped or if the virus becomes resistant to the drug, there could be a 'flare-up' or sudden return of the infection. This fact may cause liver inflammation, that could further lead to a worsening in liver function and potentially severe liver damage. Lamivudine withdrawal can cause IRIS and there may be an improvement in immune response to hepatitis B or C viruses in co-infected individuals [7,39,40]. This could lead to increased liver inflammation and potential injury.

In certain patient population lamivudine might raise the possibility for hyperbilirubinemia in some cases with severe hepatitis, suggesting that precaution is necessary in prescribing lamivudine treatment for specific patient groups [41].

Lamivudine is known to cause resistance issues, particularly in HBV infection. Resistance to lamivudine in HBV is primarily due to mutations in the HBV polymerase gene, particularly the M204V/I mutation. This resistance emerges relatively quickly, especially when lamivudine is used as monotherapy for HBV in co-infected patients. In one study, the triple mutation M204V/L180M/V173L was the most frequently encountered mutation in a group which included patients with HIV plus HBV co-infection [42].

As always, any individual undergoing lamivudine treatment need to be closely followed for any marks of liver injury via regular blood tests and clinical evaluation.

Emtricitabine

Emtricitabine belong to the class of NRTI's that inhibits the activity of the HIV reverse transcriptase enzyme, stopping the changeover of HIV RNA in DNA. It is typically prescribed for treating HIV infection in combination with other antiretroviral drugs [43].

Studies show that emtricitabine (FTC) can induce liver injury through mechanisms associated with hepatotoxicity through mitochondrial damage, which have been reported in some cases with HIV treatment, particularly when is prescribed in unification with some other antiretroviral substances like efavirenz and tenofovir [5,44,45].

One documented case detailed a patient who experienced hepatotoxicity characterized by extremely elevated aminotransferase levels following treatment with efavirenz/ emtricitabine/tenofovir. The liver injury presented mainly with hepatocellular damage rather than cholestasis, and it resolved without leading to acute liver failure or necessitating a liver transplant referral [44].

Another aspect of potential liver injury related to emtricitabine is its exacerbation of hepatitis B virus (HBV) infection upon discontinuation, particularly in long-term HBV trials. Posttreatment exacerbation happened in 23% of subjects in these trials [46].

A significant development of antibodies against the hepatitis HBe antigen failed to avert hepatic relapses in a trial, with one patient who exhibited substantial bridging fibrosis ultimately necessitating a liver transplant [45,46].

This suggests that subjects who experience advanced liver disease posses a risk for hepatic flares with decompensation if active treatment is stopped, such as in the case of modifying highly active antiretroviral treatment (HAART).

Despite that emtricitabine is effective against both HIV and HBV, this drug can cause resistance issues. Resistance to emtricitabine usually involves the same M204V/I mutation in the HBV polymerase gene as lamivudine, leading to cross-resistance with lamivudine [47].

Tenofovir

Tenofovir is a relatively new and well-tolerated nucleotide reverse transcriptase inhibitor that comes in two formulations: tenofovir disoproxilfumarate (TDF) and tenofovir alafenamide (TAF). These two formulations have different pharmacokinetics and consequently, different efficacies and side effects. Tenofovir is part of the management of HIV infection and hepatitis B virus infection [48].

The mechanisms through which tenofovir induces liver injury, particularly in the context of liver stiffness in HIV plus HBV co-infected individuals, are various. One study conducted a cross-sectional and prospective analysis of HIV/HBV co-infected adults in Ghana that were maintained under lamivudine-based antiretroviral therapy (ART) and later introduced tenofovir as part of their ART regimen. The introduction of tenofovir, a powerful inhibitor of HBV replication, was associated with significant virologic and liver fibrosis outcomes [49].

Prior to the introduction of tenofovir, a significant portion of patients on lamivudine-based ART had detectable HBV DNA, indicating ongoing HBV replication. Following the introduction of tenofovir, there was a significant decline in HBV DNA levels, suggesting that tenofovir effectively suppresses HBV replication [50]. TE values lowered substantially in patients who experienced high pre-tenofovir HBV DNA levels or higher baseline TE values associated with the presence of HBe antigen, suggesting that tenofovir may have a contribution in the stabilization or regression of liver stiffness in subjects with active HBV replication and existing liver fibrosis [37,49,50].

