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Putting the Spotlight on Anti-Retroviral Therapy (ART) Associated Drug Induced Liver Injury (DILI), The dread of Patients Living with HIV- AIDS (PLWHA)

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ABSTRACT: This narrative review explores antiretroviral therapy (ART) -associated drug-induced liver injury (DILI), a significant clinical concern in managing patients with HIV/AIDS. As ART improves life expectancy for people living with HIV, the risk of drug-related hepatotoxicity has become more prominent, often complicating therapeutic strategies. The review examines the prevalence, risk factors, and underlying mechanisms of ART-DILI, providing a comprehensive analysis of clinical manifestations and laboratory indicators that aid in diagnosis and differentiation from other liver pathologies. Current diagnostic tools, including liver function tests, imaging, and, where applicable, liver biopsies, are discussed alongside the application of causality assessment tools like the Roussel Uclaf Causality Assessment Method (RUCAM). Additionally, we highlight genetic and immunological markers that may predispose patients to hepatotoxicity, addressing the importance of HLA-B*5701 testing for abacavir hypersensitivity as a case example. The review also explores the role of ART regimen modification and pharmacovigilance in managing and mitigating DILI risk, emphasizing the need for regular monitoring and individualized therapy. By providing a broad overview of ART-DILI and identifying knowledge gaps, this review underscores the need for further research to optimize ART management and improve liver safety outcomes in people living with HIV.

KEYWORDS: ART, drug-induced liver injury, HIV/AIDS, hepatotoxicity, RUCAM, therapy.

1.0 INTRODUCTION

Liver is a vital organ in the body, capable of its initial site of contact for orally ingested foreign substances known as xenobiotics. The xenobiotics include alcohol and other substances which are highly susceptible to chemical-induced injury during their metabolisms [1,2]. Drug-induced liver injury (DILI) is an injury to the liver that is caused by medications or other toxic substances in the public health [3-5]. It is the commonest cause of acute liver failure (ALF) in the United States and one of the major causes of chronic liver disease (CLD). It is generally classified as intrinsic (or direct) and idiosyncratic; with the indirect injury now becoming a third type [6-8].

DILI is intrinsic when the drugs or the metabolites concerned have intrinsic toxicity to the liver, biliary epithelial cells, and the liver vasculature. This is predictable, dose-dependent and cause liver injury when given in high doses while idiosyncratic type is usually caused by drugs with little or no intrinsic toxicity to the liver and occurs when there is an unusual reaction of drugs in susceptible individuals [9]. According to Gu and Manautou (2013) [10]

normal biotransformation of nutrients and xenobiotics of liver can result in generation of reactive oxygen species (ROS), which can be cleared off the system by endogenous cytoprotective mechanisms like antioxidant enzymes, Phase II conjugation, vitamin C and efflux

transporters. Moreover, in some conditions, production of ROS is boosted, and the activity of antioxidants is reduced resulting in oxidative stress [2]. There are about 1000 drugs including antiretroviral therapy (ART) capable of causing DILI and it is the most frequent reason for withdrawal of approved medications from the market, hence DILI accounts for more than 50% of the cases of acute liver failure [11-12], with paracetamol being the principal offending agent [11]. This scoping review explores the role of ART in DILI, which has generated a significant clinical concern in the management of patients with HIV/AIDS. As ART improves life expectancy for people living with HIV, the risk of drug-related hepatotoxicity has become more prominent, often complicating therapeutic strategies.

1.1 Epidemiology and Risk Factors for ART induced Liver Injury

The epidemiology of ART-induced liver injury reflects the widespread use of antiretroviral therapy (ART) in managing HIV/AIDS globally, with varying incidences reported depending on geographic region, population characteristics, ART regimen, and individual patient factors [13-14]. The incidence of liver injury among patients on ART ranges from 2% to 18%, with the risk highest within the first six months of initiating therapy [15-16].

However, the prevalence and severity of liver injury can vary widely, with rates often higher in low- and middle-income countries where HIV co- infections with hepatitis B and C are more common and access to routine liver function monitoring may be limited [17-18]. ART-induced liver injury is a significant cause of morbidity and can lead to treatment interruptions or regimen changes, impacting treatment adherence and effectiveness [19-20].

One major risk factor for ART-induced liver injury is the type of antiretroviral drug. Certain drug classes, like non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs), are more frequently associated with hepatotoxicity than others [21-23]. For example, nevirapine, an NNRTI, is known to cause idiosyncratic hypersensitivity reactions leading to severe liver injury, particularly in women and individuals with higher CD4 counts at therapy initiation [8, 21]. Similarly, PIs like ritonavir and lopinavir can cause hepatotoxicity, partly due to their interaction with liver enzymes, particularly cytochrome P450, which increases the risk of drug-drug interactions and potential toxicity [24-25].

Patient-related factors also play a significant role in determining the risk of liver injury with ART [26-27]. Pre-existing liver disease, particularly chronic viral hepatitis (hepatitis B or C), is one of the most significant risk factors [26-30]. Patients with hepatitis B or C co-infection are more susceptible to ART-induced liver injury, and the co-existence of these infections not only increases baseline liver vulnerability but also complicates the management of ART, as some drugs active against HIV may also impact viral hepatitis, creating a complex interplay of viral suppression and liver toxicity [31-32]. Furthermore, alcohol use, even at moderate levels, can exacerbate ART- related hepatotoxicity, as both alcohol and ART metabolites increase oxidative stress within hepatocytes, raising the risk of liver injury [33]. Patients with higher body mass index (BMI) are also at elevated risk, as obesity is associated with non-alcoholic fatty liver disease (NAFLD), which can compound the hepatic impact of ART, leading to more severe outcomes like steatohepatitis or cirrhosis [34-35].

Genetic predispositions, though less frequently discussed, contribute to ART-induced liver injury susceptibility, with polymorphisms in genes encoding for drug-metabolizing enzymes and transporters, such as CYP450 isoforms and ATP-binding cassette (ABC) transporters, affecting individual drug metabolism rates and potential toxicity [36-37]. Studies suggest that genetic polymorphisms may explain variations in hepatotoxicity risk among different populations, with certain populations showing a higher propensity for ART-induced liver injury due to genetic variants that influence drug clearance [38-40].

Immune-related factors also influence the epidemiology of ART-induced liver injury. Immune reconstitution inflammatory syndrome (IRIS) [41-42], a phenomenon where immune recovery after ART initiation leads to a heightened inflammatory response, can result in liver injury, particularly in patients with high baseline viral loads or low CD4 counts [43]. IRIS- associated liver injury often occurs in patients with pre-existing opportunistic infections or co-infections, where rapid immune recovery results in an inflammatory response that can exacerbate liver damage [44- 49].

Other risk factors include older age and female gender, as these groups have been found to have a higher risk of ART-related liver injury, although the exact mechanisms behind these associations remain incompletely understood [50-51]. Older adults may have decreased liver function and slower drug metabolism, increasing the potential for accumulation and hepatotoxicity [52-54], while gender differences may be related to hormone levels, body composition, or immune responses. Understanding these epidemiological patterns and risk factors is crucial for identifying patients at risk, optimizing ART regimens, and implementing preventive measures like regular liver function monitoring to reduce the burden of ART-induced liver injury.

1.2 Pathogenesis and Mechanisms of ART induced liver injury

The pathogenesis of ART-induced liver injury involves a complex interplay of direct drug toxicity, immune-mediated mechanisms, mitochondrial dysfunction, hypersensitivity reactions, and metabolic alterations [55-60]. These mechanisms vary depending on the class of antiretroviral drugs and individual patient factors, including genetic predispositions and the presence of co-infections such as hepatitis B or C [61]. Understanding these mechanisms is essential for managing and preventing liver injury in patients on ART.

