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Pediatric and Adolescent Considerations in Antiretroviral-Induced Hepatotoxicity: Mechanisms, Risks, Monitoring and Management

Fahmida Akter[1], Hure Jannat Jyoti[2], Sophia Hossain[3], Sadia Afroz[4], Eshita Akter[4], Sadman Radit Aurnab[5], Aqib Hossain Khan[6], Imtiaj Hossain Chowdhury[6*]

[1]Department of Pharmacy, University of Dhaka, Dhaka, Bangladesh; [2]Department of Pharmacy, University of Asia Pacific, Dhaka, Bangladesh; [3]Department of Pharmacy, ASA University Bangladesh, Dhaka, Bangladesh; [4]Department of Pharmacy, Gono Bishwabidyalay, Dhaka, Bangladesh; [5]Department of Pharmacy, Bangladesh University, Dhaka, Bangladesh; [6]Department of Pharmacy, Jahangirnagar University, Dhaka, Bangladesh

ABSTRACT

The scale-up of Antiretroviral Therapy (ART) has transformed pediatric and adolescent Human Immunodeficiency Virus (HIV) infection into a manageable chronic disease. Children living with HIV now initiate therapy in infancy and remain on lifelong treatment, resulting in cumulative exposure to antiretrovirals and their toxicities. Hepatotoxicity, ranging from asymptomatic transaminase elevations to severe Drug-Induced Liver Injury (DILI), represents one of the most clinically significant adverse effects of ART. Although hepatotoxicity has been extensively described in adults, pediatric populations face unique vulnerabilities due to developmental pharmacokinetics, nutritional deficiencies, coinfections, and evolving metabolic risk factors during adolescence.

This review synthesizes current evidence on mechanisms of ART-related hepatotoxicity, age-specific susceptibilities, and drug class–associated risks in children and adolescents. It further explores the influence of coinfections such as hepatitis B and tuberculosis, emerging challenges including Non-Alcoholic Fatty Liver Disease (NAFLD), and the role of genetic polymorphisms in shaping hepatotoxicity risk. Current recommendations for screening, monitoring, and management are summarized, with a focus on adapting adult-derived protocols to pediatric practice. Gaps in evidence, especially in low and middle-income countries, and priorities for future research including pharmacogenomics, longitudinal studies, and non-invasive biomarkers are highlighted.

Pediatric and adolescent patients with HIV represent a vulnerable population in whom hepatotoxicity is both preventable and manageable if recognized early. Optimizing monitoring strategies and developing safer regimens are essential to safeguard long-term liver health in the next generation of people living with HIV.

Keywords: HIV; Pediatrics; Adolescents; Antiretroviral therapy; Hepatotoxicity; Drug-induced liver injury

INTRODUCTION

The global scale-up of Antiretroviral Therapy (ART) has markedly reduced HIV-related morbidity and mortality, including in pediatric populations. According to UNAIDS, an estimated 1.4 million children under 15 years were living with HIV in 2023, with approximately 1 million receiving ART [1,2]. The widespread adoption of Dolutegravir (DTG)-based regimens has further improved viral suppression and resistance outcomes in children and adolescents [3]. However, lifelong ART exposure beginning in infancy introduces the potential for cumulative drug toxicity, particularly hepatotoxicity. Children and adolescents living with HIV often require decades of continuous therapy, which increases the likelihood of liver injury from direct

Correspondence to: Imtiaj Hossain Chowdhury, Department of Pharmacy, Jahangirnagar University, Dhaka, Bangladesh; E-mail: imtiaj.chowdhury@bu.edu.bd

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drug toxicity, mitochondrial dysfunction, or metabolic complications over time [4]. Moreover, early initiation of ART may predispose patients to long-term hepatocellular stress, compounded by potential coinfections (e.g., HBV, HCV) and lifestyle factors that emerge in adulthood. [5] Thus, the cumulative burden of ART exposure represents a significant concern for lifelong liver health in people living with HIV.