The research conducted by Stockdale et al. (2015) focused primarily on liver fibrosis scores and virologic outcomes, rather than addressing DILI or changes in ALT levels. Nevertheless, the British Liver Trust, but also other sources have noted that Tenofovir's risk of DILI is relatively low due to its favorable safety profile, which often makes it a preferred choice in HIV treatment [51].

Tenofovir is considered less hepatotoxic than other medications used for HIV therapy. However, it is crucial for healthcare providers to regularly monitor liver enzyme levels, especially in patients with preexisting liver conditions or those who associate other infections, like Hepatitis B or C [52].

A study concluded that TE values were individually connected with HBV DNA viral levels, AST serum levels, and platelet counts. This highlights the complex interplay between HBV replication, liver inflammation (indicated by AST levels), and liver fibrosis (as measured by TE) [44].

Studies suggest that tenofovir may have a protective effect against liver injury by reducing HBV replication and potentially stabilizing or improving liver fibrosis.

Non-nucleoside reverse transcriptase inhibitors

Efavirenz

Efavirenz is a NNRT highly effective in suppressing HIV-1 replication. Nevertheless, the success of efavirenz therapy depends heavily on patient adherence. Efavirenz binds to a non-catalytic site on the reverse transcription, the NNRTI pocket, inhibiting its activity. Efavirenz is primarily bound to human plasma proteins, especially albumin. The metabolism of efavirenz is catalyzed by the CYP3A4 enzyme, resulting in the formation of inactive hydroxylated metabolites [53].

Several mechanisms were identified which relate to Efavirenz induction of liver injury. In vitro studies on liver cells showed that Efavirenz induced an energetic stress by suppression of mitochondrial function through accumulation of lipids mediated by AMPK [1].

In one study Efavirenz caused DILI leading to acute liver failure (ALF) as observed in 4 patients over a 6-month period. A severe form of liver injury, called fulminant liver failure with encephalopathy, was reported in a patient which later resulted in the patient's death [54].

Liver biopsies taken from patients who developed liver injuries revealed an important infiltration with various inflammatory cells, especially with eosinophils. This suggests an

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immune-mediated hypersensitivity reaction that can cause immune cells to attack liver cells [55].

Lately, the administration of the HIV-1 specific non-nucleoside reverse transcriptase inhibitor, efavirenz, has been linked to severe hepatic injury. Severe hepatotoxicity happened in 8.0% of people receiving efavirenz, with 50% of these cases detected within the first 12 weeks of treatment. The risk was substantially more important in individuals with chronic viral hepatitis (69% of cases), but also in some cases with coexisting protease inhibitors (82% of cases) [56].

The likelihood of achieving important liver toxicity in the time of treatment with Efavirenz was found to be more important in subjects with history of positive Hepatitis C antibodies, those combining Efavirenz with a protease inhibitor, and in those with alcohol consumption more than 40 grams each 24h. Each of these conditions can amplify the hepatotoxic impact of Efavirenz, leading to liver damage [57].

The risk for achieving serious liver toxicity amid Efavirenz treatment are also associated with co-medication (antiretroviral schemes in combination with a protease inhibitor) and co-infections like Hepatitis C (HCV), leading to a higher risk of severe liver toxicity. Efavirenz can cause amplified damage in an already compromised liver due to chronic HCV infection [57].

In conclusion, Efavirenz may induce liver injury by direct hepatotoxicity, hypersensitivity reactions, and the exacerbation of preexisting liver diseases. Other factors like alcohol consumption and combining Efavirenz with a Protease inhibitor can also influence possibility for liver damage, suggesting the importance of careful monitoring and patient-specific considerations during Efavirenz treatment [57].

Etravirine

Etravirine (formerly TMC125), brand name Intelence, is a NNRTI that do not share cross resistance with other NNRTIs. Etravirine has demonstrated effectiveness against HIV strains with mutations that render first-generation NNRTIs, specifically efavirenz and nevirapine, ineffective.