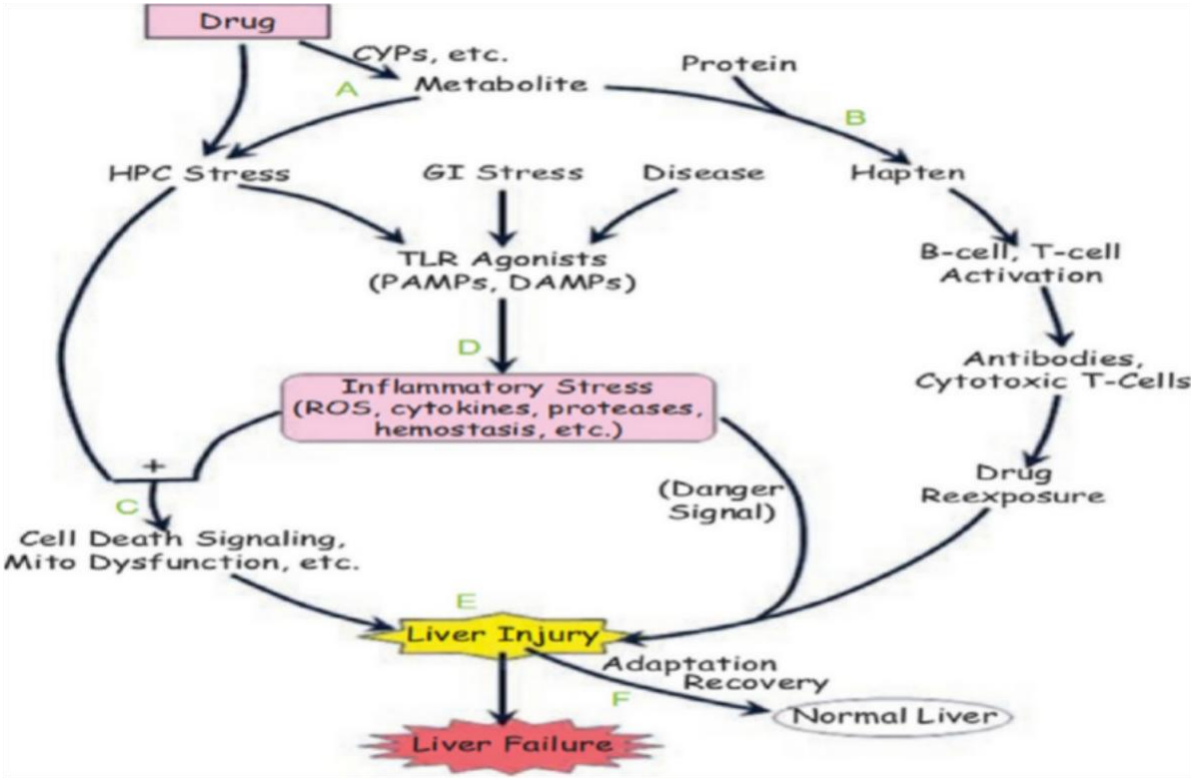

Figure 1: Diagram showing the illustration of Drug-induced liver injury culled from Roy *etal.*, (2024) [4]):

1.2.1. Direct Hepatotoxicity

Direct hepatotoxicity is a primary mechanism of liver damage caused by antiretroviral therapy (ART), particularly among drugs that heavily rely on hepatic metabolism. Key drug classes, such as non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs), are known to produce reactive metabolites during their processing in the liver (Figure 1) [4, 15-20]. The cytochrome P450 (CYP) enzyme system plays a central role in the biotransformation of these drugs [62]. However, this metabolic process can generate byproducts that are highly reactive and capable of causing cellular injury within the liver [62].

Once formed, these reactive metabolites initiate oxidative stress by generating free radicals and other reactive oxygen species (ROS), which overwhelm the liver's antioxidant defence systems [55]. When oxidative stress persists, it leads to lipid peroxidation, in which free radicals attack lipid components of cell membranes, resulting in structural damage to hepatocytes. Moreover, oxidative stress and the accumulation of reactive metabolites can directly harm DNA, proteins, and cellular organelles, compromising cellular integrity and function [55].

Nevirapine is a well-documented example of an ART drug that can cause direct hepatotoxicity through the production of reactive intermediates (Table 1) [23]. These intermediates can form covalent bonds with cellular proteins, disrupting normal protein function and inducing immune responses against modified hepatocytes. In certain individuals with specific genetic polymorphisms, such as those involving the CYP2B6 gene, nevirapine metabolism becomes altered, leading to an increased production of reactive metabolites and a heightened risk of liver injury. Thisngenetic predisposition can exacerbate hepatocyte apoptosis,or programmed cell death, which further contributes to liver damage [23, 63- 70].

In addition to nevirapine, other ART drugs like efavirenz and ritonavir also pose hepatotoxic risks due to their metabolic byproducts [71-85]. Efavirenz, for instance, undergoes extensive hepatic metabolism, with its metabolites having potential toxic effects on hepatocytes, especially when drug concentrations are elevated [71]. Ritonavir, often used as a pharmacokinetic booster in ART regimens, can also influence liver health due to its potent CYP enzyme inhibitory effects. When used in combination with other drugs metabolized through the CYP system, ritonavir can cause increased drug levels and amplify hepatotoxic effects, further stressing the liver [71-85].

Direct hepatotoxicity induced by ART drugs is, therefore, a multifactorial process. It involves metabolic byproduct formation, oxidative damage, genetic susceptibility, and immune responses against damaged liver cells. Understanding these complex interactions is vital in developing safer ART regimens and monitoring strategies for at-risk individuals, allowing for timely interventions to prevent severe liver injury [71-87].

Table 1: Hepatotoxicity in Antiretroviral Therapy: A Comparative Analysis of NNRTIs and PIs [63–87]

Class	Drug	Mode of Action	Pharmacokinetics	Pharmacodynamics	Hepatotoxicity Potential
NNRTIs	Efavirenz	Inhibits HIV-1 reverse transcriptase by binding to its allosteric site, blocking DNA polymerization.	High oral bioavailability; metabolized by CYP2B6 and CYP3A4; long half-life (~40–55 hours).	Non-competitive inhibition of reverse transcriptase; concentration-dependent viral suppression.	High risk, especially with CYP2B6 polymorphism; direct mitochondrial toxicity and oxidative stress contribute to damage.
	Nevirapine	Binds to HIV-1 reverse transcriptase, disrupting the enzyme's catalytic activity.	Rapid absorption; metabolized by CYP3A4 and CYP2B6; half-life ~25–30 hours.	Strong inducer of CYP450 enzymes; potent suppression of viral replication.	Moderate to high risk, especially in individuals with hepatitis co-infection; can cause severe idiosyncratic hepatotoxicity.
	Etravirine	Binds to reverse transcriptase and induces conformational changes that inhibit enzyme function.	Moderate oral bioavailability; extensively metabolized by CYP3A4, CYP2C9, and CYP2C19; half-life ~40 hours.	High genetic barrier to resistance; flexible binding to mutated enzymes.	Low to moderate risk; hepatotoxicity occurs rarely and is dose-dependent.
	Rilpivirine	Non-competitive inhibition of reverse transcriptase by allosteric binding.	High oral bioavailability with food; metabolized by CYP3A4; half-life ~50 hours.	Maintains activity against NNRTI-resistant strains; concentration-dependent efficacy.	Low to moderate risk; liver enzyme elevations reported, especially with baseline hepatic dysfunction.
PIs	Ritonavir	Inhibits HIV protease, preventing cleavage of viral polyproteins, essential for virus maturation.	High oral bioavailability; potent inhibitor of CYP3A4; half-life ~3–5 hours.	Boosts plasma levels of other PIs by CYP3A4 inhibition; dose-dependent effects.	High risk; severe hepatotoxicity due to mitochondrial damage, oxidative stress, and induction of liver enzymes.
	Lopinavir	Same as Ritonavir.	Given with Ritonavir for boosting; metabolized by CYP3A4; half-life ~5–6 hours.	Effective viral suppression; requires boosting to achieve therapeutic concentrations.	Moderate to high risk; increased risk with hepatitis co-infection; can cause elevations in liver enzymes.
	Atazanavir	Inhibits HIV protease and prevents the formation of mature infectious virions.	High oral bioavailability; metabolized by CYP3A4 and UGT1A1; half-life ~6–7 hours.	Less lipid effects compared to other PIs; concentration-dependent suppression of viral replication.	Moderate risk; can cause hyperbilirubinemia and rare hepatotoxicity due to UGT1A1 inhibition.
	Darunavir	Binds to HIV protease and inhibits its cleavage activity.	High oral bioavailability with food; metabolized by CYP3A4; half-life ~15 hours.	Potent against PI-resistant strains; concentration-dependent effects.	Low to moderate risk; rare hepatotoxicity, primarily in patients with underlying liver disease or hepatitis co-infection.
	Saquinavir	Same as Ritonavir.	Poor oral bioavailability; metabolized by CYP3A4; half-life ~12 hours.	Requires boosting with Ritonavir; effective against wild-type and resistant strains.	Moderate risk; rare idiosyncratic hepatotoxicity, mostly with pre-existing liver disease.
	Indinavir	Same as Ritonavir.	Moderate oral bioavailability; metabolized by CYP3A4; half-life ~1.8 hours.	Requires multiple daily doses for viral suppression; competitive inhibition of protease.	High risk; associated with severe hepatotoxicity, including hepatic steatosis and fibrosis.

1.2.2. Mitochondrial Dysfunction

Mitochondrial toxicity is a significant adverse effect associated with the use of nucleoside reverse transcriptase inhibitors (NRTIs), such as zidovudine (AZT), stavudine (d4T), and didanosine (ddI) [88-90]. These antiretroviral medications are critical in the treatment of HIV but have been shown to interfere with mitochondrial function, primarily by inhibiting mitochondrial DNA polymerase γ (pol γ) [91]. This enzyme is essential for the replication and repair of mitochondrial DNA, which is crucial for maintaining the integrity and functionality of mitochondria [89].

When pol γ is inhibited, the synthesis of mitochondrial DNA is disrupted, leading to impaired mitochondrial replication and function [90]. This dysfunction affects various cellular processes, particularly oxidative phosphorylation, which is the primary pathway through which ATP (adenosine triphosphate), the energy currency of the cell, is produced. A reduction in ATP synthesis not only compromises energy availability for hepatocytes but also results in an imbalance in cellular metabolism [88]. As ATP levels dwindle, the cell may struggle to maintain essential metabolic processes, ultimately leading to cellular stress [91].

