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REVIEW ARTICLE

Intersections of vitamin D deficiency, HIV and chronic liver diseases

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Abstract

Objectives: Despite effective antiretroviral therapy (ART), chronic liver diseases remain a leading cause of morbidity and mortality among people with HIV, with metabolic dysfunction–associated steatotic liver disease (MASLD) now the predominant etiology. Vitamin D deficiency is also highly prevalent in this population. We synthesize current evidence on the interplay between HIV, liver disease, and vitamin D deficiency, and highlight implications for risk stratification and therapeutic research in this population.

Methods: A targeted PubMed search was conducted using terms for HIV, liver disease, fibrosis, and vitamin D, supplemented by reference screening. We prioritized peer-reviewed studies and guidelines addressing liver disease epidemiology and mechanisms in people with HIV, vitamin D biology, and associations between vitamin D status and hepatic injury. Comparative data from non-HIV populations were also reviewed.

Results: People with HIV face a high burden for chronic liver diseases due to MASLD, viral hepatitis coinfections, and hepatotoxic exposures such as alcohol and ART. Pathogenesis involve persistent immune activation, hepatic stellate cell activation, and systemic inflammation. Vitamin D deficiency is frequent in people with HIV and, in non-HIV populations, correlates with higher prevalence of MASLD and fibrosis. Emerging evidence suggests plausible links

through immune modulation, oxidative stress, and fibrogenesis, though causality remains unproven.

Conclusions: The intersection of HIV, MASLD, and vitamin D deficiency is biologically plausible and clinically relevant yet underexplored. Longitudinal studies with standardized MASLD phenotyping and vitamin D assessment are warranted. Meanwhile, integrating metabolic risk assessment with vitamin D evaluation may support more holistic liver care in people with HIV, while interventional trials should clarify whether vitamin D optimization improves hepatic and extrahepatic outcomes.

KEYWORDS

antiretroviral therapy, immune activation, liver fibrosis, metabolic dysfunction-associated steatotic liver disease, viral hepatitis

GLOBAL BURDEN OF HIV AND THE RISING CHALLENGE OF LIVER DISEASE

Over the past decades, advances in combination antiretroviral therapy (ART) have transformed HIV infection from a fatal disease into a manageable chronic condition [1]. As a result, the life expectancy of people with HIV now approaches that of the general population in many settings [2]. However, this increased longevity has also unmasked a substantial burden of non-AIDS comorbidities, including cardiovascular disease, metabolic syndrome and notably, chronic liver disease [1–3]. Globally, the prevalence of chronic liver diseases continues to grow, with people with HIV particularly vulnerable due to a combination of host, viral and environmental factors [4, 5]. In this population, liver-related conditions have become leading causes of morbidity and mortality, driven not only by HIV-associated immune dysfunction but also by frequent coinfections with hepatitis B virus (HBV) and C virus (HCV), hazardous alcohol use, prior exposure to hepatotoxic first-generation ART and current use of obesity-promoting second-generation ART. These medical risks are further compounded by adverse social determinants of health, including food insecurity, psychiatric comorbidities, inconsistent access to healthcare and the pervasive burden of stigma (Figure 1) [2, 5, 6]. Viral hepatitis coinfections are especially critical in this context. Globally, it is estimated that 5–30% of people with HIV are coinfected with HBV, and up to 20–30% are coinfected with HCV, although rates vary by region and transmission patterns [7, 8]. In some cohorts of people who inject drugs, HCV coinfection prevalence can exceed 80% [8]. Additionally, hazardous alcohol use is reported in approximately 30–50% of people with HIV, which not only accelerates liver injury and worsens immune dysfunction but also undermines adherence to ART and nutritional status [9, 10]. Collectively, these challenges mean people with HIV face disproportionately high risks of liver disease progression, cirrhosis, hepatic decompensation and hepatocellular carcinoma compared to HIV-negative individuals [11]. As the prevalence of aging people with HIV grows, addressing these multifactorial risks has become an urgent public health priority. Beyond viral hepatitis and alcohol-related injury, there is recognition that metabolic conditions, such as insulin resistance, obesity and dyslipidaemia, are playing an increasingly prominent role in shaping liver health in this population. This evolving metabolic burden highlights the need to better characterize its intersection with HIV, setting the stage for further exploration of metabolic dysfunction-associated steatotic liver disease (MASLD) as the most common chronic liver disease among people with HIV.

MASLD IN PEOPLE WITH HIV: A CLINICAL CHALLENGE

MASLD, previously encompassed under non-alcoholic fatty liver disease (NAFLD), is now recognized as the leading cause of chronic liver disease worldwide, affecting approximately 38% of adults [12, 13]. MASLD also increases the risk of cardiovascular events and extrahepatic malignancies, reinforcing its significance beyond hepatic outcomes [14, 15]. Among people with HIV, MASLD prevalence ranges from 20% to over 60%, reflecting a convergence of HIV-specific mechanisms, ART-related metabolic disturbances and traditional cardiometabolic risk factors [16–19]. While earlier studies largely focused on hepatic steatosis in HCV/HIV coinfection, the burden of MASLD in people with HIV without viral hepatitis is now established [20]. A recent meta-

