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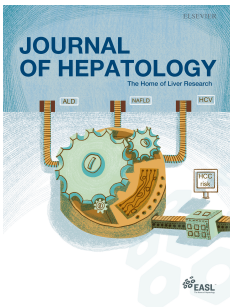

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Hepatocellular carcinoma in people living with HIV

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Summary

People living with HIV (PLWH) carry a higher risk of developing chronic liver disease and hepatocellular carcinoma (HCC). This relates to shared transmission pathways of HIV and viral hepatitis and a plethora of direct and indirect effects of HIV in the progression of chronic liver disease and HCC. In absence of active cancer treatment, the prognosis of PLWH affected by HCC is worse compared to matched controls without HIV. Evolving evidence suggests that PLWH may receive curative therapies including liver transplantation, loco-regional and systemic anti-cancer therapy for HCC with comparable benefit than people without HIV, underscoring that well controlled HIV infection should not be a barrier to the delivery of cancer care.
Nevertheless, PLWH have historically been excluded from interventional clinical trials, and most of the evidence supporting clinical decision making in this population comes from small retrospective studies, adding further challenges to the management of PLWH affected by HCC. Furthermore, whether the biology of the tumour and its microenvironment is influenced by HIV and affects response to treatment is incompletely understood. In this review we summarise the current understanding of pathophysiology, screening and management of HCC in PLWH and discuss the persisting challenges and disparities in care which may contribute to clinical outcome in PLWH.

Key points

- People living with HIV (PLWH) have higher risk of chronic liver disease and HCC compared to people without HIV (PWOH).
- The prognosis of chronic liver disease in PLWH is worse compared to PWOH
- The prognosis of HCC in PLWH is worse in the absence of therapy
- The direct role of HIV in influencing chronic liver disease and HCC progression is not clear.
- Available clinical trial testing immune-checkpoint inhibitors (ICIs) for HCC excluded PLWH
- Emerging real-world evidence supports the use of ICIs in PLWH

Introduction

According to the most recent data by the World Health Organization (WHO), there are over 39 million people living with HIV (PLWH) worldwide. Thanks to the widespread availability of combination anti-retroviral therapy (cART) to achieve suppression of HIV replication, the life expectancy of PLWH has increased to match, for most people, that of the general population. However, the risk of cancer remains higher in PLWH compared to people without HIV (PWOH) [1].

Amongst non-AIDS defining malignancies, the incidence of hepatocellular carcinoma (HCC) is constantly rising, with a 2 to 10-fold higher relative risk in PLWH compared to PWOH [2]. Available evidence indicates that the prognosis of PLWH affected by HCC is worse compared to matched PWOH, suggesting a more aggressive disease course [3].

HCC is invariably caused by chronic liver inflammation, being associated with liver cirrhosis in >80% of cases. In PLWH, due to shared routes of transmission, co-infection with hepatis B virus (HBV) and/or hepatis C virus (HCV) is frequent, making virally-induced HCC the

most common etiologic subset. In addition, multiple studies report higher prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH) in PLWH (~30-40%) compared to PWOH (~14-30%), mainly due to the metabolic impact of commonly used cART. All these factors are key contributors to the high prevalence of liver-related morbidity and mortality in PLWH [4].

In this review, we summarise existing evidence on the epidemiology, pathophysiology and management strategies for PLWH affected by HCC. Additionally, we highlight the ongoing challenges faced by physicians managing HCC in this population, with a particular focus on socioeconomic and healthcare disparities that continue to impact oncological care for PLWH.

HIV-associated HCC: epidemiology and risk factors

In the United States (US), the risk of HCC is 2.8 times higher in PLWH than in the general population [5], a pattern that is consistent across high-, low-, and middle-income countries [6]. Furthermore, liver-related mortality represents a leading cause of death not related to acquired immunodeficiency syndrome (AIDS) in PLWH in the post-cART era: up to 18% of non-HIV related death in PLWH involves a liver damage [4].
In PLWH, the prevalence of chronic HBV infection, defined as the persistence of hepatitis B surface antigen (HBsAg) in the blood, is estimated at 7.6% worldwide, with the greatest burden geographically concentrated in sub-Saharan Africa, where 69% of total HIV-HBV co-infection cases reside [7]. PLWH recognize the highest prevalence of people who inject drugs (PWID), with a global estimate of 11.8%.
The global prevalence of HCV infection, defined as anti-HCV seropositivity in PLWH is as high as 6.2% [7], rising up to 82.4% in PWID. Eastern Europe and central Asia are the macro-regions with the highest prevalence of HIV-HCV co-infection (27% of PLWH).
MASLD is an emerging threat to liver health and a leading risk factor for HCC, which often coexists with viral causes. The prevalence of MASLD worldwide mirrors that of obesity, and it has indeed increase by 50% over the past 3 decades, leading to an overall prevalence of ~30% [8]. Consequently, MASLD-related HCC accounts for around 35% of all global cases [9], and epidemiologic models estimate an increase of 130% in the United States from 2016 to 2030 [10].
Finally, PLWH are 2 to 4 times more likely to use alcohol compared to the general population [11]. The risk of hepatic fibrosis is higher in PLWH than in people without HIV for each alcohol-use category, included in people consuming low levels of alcohol [12]. However, to our knowledge, the exact rate of alcohol-related liver disease in PLWH worldwide is unknown.