In response to the impaired oxidative phosphorylation, the body can experience an accumulation of reactive oxygen species (ROS) [89-91]. These highly reactive molecules can cause further damage to cellular components, including lipids, proteins, and DNA. The oxidative stress induced by ROS can initiate a cascade of pathological processes within the liver, contributing to various liver disorders [91].One common manifestation of mitochondrial toxicity is hepatic steatosis, characterized by fat accumulation within liver cells [92]. The disruption of normal fatty acid oxidation pathways due to impaired mitochondrial function can lead to the excessive buildup of triglycerides. Initially, this condition presents as microvesicular steatosis, where small lipid droplets accumulate within hepatocytes [93]. Over time, if the mitochondrial damage persists, this can progress to macrovesicular steatosis, where larger lipid droplets replace normal hepatic architecture [94].

The accumulation of fat can lead to hepatomegaly, or enlargement of the liver, which is often asymptomatic in its early stages [95].

Severe mitochondrial toxicity may culminate in more serious conditions such as lactic acidosis, a life-threatening metabolic disturbance characterized by elevated lactate levels in the blood due to anaerobic metabolism [95]. Lactic acidosis occurs when the liver's ability to clear lactate is compromised, further stressing the already impaired hepatic function [94]. Additionally, ongoing mitochondrial dysfunction can trigger hepatocyte apoptosis, or programmed cell death, as the cells become overwhelmed by the toxic effects of accumulated ROS and energy depletion [95].

If mitochondrial toxicity is not identified and managed appropriately, it can lead to progressive liver damage and potentially culminate in liver failure [96]. This highlights the importance of careful monitoring of liver function in patients receiving NRTIs, as early detection and intervention can help mitigate the risk of severe hepatic complications [97-98]. Strategies for managing mitochondrial toxicity may include switching to alternative ART regimens with a lower propensity for mitochondrial damage, optimizing supportive care, and addressing any modifiable risk factors, such as co-infections or alcohol use, that could exacerbate liver dysfunction [100-104]. Ultimately, understanding the mechanisms and consequences of mitochondrial toxicity is crucial for improving patient outcomes in those undergoing antiretroviral therapy [98-99].

1.2.3. Immune-Mediated Mechanisms and Hypersensitivity Reactions

Immune-mediated hepatotoxicity is another mechanism observed with certain ART drugs, particularly with NNRTIs like nevirapine and abacavir, an NRTI [105-106]. These drugs can lead to hypersensitivity reactions involving the activation of CD8+ T-cells, which recognize drug-protein adducts formed by the interaction of drug metabolites with hepatocyte proteins (Figure 2) [107-108]. This response can result in an autoimmune-like reaction, with cytotoxic T-cells attacking hepatocytes [108]. In patients with genetic susceptibilities, such as the HLA-B*5701 allele in individuals receiving abacavir, these reactions can be severe, manifesting as drug rash with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome, or acute liver failure [109].

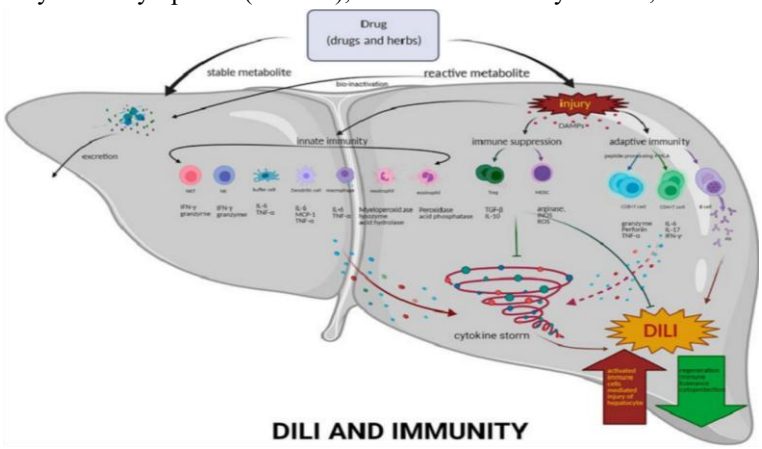

Figure2: A figure showing the relationship between the the mechanism of action of drug induced liver injury (DILI) and the immune system. Culled from Liu et al. (2021) [109]

1.2.4. Immune Reconstitution Inflammatory Syndrome (IRIS)

Immune-mediated hepatotoxicity represents a critical pathway through which certain antiretroviral therapy (ART) drugs, particularly non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as nevirapine and the nucleoside reverse transcriptase inhibitor (NRTI) abacavir, can induce liver injury [110]. This mechanism is primarily characterized by hypersensitivity reactions that occur due to the activation of CD8+ T-cells. These immune cells are pivotal in the adaptive immune response and play a significant role in recognizing and responding to foreign substances, including drug metabolites [110].

When these ART drugs are metabolized, they can form reactive metabolites that covalently bind to hepatic proteins, creating drug-protein adducts [111]. These adducts are perceived as foreign by the immune system, prompting an immune response. The activation of CD8+ T-cells occurs as they recognize these modified proteins, leading to an autoimmune-like reaction in which the immune system mistakenly targets the body's own hepatocytes. This immune-mediated attack can manifest as hepatocyte apoptosis and inflammation, further contributing to liver injury [112-116].

The severity of immune-mediated hepatotoxicity can vary significantly among individuals, particularly in those with specific genetic predispositions [117]. A well-known example is the association between the presence of the HLA-B*5701 allele and the hypersensitivity reaction to abacavir [118-120]. Individuals carrying this allele are at a significantly higher risk for developing severe adverse reactions, including hypersensitivity syndrome, which is characterized by a constellation of symptoms that may include fever, rash, gastrointestinal upset, and hematological abnormalities such as eosinophilia [121]. When the syndrome escalates, it can progress to more severe conditions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) or Stevens-Johnson Syndrome (SJS). Both DRESS and SJS are severe, potentially life-threatening conditions characterized by widespread skin eruptions, systemic inflammation, and multi-organ involvement, including acute liver failure [122-124].

In the context of nevirapine, immune-mediated hepatotoxicity is particularly concerning, as it has been associated with a risk of liver injury that may be influenced by the timing of drug initiation and prior exposure to ART [40]. Patients who have previously been exposed to nevirapine may experience a more severe reaction upon re-exposure [68]. The risk is especially pronounced in individuals with pre-existing liver conditions or co-infections, such as hepatitis B or C, which can exacerbate the hepatotoxic effects [68].

The immune-mediated response can also be exacerbated by concurrent use of other drugs that may influence hepatic metabolism or immune function, complicate the clinical picture and make it challenging to determine the primary offending agent [100-105]. Overall, immune- mediated hepatotoxicity underscores the necessity for careful patient selection, genetic screening, and ongoing monitoring in individuals receiving ART, particularly those on NNRTIs and abacavir [79-81]. Recognizing and addressing these hypersensitivity reactions promptly is crucial to preventing severe outcomes, including liver failure, and ensuring optimal management of HIV infection [69-70]. Healthcare providers should be vigilant in assessing for signs of immune-mediated liver injury, educating patients about potential symptoms, and implementing strategies to mitigate risks, such as selecting alternative ART regimens in genetically predisposed individuals [71]. Understanding the intricate relationship between immune responses and hepatotoxicity is essential for improving treatment outcomes and enhancing patient safety in the management of HIV.

1.2.5. Genetic and Idiosyncratic Factors

Genetic predispositions play a pivotal role in the susceptibility to antiretroviral therapy (ART) -induced liver injury, highlighting the complexity of individual responses to these medications [36]. Variations in genes involved in drug metabolism, transport, and immune regulation can significantly influence how a patient metabolizes antiretroviral drugs and how their immune system responds to these therapies [125].

Polymorphisms in genes encoding drug-metabolizing enzymes are particularly influential. The cytochrome P450 (CYP) enzyme system, a crucial component of hepatic drug metabolism, is comprised of several isoenzymes, including CYP2B6, CYP2D6, and CYP3A4 [126]. Variants in these CYP genes can lead to significant inter-individual differences in drug clearance. For example, polymorphisms in the CYP2B6 gene can result in slower metabolism of efavirenz, an NNRTI [127]. In individuals with these genetic variants, the reduced metabolic clearance can lead to higher plasma levels of efavirenz, increasing the risk of accumulation of toxic metabolites. This accumulation may subsequently precipitate liver injury through direct hepatotoxicity or immune-mediated mechanisms [128-130].

In addition to CYP enzymes, genetic variations in drug transporters, such as those belonging to the ATP-binding cassette (ABC) and solute carrier (SLC) families, can also affect drug bioavailability and hepatic clearance [131]. These transporters play critical roles in the hepatic uptake and excretion of drugs. Variations in transporter genes can alter the pharmacokinetics of ART drugs, potentially leading to increased systemic exposure and a heightened risk of hepatotoxicity [132].

Furthermore, genetic predispositions can extend to immune-related molecules that mediate hypersensitivity reactions [133]. For instance, individuals with certain human leukocyte antigen (HLA) alleles are at a heightened risk of developing severe hypersensitivity reactions to specific ART drugs [133]. The most notable example is the association of the HLA- B*5701 allele with hypersensitivity to abacavir, which can manifest as a severe immune-mediated reaction, resulting in liver injury among other systemic effects [134]. These immune-mediated idiosyncratic reactions are unpredictable and not necessarily related to the drug dosage,

emphasizing the importance of genetic screening in selecting appropriate ART regimens [135-136].