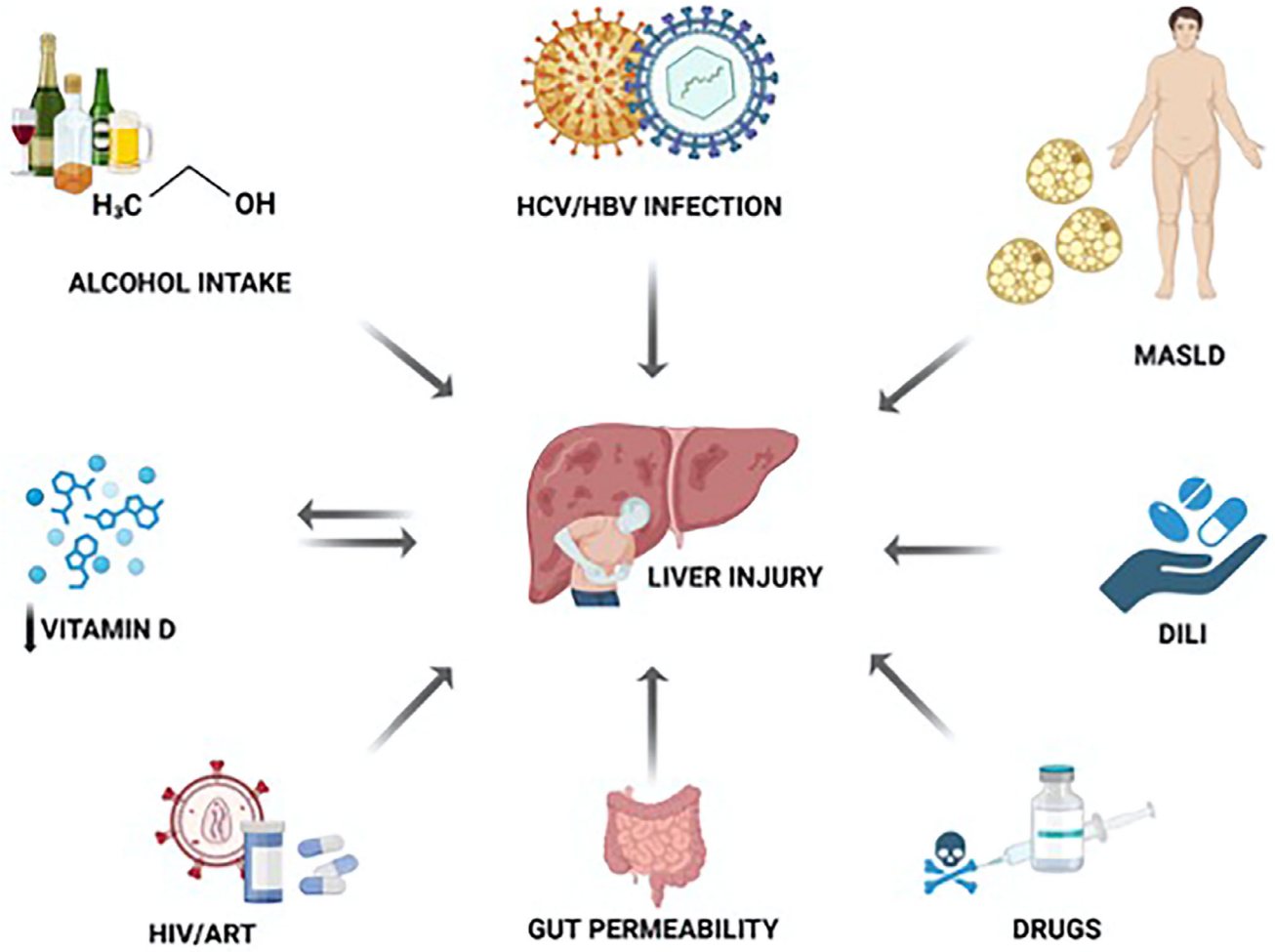

FIGURE 1 Multi-hit contributors to liver injury in people with HIV. ART, antiretroviral therapy; DILI, drug-induced liver injury; MASLD, metabolic dysfunction-associated steatotic liver disease.

analysis reported a pooled MASLD prevalence of 33.9% in this population [16], with significant liver fibrosis and metabolic dysfunction-associated steatohepatitis (MASH) reaching approximately 15% and 11%, respectively, in unselected cohorts [16, 19, 21]. These rates exceed those observed in the general population, highlighting a more aggressive disease course in people with HIV. HIV itself may contribute directly to steatosis and fibrosis through viral interactions with hepatocytes and Kupffer cells, inducing lipid accumulation and pro-fibrotic signalling, alongside secondary immunological dysfunction [5]. In parallel, chronic immune activation, characterized by elevated circulating tumour necrosis alpha-α and interleukin-6, promotes insulin resistance and hepatic stellate cell activation, accelerating liver fibrosis [22]. A recent Spanish study highlighted these interactions, showing that liver steatosis correlated with higher baseline HIV viral loads and greater current CD4 counts, likely reflecting metabolic shifts following immune restoration [23]. Alterations in gut permeability and microbial translocation, which are frequent occurrences in the context of HIV infection, further drive endotoxaemia and hepatic inflammation [22, 24]. Additionally, ART plays a significant role: older agents like dideoxynucleoside analogues were linked to mitochondrial toxicity and hepatic steatosis [22, 25]. Contemporary regimens are almost universally based on integrase strand transfer inhibitors (INSTIs), often co-formulated with tenofovir alafenamide, both of which have been associated with weight gain and obesity [26–28]. While the direct association between INSTI use and MASLD remains an area of ongoing investigation, the indirect link mediated by weight gain is well documented [26]. Nevertheless, both weight gain and obesity, as well as MASLD, are multifactorial in nature. Protease inhibitor (PI)-based regimens, particularly those boosted with ritonavir, are also well known to disrupt metabolic homeostasis. They are strongly associated with dyslipidaemia and contribute to

