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Hepatocellular cancer therapy in patients with HIV infection: Disparities in cancer care, trials enrolment, and cancer-related research

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ABSTRACT

In the highly active antiretroviral therapy (HAART) era, hepatocellular carcinoma (HCC) is arising as a common late complication of human immunodeficiency virus (HIV) infection, with a great impact on morbidity and mortality. Though HIV infection alone may not be sufficient to promote hepatocarcinogenesis, the complex interaction of HIV with hepatitis is a main aspect influencing HCC morbidity and mortality.

Data about sorafenib effectiveness and safety in HIV-infected patients are limited, particularly for patients who are on HAART. However, in properly selected subgroups, outcomes may be comparable to those of HIV-uninfected patients. Scarce data are available for those other systemic treatments, either tyrosine kinase inhibitors, as well as immune checkpoint inhibitors (ICIs), which have been added to our therapeutic armamentarium. This review examines the influence of HIV infection on HCC development and natural history, summarizes main data on systemic therapies, offers some insight into possible mechanisms of T cell exhaustion and reversal of HIV latency with ICIs and issues about clinical trials enrollment. Nowadays, routine exclusion of HIV-infected patients from clinical trial participation is totally inappropriate, since it leaves a number of patients deprived of life-prolonging therapies.

Human immunodeficiency virus (HIV) infection and natural history of stage-stratified HCC

The early 21st century has witnessed both an increasing biological and immunological knowledge of the human immunodeficiency virus (HIV) epidemic, as well as a huge evolution of medical treatments available for HIV-infected patients. The advent of highly active antiretroviral therapy (HAART) has considerably extended the life expectancy of these subjects [12], and has converted HIV infection into a chronic disease [12,109]. HAART can restore immune function, lower plasma viral RNA load, and decrease morbidity and mortality of acquired immune deficiency syndrome (AIDS)-related complications [121,94]. As a consequence of this positive impact on survival, the occurrence of other chronic, non AIDS-related, morbidities has increased [121,94,16,171,91]. Previously published data on HIV-infected patients receiving medical care in Europe showed that leading causes of mortality are: AIDS-related cancers (29%), non-AIDS-defining cancers (15%), liver diseases (13%), and cardiovascular diseases (11%) [151].

The observation that chronic liver disease is a significant cause of mortality in HIV-infected patients in the era of HAART is not unexpected. Indeed, co-infection with hepatitis B (HBV) or C (HCV) is quite common among HIV-infected patients, due to shared transmission modalities, although the prevalence of co-infection varies greatly according to the geographic origin of infected patients [145,158]. In Western countries, approximately 30% of HIV-positive subjects has HCV co-infection [158], and an increasing morbidity and mortality of

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HIV-infected patients due to HCC has been reported, accounting for more than 40% of liver-related death [141].

As a well known complication of liver cirrhosis in more than 80% of incident cases, HCC is an extremely complex condition, due to the combined influence of different etiologic factors, severity of primary chronic liver disease, and extent of disease [126,140]. Co-infection of HIV with either HBV or HCV might be associated with rapidly progressive liver disease, and the risk of HCC increases when patients develop cirrhosis [91,151]. Available epidemiologic evidence suggests a seven-fold increase in the incidence of HCC in HIV-positive subjects with hepatitis, when compared with HIV-negative controls [127]. Traditionally, the increased risk associated with HIV infection has been explained by the synergistic oncogenic effect of hepatitis, leading to a faster progression of liver fibrosis in the context of immune-impairment [73], which can be further worsened by other associated factors, including increased oxidative stress from HAART [89], excessive alcohol consumption [99], impaired cell mediated immune response [73], and dysbiosis of the gut microbiota [170]. Indeed, the altered intestinal permeability triggered by HIV infection through depletion of mucosal $CD4^+$ *T* lymphocytes, especially T helper 17 (Th17) cells, and altered epithelial function enables microbial translocation such as bacterial lipopolysaccharide, with secondary immune activation by interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) [170,153,120]. This protracted cytokine release enables the development of liver fibrosis, and can activate Toll-like receptors (TLR)−4 and −9[119]. Consistently, compared with HIV-negative cases, HIV-associated HCCs have been shown to present at a younger age, and are often characterized by a higher tumor burden, supporting the hypothesis of an accelerated hepatocarcinogenesis [19,133]. Also, elevated levels of α-fetoprotein (AFP) are common in HIV/HCV coinfected patients, independently of HCC stage, and liver fibrosis severity [19,17]. Interestingly, patients with cirrhosis who are co-infected with HIV and HCV often present at radiologic diagnosis an infiltrative-type HCC, with portal vein thrombosis [92], which is usually characterized by considerably poorer long-term survival. Yet, diverging evidence shows that HIV seropositivity impacts on the outcome of patients with HCC [19,17,132,10,93]. Case cohort analyses indicate that HIV co-infection does not have a detrimental effect on clinical outcome, provided the widespread use of standardized screening programs and the broader acceptance of the Barcelona Clinic Liver Cancer (BCLC) staging algorithm [93], likely the consequence of effective treatments, and of an extended access to anticancer drugs for HIV patients. Nevertheless, these conclusions may not be applicable to HIV+ patients with low $CD4^+$ cell counts, or failure to maintain undetectable plasma viral load on HAART, as both conditions are recognized risk factors for end-stage liver disease. Remarkably, a multicenter case–control study showed that undetectable plasma HIV RNA, rather than $CD4^+$ cell counts predicted longer survival in HCV-coinfected patients, suggesting that an adequate suppression of viral replication by HAART might reduce the influence of HIV on HCV-induced liver fibrosis, and slow the progression of fibrosis [18]. Conversely, in a recently reported global collaborative study, despite adequate antiretroviral treatment, HIV seropositivity adversely influenced the prognosis in a multicohort of patients with untreated HCC, where survival estimates were not biased by the effect of active anticancer treatment [128]. In an adjusted analysis, HIV infection increased the hazard ratio (HR) for death by 24% ($P = .0333$), independently of BCLC stage ($P < .0001$), Child-Turcotte-Pugh class ($P < .0001$), AFP levels ($P < .0001$), geographical origin ($P < .0001$), and male sex [128]. Still, the clinical behavior of HCC in HIV-infected patients is not clearly defined [139], and different studies showed overall comparable survival rates regardless of HIV status, thus refuting HIV adverse prognostic association [19,132,10,93].