Mitochondrial toxicity associated with NRTIs, such as zidovudine and stavudine, is another area where genetic predisposition is critical [137]. Variants in mitochondrial DNA polymerase γ (pol γ) can impair the enzyme's function, which is essential for mitochondrial DNA replication and repair. Patients with such genetic variations may be more susceptible to the mitochondrial toxic effects of NRTIs, leading to complications such as lactic acidosis, hepatic steatosis, and hepatocyte apoptosis. Additionally, idiosyncratic drug reactions often occur independently of the dose administered and may be influenced by a combination of genetic, environmental, and host factors. These unpredictable responses can manifest as immune-mediated reactions, as observed with nevirapine. The activation of CD8+ T-cells in response to drug-protein adducts formed by nevirapine metabolism can lead to hepatic inflammation and damage, highlighting how genetic factors can contribute to the variability in clinical outcomes among patients receiving ART.

The interplay of genetic predispositions underscores the necessity for personalized medicine in the treatment of HIV. Genetic testing for polymorphisms related to drug metabolism and immune response can aid clinicians in identifying patients at risk for ART-induced liver injury, thereby allowing for more informed decisions regarding treatment selection and monitoring. This tailored approach can enhance the safety and efficacy of ART regimens, ultimately improving patient outcomes and minimizing the risk of severe hepatic complications. Understanding the genetic factors that contribute to ART-induced liver injury is crucial in developing strategies for risk assessment and management, paving the way for advancements in individualized HIV care.

1.2.6. Steatosis and Lipid Metabolism Disorders

Some antiretroviral therapy (ART) drugs, particularly protease inhibitors (PIs), have been shown to significantly interfere with lipid metabolism, leading to hepatic steatosis, commonly known as fatty liver [60]. The impact of PIs on lipid homeostasis is multifaceted and involves complex biochemical pathways. PIs, including drugs such as ritonavir, indinavir, and lopinavir, have been observed to inhibit critical lipid-regulating enzymes, particularly sterol regulatory element-binding proteins (SREBPs) [138]. SREBPs play an essential role in the regulation of lipid synthesis, including cholesterol and fatty acid metabolism, by promoting the transcription of genes involved in these processes [139].

The inhibition of SREBPs by PIs disrupts normal lipid metabolism, resulting in altered lipid homeostasis [140]. Specifically, this disruption leads to an abnormal accumulation of triglycerides within hepatocytes, a hallmark of steatosis [141]. The liver, being a central organ for lipid metabolism, is particularly vulnerable to such disturbances. When triglyceride synthesis outpaces fatty acid oxidation and lipoprotein export, excess fat accumulates within liver cells, manifesting as hepatic steatosis [142]. Over time, this condition can evolve into non-alcoholic steatohepatitis (NASH), where fat accumulation is associated with inflammatory responses and hepatocyte injury [143].

NASH is characterized by a triad of findings: steatosis, inflammation, and hepatocyte ballooning degeneration [144]. The inflammatory component is particularly concerning as it can trigger further hepatic injury, leading to fibrogenesis and potentially culminating in advanced liver disease [145]. In individuals with pre-existing metabolic conditions such as obesity, insulin resistance, or type 2 diabetes, the risk of developing ART-induced steatosis is significantly heightened [146]. These metabolic conditions often exacerbate the underlying dysregulation of lipid metabolism, creating a vicious cycle where steatosis can rapidly progress to more severe liver pathologies [147].

The interplay between ART-induced steatosis and metabolic syndrome is particularly problematic. Insulin resistance, a common feature of metabolic syndrome, can promote lipogenesis and inhibit fatty acid oxidation, leading to an exacerbation of hepatic fat accumulation [148]. Patients already burdened with excess body weight may find that the addition of PIs to their treatment regimen compounds their risk of hepatic fat deposition,

thus increasing the likelihood of progressing to liver fibrosis or cirrhosis [149]. As liver fibrosis develops, the architecture of the liver becomes disrupted, which can lead to complications such as portal hypertension, hepatic insufficiency, and hepatocellular carcinoma [150].

Moreover, the presence of hepatic steatosis has been linked to a broader spectrum of metabolic dysregulations, including dyslipidemia and increased cardiovascular risk [151]. The accumulation of triglycerides in the liver is not merely a local phenomenon; it is often associated with systemic changes in lipid profiles, contributing to the development of atherogenic dyslipidemia characterized by elevated levels of triglycerides and reduced high-density lipoprotein (HDL) cholesterol [152-153]. This situation can further predispose patients to cardiovascular diseases, compounding the risks associated with ART [153-160].

To mitigate the risks associated with ART-induced hepatic steatosis, careful monitoring of liver function and lipid profiles is essential [154, 160]. Clinicians must be vigilant in assessing patients' metabolic status before and during ART, especially when prescribing PIs. Lifestyle interventions, such as weight management, dietary modifications, and physical activity, can play a critical role in managing and potentially reversing steatosis [154]. Additionally, considering alternative ART regimens that have a more favorable impact on lipid metabolism may be warranted, particularly in patients with existing metabolic risks [154].

In summary, the interference of PIs with lipid metabolism poses a significant challenge in managing HIV-infected patients,

especially those with underlying metabolic conditions [150]. The progression from hepatic steatosis to steatohepatitis and, ultimately, to liver fibrosis underscores the importance of understanding the metabolic consequences of ART [149]. Comprehensive management strategies that encompass both effective viral suppression and the maintenance of metabolic health are crucial for optimizing patient outcomes in this population [148].

1.2.7. Oxidative Stress and Inflammation

Many antiretroviral therapy (ART) drugs induce oxidative stress in hepatocytes, a phenomenon that significantly contributes to liver injury [8]. This oxidative stress arises primarily from the production of reactive oxygen species (ROS) during the metabolism of ART drugs [161-162]. These highly reactive molecules can arise from various metabolic processes, including the mitochondrial metabolism of drugs, the activity of drug- metabolizing enzymes, and the interaction of drugs with cellular components. In hepatocytes, the excessive accumulation of ROS can result in a cascade of oxidative damage affecting lipids, proteins, and DNA [8].

The oxidative damage to lipids, also known as lipid peroxidation, alters the structural integrity and fluidity of cell membranes, compromising hepatocyte function. The damage to cellular proteins can disrupt enzymatic activities and lead to the formation of protein adducts, which may further invoke immune responses [160]. Additionally, oxidative stress inflicts damage on hepatocyte DNA, potentially leading to mutations and promoting cellular apoptosis or necrosis. The cumulative effect of these damages exacerbates hepatocyte injury, resulting in impaired liver function [160].

In response to oxidative stress, hepatocytes and surrounding cells initiate inflammatory responses. This process is mediated by the activation of pro- inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) [8]. TNF-α is particularly noteworthy as it can induce apoptosis in hepatocytes and stimulate the production of other inflammatory mediators, thereby amplifying the inflammatory cascade. IL-6, on the other hand, is involved in the acute phase response and can further promote inflammation and fibrosis in the liver [8]. The activation of these cytokines leads to a recruitment of immune cells to the liver, perpetuating inflammation and tissue damage [161].

The impact of oxidative stress is especially pronounced in patients with pre-existing liver diseases or conditions that heighten susceptibility to oxidative damage. For instance, individuals with chronic viral hepatitis, fatty liver disease, or alcohol use disorder often exhibit increased oxidative stress and diminished antioxidant defenses [8, 161]. The combined effect of ART-induced oxidative stress and these underlying conditions can create a scenario where hepatocyte injury is amplified, accelerating the progression to more severe liver diseases such as fibrosis or cirrhosis [162].

Moreover, patients with metabolic syndrome are at an elevated risk for ART-related oxidative stress due to inherent metabolic dysregulations. The interplay between obesity, insulin resistance, and inflammation can exacerbate the oxidative environment within the liver. In these individuals, the liver's capacity to manage ROS is further compromised, as metabolic disorders can deplete antioxidants and enhance ROS production, leading to a vicious cycle of oxidative stress and liver injury [160-162].

In addition to direct hepatocyte damage, oxidative stress can stimulate hepatic stellate cells (HSCs), the principal cells involved in liver fibrosis. Upon activation, HSCs transform into myofibroblast-like cells that produce excess extracellular matrix components, leading to fibrosis. The continuous cycle of hepatocyte injury, inflammation, and fibrosis not only compromises liver architecture but can also lead to portal hypertension and liver failure if not addressed [161].

To combat oxidative stress induced by ART, it is essential to monitor liver function closely and consider strategies aimed at enhancing antioxidant defenses. These may include dietary interventions rich in antioxidants, such as vitamins C and E, which can help neutralize ROS and mitigate oxidative damage. Additionally, lifestyle modifications that reduce the burden of oxidative stress, such as limiting alcohol consumption and managing metabolic syndrome, are crucial in safeguarding liver health in patients undergoing ART [162]. In summary, the induction of oxidative stress by ART drugs represents a significant pathway through which liver injury occurs. Understanding the mechanisms underlying oxidative damage and the role of inflammatory cytokines is vital for developing targeted interventions that can mitigate liver injury and improve patient outcomes in those receiving ART. By addressing both the direct effects of ART on hepatocytes and the broader context of coexisting conditions, healthcare providers can implement more effective management strategies to preserve liver health in patients living with HIV [8].