insulin resistance through direct and indirect mechanisms, including interference with glucose transporter activity and promotion of visceral adiposity [22]. Furthermore, traditional risk factors such as obesity, type 2 diabetes, hypertension and sedentary lifestyles are common in this population and interact with these HIV-specific mechanisms [5]. Several studies demonstrated associations between higher body mass index (BMI) and liver steatosis in people with HIV and well-controlled infection on long-term ART [20, 27, 29]. Given this convergence of viral, immunological and metabolic hits, the European AIDS Clinical Society (EACS) recommends screening for MASLD-associated liver fibrosis in people with HIV who are overweight, have metabolic syndrome, elevated transaminases or prior exposure to older ART [17, 30]. This proactive approach is crucial, as even in the absence of HBV or HCV coinfection or significant alcohol use, people with HIV face increased risk of liver fibrosis. Despite this growing recognition, many aspects of MASLD pathogenesis in people with HIV remain incompletely understood. The complex interplay of chronic immune activation, microbial translocation, ART-induced metabolic changes and conventional cardiometabolic risks underscores the multifactorial nature of liver disease in this setting. Yet, important gaps persist, particularly in disentangling the mechanisms that drive MASLD and fibrosis progression, and identifying modifiable factors that could alter its course. Notably, disturbances in vitamin D metabolism have emerged as a potentially relevant yet underexplored contributor, warranting closer examination in the context of HIV-associated liver disease.

VITAMIN D DEFICIENCY IN HIV: INTERSECTING PATHWAYS AND SYSTEMIC COMPLICATIONS

Vitamin D has two primary sources: dietary intake of vitamin D3 from foods such as fatty fish, eggs, dairy products and fortified items and cutaneous synthesis, where exposure to ultraviolet B (UVB) radiation from sunlight converts 7-dehydrocholesterol in the skin into previtamin D3 [31]. Once in circulation, vitamin D3 is first hydroxylated in the liver by CYP2R1 to 25-hydroxyvitamin D [25(OH)D], the main circulating marker of vitamin D status. It is again hydroxylated in the kidneys by CYP27B1 into the biologically active hormone 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]. This active form exerts pleiotropic effects on target organs: it regulates parathyroid function and calcium-phosphate homeostasis, promotes bone mineralization, modulates immune responses by shaping T-cell differentiation and cytokine production, maintains gut barrier integrity and nutrient absorption and contributes to glucose homeostasis through actions on pancreatic β-cells and hepatic insulin sensitivity. Together, these pathways underscore vitamin D's central role in skeletal, metabolic and immune health. According to the Institute of Medicine, vitamin D insufficiency is defined as serum 25(OH)D levels between 30 and 50 nmol/L, while deficiency is classified as levels below 30 nmol/L. Similarly, EACS defines deficiency as serum 25(OH)D < 25 nmol/L and insufficiency as <50 nmol/L [30]. However, the International Osteoporosis Foundation and Endocrine Society commonly use <50 nmol/L to define deficiency and 50–74 nmol/L for insufficiency [32, 33]. These thresholds are grounded in evidence showing that parathyroid hormone (PTH) levels decrease and fall risks are reduced above ∼75 nmol/L, while severe deficiency (<25 nmol/L) dramatically heightens the risk of osteomalacia and impaired mineralization [31]. Although vitamin D deficiency is relatively common in the general population, with data showing a prevalence of about 16%, HIV-specific mechanisms further aggravate this risk [34]. Vitamin D deficiency is highly prevalent among people with HIV, with studies across Europe and North America reporting rates ranging from 58% to over 85% [35]. The burden of vitamin D deficiency in people with HIV is partly driven by traditional factors, such as inadequate sunlight exposure, low dietary intake, obesity, aging and darker skin pigmentation, much like in the general population. However, HIV-specific mechanisms markedly amplify this burden [36]. Chronic HIV infection is characterized by persistent inflammation, immune dysregulation and low CD4 counts, along with monocyte/macrophage dysfunction and residual viral replication. These factors collectively impair both hepatic and extra-renal conversion of vitamin D to its active forms [36]. Vitamin D synthesis, initiated in the skin via UVB exposure, relies on subsequent hepatic 25-hydroxylation and renal 1α-hydroxylation. However, HIV itself and certain ART disrupt these pathways [35, 36]. PIs, particularly when boosted with ritonavir, potentially inhibit hepatic 25-hydroxylase and renal 1α-hydroxylase, while also mildly blocking 24-hydroxylase, leading to reduced production of 1,25$(OH)_2$D and dysregulated calcium-PTH feedback [37]. Non-nucleoside reverse transcriptase inhibitors such as efavirenz induce CYP24 and CYP3A4, accelerating vitamin D catabolism, a process intensified by common genetic polymorphisms like CYP2B6 G516T [38]. Clinical studies support these mechanisms: several cohorts have documented persistent PTH elevations in patients on boosted PI regimens despite vitamin D repletion, and longitudinal analyses show increased rates of deficiency under efavirenz treatment [39, 40]. Additionally, tenofovir disoproxil fumarate independently influences vitamin D metabolism and is