Probably, the survival heterogeneity within each BCLC stage, a recognized feature of HCC, may be even wider in HIV-infected patients with HCC [13,101,61,59]. socioeconomic and geographical differences, as well as long-term HIV control, might also contribute to limit both access and eligibility to oncologic treatments, thus potentially affecting patients' outcome, independently of any true immunobiologic effect of HIV [43]. Nevertheless, previously published studies have recognized anticancer treatment as a key prognostic factor in HIV-infected patients [124,164,48,49,110,44]. In one of the largest series ever reported [132], which demonstrated HIV to adversely influence the prognosis of HCC, 60% of the patients with HIV-associated HCC received best supportive care compared with 38% of the HIV-negative controls ($P = .02$), emphasizing that the unfavorable prognostic role of HIV infection might be at least partly related to an imbalance in treatment allocation across subgroups. Treatment imbalance is also a feature of another study [10], though a significantly higher proportion of HIV-positive patients received active anticancer treatment compared with HIV-negative patients (65.4%, vs 85.6%, respectively; $P < .001$). The study showed an unexpectedly high 12.8 months median OS in 27 consecutive HIV-infected patients with unresectable HCC treated with sorafenib. Yet, only 19% of patients harbored a BCLC stage C, which limits reproducibility of these data. Moreover, patients who were HIV-positive seemed disadvantaged by the lower probability of receiving treatment at recurrence (61% of HIV-positive patients vs 86.2% of HIV-negative cases, $P < .001$), underlining that the unfavorable prognostic role of HIV status might have been partially influenced by the different treatment allocation across patients' subgroups. Moreover, available data describing the incidence and clinical outcome of HCC in the HAART era are often biased by small cohort size from single centers or tertiary referral hospitals, and short follow-up. Further studies exploring the immunobiology of HIV-associated HCC are straightaway required.

In this review, we highlight the role of HIV infection on HCC pathogenesis, summarize recent advances in medical knowledge and specific pathways involvement as well as latest report on immunotherapy. It also offers some insights on evidence-based data and clinical trial inclusion of HIV-positive patients.

HIV infection and pathogenesis of HCC

The role of HIV on HCC development has long been investigated. In vivo studies on murine models have reported the involvement of the HIV tyrosine aminotransferase (*Tat*) gene [116,33,4]. Tat promotes proliferation and protects cells from apoptosis [181,25], has angiogenic properties [53,2] and induces expression of several cytokines [147,172], growth factors [52], and transcription factors [41]. Transgenic mice bearing a *Tat* transgene showed a greater incidence of HCC and other extra-hepatic malignancies [103].