Pathogenic mechanisms of liver carcinogenesis in PLWH

HIV infection increases the risk of HCC through both direct and indirect mechanisms. While the precise direct role of HIV in hepatocarcinogenesis remains unclear, data from mouse models genetically modified to express HIV proteins in the liver, suggest a potential pro-oncogenic effect of the viral protein *Tat* [13]. However, due to the scarcity of immune competent preclinical models for HIV-positive viral hepatitis, the direct effect of HIV in HCC development in the context of HBV and/or HCV co-infections remains poorly understood, and there is no clear evidence of a direct synergy between HIV and viral hepatitis in HCC development. Indeed, aside from causing immune suppression, there is not any evidence that suggests a direct role of HIV in facilitating HBV replication. Whereas in the absence of cART, the HIV-envelope protein gp120 may directly promote HCV replication via TGFbeta production. In vitro data indicated indeed that this effect could be abolished by blocking the

HIV receptors CCR5 and CXCR4 on hepatocytes, suggesting a direct interaction between HCV replication and these receptors [14].

The indirect oncogenic effects of HIV are primarily linked to immune-mediated mechanisms and the virus's pro-fibrotic impact on the liver microenvironment. These immune-mediated mechanisms can be categorized into those associated with advanced HIV and profound immune depletion, and those occurring despite well-controlled HIV infection [15].

PLWH have a higher risk of developing HCC, with this risk being inversely correlated with CD4 count [16] [6]. In HIV/HCV co-infected patients, lower CD4 counts, higher HIV RNA levels, and prolonged HIV viremia are associated with an increased risk of HCC [17]. In the post-cART era, immune-mediated mechanisms beyond HIV-induced immune suppression are gaining importance. Chronic HIV infection—even when well-controlled—leads to T-cell overactivation, systemic chronic inflammation, and immunological alterations commonly referred to as "immune exhaustion" [18]. Specifically, significant immune dysfunction affects both the innate (e.g., macrophages, NK cells, dendritic cells) and adaptive immune compartments (e.g., T and B cells) in PLWH with well-controlled infection. This dysfunction is linked to tumor immune escape, potentially contributing to increased cancer risk [18]. Chronic HIV antigen stimulation induces the expression of immune checkpoint molecules—such as PD-1, CD57, TIGIT, Tim-3, CD160, and Lag-3—on various immune cell subsets, leading to a dysfunctional immune state. Additionally, PLWH exhibit higher immune senescence in peripheral lymphocytes, which precedes cancer development [19]. Immune-exhausted T cells gradually lose their ability to produce cytokines, proliferate, and exert cytotoxic functions [18]. Notably, immune checkpoint inhibitors (ICIs) commonly used in oncology have been shown to restore HIV-infected lymphocyte function in vitro by disrupting HIV latency, further highlighting shared dysfunctional pathways between chronic HIV infection and cancer [20].

PLWH also experience accelerated liver fibrosis, particularly in cases of suboptimal CD4 count recovery [21]. Persistent CD8 activation—often following CD4 depletion—leads to increased levels of pro-fibrotic cytokines such as IL-4, IL-5, and TGF-beta, which promote liver fibrosis [22]. This effect is especially evident in HIV/HCV co-infected individuals, regardless of well-controlled HIV infection or successful HCV clearance. Mechanisms contributing to this phenomenon include hepatic CD4 cell depletion, leading to a shift toward pro-fibrotic Th2 cytokines [23], NK cell depletion [24], and increased gut bacterial translocation, which activates intrahepatic macrophages [25].
Moreover, HIV infection is often associated with metabolic dysfunctions and insulin resistance [26], which can lead to hepatic steatosis and subsequent fibrosis. These alterations can be attributed to virus-specific factors, such as immune dysfunction and mitochondrial toxicity; the effects of combination antiretroviral therapy (cART)—for instance, protease inhibitors like lopinavir/ritonavir [27], nucleoside reverse transcriptase inhibitors (NRTIs) such as zidovudine/lamivudine [28], all of which can contribute to insulin resistance; and the co-existence of other *noxa*, including alcohol consumption or illicit drug use [29] [30].

The immunological tumour microenvironment (TME) plays a central role in determining the emergence of HCC and influencing its progression [31]. However, due again to the difficulties in generating immune competent pre-clinical model of HCC in the presence of HIV infection, specific data about the composition of the TME in this setting are scarce [32]. Preclinical data from humanized mice models immune reconstituted with human fetal livers, infected with HIV and subsequently treated with cART, provides insights on the mechanism of liver fibrosis in the presence of cART treated HIV [33]. In particular, the mice reported accelerated liver fibrosis when infected with HIV and receiving cART. This was showed to be due to M2 macrophage accumulation and subsequent TGFbeta and IFN-I secretion, leading to hepatic stellate cells activation. Interestingly, IFN-I blockade was able to reverse the fibrotic process. The authors also identified high serum markers of macrophages activation