Hepatotoxicity is a well-recognized complication of ART and includes asymptomatic transaminase elevations, immune-mediated hypersensitivity hepatitis, mitochondrial hepatopathy, steatosis, and fulminant hepatic failure [6]. While much of the evidence base arises from adult studies, children and adolescents have distinct risk profiles. Developmental differences in hepatic enzyme maturation, nutritional vulnerabilities, and coinfections such as Hepatitis B Virus (HBV) and Tuberculosis (TB) can magnify susceptibility to Drug-Induced Liver Injury (DILI). Furthermore, adolescents face emerging risk factors such as obesity, metabolic syndrome, and Non-Alcoholic Fatty Liver Disease (NAFLD), which intersect with ART-related hepatotoxicity [7,8].

While Antiretroviral Therapy (ART) has dramatically improved survival and quality of life for children and adolescents living with HIV, its lifelong administration presents a dual challenge: Sustaining virologic control while minimizing cumulative toxicity. Hepatotoxicity, in particular, has emerged as a significant concern in pediatric populations exposed to ART from infancy. The interplay of immature hepatic enzyme systems, coinfections such as Hepatitis B Virus (HBV) and Tuberculosis (TB), and nutritional deficiencies may exacerbate the risk of Drug-Induced Liver Injury (DILI) in children [9,10]. In adolescents, additional risk factors including obesity, insulin resistance, and Non-Alcoholic Fatty Liver Disease (NAFLD) compound these vulnerabilities [10,11]. These realities underscore the importance of age-appropriate pharmacovigilance, with regular liver function monitoring, individualized regimen selection, and the availability of less hepatotoxic alternatives. Integrated care approaches that address nutritional support, screening for metabolic syndrome, and proactive management of coinfections are essential to reduce the long-term burden of ART-related liver injury [12]. As ART initiation now routinely begins in infancy and continues lifelong, ongoing research into safer formulations, pediatric-specific dosing guidelines, and predictive biomarkers for hepatotoxicity is critical to ensuring durable, safe, and effective HIV treatment across the pediatric age spectrum.

Despite its clinical relevance, pediatric ART hepatotoxicity remains under-characterized. Most current monitoring guidelines are adapted from adult data, with limited pediatric-specific evidence. This review aims to synthesize available data on ART-induced hepatotoxicity in children and adolescents, emphasizing mechanisms, age-related vulnerabilities, drug class–specific risks, comorbid conditions, monitoring, and management strategies.

MATERIALS AND METHODS

This review followed a systematic approach to identify, evaluate, and synthesize evidence on antiretroviral therapy (ART)–induced hepatotoxicity in pediatric and adolescent populations. A comprehensive literature search was conducted in PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. Search terms included combinations of: "HIV," "children," "adolescents," "antiretroviral therapy," "hepatotoxicity," "drug-induced liver injury," "NNRTI," "PI," "INSTI," "NRTI," "nevirapine," "dolutegravir," "liver enzymes," "NAFLD," and "toxicity."

Eligible studies included randomized trials, observational cohorts, pharmacokinetic studies, case series, and systematic reviews evaluating hepatic outcomes in individuals receiving ART. Publications were excluded if they lacked liver-related outcomes, or were commentaries without primary data. Titles and abstracts were screened, followed by full-text review of potentially relevant articles. Data extraction focused on hepatotoxicity mechanisms, incidence, drug-specific risks, comorbidities, monitoring practices, and long-term outcomes.

Findings were synthesized qualitatively due to heterogeneity in study designs, populations, and outcome definitions. Evidence was integrated to provide a comprehensive assessment of pediatric-specific hepatotoxicity patterns and clinical implications.