1.2.8. Drug-Drug Interactions

Antiretroviral therapy (ART) drugs, especially protease inhibitors (PIs), have well-documented interactions with other medications that are metabolized through the cytochrome P450 (CYP) enzyme system [163-170]. This system is pivotal in drug metabolism, and any alterations in its activity can significantly impact the pharmacokinetics of co-administered medications [171]. These interactions can manifest as either inhibition or induction of liver enzymes, resulting in altered drug levels that may lead to toxic metabolite accumulation or inadequate clearance of medications. Such alterations can greatly increase the risk of hepatotoxicity in patients receiving ART [172-180].

For instance, ritonavir, one of the commonly used PIs, is recognized as a potent inhibitor of the CYP3A4 enzyme [181-185]. This inhibition can have far -reaching effects on the metabolism of numerous other drugs that rely on CYP3A4 for clearance [182,183]. When ritonavir is co-administered with medications such as statins or antifungal agents, it can lead to elevated plasma

concentrations of these drugs. The increased levels of statins, for example, can raise the risk of statin-related side effects,including myopathy and liver injury, while antifungal agents may exacerbate existing liver conditions. The resultant increase in drug concentrations can lead to a complex interplay that further compromises liver function, especially in patients already at risk due to pre-existing liver conditions or other factors [181].

The pathogenesis of ART-induced liver injury is multifaceted and involves both direct and indirect mechanisms that jeopardize hepatocyte integrity [1,5,12]. Direct mechanisms include the hepatotoxic effects of certain ART drugs, which can result in cellular injury through pathways such as oxidative stress, mitochondrial toxicity, and immune-mediated damage. Indirect mechanisms, on the other hand, may involve drug-drug interactions that modify the metabolic clearance of other medications, leading to toxic effects on the liver.

The severity of liver injury observed in patients undergoing ART is influenced by various factors, including the specific ART regimen prescribed, patient-related characteristics such as age, sex, genetic predispositions, and the presence of co-infections or comorbid conditions. For example, patients with chronic viral hepatitis, obesity, or diabetes may have a heightened vulnerability to liver injury due to the synergistic effects of these conditions alongside ART. Genetic polymorphisms affecting drug metabolism and immune response can further complicate the clinical picture, leading to idiosyncratic reactions in susceptible individuals [186- 195]. Understanding the intricate mechanisms behind ART-induced liver injury facilitates targeted monitoring and management strategies. Regular liver function tests are crucial for early detection of hepatic dysfunction, allowing healthcare providers to make timely adjustments to the ART regimen or intervene to prevent further liver damage. This monitoring is particularly important in populations at higher risk for liver injury due to genetic or environmental factors.

1.3. Clinical Presentation and Diagnosis of ART induced liver injury

The clinical presentation of ART-induced liver injury (DILI) can vary widely among patients. Some individuals may exhibit asymptomatic elevations in liver enzyme levels, which can go unnoticed without routine monitoring [60, 196-197]. Conversely, others may progress to more severe manifestations, including acute liver failure, characterized by rapid deterioration of liver function and the potential for life-threatening complications [17]. The manifestations of DILI depend on several variables, including the specific ART drug involved, the dosage administered, the duration of therapy, and individual patient characteristics such as genetic predispositions and pre- existing liver disease [17, 15-20].

Early recognition and accurate diagnosis of ART-induced liver injury are critical to preventing the progression of hepatic complications. Clinicians must maintain a high index of suspicion for liver injury in patients receiving ART, particularly when they present with nonspecific symptoms such as fatigue, jaundice, or abdominal pain. Prompt investigation through liver function tests and imaging studies, if warranted, can aid in distinguishing between drug-induced liver injury and other potential causes of hepatic dysfunction [18].

1.3.1 CLINICAL PRESENTATION

1. Asymptomatic Elevation of Liver Enzymes: Many patients initially present with asymptomatic elevations in serum transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), often detected during routine monitoring. Mild elevations are common and may not necessitate discontinuation of ART, though they warrant close follow-up to detect further elevations or other symptoms of hepatotoxicity [19-21].

2. Hepatitis with Clinical Symptoms: Some patients progress to symptomatic hepatitis, presenting with symptoms like malaise, fatigue, nausea, right upper quadrant abdominal pain, and jaundice. This may be accompanied by laboratory findings of significantly elevated ALT and AST levels, typically more than three times the upper limit of normal, with ALT levels often being higher than AST [26-27].

3. Cholestatic Liver Injury: Certain ART drugs, such as some protease inhibitors, may lead to cholestatic injury, presenting with symptoms like pruritus, dark urine, pale stools, and jaundice. Laboratory findings include elevated alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) levels, with mild-to-moderate increases in bilirubin levels [5-7].

4. Mixed Hepatocellular-Cholestatic Injury: Some patients experience a mixed pattern of liver injury with features of both hepatocellular and cholestatic damage. This may manifest as a combination of elevated ALT, AST, and ALP, along with symptoms like jaundice and fatigue [10].

5. SevereHepatotoxicityandLiver Failure: In rare cases, patients may develop acute liver failure, especially with drugs known to cause immune-mediated reactions (e.g., nevirapine) or severe mitochondrial toxicity (e.g., certain NRTIs like didanosine and stavudine). Symptoms include confusion, coagulopathy (elevated INR), and encephalopathy, reflecting severe hepatic impairment. These cases are life- threatening and require immediate medical attention [16].

6. Immune Reconstitution Infla mmatory Syndrome (IRIS): In patients with co-infections like hepatitis B or C, the initiation of ART may trigger an immune reconstitution response, characterized by a flare- up of underlying infections. This can cause abrupt and severe liver inflammation, jaundice, and worsening hepatic function, often mistaken for ART-induced liver toxicity. The patient's

clinical history and timing relative to ART initiation are crucial in identifying IRIS as the underlying cause [41, 44].

1.4. Diagnosis of ART induced liver injury

Diagnosing ART-induced liver injury requires a comprehensive assessment, as the clinical picture can mimic other hepatic diseases [198]. Diagnosis is typically a process of exclusion, involving clinical history, laboratory evaluations, and imaging [198].

1.4.1. Clinical History: A thorough medication history is a cornerstone of evaluating potential drug-induced liver injury (DILI) in patients receiving antiretroviral therapy (ART). This comprehensive assessment begins with documenting the specific ART regimen being utilized by the patient, which includes the exact names of the medications, their dosages, and the duration of treatment [199]. Each class of antiretroviral drugs, including nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase inhibitors, carries its own risk profile for hepatotoxicity. Understanding which drugs the patient is taking, along with their treatment history, can provide valuable insights into the likelihood of liver injury [198].

Furthermore, it is crucial to consider any recent modifications to the treatment plan. Changes in medication can occur for various reasons, such as the management of side effects, development of drug resistance, or the introduction of new agents to optimize therapy [200]. Each adjustment may influence the patient's risk for liver injury, especially if a new drug with a known hepatotoxic profile has been added. Documentation of the timing of these changes, as well as any clinical rationale for switching medications, can assist in correlating changes in liver function tests with specific therapeutic interventions [200].

In addition to the current ART regimen, prior episodes of hepatotoxicity warrant careful consideration. Patients who have experienced liver injury in the past, whether attributed to ART or other medications, are often at an increased risk for recurrent episodes. It is essential to identify the specific drugs involved in previous incidents, as well as the severity and duration of the liver injury. Knowledge of past drug allergies is also critical, as these can indicate heightened sensitivity to certain medications, potentially leading to adverse reactions if reintroduced [201].

A comprehensive medication history must also encompass the use of alcohol, which is a well-known hepatotoxin. Alcohol consumption can exacerbate liver injury, especially in individuals already at risk due to ART. It is vital to ascertain the frequency, amount, and duration of alcohol use to gauge its potential contribution to hepatic dysfunction [200].

Additionally, the use of herbal supplements and over-the-counter medications should not be overlooked. Many patients may self-medicate with herbal remedies or alternative treatments that can interact with ART or have hepatotoxic effects on their own. For instance, certain herbal supplements like kava, chaparral, or comfrey have been associated with liver injury and could complicate the clinical picture [198].

Understanding all medications the patient is taking, including prescribed medications, over-the-counter drugs, and herbal supplements, allows for a holistic view of the potential risk factors contributing to liver injury. This detailed medication history provides essential information to healthcare providers, aiding in the early detection of hepatotoxicity, guiding
management decisions, and ultimately improving patient outcomes in those receiving ART [198].