and IFN-I production in PLWH treated with cART compared to PWOH. These findings, despite not focusing on HCC, highlight the ability of well-controlled HIV to alter the liver immune environment. If these changes also apply to HCC in PLWH is not clearly understood and, nowadays, no pre-clinical models of HCC in the context of HIV have been generated. In humans, the largest available study published by our group in 2023 showed that the TME of early HCC in PLWH is associated with intratumoural infiltrates enriched in regulatory T cells and immune- exhausted CD8+PD-1+ T cells compared with a matched cohort of HCC in PWOH. These findings were also corroborated by the evidence of downregulation of gene signatures related to innate and adaptive immune response on targeted transcriptomic analyses. However, no differences were found in the TCRbeta clonality of intra-tumoral T cells, suggesting a possible role of HIV in driving a more pronounced dysfunction in the adaptive phase of the immune response.
Interestingly, almost all the patients were well-established on cART, and none of the findings was associated with peripheral CD4+ T cell count, nor other HIV-specific characteristics [34]. Whether these differences apply to uHCC and might influence response to ICI is currently not known. Pre-clinical and clinical dedicated studies are urgently needed to better elucidate the role of HIV in shaping the HCC-TME and response to anti-cancer treatments in PLWH.

Management of HCC risk factors in PLWH.

Due to the frequent co-existence of HIV with other HCC risk factors, specific considerations apply to PLWH in this context.

HBV-HIV co-infection.
Due to the high rate of HIV/HBV co-infection, international guidelines recommend that all PLWH should be tested for HBV, and vice versa [35-37]. Consequently, clinical management relies on HBV virological status and three serological profiles can be identified: 1) HBsAg-negative, anti-HBs-negative, and anti-HBc-negative (PLWH without HBV and therefore susceptible to HBV infection); 2) HBsAg-negative, anti-HBs negative/positive, and anti-HBc-positive (PLWH with previous HBV infection or “occult” HBV infection); 3) HBsAg-positive, anti-HBs negative, and anti-HBc-positive (PLWH with active HBV infection). For PLWH without HBV infection, HBV vaccination is recommended, although it has been demonstrated that response to the recombinant vaccines could be significantly lower compared to PWOH [38]. In these individuals, a higher dose (40 μg) or four vaccine doses could be needed to achieve an effective response [39].
Compared to HBV-monoinfected patients, HBsAg-positive PLWH display higher HBV replication levels and they are more prone to develop liver-related events, including the development of cirrhosis, hepatic decompensation, HCC, and liver-related death [40, 41]. For these reasons, international guidelines [35-37] recommend that all PLWH with HBV-coinfection should receive cART including TDF or TAF plus either lamivudine or emtricitabine, as soon as possible and regardless of CD4 cell count.

HCV-HIV coinfection.

All PLWH require screening for HCV infection [35]. HCV-seronegative patients at risk for HCV infection need to repeat testing annually, while HCV-seropositive patients should be tested for HCV RNA. Those testing positive for HCV RNA require HCV genotyping and staging of the severity of liver disease. This is clinically relevant given that risk of progression to cirrhosis and decompensation is threefold higher in HCV/HIV co-infected patients, compared to those with HCV monoinfection, especially in PLWH with low CD4+ T cell count [42]. Although cART may slow the rate of HCV-related liver disease progression in PLWH, the risk is still higher than in HCV monoinfected patients [43].
Overall, DAAs are effective in achieving sustained virological response (SVR) in patients with HCV/HIV co-infection [44-47].

Alcohol-related liver disease (ARLD)
All PLWH need to be screened for substance use disorders (SUDs), including alcohol use disorder (AUD). Alcohol and HIV infection have synergistic effects in the progression of liver fibrosis and end-stage liver disease, with pathogenic mechanisms including enhanced oxidative stress and inflammation and impaired immune response. Data about the direct synergistic effect of alcohol and HIV in HCC development, aside from accelerated liver inflammation are not available. Alcohol consumption is associated with all-cause and liver-related mortality in PLWH [48] [49] and staging of severity of liver disease in PLWH with positive screening test for AUD should follow recommendations from guidelines, similarly to PWOH [50].
Clinical challenges in this setting are represented by potential barrier to adherence to cART, the increased risk for cART-related DILI and altered ARV liver metabolism in patients with advanced ARLD and cirrhosis, and potential DDIs with pharmacological AUD treatments.

MASLD
Management of MASLD in PLWH represents a clinical challenge given the complex relationship between HIV infection and steatotic liver disease. While opportunistic infections and malnutrition had represented the main mechanisms leading to the development of steatotic liver disease in the era before the advent of highly effective cART, currently the increased life expectancy of PLWH exposes these individuals to the same cardiometabolic risk factors for the development of MASLD that are observed in uninfected patients. Moreover, cART increases the risk of metabolic dysfunction and insulin resistance through different pathways, with older ART regimens and protease inhibitors being associated with lipodystrophy and mitochondrial damage and modern cART being associated with weight gain and insulin resistance [51]. Thus, metabolic comorbidities commonly observed in patients with MASLD could represent both an adverse event of cART and a limiting factor in the choice of antiviral therapy, requiring a personalized approach based on virological and metabolic factors and specific metabolic adverse events of ARV therapy. Particularly, the duration of cART appears to be a major determinant of the risk of developing steatotic liver disease and metabolic comorbidities [52, 53].
For all these reasons, all PLWH should be screened for liver steatosis by abdominal ultrasound and for cardiometabolic risk factors. In those with ultrasound evidence of steatosis, non-invasive staging of the severity of liver disease should follow algorithms proposed by current guidelines [9].