LITERATURE REVIEW

Mechanisms of antiretroviral-induced hepatotoxicity

Antiretroviral Therapy (ART) has significantly improved survival and quality of life in people living with HIV. However, hepatotoxicity remains one of its most clinically relevant adverse effects, contributing to treatment interruptions and morbidity [13]. The mechanisms of antiretroviral-induced liver injury are multifactorial, involving direct drug toxicity, mitochondrial dysfunction, immune-mediated hypersensitivity reactions, and altered hepatic metabolism. These processes may lead to steatosis, oxidative stress, apoptosis, and inflammation, ultimately culminating in hepatocellular injury. Understanding these mechanisms is crucial for early detection, prevention, and management of ART-related liver complications (Figure 1).

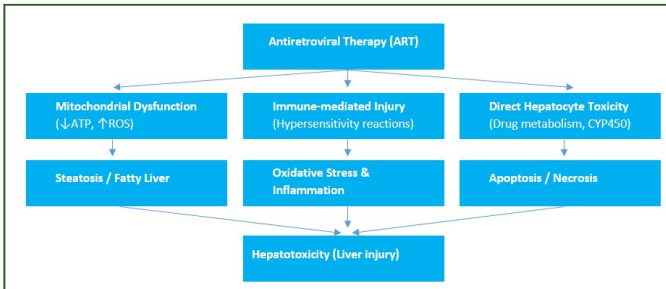

Figure 1: Flow diagram of antiretroviral-induced hepatotoxicity.

Direct hepatocellular toxicity: Many antiretrovirals undergo hepatic metabolism, and toxic metabolites can directly injure hepatocytes. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), particularly nevirapine, are associated with hepatocellular necrosis due to reactive intermediate metabolites [14]. Protease Inhibitors (PIs), metabolized by cytochrome P450 isoenzymes, may cause hepatotoxicity through direct cytotoxicity and metabolic disturbances.

Mitochondrial dysfunction: Nucleoside Reverse Transcriptase Inhibitors (NRTIs) are implicated in mitochondrial hepatotoxicity. Older NRTIs such as Stavudine and Didanosine inhibit mitochondrial DNA polymerase-γ, leading to impaired oxidative phosphorylation, lactic acidosis, and hepatic steatosis [15]. Although these agents are largely phased out, their long-term use in older pediatric cohorts highlights the importance of cumulative toxicity.

Immune-mediated injury: Idiosyncratic, immune-mediated liver injury occurs with certain antiretrovirals. Abacavir hypersensitivity reaction, strongly associated with the HLA-B*57:01 allele, may present with hepatitis alongside systemic symptoms [16]. Nevirapine can also trigger immunoallergic hepatitis, particularly within the first 6–12 weeks of initiation, and appears more frequent in younger children and females [17].

Metabolic and steatotic injury: Protease inhibitors and Integrase Strand Transfer Inhibitors (INSTIs), particularly dolutegravir, are associated with weight gain and metabolic derangements. These changes predispose to NAFLD, an increasingly recognized cause of liver morbidity in adolescents living with HIV. As these individuals transition into adulthood, the interplay of ART, obesity, and hepatic steatosis becomes an increasingly important concern for long-term liver health [18,19].

Drug–drug interactions: Children with HIV often receive concomitant therapies, including TB drugs (isoniazid, rifampicin), antifungals, and anticonvulsants. These agents may potentiate ART hepatotoxicity through overlapping toxicities or cytochrome P450–mediated interactions [20].

Age-related vulnerabilities

Children and adolescents experience hepatotoxicity differently from adults due to developmental and contextual factors.

Immature hepatic enzyme systems: Neonates and young children exhibit delayed maturation of hepatic phase I (CYP450) and phase II (Glucuronidation, Sulfation) enzymes. This enzyme immaturity impairs drug clearance and predisposes to accumulation of parent compounds or toxic metabolites, thereby increasing vulnerability to hepatotoxic injury [21]. Clinically, this risk is exemplified by drugs like Nevirapine and Efavirenz, which have been associated with significant liver toxicity—stemming from immune-mediated injury, mitochondrial dysfunction, ER stress, and impaired bile acid transport [22].