linked to alterations in bone turnover markers [41]. These disruptions compound broader HIV-related insults to skeletal health, including ART-associated lipodystrophy, imbalances in osteoblast and osteoclast activity, chronic inflammation and shared risk factors such as low BMI, aging, smoking and hypogonadism [35, 36]. As a consequence, vitamin D deficiency in people with HIV has been associated not only with osteopenia, osteoporosis and increased vertebral fracture risk, but also with systemic complications [35, 42, 43]. A few studies in people with HIV have suggested an association between vitamin D deficiency and cardiovascular disease, including increased carotid intima-media thickness and a higher prevalence of coronary artery calcification [44]. In a study of 1811 people with HIV, type 2 diabetes was associated with a significantly increased likelihood of vitamin D deficiency, defined as serum 25(OH)D levels below 50 nmol/L, with an odds ratio of 1.85 (95% confidence interval, 1.03–3.32) [42]. Moreover, vitamin D deficiency has been linked to elevated interleukin-6, activated monocyte subsets (CX3CR1+, CCR2+) and oxidative stress markers, suggesting a contributory role in the chronic immune activation that characterizes HIV infection [45]. Emerging research suggests that vitamin D deficiency may aggravate key cardiometabolic processes by impairing pancreatic β-cell function, reducing peripheral glucose uptake and disrupting hepatic lipid metabolism [46, 47]. These mechanisms contribute to insulin resistance and adverse lipid profiles. Consistently, studies have shown that vitamin D deficiency is associated with higher insulin resistance, elevated triglycerides and markers of endothelial dysfunction, collectively heightening cardiovascular risk [46–48]. In 554 healthy adults, vitamin D insufficiency defined as serum 25(OH)D < 75 nmol/L was associated with increased arterial stiffness and endothelial dysfunction [48]. Vitamin D deficiency has also been linked to increased visceral adiposity and dysregulation of adipokines such as adiponectin and leptin, further reinforcing a pro-steatotic and pro-inflammatory milieu that may accelerate hepatic fat accumulation and fibrosis [49, 50]. These mechanisms are particularly relevant given the elevated burden of metabolic syndrome and MASLD in people with HIV. Beyond these metabolic and inflammatory effects, vitamin D exerts direct immunomodulatory actions. Its receptor and activating enzymes are expressed across nearly all immune cell types, where vitamin D promotes regulatory T-cell differentiation, tempers NF-κB signalling, shifts Th1/Th2 balance and enhances local $1,25(OH)_2D$ production by monocytes [51]. This, in turn, upregulates antimicrobial peptides such as defensins and cathelicidin, the latter of which has demonstrated direct anti-HIV activity in vitro [52, 53]. Collectively, these pathways highlight that vitamin D deficiency in HIV extends beyond the skeleton, intersecting with metabolic, cardiovascular and immune vulnerabilities that compound long-term health risks in this population.

VITAMIN D, LIVER DISEASE AND COMPOUNDING RISKS IN HIV

Vitamin D's influence extends importantly to liver pathology (Figure 2). In viral hepatitis, vitamin D deficiency, defined in most studies as serum 25(OH)D levels <50 nmol/L, is highly prevalent among patients with chronic HBV and HCV infections. A meta-analysis of 641 patients with chronic HBV reported a combined prevalence of 56%, while several studies have demonstrated that low vitamin D levels correlate with higher HBV DNA levels, increased transaminases and more advanced fibrosis stages [54, 55]. Some reports even suggest genotype-specific differences, such as greater deficiency among patients infected with HBV genotype B compared to genotype C, possibly reflecting differential impacts on hepatic vitamin D metabolism or immune modulation [56]. The association between vitamin D deficiency and HCV is even more extensively documented. Patients with chronic HCV often exhibit markedly reduced serum 25(OH)D levels, which have been linked to higher HCV RNA loads, more severe necroinflammatory activity and accelerated fibrosis progression [57, 58]. In a meta-analysis of over 3000 patients with chronic hepatitis C, low baseline vitamin D, defined as serum 25(OH)D levels <50 nmol/L, was associated with both increased histologic severity of liver disease and poorer responses to interferon-based therapy—also adjusting for interleukin 28B genetic variants, underscoring its relevance not only as a biomarker of liver injury but also as a potential modulator of antiviral immunity [59]. The liver expression of vitamin D receptor has also been documented in hepatocytes and cholangiocytes of people with HCV, lower concentrations being associated with the severity of liver damage in terms of both necroinflammation and fibrosis [57]. Additional mechanistic studies have proposed that vitamin D deficiency may exacerbate HCV-induced oxidative stress and pro-fibrotic signalling through transforming growth factor-β (TGF-β) and tissue inhibitor of metalloproteinases-1 pathways, further driving hepatic stellate cell activation and fibrogenesis [60]. Coinfections with HBV and HCV are notably more prevalent among people with HIV than in the general population, and they accelerate progression to cirrhosis and liver failure. They compound vitamin D deficiency through multiple mechanisms including heightened