Surveillance for HCC in PLWH

Detection of hepatocellular carcinoma at early stages is imperative for favourable outcomes and despite potential bias, patients enrolled in surveillance programs achieve better overall survival outcomes compared to those not undergoing screening [54]. Indeed, while median overall survival is >5 years in patients with BCLC stage 0/A, the survival is reduced to <6 months in patients with BCLC stage D [55, 56], underscoring the importance of an asymptomatic diagnosis of HCC in a context of preserved liver function.
Even though the risk for HCC development is significantly higher in PLWH (~0.75 cases per 1000 person-years) compared to the general population (0.1 cases per 1000 person-years), the overall incidence remains well below the proposed cut-off of 1.5%/year for cost-effective surveillance programs [57-60]. Therefore, current guidelines do not recommend HCC screening in all PLWH but recommend screening depending on the underlying liver disease in line with recommendations for PWOH. The risk for HCC development is profoundly influenced by the aetiology, activity and severity of the underlying liver disease not only in PWOH but also those living with HIV infection [61]. Therefore, recently published European

Association for the Study of the Liver (EASL) guidelines recommend surveillance with bi-annual sonography and alpha-fetoprotein (AFP) evaluation in all patients with established cirrhosis independent of the underlying liver disease unless patients have a relatively high risk of death from non-HCC causes or could not be offered any treatment for HCC (e.g., patients with decompensated cirrhosis ineligible for liver transplantation). The guideline panel also acknowledged the increased risk of HCC development in patients with advanced fibrosis without cirrhosis but concluded that evidence is insufficient to recommend HCC surveillance in this subgroup [62]. While data on surveillance programs or tools for risk stratification specific for PLWH are generally scarce and recommendations must be extrapolated from PWOH, a number of recent studies evaluated performance of surveillance in PLWH.

A European multi-cohort study evaluated the performance of the PAGE-B score, which includes patients' age, gender and platelets [63], as a biomarker to predict the risk of HCC in people living with HIV/HBV coinfection. While patients with a score <12 points had a risk for HCC development below the recommended threshold for screening (<0.2%/year), those with ≥12 points had a substantial risk and should therefore undergo screening [64]. Sustained virologic response (SVR) following direct-acting antiviral (DAA) treatment for HCV-coinfection has been shown to reduce the incidence of HCC development in PLWH, even though the risk likely remains elevated as compared to PLWH never infected with HCV. Indeed, two large European cohort studies reported an HCC incidence of ~1% per year in patients with HCV/HIV coinfection and cirrhosis who achieved SVR [65]. Even though this value is below the 1.5% HCC incidence/year cut-off for cost-effective surveillance derived from a decision-analysis model, indefinite screening is still recommended in this patient population [59] [62]. In line with the recent EASL guideline [62], validated risk stratification tools to focus screening efforts on patient subgroups with a relevant risk for HCC development are a research priority to not only save costs but also reduce other potential screening-derived harm such as psychological distress and unnecessary procedures in PLWH and cirrhosis. This is particularly important in PLWH, as they already require frequent medical visits for their condition, which can lead to increased psychological burden. Intensified surveillance for various other cancer types further adds to their time commitment, making efficient and targeted screening approaches even more crucial. Indeed, a recent prospective multicentre study involving 23 Spanish centres evaluating an 'untargeted' surveillance approach for non-AIDS-defining malignancies only identified a single HCC case among 124 patients with advanced fibrosis/cirrhosis or chronic HBV infection [66].

Management of HIV-associated HCC

Early and intermediate stage HCC

Differently from other malignancies occurring in PLWH, e.g., Kaposi's sarcoma, non-Hodgkin lymphoma, anal cancer and invasive cervical cancer, where specific guidelines exist for PLWH [67, 68], no specific recommendations are available for the treatment of PLWH affected by HCC. Therefore, most of the indications that clinicians follow derive from real-world studies.
Based on these premises, the staging and treatment of HCC in PLWH should follow the guidelines dictated by the Barcelona Clinic Liver Cancer (BCLC) algorithm. This not only considers tumour-related factors, but also liver function, the presence of portal hypertension and the physical status [69]. These factors should guide treatment decision in PLWH affected by HCC as they do for PWOH.

Available real-world studies in PLWH well-established on cART receiving curative loco-regional treatments (e.g., thermal ablation, macro-wave ablation) for early and intermediate

HCC indicate that the outcomes are comparable to those of PWOH [70]. Therefore, the oncological indications for LRT in the curative setting in PLWH are the same for PWOH [71].