Nutritional status: Malnutrition, still common in many HIV-endemic regions, compromises hepatic resilience. Protein-energy malnutrition impairs detoxification pathways, while micronutrient deficiencies (vitamin A, selenium, zinc) exacerbate oxidative stress [23]. Conversely, in high-income settings, rising rates of obesity in HIV-infected adolescents contribute to metabolic liver injury.

Hormonal and metabolic changes in adolescence: Puberty introduces hormonal fluctuations and shifts in body composition that alter drug pharmacokinetics. Increased insulin resistance and lipid abnormalities during adolescence interact with ART-associated metabolic effects, compounding liver risk [24].

Cumulative lifetime exposure: Unlike adults who initiate ART later, children are exposed from birth or early infancy, leading to decades of potential drug–liver interaction. Even subclinical injuries in early life may predispose to fibrosis, cirrhosis, or NAFLD in adulthood [25].

Adherence and behavioral risk factors: Adolescents face unique challenges, including poor adherence, alcohol or substance use, and irregular health service utilization. These factors increase the likelihood of treatment interruptions, regimen switches, and repeated liver insults (Table 1) [26].

Table 1: Key risk factors for antiretroviral-associated hepatotoxicity in children and adolescents.

Category	Risk factor	Notes/Examples
Age-related [27]	Immature hepatic enzymes	Slower clearance of NNRTIs in neonates/young children
	Pubertal hormonal changes	Altered drug metabolism, increased metabolic risk
Nutritional [29]	Malnutrition	Impaired hepatic detoxification, oxidative stress
	Obesity/metabolic syndrome	NAFLD in adolescents, worsened by PIs/INSTIs
Drug-related [27-29]	NRTIs (Stavudine, Didanosine)	Mitochondrial toxicity, lactic acidosis
	NNRTIs (Nevirapine)	Hypersensitivity hepatitis, especially in young children
	PIs/INSTIs	Dyslipidemia, weight gain, steatosis
Comorbidities [30]	HBV/HCV co-infection	Increased hepatotoxicity risk with ART
	TB co-treatment	Isoniazid/rifampicin overlapping toxicity
Genetic [31]	HLA-B*57:01 allele	Abacavir hypersensitivity with hepatitis
	CYP450 polymorphisms	Altered NNRTI metabolism
Behavioral [32]	Poor adherence, alcohol/substance use	Repeated hepatotoxic insults, treatment interruptions

Drug class–specific hepatotoxicity in children and adolescents

Nucleoside Reverse Transcriptase Inhibitors (NRTIs): NRTIs form the backbone of pediatric ART regimens. Older NRTIs such as Stavudine (d4T) and didanosine (ddI) are well known for mitochondrial toxicity, leading to hepatic steatosis and lactic acidosis [33]. Although these agents are no longer recommended by the World Health Organization (WHO) and have been phased out of most programs, many children initiated on them in earlier years may still face long-term hepatic consequences. Newer NRTIs such as Tenofovir Disoproxil Fumarate (TDF), Tenofovir Alafenamide (TAF), Lamivudine (3TC), and Abacavir (ABC) are considerably safer, but occasional hepatotoxicity has been documented. Abacavir carries the risk of hypersensitivity hepatitis in HLA-B*57:01–positive individuals, although this allele is less prevalent in African populations [31].

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs): Nevirapine remains one of the most studied causes of pediatric ART-related hepatotoxicity. It is strongly associated with immune-mediated hepatitis, typically within 6–12 weeks of initiation, particularly in children under two years, females, and those with higher CD4 counts at ART initiation [34]. Clinical trials and cohort studies have reported hepatotoxicity rates of up to 8–10% in pediatric populations. Efavirenz, now more common in adolescents, is generally safer but may cause mild transaminase elevations [35].

Protease Inhibitors (PIs): Ritonavir-boosted lopinavir (LPV/r) was historically the cornerstone of first-line pediatric ART [36]. PIs are associated with metabolic complications including hyperlipidemia and insulin resistance, which predispose to secondary NAFLD [37]. Direct hepatotoxicity is less common but has been observed, especially in the presence of HBV or HCV co-infection. Darunavir, increasingly used in second-line therapy, has a relatively favorable hepatic safety profile but requires monitoring [38].