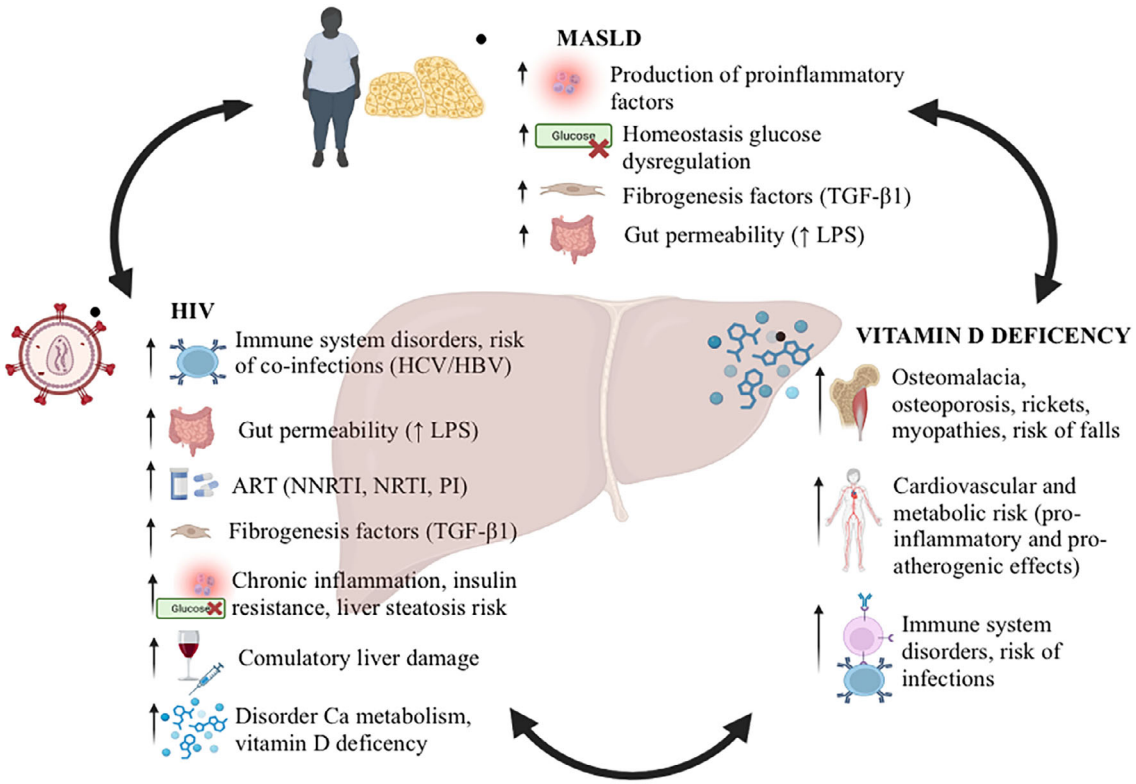

FIGURE 2 Interplay of MASLD, vitamin D deficiency and HIV in liver injury. ART, antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; LPS, lipopolysaccharide; MASLD, metabolic dysfunction-associated steatotic liver disease; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; TGF-β, transforming growth factor-beta. [Correction added on 25 September 2025, after first online publication. Figure 2 has been corrected in this version.]

systemic inflammation, mitochondrial dysfunction and pro-fibrotic signalling cascades involving TGF-β, hypoxia-inducible factor 1-alpha and the Hippo-YAP pathways [61, 62]. Consistent with these interactions, vitamin D deficiency has been reported in up to 40% of patients with HIV/HCV coinfection, highlighting the added burden of micronutrient disturbances in this high-risk group [63]. In this population, vitamin D deficiency has been associated with the severity of liver disease, including liver fibrosis and hepatic necroinflammation (Table 1) [64–68]. Interestingly, in our recent study of 321 individuals with HIV/HCV coinfection, we found that elevated fibroblast growth factor 23 (FGF23) levels, defined as >241 RU/mL, were independently associated with a higher incidence of all-cause mortality (66.1 vs. 37.5 per 1000 person-years) and with increased risk of liver fibrosis. Notably, mediation analysis indicated that 57% of the excess mortality risk associated with elevated FGF23 was not attributable to advanced liver fibrosis, suggesting that FGF23 may serve as a broader prognostic marker in this population [69]. Mechanistically, FGF23 inhibits renal 1α-hydroxylase (CYP27B1), thereby reducing the conversion of 25(OH)D into active $1,25(OH)_2D$, while simultaneously stimulating 24-hydroxylase (CYP24A1) to accelerate vitamin D catabolism. This dual action ultimately lowers circulating calcitriol levels, impairing calcium and phosphate absorption and contributing to systemic and hepatic consequences [70]. In alcoholic liver disease, vitamin D deficiency, often exacerbated by poor nutritional intake, further compounds hepatic injury by worsening gut barrier dysfunction and promoting increased intestinal permeability [71]. This facilitates the translocation of lipopolysaccharide into portal circulation, which activates hepatic macrophages via TLR4 signalling, propagating pro-inflammatory cytokine release and hepatic stellate cell activation, thereby accelerating steatosis and fibrosis [72].