Specifically, etravirine is effective against the mutation K103N, which reduces the effectiveness of efavirenz, and the mutation Y181C, which reduces the effectiveness of nevirapine. The effectiveness of etravirine is likely connected to its molecular flexibility as a diarylpyrimidine (DAPY) compound, which enables it to bind with reverse transcriptase in various forms, leading to a more stable interaction with the enzyme, even in the presence of mutations.[58].

Studies on the safety and efficacy of etravirine in HIV-1/Hepatitis B and/or C virus (HBV/HCV) co-infected subjects, suggest that etravirine, does not produce substantially rise in the risk of liver toxicity when correlated with placebo, despite the possibility to have mild to advanced liver stiffness [59,60].

In a group involving 211 subjects starting etravirine, including a significant proportion with HCV co-infection, the incidence of hepatotoxicity was notably low, with only one co-infected patient developing grade 3-4 liver toxicity. This suggests that etravirine is generally safe for use in HIV/HCV co-infected people, even those that already have advanced liver stiffness, across various antiretroviral regimens [59].

Similarly, a combinate analysis from the Phase III DUET trials, which included a subset of subjects co-infected with HIV-1 and HBV/HCV, showed that etravirine has a security profile similar to that of placebo over 96 weeks. The proportion of hepatic adverse events (AEs) was much higher among co-infected patients rather patients with no other infection associated in both etravirine and placebo groups, which is consistent with the underlying hepatitis.

However, there was not found notable difference in the incidence of hepatic AEs among etravirine and placebo groups among co-infected patients, indicating that etravirine does not exacerbate liver toxicity in this population[60].

Nevirapine

Nevirapine (marketed under the trade names Viramune by Boehringer Ingelheim Ltd) is the first NNRT to be approved for use. Clinical studies demonstrated that therapies including nevirapine can conduct to sustained virological, immunological responses in roughly 50% of antiretroviral-naive patients.

Additionally, nevirapine can be effectively employed as a component of salvage therapies and as part of a strategy to simplify protease inhibitor-containing regimens.

In general, it was shown its effectiveness in the cases with depressed CD4 cell count [61].

It was shown that nevirapine induces liver injury through fatty acid biosynthesis up-regulation in onset and rate-limiting genes of fatty acid biosynthesis. High levels of these fatty acids can lead to a variety of intracellular imbalances, potentially disrupting normal liver cell functions.

Another mechanism is β-oxidation through up-regulation of acyl-coA synthetase long-chain

enzyme family (ACSL), which has a vital role in lipid biosynthesis and fatty acid deterioration. Elevated fatty acid β-oxidation may lead to mitochondrial dysfunction, resulting in a phenomenon called 'uncoupling,' which could ultimately result in cell death [62,63].

Nevirapine differentially regulate genes of the respiratory ETC from mitochondria causing disruptions and potentially contributing to liver damage. Aside from mitochondrial toxicity as other reverse transcriptase inhibitors, nevirapine induces changes in the antigen presentation pathway. Pathway analysis following exposure to Nevirapine predicted an elevation in the expression of both MHC class I and II.

Alterations of these critical components that are part of the immune system can conduct to immune responses that may contribute to liver damage [62,63].

Nevirapine treatment have been linked with a risk of important hepatotoxicity, occurring up to 10% of cases, with risk factors including hepatitis co-infection, progressive liver disease, but also increased liver enzymes serum levels in the beginning of treatment [64,65].

Hepatotoxicity, defined as a significant increase in liver enzymes, was observed in 12.5% of patients on nevirapine, with risk factors including previous antiretroviral exposure, hepatitis C co-infection, and higher baseline liver enzyme levels [65].

Hepatotoxicity associated with nevirapine was more often encountered in subjects who associate the infection with hepatitis C or B, but also those coadministered protease inhibitors, with important hepatotoxicity occurring meanwhile therapy [66].

These mechanisms can function individually or synergistically and collectively contribute to the potential liver toxicity seen with Nevirapine administration. It's critical to monitor liver function for anyone undergoing long-term treatment with this medication.