Integrase Strand Transfer Inhibitors (INSTIs): Integrase inhibitors such as Dolutegravir (DTG) and Bictegravir (BIC) are now preferred first-line options for children and adolescents due to high efficacy and tolerability [39,40]. Clinical trials, including IMPAACT P1093 and ODYSSEY, demonstrated good hepatic safety, with minimal grade 3–4 transaminase elevations. However, INSTIs are linked to weight gain and metabolic alterations, raising long-term concerns about NAFLD in adolescents [41]. Pediatric-specific longitudinal data remain limited (Table 2).

Table 2: Antiretroviral class–specific hepatotoxicity in children and adolescents.

Drug class	Common agents (Peds)	Mechanism of injury	Typical presentation	Notes
NRTIs	3TC, ABC, TDF, TAF (older: d4T, ddI)	Mitochondrial toxicity, hypersensitivity (ABC)	Steatosis, lactic acidosis, hepatitis	d4T/ddI largely phased out; ABC requires HLA-B*57:01 testing
NNRTIs	Nevirapine, Efavirenz	Immune-mediated hypersensitivity	Acute hepatitis, rash-hepatitis syndrome	Nevirapine risk highest in young children and females
PIs	LPV/r, Darunavir	Metabolic derangements, direct hepatotoxicity	Dyslipidemia, insulin resistance, transaminase elevations	Contributes to NAFLD risk in adolescents
INSTIs	Dolutegravir, Bictegravir	Weight gain, metabolic changes	Subclinical steatosis, mild ALT elevations	Generally safe; long-term pediatric outcomes unknown

Comorbidities and contextual risks

Viral hepatitis co-infection: Children with HIV frequently acquire HBV or HCV *via* vertical transmission or early exposure. Co-infection accelerates liver injury and increases ART-related hepatotoxicity [42]. In such cases, ART regimens must include agents active against HBV (TDF or TAF plus 3TC or FTC) to prevent reactivation or flare. Monitoring should be more intensive, with baseline and periodic HBV DNA or HCV RNA testing where feasible.

Tuberculosis co-treatment: HIV–TB co-infection is common in children, especially in sub-Saharan Africa. Standard TB therapy (isoniazid, rifampicin, pyrazinamide) carries intrinsic hepatotoxic risk, which may be additive with ART. Pediatric studies show DILI incidence of 5–15% during concomitant ART and TB treatment, with risk factors including malnutrition, female sex, and elevated baseline liver enzymes [43].

Malnutrition and micronutrient deficiency: Protein-energy malnutrition impairs hepatic glutathione-mediated detoxification, increasing vulnerability to oxidative stress and hepatocellular injury. In resource-limited settings, this synergizes with ART toxicity. Conversely, in high-income countries, pediatric HIV survivors face rising obesity rates, leading to NAFLD risk [44,45].

Genetic susceptibility: Pharmacogenomic studies highlight genetic predispositions to hepatotoxicity. NAT2 polymorphisms affect isoniazid metabolism, increasing TB-related hepatotoxicity,

while CYP2B6 variants alter NNRTI metabolism [46]. Screening for HLA-B*57:01 before abacavir initiation is recommended where feasible, though its predictive value in pediatrics is understudied.

Emerging NAFLD and NASH: Non-alcoholic fatty liver disease is now recognized as a leading cause of chronic liver disease in adolescents with HIV, particularly those exposed to long-term ART and with obesity or metabolic syndrome. Studies show NAFLD prevalence of 15–30% in perinatally infected adolescents in high-income settings, though under-diagnosed in low-income regions due to lack of imaging and biomarkers (Figure 2) [47].