Among people with HIV, these processes converge with particularly deleterious synergy, especially in MASLD. In a cross-sectional study involving 89 nondiabetic people with HIV on stable or initiating ART, insulin resistance remained significantly correlated with vitamin D insufficiency, defined as serum 25(OH)D levels <75 nmol/L, even after adjusting for age, HIV duration, ART exposure, lipodystrophy, BMI and visceral

TABLE 1 Studies ($n = 7$) on vitamin D and liver diseases in people with HIV.

Study	Design / Country	N	Age (yrs)	Male (%)	Vitamin D deficiency/ insufficiency (%, definition)	BMI (kg/m^2)	Diabetes (%)	Duration HIV infection (yrs)	Vitamin D concentration	MASLD (%)	HCV (%)	HBV (%)	Liver assessment method	Main findings
Milazzo 2011	Retrospective/ Italy	237	45 (41–49)	68.3	68% (<30 ng/mL)	23.6 (21.2–25.3)	NA	14 (9–19)	23.4 ng/mL (16.7–33.7)	57	39	NA	Liver biopsy	Low vitamin D was independently associated with advanced fibrosis in HIV/HCV coinfected patients
Terrier 2011	Retrospective/ France	189	39.5 (±4.8)	77.2	63% insufficiency (11–30 ng/mL); 23% deficiency (≤10 ng/mL)	22.7 (±3.2)	NA	12 (0.5–18.5)	18.5 ng/mL (±9.8)	NA	100	NA	Liver biopsy	Low vitamin D correlated with severe liver fibrosis
El-Maouche 2013	Prospective/ United States	116	49.9 (46.5–53.3)	63	41% (<15 ng/mL)	Obese 22%	NA	NA	19 ng/mL (11–26)	NA	100	NA	Liver biopsy	Vitamin D deficiency not associated with fibrosis or bone mineral density
Avihingsanon 2014	Prospective / Thailand	130	42 (37–48)	85.4	47.9% insufficiency (20–30 ng/mL); 13.7% deficiency (≤20 ng/mL)	Overweight 15.8%	NA	NA	27 ng/mL (22.4–34.3)	NA	100	NA	Transient elastography, FIB-4, APRI	Significant fibrosis associated with HIV, FIB-4 >1.45, and hypovitaminosis D
Guzman-Fulgencio 2014	Retrospective / Spain	174	40.8 (37.3–44.6)	74.7	15.5% (<25 nmol/L)	22.5 (20.4–24.3)	NA	NA	19.2 ng/mL (13.0–22.4)	NA	100	0	Liver biopsy	Vitamin D deficiency was associated with liver disease severity on biopsy, not with HCV treatment failure
Milic 2020	Retrospective / Italy	707	53.5 (±8.2)	76.2	NA (<50 nmol/L)	24.6 (±4.2)	18.3	275 (median)	NA	39.7	0	0	Transient elastography	Vitamin D insufficiency significantly associated with MASLD and fibrosis
Calza 2024	Retrospective / Italy	413	52.2 (±10.1)	78.9	13.3% (<10 ng/mL)	23.0 (±3.1)	9.2	14.3 (±7.2)	31.2 ng/mL (±21.5)	32.7	7	5.6	Transient elastography	Factors independently associated with vitamin D deficiency: MASLD, hypertension, overweight, metabolic syndrome, triglycerides, bone mineral density

Note: Continuous variables are expressed as mean ± standard deviation or median and interquartile range, and categorical variables are presented as percentages.

Abbreviations: APRI, AST-to-platelets ratio index; BMI, body mass index; FIB-4, fibrosis 4 index; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MASLD, metabolic dysfunction-associated steatotic liver disease; NA, not available.