Even if data on surgical outcomes for resectable HCC in PLWH are limited, HIV-infection by itself is not a general contra-indication to surgery [72]. Data about liver resection for HCC in PLWH derive from small retrospective series, including heterogeneous group of patients and based on different endpoints [73]. This prevents from drawing definitive conclusions on the best curative approach to follow in PLWH affected by early-stage HCC. Some retrospective evidence reported worse survival after liver resection for HCC in the presence of HIV-infection [74], however this was not confirmed by other series [75, 76], which identified tumour-related factors as main prognostic factors in this population. One small study including 27 PLWH receiving hepatectomy for early-stage HCC identified among other oncological factors, CD4 count < 200 cells/ µL as the only HIV-related independent negative prognostic factor for mortality [76]. Based on the yet scarce available evidence, and in the absence of dedicated guidelines, oncological indications to resection for early-stage HCC can mirror that of PWOH [73]. Despite the absence of HCC-specific guidelines for surgery in PLWH, it remains fundamental to refer to the international guidelines for the management of PLWH receiving elective surgery [77]. In general, HIV-RNA and CD4 count should be tested at least 6 months prior to surgery in all PLWH receiving elective procedures. In the case of undetectable viral load and CD4 count > 200 cells/ µL, the surgical plan can proceed as per PWOH. In the case of sub-optimal HIV-RNA control or suppressed CD4 count, HIV-specialist review is required prior to proceed to surgery. Furthermore, independently from the baseline viral status, consultation with an HIV-care provider is needed to advise on peri-operative cART interruption if dictated by the surgical circumstances, as well as on possible drug-to-drug interactions between cART and surgery-associated medications [77].

From an oncological point of view, orthotopic liver transplant (OLT) is considered for PLWH according to the BCLC algorithm [69], with HCC specific criteria following the local guidelines adopted for PWOH [78, 79]. This is indeed important to reinforce that HIV infection does not represent an exclusion criterion for solid organ transplants, including OLT [80] for HCC or any other causes [81]. Specific virological criteria need however to be met to ensure optimal post-transplant outcomes in PLWH. The criteria generally adopted in most transplant centres include CD4 count of at least 100 cells/µL, sustained HIV-RNA < 50 copies/ml, absence of active opportunistic infections, no history of visceral Kaposi's sarcoma, chronic cryptosporidiosis, primary central nervous system lymphoma, drug-resistant fungal infections, or progressive multifocal leukoencephalopathy used to be exclusion criteria. History of opportunistic infection used to be part of the exclusion criteria; however, this is currently no longer considered by most of the guidelines [37, 80, 82, 83]. The HIV-RNA target should be met and maintained for at least 3 months prior to OLT; however, if the target cannot be reached before OLT, this is commonly accepted to include otherwise eligible patients if HIV-RNA control is confidently predicted to happen post-OLT [83]. The length of HIV-RNA viral control prior to transplant has been possibly associated with the risk of acute rejection: longer the duration of HIV-RNA control, lower the risk of acute rejection. However, these data mainly derive from kidney transplant recipients, and a clear cut-off for the viral control duration has not been established. Therefore, as reported above, most of the guidelines usually recommend at least 3 months of adequate viral suppression [83]. When the specific virological criteria are followed, transplant can be safely performed in PLWH, and most recent evidence are concordant in reporting that OLT-specific outcomes and post-OLT HCC recurrence rate are comparable to matched PWOH cases [84-88]. The risk of acute rejection (< 6 months post-transplant) has been reported to be higher in PLWH, mostly in those receiving kidney [89] and heart transplant [90], and this has been mainly attributed to possible drug to drug interactions between post-transplant immune suppressant and cART [91]. In general, cART regimens containing protease inhibitors or boosters (e.g. cobicistat) should be avoided in the post-transplant setting [92]. Extensive discussion of the post-OLT pharmacological regimens is beyond the scope of this review. This is however

pivotal to strengthen the absolute need for the involvement of a multidisciplinary team with dedicated expertise in cART management [93] when OLT is performed in PLWH. Finally, despite the risk of solid tumour in patients receiving OLT is higher compared to the general population [94], mainly due to the need for life-long immune-suppression, the risk of non-HCC cancers post OLT in PLWH is not higher compared to matched controls without HIV. Therefore, well-controlled HIV-infection does not appear to synergistically increase the general risk of solid tumours after solid organ transplant in PLWH [95].

Few real-world studies have assessed the use of trans-arterial chemoembolization (TACE) performed in the palliative setting for intermediate stage HCC in PLWH. Initial data showed worse survival outcomes in PLWH compared to PWOH. These results have been summarised by a pooled meta-analysis of 6 real-world studies in 2021. This included a total of 305 PLWH affected by HCC receiving TACE and showed an almost doubled risk of death at 1 and 2 years compared to PWOH [71]. However, it is worth reporting the high heterogeneity of the studies included in the meta-analysis and the presence of selection biases which potentially impacted the overall results. Most of the studies included reported indeed worse baseline prognostic factors in PLWH [96-98], and the proportion of patients receiving TACE with curative intent was higher in the PWOH control cohort. Furthermore, the meta-analysis included HIV/HCV co-infected patients prior to the availability of DAA to treat HCV [98-100]. This is in fact well-known that the prognosis of HCV infection in PLWH was significantly worse than HCV mono-infected patients in the pre-DAA era [101, 102]. Interestingly, the studies where matching for baseline prognostic factors was performed, did not show any differences in terms of overall survival [71, 97]. None of the available evidence reported on the risk of adverse events from TACE in PLWH. Therefore, despite the absence of dedicated studies and guidelines, there is not any evidence to consider different oncological indications to TACE for intermediate stage HCC in PLWH [71].