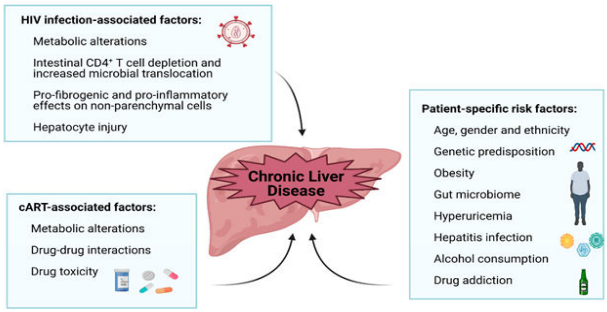

Figure 2: Pathways contributing to hepatotoxicity in children and adolescents with HIV [22].

Clinical spectrum and monitoring

Spectrum of hepatotoxicity: The clinical manifestations range from asymptomatic transaminase elevation to fulminant hepatic failure. Most children experience mild, transient enzyme elevations. Severe outcomes such as lactic acidosis with older NRTIs or immune-mediated hepatitis with Nevirapine are less common but clinically significant [48,49]. Chronic injury, including fibrosis and NAFLD, is increasingly observed in adolescents transitioning to adult care [47].

Grading and definitions: Pediatric hepatotoxicity is graded using the Division of AIDS (DAIDS) toxicity tables: Grade 1 (mild) ALT/AST elevation to Grade 4 (life-threatening) [50]. Causality is often assessed using the RUCAM (Roussel Uclaf Causality Assessment Method), though pediatric-specific validation is limited [51].

Monitoring recommendations: Guidelines recommend baseline liver function testing before ART initiation or modification, with repeat testing at 2–4 weeks, 3 months, and every 6–12 months thereafter. In higher-risk children (HBV/HCV co-infection, TB co-treatment, use of nevirapine or PIs), more frequent monitoring is advised [52]. Non-invasive fibrosis assessment tools such as APRI and FIB-4 are under study but not validated for routine pediatric use (Table 3).

Table 3: Monitoring schedule for children and adolescents on ART.

Time point	Recommended tests	High-risk populations (e.g., HBV/HCV, TB therapy, NNRTIs)
Baseline	ALT, AST, bilirubin, HBV/HCV serology, nutritional assessment	Add HBV DNA or HCV RNA if feasible
2–4 weeks after ART initiation	ALT, AST	Monitor closely if on Nevirapine or TB co-treatment
3 months	ALT, AST, bilirubin	Add lipids if on PI/INSTI
6–12 months	ALT, AST	More frequent (every 3 months) if co-infected or on high-risk regimens
Annually	ALT, AST, bilirubin, metabolic panel	Add FibroScan/APRI if available

Management strategies

General principles: Management depends on severity, causality, and clinical status. Mild, asymptomatic enzyme elevations may only require continued monitoring. Moderate to severe hepatotoxicity may necessitate dose interruption, regimen switch, or hospitalization in fulminant cases [53].

Grade-based approach:

- **Grade 1–2 (Mild/moderate):** Continue ART with close monitoring.
- **Grade 3 (Severe):** Interrupt suspect drug(s); investigate for alternative etiologies (viral hepatitis, TB drugs).
- **Grade 4 (Life-threatening):** Discontinue all hepatotoxic agents; provide supportive care; restart with safer regimen once stable.

Switching strategies: If Nevirapine-induced hepatitis occurs, the drug should be permanently discontinued and replaced with an INSTI or PI [54]. In cases of Abacavir hypersensitivity, rechallenge is contraindicated, and alternative NRTIs must be selected. Children with HBV co-infection should always remain on HBV-active ART, even if hepatotoxicity occurs, to prevent viral reactivation [55].

Adjunctive measures: Optimizing nutrition, treating viral hepatitis, and managing metabolic syndrome are essential components of hepatotoxicity management. Vaccination against HBV and avoidance of hepatotoxic concomitant drugs when possible should be emphasized [56]. In adolescents, counseling on alcohol and substance use is important.