adiposity [73]. Consistent with these findings, additional studies linked low vitamin D to an increased risk of type 2 diabetes in this population [42, 44]. Beyond glycaemic outcomes, low vitamin D levels have also been linked to MASLD and related hepatic complications. Several case–control and cross-sectional studies consistently demonstrate inverse relationships between serum 25(OH)D levels and hepatic steatosis, fibrosis and lobular inflammation, independent of age, BMI or classic metabolic factors [74, 75]. Experimental models reinforce this association: vitamin D-deficient rodents display more pronounced hepatic steatosis, higher NAFLD activity scores, increased expression of pro-inflammatory cytokines such as tumour necrosis factor alpha and interleukin-6, reduced adiponectin levels and compromised gut barrier integrity, all contributing to endotoxaemia and hepatic macrophage activation [76]. Vitamin D deficiency is compounded by chronic HIV-related inflammation and ART effects, amplifying insulin resistance and dyslipidaemia, which are central drivers of MASLD [5, 22]. Meanwhile, MASLD-induced hepatic dysfunction can diminish local 25-hydroxylation capacity, perpetuating a vicious cycle of worsening vitamin D deficiency and liver injury [77]. Additionally, chronic bacterial translocation in HIV maintains hepatic macrophage activation and fibrogenesis, linking gut barrier dysfunction, systemic inflammation and vitamin D deficiency into a unified pathogenic framework [78, 79]. Beyond these indirect mechanisms, vitamin D also directly shapes metabolic and immune environments relevant to MASLD: deficiency is associated with increased visceral adiposity, dysregulated adipokines such as a reduced adiponectin and elevated leptin and heightened oxidative stress, fostering a pro-steatotic and pro-fibrotic hepatic milieu. Emerging clinical data highlight these intersections. In our multicentre study of 707 people with HIV, vitamin D insufficiency, defined as serum 25(OH)D levels <50 nmol/L, was significantly associated with MASLD and fibrosis on univariate analysis and frailty was independently linked to greater liver fibrosis [80]. Given that low vitamin D has also been tied to higher frailty scores in both HIV and general aging populations, this suggests another dimension by which vitamin D deficiency may indirectly accelerate liver disease progression [81, 82]. Similarly, in a cross-sectional study of 413 people with HIV, vitamin D deficiency, defined as serum 25(OH)D levels <50 nmol/L, remained significantly associated with MASLD, metabolic syndrome, hypertension, elevated BMI, waist circumference, reduced bone mineral density and hypertriglyceridaemia, even after multivariate adjustment [83]. Together, these data underscore the multifaceted impact of vitamin D deficiency on metabolic and hepatic health in people with HIV, positioning it as a key factor intertwined with insulin resistance, cardiometabolic risk and progressive liver disease. Sex dimorphism further complicates this interplay. Vitamin D pathways are influenced by sex hormones, notably oestrogens and androgens, which modulate circulating vitamin D levels, vitamin D–binding protein and potentially vitamin D activation [84]. In HIV, where sex-specific differences are well documented, a study of 1472 people with HIV from our team found that women had a lower overall prevalence of MASH with fibrosis compared to men, yet showed a sharp increase around perimenopause [85]. This likely reflects hormonal shifts that reduce the protective effects of oestrogen on both vitamin D metabolism and hepatic lipid homeostasis, thereby increasing susceptibility to MASLD progression.

This convergence across viral hepatitis, alcoholic liver disease and MASLD, all amplified by vitamin D deficiency, highlights why vitamin D is increasingly regarded not merely as a passive biomarker but as a potentially modifiable factor that could influence the trajectory of liver disease in people with HIV. It also underscores the need for integrated strategies that address vitamin D status alongside ART optimization, metabolic management and liver health monitoring to mitigate the compounded hepatic and systemic risks in this vulnerable population.

VITAMIN D STATUS, LIVER DISEASE AND CLINICAL OUTCOMES IN PEOPLE WITH HIV

Multiple observational studies report associations between low vitamin D levels and adverse outcomes in people with HIV, including AIDS progression and higher mortality [86]. In the EuroSIDA cohort, higher serum 25(OH)D levels were linked to lower mortality and fewer AIDS events [87]. However, randomized evidence to date does not support a causal protective role of vitamin D. In a large double-blind placebo-controlled trial of 4000 people with HIV, high-dose vitamin D_3 supplementation did not reduce mortality, tuberculosis incidence or HIV progression in individuals initiating ART with baseline deficiency [88]. Similarly, no consistent benefits were observed for comorbidities, weight or viral suppression [89]. In chronic liver disease more broadly, vitamin D deficiency has been linked to higher risks of cirrhosis and hepatocellular carcinoma in retrospective cohorts, but these studies again cannot exclude reverse causality or confounding [90]. Mendelian randomization analyses have further failed to demonstrate a causal relationship between vitamin D levels and alcoholic liver disease [91]. In a meta-analysis on patients with MASLD, vitamin D supplementation did not improve liver enzymes, insulin

resistance, glucose metabolism parameters and lipid levels [92]. While a recent meta-analysis of randomized controlled trials (RCTs) in chronic liver disease found significantly reduced alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, triglycerides and insulin in the vitamin D-supplemented group, the effect was modest [93]. In addition, there were no differences in survival or liver fibrosis markers. Further RCTs with adequate power are warranted to clarify the results. Taken together, the current evidence does not support that optimizing vitamin D levels improves clinical outcomes in people with HIV with liver disease. Supplementation should not be equated with therapeutic benefit, and future well-powered, disease-specific interventional trials, with specific studies targeting people with HIV, are required to determine whether vitamin D plays a causal role in modifying disease course or prognosis.