Rilpivirine

Rilpivirine, also known as Edurant, is a second-generation non-nucleoside reverse transcriptase inhibitor that possess a much more important potency and less adverse effects compared to older NRTI's. When used in combination with drugs that induce CYP3A4 liver enzymes, such as carbamazepine and phenytoin, it can happen a decline in effectiveness, but also the probability of resistance due to decreasing plasma concentrations [67].

The mechanisms through which rilpivirine might induce liver injury appear to be related to its pharmacokinetics, potential for drug interactions, and effects on hepatic enzymes. Rilpivirine is metabolized in the liver and is a substrate of hepatic cytochrome P450 3A4. The substances that can block this isoenzyme can affect the serum levels of rilpivirine, potentially leading to altered hepatic function or injury in susceptible individuals [68].

For instance, rifamycins, anticonvulsants, can cause a depletion of rilpivirine levels, while macrolides, azoles, and protease inhibitors may increase its levels.

The absorption of rilpivirine requires an acidic gastric environment. The medication that can cause raise of the gastric pH, should not be used with rilpivirine, indicating a delicate balance in its absorption that might, in certain conditions, affect its metabolism and potentially its hepatic safety profile [68].

Clinical data suggest that rilpivirine is connected with a good security profile, showing a lower incidence of central nervous system symptoms compared to efavirenz and a generally low rate of hepatotoxicity. This implies that while rilpivirine can induce liver injury, its likelihood appears to be lower compared to some other antiretrovirals, potentially due to its metabolic profile and interactions [68-70].

Rilpivirine treatment has been connected with better fats parameters despite efavirenz or protease inhibitors, indicating a potentially beneficial effect on metabolic processes that could indirectly suggest a lower hepatotoxicity risk [71].

Doravirine

Doravirine is a recently approved single dose per day administered NNRTI which has been indicated for the therapy of HIV-1 in patients who are therapy-naive or in those patients with undetectable viral loads. In clinical trials, doravirine has demonstrated that it's efficacy and better pharmacokinetics and/or safety profile when compared to efavirenz and darunavir.

Additionally, doravirine has been shown to be potent in suppressing viral multiplication, also in patients who have transmitted NNRTI mutations, like K103N and G190A [72].

Doravirine has been evaluated in healthy subjects and HIV-infected individuals for its pharmacokinetics, safety, and efficacy. The main method by which Doravirine is metabolized is by CYP3A4 and also a small percentage is eliminated via renal excretion. Its metabolism pathway suggests that doravirine undergoes

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oxidative metabolism in the liver, which could potentially contribute to liver injury under certain conditions or in susceptible individuals [73,74].

Also, there is possibility for drug-drug synergy that can interfere with its plasma levels with the possibility to affect its safety profile, including its impact on the liver. Doravirine is less likely to cause significant drug interactions, as it does not inhibit or induce drug-metabolizing enzymes to a significant extent.

In clinical studies, doravirine has shown a good safety profile [75].

The majority of the adverse events reported were of a mild to moderate intensity and transient nature. There was no apparent relationship between the frequency or intensity of these events and the doravirine dose. Notably, no significant central nervous system events other than headache were reported, and the incidence of rash was low. These findings indicate a relatively low potential for hepatotoxicity associated with doravirine [75,76].

In one study involving treatment-naive HIV-infected individuals, a subject had experienced a serious adverse event manifested with elevated liver enzymes [76].

This event overlapped with the diagnosis of hepatitis C infection and was thought as probably not connected to doravirine. This indicates that while doravirine may be associated with elevated liver enzymes, such events are rare and may not be directly attributable to the drug.

Given doravirine's metabolism via CYP3A4, there is potential for drug-drug interactions that could affect its plasma levels and possibly its safety profile, including its impact on the liver. Nevertheless, doravirine has a low likelihood of causing notable drug interactions, since it neither inhibits nor significantly induces drug-metabolizing enzymes.