In summary, in the cART era, PLWH established on cART affected by early or intermediate HCC can be safely offered the same therapeutic options-including OLT- as PWOH. However, the frequent coexistence of advanced liver fibrosis and portal hypertension, along with polypharmacy related to lifelong cART, necessitates a multidisciplinary approach involving specialists from different medical fields for optimal HCC management at all stages. When general anaesthesia or prolonged fasting is required, early consultation with HIV specialists is crucial to prevent drug-drug interactions (DDIs) and ensure uninterrupted cART exposure.

Advanced/Unresectable HCC

The prognostic role of HIV in patients receiving anti-cancer therapy for HCC is still unclear. However, PLWH are less likely to receive systemic therapy for HCC at recurrence and have higher probability to receive exclusive palliative care [99]. Solid prospective clinical data on the effect of systemic anti-cancer therapies for HCC in PLWH are currently lacking, because this subgroup is usually excluded from pivotal phase III trials.

In the tyrosine kinase inhibitor (TKI) era, the exclusion of PLWH from clinical trials was motivated by the risk of drug-to-drug interactions and increased or overlapping toxicities with combined anti-retroviral therapy (cART) [103]. Post-approval real-world data for sorafenib in PLWH, indicate that the overall survival may be inferior to that reported in the SHARP trial [104], while the safety profile appears overall consistent with that observed in PWOH [105]. It is important to note the heterogeneity of the available studies, their retrospective nature, which may affect the accuracy of adverse event reporting, and the small sample sizes in the absence of pooled meta-analyses. Moreover, the available evidence lacks sufficient power to differentiate between the potential prognostic impact of HIV infection on HCC progression and its interaction with the efficacy of sorafenib [104].

PLWH were also excluded from the REFLECT [106], CELESTIAL [107] and RESORCE [108] trials, therefore scattered data are available about the safety, efficacy and possible interactions between the TKIs currently approved for the treatment of HCC and cART.
Sorafenib undergoes a first oxidative metabolism via CYP3A4 and a second glucuronidation metabolism via UGT1A9 [109], therefore caution is advised when co-administered with protease inhibitors, which inhibit CYP3A4, or non-nucleotide reverse transcriptase inhibitors, which induce the same cytochrome [110]. However, no dedicated studies have been conducted in this setting in patients with HCC. A phase II study conducted in PLWH affected by Kaposi's sarcoma treated with sorafenib, reported indeed high incidence of adverse events, and a 3.8-fold increase in the CYP3A4 metabolite sorafenib-N-oxide in patients receiving ritonavir as cART, possibly explaining the higher rate of adverse events [111]. An alternative cART regimen is therefore recommended in PLWH treated with sorafenib. Fewer data are available regarding the safety and the pharmacodynamics of lenvatinib and regorafenib in PLWH [112]. However, both lenvatinib and regorafenib are mainly metabolized by CYP3A4 and aldehyde oxidase [109], and caution is required when co-administered with ART agents (e.g., ritonavir) which are known to inhibit the activity of these pathways due to the risk of increased concentration of lenvatinib.
No data are available about the safety and efficacy of cabozantinib in PLWH affected by HCC. The phase I AMC-087 study [113] investigated the pharmacodynamics of cabozantinib in PLWH affected by various types of cancers receiving cART. Patients were assigned to different dose levels depending on the type of cART they were receiving (CYP3A4 inhibitors-inducer or non-interacting). The authors concluded that the initial recommended dose for cabozantinib in PLWH receiving anti-retroviral therapy with inhibitory effect on CYPRA4 (ritonavir or cobicistat-boosted) is 20 mg, and 60 mg if on CYPRA4 inducers (efavirenz or etravirine-based).

Since the positive results of the IMbrave150 study [114] in 2020, immunotherapy-based combinations, with immune-checkpoint inhibitors (ICIs) targeting the programmed death (PD)-1/ PD-L1 pathway represents the backbone of systemic first-line therapy for advanced/unresectable HCC.