Long-term outcomes

Recovery and reversibility: Most children with ART-related hepatotoxicity experience full biochemical recovery after drug withdrawal or substitution. However, subclinical damage may persist, particularly in those with repeated episodes of Drug-Induced Liver Injury (DILI) or concurrent risk factors.

Fibrosis and cirrhosis: Persistent hepatic inflammation may progress to fibrosis and cirrhosis, particularly in children with viral hepatitis co-infection or metabolic risk factors. Elastography studies in perinatally infected adolescents report early signs of fibrosis in 10–15% despite viral suppression [57].

Hepatocellular Carcinoma (HCC) Risk: While pediatric HCC remains rare, chronic HBV co-infection combined with ART-induced hepatotoxicity may increase lifetime risk [58]. A few case reports document HCC in perinatally HIV-infected adolescents with longstanding HBV co-infection. Surveillance strategies should be considered in high-risk populations [59].

Psychosocial and quality of life outcomes: Adolescents experiencing recurrent hepatotoxicity may require regimen switches that limit treatment options, creating anxiety about drug failure [60]. Chronic illness burden, frequent monitoring, and dietary restrictions may further impact adherence and quality of life (Table 4).

Table 4: Long-term outcomes of ART-related hepatotoxicity in children and adolescents.

Outcome	Frequency/Prevalence	Risk Factors	Notes
Biochemical recovery	70–80% after drug discontinuation	Mild/moderate DILI, early detection	Majority recover fully
Persistent ALT elevation	20–30% in longitudinal studies	Recurrent DILI, HBV/HCV, obesity	May progress to fibrosis
Fibrosis	10–15% of perinatally infected adolescents	HBV/HCV, PIs, obesity, malnutrition	Underdiagnosed in LMICs
Cirrhosis	Rare but reported in teens	Chronic HBV/HCV, repeated hepatotoxicity	Requires lifelong surveillance
HCC	Rare case reports	HIV/HBV co-infection, chronic liver disease	Lifelong risk persists

Future perspectives

Safer ART regimens: The shift toward integrase inhibitors (Dolutegravir, Bictegravir) in pediatric populations is promising, with reduced hepatotoxicity compared to NNRTIs and PIs [61]. Ongoing surveillance for metabolic consequences and NAFLD is essential. Development of long-acting injectable ART formulations may reduce cumulative hepatic exposure but requires pediatric safety studies.

Precision medicine approaches: Pharmacogenomic testing (e.g., HLA-B*57:01, CYP2B6 polymorphisms) should be integrated into pediatric HIV programs where feasible. Tailoring ART based on genetic risk may prevent idiosyncratic hepatotoxicity and optimize drug safety [62].

Improved monitoring tools: Non-invasive methods such as transient elastography, MRI-based fat quantification, and serum fibrosis biomarkers need validation in children [63]. These tools could replace invasive biopsies for longitudinal monitoring.

Research gaps:

- Lack of long-term prospective cohorts of perinatally infected children to assess chronic liver outcomes.
- Limited data from Low and Middle-Income Countries (LMICs), where hepatotoxicity burden is likely higher.
- Under-exploration of sex and puberty-related differences in susceptibility.
- Few interventional trials evaluating adjunctive therapies (antioxidants, hepatoprotective agents) in pediatric populations.

CONCLUSION

ART has transformed pediatric HIV into a chronic, manageable condition, but hepatotoxicity remains a clinically significant complication. The risk is shaped by drug class, host factors, co-morbidities, and environmental context. While most children recover fully, a subset progress to chronic liver disease, fibrosis, or cirrhosis, especially when additional risk factors such as HBV/HCV, TB treatment, or obesity are present.

Future strategies must focus on safer regimens, pharmacogenomic screening, improved monitoring, and targeted interventions to mitigate hepatotoxicity. Strengthening pediatric-specific research and ensuring access to diagnostic tools in LMICs will be critical to safeguard long-term liver health in children and adolescents living with HIV.

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