Limitations

The intricacy of HIV-related liver fibrosis arises from numerous factors that contribute to its development and progression, making it difficult to fully comprehend. There are several obstacles that impede our comprehension of the mechanisms and effective management of this condition, such as the intricacy of patient populations, the interplay between HIV and ART co-infections at the molecular and cellular levels that are not entirely understood, unclear pathways for the precise mechanism by which HIV causes liver fibrosis development, and diagnostic challenges because current non-invasive tests (e.g., transient elastography and serum biomarkers) have limitations in sensitivity and specificity for detecting liver fibrosis in HIV-infected people; however, liver biopsies are invasive and carry risks, and there is limited data due to the scarcity of long-term studies on the development of liver fibrosis in PLWH.

To address these limitations, we suggest conducting extensive research, such as setting up large and diverse cohorts to study the progression of liver damage in PLWH who are on various ART regimens and co-infections. Additionally, we propose molecular studies, including single-cell RNA sequencing and proteomics, to unravel the intricate interactions between HIV, the immune system, and liver cell biology.

Furthermore, we recommend establishing national and international registries for longitudinal data collection to gather long-term data on HIV-related liver fibrosis. Lastly, we suggest the development of new serum biomarkers with higher sensitivity and specificity for liver fibrosis in HIV patients.

Conclusions

This review delineates the multifaceted challenges and considerations connected in the treatment of liver fibrosis in PLWH, particularly those receiving reverse-transcriptase inhibitors, as this class was the first introduced for the treatment of HIV infection and seems to carry the greatest risk for liver fibrosis development.

The review highlights the intricate interplay between HIV infection, antiretroviral therapy (ART), and liver health, shedding light on the possibility of hepatotoxic effects of nucleoside and non-nucleoside reverse-transcriptase inhibitors.

Individuals with HBV or HCV co-infection are more likely to have liver damage before starting antiretroviral therapy (ART), which increases their susceptibility to hepatotoxicity from ART.

The mechanisms of liver injury during ART include mitochondrial dysfunction, oxidative stress, and immune-mediated hypersensitivity reactions contribute to liver injury, highlighting the liver's vulnerability due to its bioenergetic demands. The clinical manifestations of ART produced liver toxicity range from moderate liver enzymes elevation to severe hepatitis and liver failure. It was also noted a paradoxical worsening of liver health in some patients due to IRIS following the beginning of ART.

The relationship between ART, particularly reverse-transcriptase inhibitors, and liver health is complex in HIV patients, calling for a nuanced approach to HIV treatment, balancing the pro's of

viral suppression with the potential danger of liver toxicity.

Future research can include long-term studies on liver health in HIV patients, development of less hepatotoxic drugs, or novel therapeutic strategies for managing drug-induced liver injury.

In clinical practice healthcare providers should prioritize personalized treatment strategies, regular monitoring of liver function, and the exploration of less hepatotoxic ART regimens to mitigate the risk of liver fibrosis in this vulnerable population.

Future Research

Recent work conducted by researchers at the University of Michigan has unveiled the potential of employing human liver organoids for drug toxicity testing. These three-dimensional structures, derived from stem cells, exhibit a superior capacity for predicting liver toxicity when compared to conventional animal testing. This innovation holds the promise of enhancing the safety of new medications [77].

We suggest extensive research involving the establishment of substantial and diverse cohorts to follow the progression of liver fibrosis in individuals living with HIV under various ART regimens and co-infections.

Additionally, we propose molecular studies, such as single-cell RNA sequencing and proteomics, to explore the complicated interplay between HIV, the immune system, and liver cell biology.

Longitudinal data collection is also crucial, which can be achieved by setting up national and international registries to gather long-term data on HIV-related liver fibrosis. Finally, we recommend the development of innovative serum biomarkers with improved sensitivity and specificity for liver fibrosis in HIV patients.

Another suggestion is to promote collaboration between hepatologists, infectious disease specialists, and immunologists to provide comprehensive care and gather multifaceted data.

It is also necessary to develop and implement standardized protocols for diagnosing and monitoring liver fibrosis in HIV-infected populations globally.

In addition, addressing socioeconomic barriers through strengthening global health initiatives to improve access to diagnostics, treatment, and research is crucial.

Lastly, investing in local healthcare infrastructure and training to enhance the capability to diagnose and manage liver fibrosis in PLWH is essential.

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Conflicts of Interest

The authors declare no conflicts of interest.

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