Differently from TKIs, due to the different metabolic pathway, the risk of metabolic drug-to-drug interactions between cART and ICIs is virtually absent [115].
However, PLWH have been excluded from all therapeutic clinical trials testing ICIs in HCC, mainly due to the fear of HIV reactivation. A phase I trial has been specifically conducted to test the safety of pembrolizumab, an PD-1 antibody, in PLWH and well controlled viremia affected by different types of solid tumours, confirming the safety and efficacy of this approach in the presence of well-controlled HIV infection and preserved CD4 count [116]. Furthermore, recent data from the CATCH-IT consortium, mainly including patients affected by lung cancer, have reported ICIs to be safe and effective in PLWH with well-controlled HIV infection [117]. The study also included patients treated with dual checkpoint inhibition (anti-PD1 + anti-CTLA4), providing the best evidence so far in support of the use of this approach in PLWH. A small cohort of patients affected by HCC- mainly receiving anti-PD1 monotherapy-was part of the CATCH-IT cohort [117]. No changes in CD4 count, nor HIV viraemia were reported during treatment, despite 30% of the whole population- but none of the patients affected by HCC- having a baseline CD4 count < 200 cells/μL . More recent data from the largest HCC-international consortium collecting real-life data of patients receiving ICIs for HCC, reported on the safety and preserved anti-cancer activity of ICIs in PLWH. The study also included a small group of patients treated with atezolizumab plus bevacizumab, in which no new safety concerns emerged [118]. The incidence of immune-related AEs (irAEs) of grade 3 or higher was 22% in PLWH and 13.0% in PWOH; data about the needs for steroids are not available. In the same study, the incidence of hepato-toxicity, also including non-ir liver-related AEs, was 6.5% in PLWH. However, data about the management of irAEs and the outcomes were not reported by the authors. Therefore, more

specific information about the risk and the management of irAEs in PLWH cannot be reported.

Furthermore, the available evidence does not allow to derive any conclusions on which type of ICI-based regimen might be preferred in PLWH. Similarly, there are no data comparing the efficacy and safety of ICIs over TKIs in PLWH, and prospective clinical trials are unlikely to be performed in the future. However, the existing real-world evidence, showed similar efficacy of ICIs in PLWH and PWOH, without safety concerns in terms of immune-related adverse events. All the aforementioned studies conducted in uHCC mainly included patients well-established on cART , HIV viral load <200 copies/ml and CD4 count ≥200 cells/μL. The published prospective clinical trials testing ICI in PLWH for oncological indications other than HIV required patients to have a viral load <200 copies/ml at study entry, and had a baseline CD4 count cut-off ranging from ≥50 cells/μL [119] to ≥100 cells/μL [120]; no differences in the oncological outcomes was observed based on the baseline CD4 count level. No specific data about the impact of CD4 count on outcomes from ICI in HCC exist; however, as per available international guidelines for PLWH affected by malignancies, modifications to cancer treatment should not be made solely based on HIV status [67]. The main indication remains to establish all the patients on cART before starting anti-cancer treatments and those already on treatment must continue the anti-retroviral therapy; furthermore, counseling with specialized pharmacist is required to rule-out any possible interactions, which as previously discussed is less likely with ICIs as opposed to TKIs. Adequate prophylaxis for opportunistic infections should be provided as per local guidelines based on the CD4 count, taking into account that ICIs, differently from other anti-cancer treatments, have not been reported to lower the CD4 count [35, 117]. Therefore, the need for ICIs *per se* does not represent an indication to start prophylaxis for opportunistic infections, unless otherwise required [35]. Moreover, there is not any indications to aim for a specific CD4 count prior to therapy commencement. As HIV viraemia is more reflective of infection control than the CD4 count, this is suggested to monitor the HIV-viraemia more frequently in PLWH receiving anti-cancer therapy, in particular in those not already established on cART [67]. This further highlights the need for optimal multidisciplinary management in the oncology care of PLWH. All the available guidelines mainly refer to patients requiring chemotherapy. In the absence of guidelines dedicated to PLWH receiving ICIs, the same recommendations should be followed.

In summary, prospective trial data for uHCC treatment in PLWH are lacking. Available real-world data suggests that TKIs have higher risk for drug-to-drug interaction with the cART, and possible worse survival outcomes in PLWH compared to PWOH. ICIs-based therapies, despite not being tested against TKIs in this population, appear safe and effective in the presence of well-controlled HIV infection, therefore the indication for ICIs-based therapies in PLWH with well-controlled HIV-infection, should follow that of PWOH. Furthermore, the inclusion of PLWH with well-controlled HIV in therapeutic clinical trials is supported by the current real-world data and remains pivotal to generate high-quality evidence in terms of efficacy and safety.

Disparities in the care of PLWH affected by chronic liver disease and HCC

PLWH are an underserved group in the cancer care continuum. In terms of modifiable risk factors for chronic liver disease and HCC, not only are PLWH more likely to be co-infected with HBV and HCV, but they are also burdened by higher rates of alcohol use, the reduction of which has been shown to reduce the risk of HCC [121]. In addition, some studies have reported low uptake of preventive measures such as HBV vaccination among PLWH [5]. These factors are driven on the one hand by HIV-related stigma, which operates through inequitable social structures and leads many PLWH to adopt less healthy lifestyles, as described by Meyer's minority stress model [122]. On the other hand, HIV itself is often more prevalent among marginalized groups, such as sexual and gender minorities and racially minoritized communities, where this stigma may be even more pronounced [123].

In terms of disparities in active treatment, the most urgent issue to be addressed is inclusivity in clinical trials. Around 50% of cancer clinical trials that were open and recruiting in 2022 excluded PLWH outright, despite a joint statement from ASCO and Friends of Cancer Research (FCR) in 2017 recommending that PLWH should not be excluded from clinical trials without justification [124]. Regarding HCC, all the pivotal trials testing systemic therapies excluded PLWH.