1.4.2. LABORATORY EVALUATION

1.4.2.1. Liver Enzymes: Monitoring liver function tests is crucial for the early detection and management of antiretroviral therapy (ART) - induced liver injury (DILI). Key biomarkers include alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and total bilirubin. Each of these tests provides valuable information regarding the liver's condition and function, helping clinicians assess the extent and nature of liver injury [1-5]. Elevations in ALT and AST are particularly significant as they primarily reflect hepatocellular injury. ALT is found predominantly in the liver, making it a more specific marker for liver damage compared to AST, which is also present in other tissues such as the heart and muscles. When hepatocytes are damaged, as seen in cases of DILI, ALT levels tend to rise significantly. A marked elevation in these enzymes can indicate acute liver cell injury, which may be a result of direct hepatotoxicity from ART drugs or other factors affecting the liver.

Monitoring these enzymes can help determine the severity of liver damage and guide clinical decisions regarding ART management [200-203]. In addition to ALT and AST, monitoring ALP and GGT is essential, as their elevation points towards cholestatic liver injury. ALP is an enzyme related to the bile ducts, and its increase may indicate biliary obstruction or cholestasis, conditions where bile flow is impaired. Similarly, GGT is involved in the metabolism of glutathione and is often elevated in liver disease, particularly when cholestasis is present. Elevated GGT levels may also signify alcohol use or drug- induced liver injury, as GGT is sensitive to liver stress. Together, elevated ALP and GGT levels can provide insight into the biliary function of the liver and help distinguish between hepatocellular injury and cholestasis [10, 40-42].

Total bilirubin is another vital marker that should be routinely monitored. It is produced from the breakdown of hemoglobin and is conjugated in the liver. Elevated total bilirubin levels may indicate impaired liver function, particularly in cases where liver cells are unable to process and excrete bilirubin effectively due to damage or dysfunction. Hyperbilirubinemia can lead to jaundice, a visible manifestation of liver injury that occurs when bilirubin accumulates in the bloodstream. Monitoring total bilirubin levels can assist clinicians in evaluating the liver's excretory function and the overall impact of ART on hepatic health [198].

Regular monitoring of these liver function tests not only allows for the detection of ART-induced liver injury at an early stage but also aids in the assessment of the progression or resolution of liver damage. It informs clinicians about the necessity to adjust ART regimens or initiate further investigations, thereby playing a vital role in patient management. By closely tracking these biomarkers, healthcare providers can enhance the safety and efficacy of ART, ultimately improving patient outcomes and minimizing the risk of severe hepatic complications [198].

1.4.2.2. Liver Function Tests: Evaluating liver synthetic function is crucial in the context of assessing liver health, particularly in patients undergoing antiretroviral therapy (ART). Two key tests for this purpose are serum albumin and prothrombin time (PT) or International Normalized Ratio (INR) [201-202]. These tests provide important insights into the liver's ability to produce essential proteins and maintain hemostasis, which are critical functions compromised in advanced liver disease [202].

Serum albumin levels serve as a marker of the liver's synthetic capacity. Albumin is a protein synthesized exclusively by the liver and plays a vital role in maintaining oncotic pressure, transporting various substances, and contributing to overall protein balance in the body. When liver function is impaired due to injury or disease, the production of albumin decreases, leading to lower serum albumin levels. Hypoalbuminemia can manifest as edema or ascites due to decreased oncotic pressure. In patients receiving ART, monitoring albumin levels can help identify significant liver dysfunction, guiding clinical decisions regarding further evaluation and management [202- 203].

Prothrombin time (PT) and INR are critical tests that assess the coagulation status of the blood, reflecting the liver's ability to produce clotting factors. The liver synthesizes most of the proteins involved in coagulation, and any impairment in liver function can lead to an increase in PT and INR. Prolonged PT/INR indicates a delay in coagulation, which can increase the risk of bleeding and signifies severe liver dysfunction. In the context of ART, monitoring PT/INR can be particularly important for identifying patients at risk of hemorrhagic complications, especially in those who may already have liver involvement due to chronic hepatitis, alcohol use, or other co-morbidities [203].

The combination of serum albumin and PT/INR results provides a comprehensive overview of hepatic synthetic function. An isolated decrease in albumin with a prolonged PT/INR indicates a significant compromise in liver function, suggesting that the liver is unable to produce proteins adequately due to extensive hepatocyte damage or loss of functional liver mass. This scenario can be indicative of advanced liver disease, such as cirrhosis, and may necessitate more aggressive management or referral to a specialist for further evaluation and potential intervention [200, 203].

In the management of patients on ART, recognizing the implications of altered synthetic function is crucial. Impaired liver synthesis can complicate the clinical picture, influencing drug metabolism, increasing the risk of adverse effects, and necessitating modifications to the treatment regimen. Regular monitoring of serum albumin and PT/INR, therefore, is not only essential for evaluating liver function but also serves as a critical component of the overall care plan for patients receiving antiretroviral therapy, ultimately contributing to improved patient safety and treatment outcomes [203].

1.4.2.3. Viral Hepatitis Serologies: Co-infections with hepatitis B virus (HBV) or hepatitis C virus (HCV) are prevalent among individuals living with HIV, significantly impacting their overall health and management [204]. The co-occurrence of these viral infections poses unique challenges in the treatment of HIV, particularly in the context of antiretroviral therapy (ART). It is crucial to recognize and exclude active HBV or HCV infection or any potential reactivation of these viruses, especially in patients undergoing immunological recovery [204].

The intersection of HIV and viral hepatitis creates a complex clinical scenario. Hepatitis B and C are both bloodborne viruses that primarily affect the liver and can lead to chronic liver disease, cirrhosis, and hepatocellular carcinoma. People living with HIV are at an increased risk of acquiring HBV and HCV due to shared transmission routes, such as unprotected sexual contact, needle sharing, and other risk factors associated with HIV transmission. The presence of HBV or HCV co-infection can complicate the management of HIV infection by influencing the choice of ART, necessitating a more tailored approach to treatment [204].

Active infection with HBV or HCV can lead to significant liver-related morbidity and mortality. In patients with chronic hepatitis, the introduction of ART can trigger immune reconstitution inflammatory syndrome (IRIS), a condition characterized by an exaggerated immune response against previously undetectable viral antigens due to the recovery of CD4+ T-cells. IRIS can result in the reactivation of chronic hepatitis B or C, leading to acute exacerbations of liver disease, jaundice, and in severe cases, acute liver failure. Therefore, before initiating ART, it is essential to screen for both HBV and HCV infections through serological tests such as HBsAg, anti-HCV antibodies, and viral load assessments [204, 205].

For individuals who test positive for HBV or HCV, additional diagnostic workup is necessary to determine the extent of liver disease, including liver function tests, imaging studies, and possibly liver biopsy or elastography. Management strategies may need to be adjusted accordingly, as the presence of viral hepatitis can influence the choice of ART drugs. For instance, certain nucleos(t) ide reverse transcriptase inhibitors (NRTIs) used in ART have activity against HBV, making them beneficial for patients with HIV and HBV co-infection.

However, other ART drugs may exacerbate liver disease or interact negatively with antiviral treatments for hepatitis [203- 205].

Regular monitoring of liver function and viral load is vital in patients with HIV-HBV or HIV-HCV co-infection. Clinicians must maintain

vigilance for signs of acute liver injury or exacerbation, particularly in the setting of ART initiation or modification. This proactive approach includes educating patients about the potential risks of liver disease progression and the importance of adhering to both HIV and hepatitis treatments [204].

1.4.2.4. Autoimmune Markers: In cases where immune-mediated liver injury is suspected in patients undergoing antiretroviral therapy (ART), testing for autoantibodies is a crucial step in differentiating ART- related drug-induced liver injury (DILI) from autoimmune hepatitis.[202] Autoimmune hepatitis is a chronic liver disease characterized by inflammation and damage to liver cells, driven by an aberrant immune response against liver antigens. The overlap in clinical presentations between autoimmune hepatitis and ART-DILI can make accurate diagnosis challenging, necessitating the use of serological tests to inform clinical decisions [205].

The presence of autoantibodies is a hallmark of autoimmune hepatitis. Among the most commonly tested autoantibodies are antinuclear antibodies (ANA) and anti-smooth muscle antibodies (ASMA). ANA are a group of antibodies that target various nuclear components and are often elevated in autoimmune conditions, including systemic lupus erythematosus and autoimmune hepatitis. ASMA, on the other hand, specifically targets smooth muscle proteins and is frequently associated with autoimmune hepatitis.

When assessing a patient suspected of having immune-mediated liver injury, healthcare providers should consider the following steps. First, a thorough clinical evaluation, including a detailed history and physical examination, should be performed to identify any signs and symptoms indicative of autoimmune hepatitis, such as jaundice, fatigue, or arthralgia. Next, serological tests for ANA and ASMA should be ordered. A positive ANA test can be indicative of autoimmune activity, but it is not exclusive to autoimmune hepatitis, as it can also be found in various other autoimmune disorders. ASMA positivity, especially when combined with elevated immunoglobulin G (IgG) levels, raises suspicion for autoimmune hepatitis.

In addition to ANA and ASMA, other autoantibodies such as anti- liver/kidney microsomal antibodies (LKM-1) and anti-soluble liver antigen (SLA) antibodies may also be tested. The presence of LKM-1 is particularly associated with autoimmune hepatitis type 2, which commonly affects younger individuals and can present with acute liver failure. In cases where these autoantibodies are detected, further investigations may be warranted to confirm a diagnosis of autoimmune hepatitis, which may include liver biopsy to assess for characteristic histological features such as portal inflammation and interface hepatitis.