PRACTICAL MANAGEMENT OF VITAMIN D IN PEOPLE WITH HIV WITH LIVER DISEASE

Vitamin D deficiency is common in chronic liver diseases [94] and in people with HIV, who may have additional risks, including malabsorption, impaired hepatic metabolism and ART-induced catabolism of vitamin D metabolites [63]. It is reasonable to measure serum 25(OH)D in people with HIV with liver disease. Targets differ by guideline: osteoporosis/endocrine societies generally consider ≥75 nmol/L sufficient, whereas EACS targets ≥50 nmol/L (with normal PTH) [33, 94]. In practice, clinicians should aim for at least ≥50 nmol/L, with consideration of ≥75 nmol/L in those with low bone mineral density, fractures, elevated PTH or persistent risk [33, 94, 95]. When supplementation is indicated, it is important to tailor to baseline level and disease severity [94]. Severe deficiency (<12.5 nmol/L) may be treated with cholecalciferol 50,000 IU weekly for 12 weeks, followed by monthly maintenance. For levels between 12.5 and 37.5 nmol/L, the same weekly regimen for 4 weeks followed by monthly maintenance is appropriate. Moderate deficiency (40–75 nmol/L) is often corrected with a monthly 50,000 IU dose. Patients with low normal (50–75 nmol/L) or >37.5 nmol/L with ongoing risk may benefit from daily supplementation of 800–2000 IU. Higher daily doses (2000–4000 IU/day) may be needed in cirrhosis, obesity or with interacting ART, with monitoring [96]. In advanced liver disease, calcifediol (25(OH)D) may offer pharmacokinetic advantages, though comparative evidence versus cholecalciferol remains limited [95]. Serum 25(OH)D should be reassessed after 8–12 weeks, especially in high-risk or non-adherent patients; then monitoring could be extended to 6–12 month intervals once sufficiency is achieved. Beyond supplementation, nutritional and lifestyle interventions should be emphasized. A diet including fatty fish, fortified dairy or plant-based milks and eggs provides natural vitamin D intake, while adequate calcium intake supports bone health. Safe sunlight exposure, moderation of alcohol and weight control are additional pragmatic measures. In people with HIV, correcting vitamin D deficiency supports not only skeletal health, but may also potentially influence liver and immune outcomes, though definitive evidence remains limited [97, 98].

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

Among people with HIV, vitamin D deficiency is common, particularly in those with liver disease, metabolic syndrome or chronic HBV or HCV coinfections [35, 42, 64]. Growing evidence suggests that low vitamin D levels may aggravate insulin resistance, dyslipidaemia, immune activation and hepatic fibrogenesis, key drivers of MASLD and other chronic liver diseases in this population [22, 35, 36]. Despite these biologically compelling links, the current literature is constrained by predominantly cross-sectional studies, heterogeneous study populations, inconsistent definitions of deficiency and a marked lack of RCTs directly evaluating the impact of vitamin D supplementation on liver outcomes. Notably, some recent RCTs in people with HIV, although not specifically addressing MASLD, have demonstrated that vitamin D supplementation can improve other clinically relevant outcomes, such as endothelial function, carotid intima-media thickness and markers of immune activation, further supporting the potential benefits of optimizing vitamin D status [99]. These findings reinforce the biological plausibility of broader metabolic and vascular benefits, though targeted trials on liver-specific endpoints remain lacking. These limitations hamper the development of clear, evidence-based guidelines for screening and intervention. Nonetheless, given the intricate ties among vitamin D status, metabolic health and immune regulation, routine assessment and targeted supplementation appear prudent, especially for people with HIV with established liver disease or high metabolic risk. The EACS already recommends vitamin D screening in individuals with low bone mineral density, increased fracture risk or classic risk factors such as darker skin pigmentation, limited sun exposure, malabsorption, obesity, chronic kidney disease and certain ART regimens known to reduce vitamin D levels [30]. While optimal 25(OH)D

targets remain to be defined for this unique population, adopting a multidisciplinary approach, thus engaging hepatologists, endocrinologists, infectious disease specialists and nutritionists, will be essential to tackle the multifactorial drivers of liver and metabolic disease in people with HIV. Looking ahead, robust longitudinal and interventional studies, including mechanistic investigations, are needed to determine whether correcting vitamin D deficiency can meaningfully alter the trajectory of liver disease and metabolic complications in people with HIV.

CONCLUSIONS

Significant progress has been made in elucidating the associations among vitamin D deficiency, HIV infection and chronic liver disease, yet our understanding remains limited by largely cross-sectional evidence, heterogeneous cohorts and a shortage of rigorous interventional trials. These gaps restrict our ability to establish causality or define optimal management strategies. Still, the intersection of vitamin D with metabolic, hepatic and immune pathways highlights an important, and potentially modifiable, axis of disease progression in people with HIV. In this context, routine screening for vitamin D deficiency, judicious supplementation and comprehensive nutritional counselling represent practical interim measures while awaiting more definitive data. Public health initiatives that promote balanced diets and raise awareness in at-risk communities may further support liver health and mitigate metabolic complications. Ultimately, advancing our knowledge through prospective studies will be crucial to determine whether targeted vitamin D interventions can reduce liver injury and metabolic deterioration, opening new avenues to improve long-term outcomes in people with HIV.

AUTHOR CONTRIBUTIONS

FF, AD and GS contributed to the study conception, design, data acquisition, interpretation and drafting of the manuscript. SNM, SS, BL, GG and SP were involved in study conception and interpretation. All authors reviewed and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

SS has served on an advisory board for Novo Nordisk. GS has acted as a speaker for Merck, Gilead, Abbvie, Novo Nordisk, Eli Lilly, Merck and served as an advisory board member for Gilead, GlaxoSmithKline, Novo Nordisk. FF, AD, SNM, BL, GG and SP have nothing to disclose.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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