Treating PLWH can be challenging due to possible interactions between experimental therapies and cARTs, possible comorbidities and the lack of data in this population. However, the exclusion of PLWH from clinical trials prevents researchers from collecting efficacy and safety data on new therapies in this group, leading to a vicious cycle that ultimately excludes PLWH from the latest and potentially life-saving treatments. Finally, PLWH are more likely not to receive standard cancer care, as recently shown in a US population-based study, with people who inject drugs and black people being the most disadvantaged groups. The reasons for these disparities are multifactorial, and while most are related to the general barriers that PLWH face in accessing health services, such as stigma and socio-economic marginalization, others are related to the lack of training of oncologists in the management of cancer in PLWH [125].

Moreover, co-infection of HIV and HBV or HCV is more prevalent in those geographical areas such as sub-Saharian Africa, eastern Europe, and central Asia, where the availability of resources might be limited compared to the global north [126]. In these contexts, where diagnosing and managing liver disease can be more challenging due to limited access to diagnostic tools, and advanced therapies like immunotherapy or liver transplantation, effective prevention strategies, including screening for hepatitis viruses, promoting campaigns against tobacco consumption and alcohol abuse, addressing metabolic risk factors, and ensuring access to appropriate cART are even more crucial [127, 128].

Conclusions and Future Directions.

The risk of chronic liver disease and HCC is higher in PLWH. HIV-induced immune suppression has historically been considered the main factor leading to this epidemiological trend. However, emerging evidence in the post-cART era indicates that HCC developing in the context of HIV infection—even when well controlled—may exhibit distinct immunological and biological characteristics. Furthermore, all therapeutic clinical trials in HCC have inevitably excluded PLWH based on the presence of HIV antibodies, resulting in a lack of high-quality clinical data to guide treatment strategies for PLWH affected by HCC; while recent real-world studies suggest that available oncological treatments can be safely administered to PLWH established on cART. These considerations highlight the need to include PLWH with well-controlled HIV in interventional clinical trials and emphasize the importance of a multidisciplinary approach to optimize both HIV and oncological outcomes.

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Figure 1

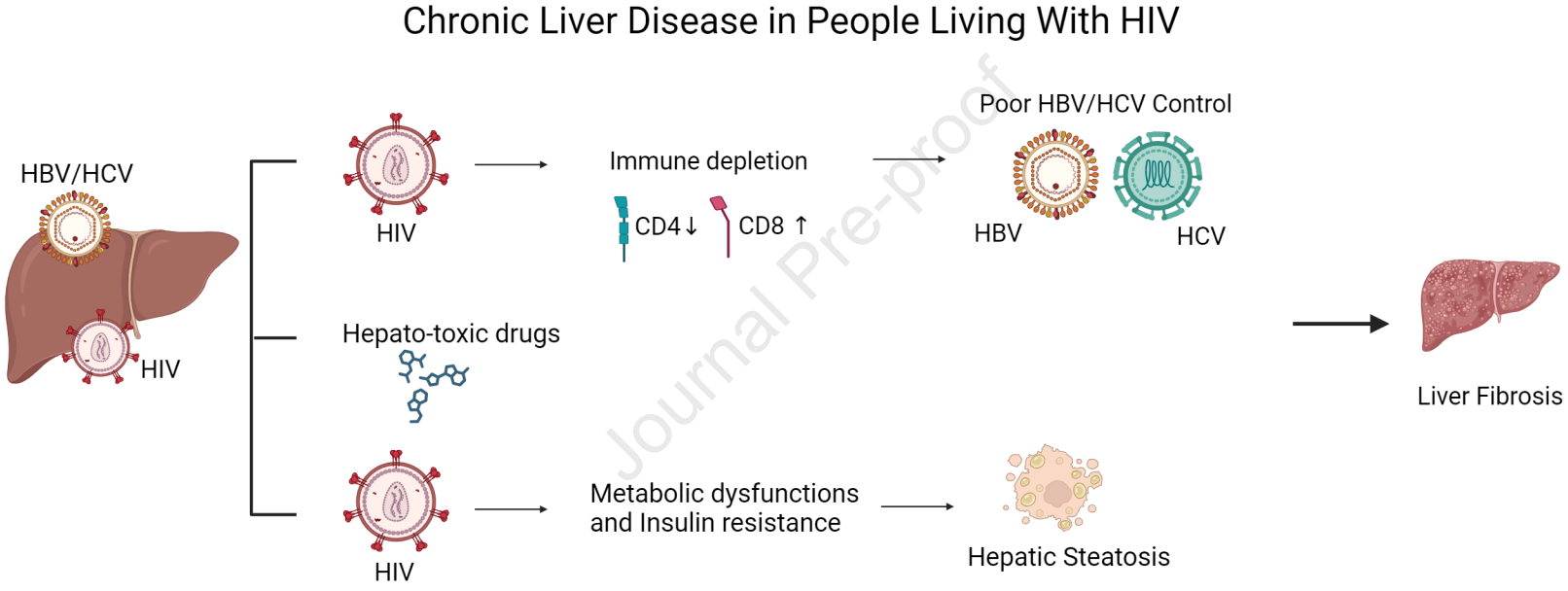

Figure 2

Hepatocarcinogenesis in People Living With HIV