It's also important to note that the identification of autoimmune hepatitis can influence management decisions. While ART-DILI may require discontinuation or adjustment of specific antiretroviral agents, autoimmune hepatitis may necessitate immunosuppressive therapy, such as corticosteroids, to control inflammation and prevent further liver damage.

1.4.2.5. Imaging Studies: Ultrasound and computed tomography (CT) scans are invaluable imaging modalities in the evaluation of liver health and function, particularly in the context of suspected antiretroviral therapy (ART) -induced liver injury (DILI) [203]. These imaging techniques provide detailed insights into the liver's structural integrity and can help differentiate between various underlying causes of liver disease [206].

Ultrasound is often the first imaging test performed due to its accessibility, cost-effectiveness, and lack of ionizing radiation. It uses high-frequency sound waves to create real-time images of the liver and surrounding structures. Through ultrasound, clinicians can assess liver size, echogenicity, and vascular flow, which can indicate various liver conditions. For instance, an increase in echogenicity may suggest fatty infiltration or steatosis, while changes in liver size or the presence of lesions can indicate potential liver pathology.

Ultrasound is particularly useful for identifying biliary obstruction, where gallstones or tumors may block the bile ducts, leading to cholestasis and liver injury. It can also detect fluid collections such as abscesses or ascites, which can arise from liver disease or other conditions [207].

Computed tomography (CT) scans, on the other hand, provide a more detailed cross-sectional view of the liver and surrounding structures compared to ultrasound. CT scans are particularly beneficial in assessing liver masses, which could be benign tumors, metastatic lesions, or hepatocellular carcinoma. The use of contrast- enhanced CT can help delineate the vascular supply of liver lesions, aiding in the differential diagnosis. Additionally, CT scans can evaluate the hepatic vasculature, which is crucial for identifying conditions such as portal vein thrombosis or hepatic vein obstruction. While CT scans expose patients to ionizing radiation, they can be instrumental in cases where a more comprehensive evaluation is needed, especially when the ultrasound results are inconclusive or when there is a high suspicion of malignancy [203].

In instances where chronic liver disease or steatosis is suspected, liver elastography may be utilized to assess liver stiffness, which is a non-invasive way to estimate liver fibrosis. Elastography, often performed in conjunction with ultrasound (as in transient elastography), measures the velocity of shear waves propagating through the liver tissue. Increased liver stiffness typically correlates with the degree of fibrosis, providing valuable information about the extent of liver damage. This assessment is crucial in managing patients at risk for liver complications, as it can help guide treatment decisions, including the need for closer monitoring or therapeutic interventions [207-208].

1.4.2.6. Liver Biopsy: A liver biopsy is a diagnostic procedure that involves obtaining a small sample of liver tissue for microscopic examination. While it is not routinely performed in cases of ART- induced liver injury (DILI), it can be a critical tool in specific situations,

particularly when the diagnosis remains ambiguous or when severe liver injury continues despite modifications to antiretroviral therapy [204]. The decision to perform a liver biopsy is typically made after careful consideration of the patient's clinical presentation, laboratory findings, and imaging results. In cases where there is uncertainty regarding the cause of liver dysfunction, or when patients exhibit persistent liver enzyme elevations that do not improve with changes in their ART regimen, a liver biopsy can provide definitive histological information that guides further management [209].

Histopathological examination of liver tissue can reveal various abnormalities associated with liver injury. For instance, steatosis, or fat accumulation within hepatocytes, may be identified, indicating a potential link to nucleoside reverse transcriptase inhibitors (NRTIs) or protease inhibitors (PIs). The presence of inflammation may suggest a hepatocellular injury that is immune-mediated or due to direct hepatotoxic effects of ART drugs. Pathologists may identify specific patterns of inflammation, such as portal inflammation or interface hepatitis, which can help differentiate between drug-induced liver injury and other liver conditions, such as autoimmune hepatitis or viral hepatitis [210].

Cholestasis, characterized by the impairment of bile flow, can also be assessed through biopsy. Histological signs of cholestasis may include the presence of bile duct proliferation or bile pigment accumulation in hepatocytes. Recognizing cholestatic features can aid in understanding the mechanisms underlying liver injury, particularly with certain antiretroviral agents known to induce cholestasis [211].

Fibrosis, which refers to the excessive accumulation of connective tissue in the liver, can also be evaluated through biopsy. The degree of fibrosis is a critical factor in determining liver health and guiding treatment strategies. Histological grading of fibrosis can help predict the risk of progression to cirrhosis and guide management decisions, including the potential need for more intensive monitoring or interventions to address liver damage [210-212]. In addition to identifying specific liver injury mechanisms, a liver biopsy can also provide information on co-existing liver conditions. For example, patients with chronic viral hepatitis or fatty liver disease may have overlapping histological features that complicate the diagnosis. Identifying these conditions through biopsy is crucial for tailoring appropriate therapeutic approaches and ensuring comprehensive patient care [210]. Although a liver biopsy is an invasive procedure and carries certain risks, including bleeding and infection, its benefits in complex cases may outweigh these risks. The detailed histopathological information obtained can significantly enhance the understanding of the underlying liver injury and inform future management strategies, ultimately improving patient outcomes [212].

1.2.4.7. Causality Assessment: Tools such as the Roussel Uclaf Causality Assessment Method (RUCAM) and the Drug-Induced Liver Injury Network (DILIN) scoring system are invaluable in the clinical evaluation of suspected drug-induced liver injury (DILI), including cases associated with antiretroviral therapy (ART) [205]. These systematic assessment tools enable clinicians to determine the likelihood that specific ART medications are responsible for liver injury and provide a structured approach to evaluating the causality of liver dysfunction [203].

The RUCAM scoring system is one of the most widely recognized tools for assessing drug-induced liver injury. It employs a set of criteria to calculate a score that helps categorize the causality as "certain," "probable," "possible," or "unlikely." The method evaluates several key factors, including the temporal relationship between drug administration and the onset of liver injury, the presence of other potential causes of liver dysfunction, and the pattern of liver enzyme elevations [205]. For instance, the timing of liver enzyme elevations in relation to the initiation of ART is crucial; an increase in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) shortly after starting a new medication may strongly suggest a causal link. Additionally, the scoring system considers the resolution of liver injury after the drug is discontinued or the dose is adjusted, which can further support or refute the association between the medication and liver damage [205].

Similarly, the DILIN scoring system offers a comprehensive framework for evaluating DILI cases. This tool incorporates clinical data and laboratory findings to categorize the severity and causality of liver injury [203]. The DILIN system emphasizes the importance of assessing the clinical context, including the presence of risk factors such as underlying liver disease, co-morbidities, and concurrent medication use. By systematically evaluating these factors, clinicians can gain insights into whether ART drugs are contributing to liver injury or if alternative explanations are more plausible [205].

Both assessment methods encourage thorough documentation of clinical history, including the patient's medication regimen, duration of treatment, and any previous adverse reactions to medications.

This comprehensive approach helps identify patterns that might indicate an association between ART drugs and liver injury, enhancing the overall understanding of individual patient cases [205].

Utilizing these assessment tools also facilitates communication among healthcare providers and may aid in clinical decision-making regarding the continuation or modification of ART regimens. A structured assessment can help identify patients who may require closer monitoring or alternative therapeutic strategies, reducing the risk of severe liver injury and optimizing treatment outcomes [203].

In addition to clinical assessments, these scoring systems can contribute to research efforts aimed at understanding the mechanisms underlying ART-induced liver injury. By gathering and analyzing data from multiple cases, researchers can identify trends, risk factors, and potential genetic predispositions associated with liver toxicity. This knowledge is critical for informing future guidelines and recommendations regarding ART prescribing practices, ultimately improving patient safety and enhancing the management of individuals

living with HIV [205].

1.2.4.8. Genetic Testing: In certain cases, genetic testing is emerging as a valuable tool for identifying individuals at higher risk of antiretroviral therapy-induced liver injury (ART-DILI) [181]. One prominent example is testing for the HLA-B5701 allele, which has been strongly associated with hypersensitivity reactions to abacavir,
a nucleoside reverse transcriptase inhibitor (NRTI) [177-180]. This hypersensitivity reaction can manifest as a range of clinical symptoms, including fever, rash, gastrointestinal disturbances, and, importantly, immune-mediated liver injury. By identifying patients who carry the *HLA*-B5701 allele, clinicians can make informed decisions regarding the use of abacavir, thereby preventing severe adverse reactions that could compromise liver function [195].
The importance of genetic testing extends beyond just HLA-B*5701
[187]. Variations in other genes involved in drug metabolism and immune response may also predispose individuals to ART-DILI. For instance, polymorphisms in genes encoding cytochrome P450 enzymes, which are critical for the metabolism of many antiretroviral drugs, can influence how quickly or efficiently a drug is processed in the liver [190-192]. Individuals with certain genetic variants may metabolize drugs more slowly, resulting in elevated drug levels and
an increased risk of toxic effects, including hepatotoxicity. Identifying these genetic predispositions through comprehensive pharmacogenetic testing can help personalize treatment plans, ensuring that patients receive therapies that are both effective and safe.
As genetic testing becomes more accessible and cost-effective, its role in the management of ART-DILI is likely to expand. Integrating genetic testing into clinical practice may facilitate the identification of patients who are particularly susceptible to drug-induced liver injury, allowing for more proactive monitoring and risk management strategies. For example, patients identified as having a higher risk for liver injury could be monitored more closely with regular liver function tests, enabling early detection of any elevations in liver enzymes and prompt intervention if necessary [188-189].
Furthermore, genetic testing can inform decisions about alternative therapies. If a patient is found to have a genetic predisposition to adverse reactions from certain ART drugs, healthcare providers can explore alternative medications that are less likely to cause liver injury, ensuring that patients receive optimal care while minimizing the risk of severe side effects [182-185].
The increasing recognition of the role of genetics in drug response aligns with the broader movement towards personalized medicine, where treatment strategies are tailored to individual patient profiles. As our understanding of pharmacogenetics deepens, there is potential for developing guidelines that incorporate genetic testing
into routine care for patients receiving ART. This could help establish best practices for the use of specific antiretroviral agents, improving outcomes for individuals living with HIV [186-192].

1.5. Differential Diagnosis

The differential diagnosis of ART-induced liver injury encompasses a range of hepatic conditions that can mimic or complicate the clinical picture of drug- induced hepatotoxicity. Chronic viral hepatitis, such as hepatitis B or C, remains a significant consideration, especially in patients with HIV co- infection [204]. Viral hepatitis can lead to liver enzyme elevations and symptoms that may overlap with ART-related liver injury. It is essential to assess the patient's viral hepatitis serology to exclude viral reactivation or exacerbation, particularly if there has been a recent initiation or adjustment in ART [204].
Non-alcoholic fatty liver disease (NAFLD) and its progressive form, non- alcoholic steatohepatitis (NASH) , are also relevant, as metabolic factors like obesity, insulin resistance, and dyslipidemia are common in individuals with HIV [142, 151]. ART medications, especially certain antiretrovirals, can exacerbate or initiate lipid metabolism alterations, contributing to hepatic steatosis. Differentiating steatosis-induced liver injury from ART-DILI often requires imaging and, in some cases, liver biopsy to reveal histopathologic changes specific to NAFLD/NASH [142, 151].
Autoimmune hepatitis can present with transaminase elevations and jaundice, similar to ART-induced liver injury, particularly in patients receiving ART drugs associated with immune-mediated hepatotoxicity, such as nevirapine. Testing for autoimmune markers, including antinuclear antibodies (ANA) and anti-smooth muscle antibodies (ASMA) , may aid in excluding autoimmune hepatitis, although a biopsy may be required to confirm the diagnosis when autoimmune hepatitis is strongly suspected
[204-205].
Alcoholic liver disease is another differential consideration, especially in patients with a history of alcohol use. Alcohol intake can exacerbate ART- related hepatotoxicity and contribute to liver enzyme elevations [2]. A thorough history of alcohol consumption is necessary, and the presence of characteristic histologic findings, such as Mallory-Denk bodies on biopsy, can support the diagnosis. Drug-drug interactions should be carefully assessed, as many antiretrovirals are metabolized by the liver and can interact with other medications, leading to hepatotoxicity. This is especially true for protease inhibitors and non-nucleoside reverse transcriptase inhibitors, which influence hepatic enzyme activity, potentially leading to liver injury when combined with hepatotoxic drugs [187].
Biliary disease, including cholelithiasis and cholangitis, can mimic cholestatic liver injury associated with certain ART drugs. Imaging, such as ultrasound, is essential to rule out biliary obstruction or gallbladder disease in patients presenting with elevated alkaline

phosphatase and bilirubin levels.

Wilson's disease and hemochromatosis, although rare, may present with chronic liver enzyme elevations and are important to consider, especially in cases of unexplained liver injury in younger patients. Evaluating serum ceruloplasmin and ferritin, as well as genetic testing when indicated, may help exclude these metabolic liver diseases from the differential diagnosis of ART-DILI.

1.6. Monitoring and Management Strategies

Monitoring and management of ART-induced liver injury require a proactive, individualized approach to minimize hepatic damage while maintaining effective antiretroviral therapy and is dependent on severity (Table 2.0) . Regular monitoring of liver enzymes is essential, particularly during the initiation and early months of ART, as hepatotoxicity commonly emerges within this timeframe. Baseline liver function tests, including alanine aminotransferase (ALT) , aspartate aminotransferase (AST) , alkaline phosphatase (ALP) , and bilirubin, should be conducted before starting ART. Patients at increased risk, such as those with pre-existing liver disease or co-infections like hepatitis B or C, may benefit from more frequent liver enzyme assessments, typically every 2–4 weeks for the first three months and then at longer intervals if results remain stable [199-205].

Dose adjustments and drug substitutions are critical strategies when signs of hepatotoxicity appear. Mild and asymptomatic transaminase elevations often do not necessitate ART discontinuation, as they may normalize with continued treatment or temporary dose reductions. For moderate to severe elevations or symptomatic liver injury, adjusting the ART regimen by substituting the suspected offending agent with a less hepatotoxic alternative is generally advisable. For instance, switching from nevirapine or efavirenz to integrase inhibitors can be beneficial in patients experiencing immune-mediated hepatotoxicity [202].

Rechallenge with the suspected ART drug can be considered in patients where alternative regimens are limited, although this approach carries the risk of recurrence and should only be attempted under close monitoring. In cases where liver enzyme elevations exceed five times the upper limit of normal or are accompanied by symptoms such as jaundice or abdominal pain, the implicated drug should be promptly discontinued to prevent further liver damage [204].

Supportive care is important for managing symptomatic cases, particularly those presenting with nausea, vomiting, or malaise. In severe instances of liver dysfunction, hospitalization may be necessary for monitoring and supportive interventions, including intravenous fluids and electrolytes to manage dehydration. Patients presenting with signs of acute liver failure, such as coagulopathy, encephalopathy, or rapid deterioration in liver function, require immediate referral to a specialist and potential consideration for liver transplantation.

Adjunct therapies and lifestyle modifications can play a supportive role in managing ART-DILI. Patients should be advised to avoid alcohol and other hepatotoxic substances to reduce cumulative liver stress. Additionally, antiviral treatment of hepatitis B or C co-infections may help stabilize liver function in co-infected patients, as viral suppression can reduce the overall burden on the liver.

Education and counseling are key components of management, as they promote patient adherence and understanding of the risks and symptoms associated with hepatotoxicity. Patients should be encouraged to report any signs or symptoms of liver injury, such as jaundice, dark urine, or right upper quadrant pain, early to allow for prompt intervention.

1.7. Prevention of ART induced liver injury

Prevention of ART-induced liver injury hinges on early risk assessment, cautious drug selection, and patient education. Screening for liver disease and evaluating risk factors, such as hepatitis B or C co-infections, obesity, and alcohol use, are crucial before initiating ART. Using ART regimens with a lower hepatic risk profile, particularly in patients with existing liver conditions, can reduce the incidence of hepatotoxicity. For instance, selecting integrase strand transfer inhibitors (INSTIs) over protease inhibitors or certain non-nucleoside reverse transcriptase inhibitors (NNRTIs) may be beneficial in reducing the likelihood of liver injury.

Routine monitoring during the first three months of treatment allows early detection of hepatic abnormalities, especially in high-risk patients. Regular liver enzyme assessments combined with patient awareness of early symptoms can facilitate timely intervention and minimize severe outcomes. Additionally, managing lifestyle factors such as alcohol intake and maintaining a balanced diet with adequate hydration supports overall liver health and lessens hepatic strain during ART [213].

2.0. CONCLUSION

ART-induced liver injury is a significant challenge in HIV management, necessitating an integrated approach that combines vigilant monitoring, tailored drug selection, and proactive patient engagement. Recognizing and managing hepatotoxicity early can improve treatment adherence and outcomes, preserving liver health while maintaining effective HIV suppression. Through these strategies, healthcare providers can better navigate the complexities of ART in patients at risk for liver injury, ultimately enhancing patient safety and quality of life.

AUTHOR'S CONTRIBUTIONS

SOI, SOA, EOO, MCI, BF, DOA, DBA , SL, and AAB conceptualized and designed the study and contributed to drafting and revising the manuscript. SOI, SOA, EOO, MCI, BF, DOA, DBA and SL contributed to data collection, and manuscript review, SOI, SOA,

EOO, MCI, BF, DOA, DBA and SL participated in study design, and critically reviewed the manuscript for important intellectual content. SOI, SOA, EOO, MCI, BF, DOA, DBA, SL, and AAB assisted with the literature review, data visualization, and preparation of initial manuscript drafts. All authors provided methodological expertise, and contributed significantly to manuscript revisions. All authors supported data acquisition and provided feedback on the manuscript drafts. All authors contributed to the manuscript structure, final proofreading, and editing for clarity and coherence; all authors have read and approved the final manuscript

Declarations

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Availability of data and materials

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

Competing interests

All authors declare that they have no competing interests.

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