The relationship between HIV decreased immuno-surveillance, manifesting as a low $CD4^+$ cell count, and HCC has gained increasing attention in recent studies [23,31]. A $CD4^+$ count less than 200 cells/mmc has been significantly associated with HCC, but not with cirrhosis, suggesting that immune suppression may be directly involved in carcinogenesis [23,68]. A decreased cancer immuno-surveillance is of particular relevance in HIV/HCV co-infected patients treated with interferon-free anti-HCV direct-acting antivirals (DAAs)-based therapy [32,29]. The sudden inhibition of HCV production, and the consequent disruption of the inflammatory/immune phenotype, may be responsible of a decreased immune surveillance. This modification of the immune microenvironment may allow growth of clones of cancer cells originating the primary tumor. The abrupt reduction of liver natural killer (NK) cells and of their cytotoxic functions [149] have been claimed as a further risk factor for the development of HCC in HIV-positive patients [78], whose impaired immune system may have reduced NK cells even before anti-HCV therapies. This prompted a controversial debate due the unexpected high rate and pattern of HCC recurrence after ablation or surgical resection while on DAAs-based therapies [138]. Though a direct influence of DAAs on tumor cell growth cannot be entirely rejected, it is however highly improbable. For instance, HIV protease inhibitors have been shown to exert antitumoral properties in murine models [54], and growth inhibitory effects in vitro, on a number of malignant cancer cell

lines [40]. Nevertheless, growing evidence suggests that the increased risk of malignancy is not merely driven by patient's immunological status, an issue of huge significance in the HAART era where reconstitution of quantitatively average $CD4^+$ cell count is possible. Complex signaling pathways are involved in the pathogenesis and development of HCC with a major risk of developing HCC despite adequate HIV control, or HCV clearance [32].

Though HIV infection alone may not be sufficient to promote hepatocarcinogenesis [17], the complex interaction of HIV with hepatitis is a main aspect influencing HCC morbidity and mortality in HIV co-infected patients [60]. Persistent inflammation of the liver parenchyma almost always precedes HCV-induced HCC, with activated hepatic stellate cells (HSCs) and signals derived from inflammatory cells whose cross-talk is especially relevant to hepatic fibrogenesis, ultimately leading to an increased risk of HCC development [87]. Additional transcriptional events contributing to HSC activation include dysregulation of Wnt/β-catenin, hedgehog, and GATA4 signaling [184,39,107]. The multifaceted network of intracellular events during HSC activation includes regulatory pathways affecting, among others, the intracellular inflammasome activation, a recognized key transducer of signals derived from inflammatory cells that is critical to fatty liver disease [176]. HIV can directly infect parenchymal and non-parenchymal liver stromal cells, including Kupffer [67] and HSCs [163]; it induces collagen I expression, secretion of the proinflammatory cytokine monocyte chemoattractant protein 1 (MCP-1), and reactive-oxygen species overproduction [95]. The convergence of direct profibrogenic effects and of proinflammatory pathways upregulated by HCV and HIV on HSC provides evidence supporting the accelerated course of fibrosis observed in the context of co-infection.

Different host-related aspects have been shown to influence HCC predisposition, inducing a proliferation advantage and/or an altered immune response, factors ultimately altering the progression rate from cirrhosis towards tumor.

Immune activation is differently regulated as a consequence of underlying hepatotropic infection in HIV+ individuals [75]. Studies on HIV/HCV-coinfected patients have revealed changes in levels of soluble markers connected to immune activation (soluble CD14, CD163, autotaxin, and Mac2BP) during antiviral therapy for HCV, suggesting immune dysfunction as a key mechanism in HIV/HCV coinfection [83]. The host immune response to HBV-encoded antigens is responsible for necroinflammatory liver disease [30]; furthermore, HBV replication causes cyclical phases of hepatocellular necrosis, inflammation and subsequent regeneration, where a cytokines-enriched microenvironment, directed by IL-6 and IL-22 signaling and by activation of the nuclear factor-κB (NF-κB) and signal transducer and activator of transcription 3 (STAT3) pathways [55], confers a survival advantage to chronically damaged hepatocytes. Furthermore, chronic inflammation is associated with oxidative stress [50], which promotes DNA damage and modulates intracellular signaling, alters gene expression, and induces the expression of adhesion cell molecules ([160].). The protein X (HBx), one of the four proteins encoded by the HBV genome, exerts its oncogenic effects by dysregulating multiple pathways involved in cell cycle, apoptosis, and immunity [177]. In HIV-positive subjects, HBx has been shown to enable HIV-1 transcription by stimulating the binding of transcriptional regulatory proteins CCAAT/enhancer-binding protein beta (C/EBP), cAMP-response element-binding protein 1 (CREB1), and cAMP-response element-binding protein 2 (CREB2) to HIV long terminal repeats, providing evidence of potential synergy of HBV in HIV-1 replication during HBV/HIV-1 co-infection [112]. Moreover, loss of $CD4^+$ and $CD8^+$ *T* cell responses and of the antigen presentation processes influences viral kinetics, favoring unrestrained viral replication and progression to fibrosis, cirrhosis, and HCC [73].

Systemic therapy and real world data for the treatment of advanced HCC in patients with HIV

The Sorafenib Hepatocellular Carcinoma Assessment Randomised Protocol (SHARP) trial, an international, multicenter, phase III randomized placebo-controlled study of 602 patients with advanced HCC, showed that the multitargeted tyrosine kinase inhibitor (TKI) sorafenib (endowed by both anti-angiogenic and anti-proliferative properties) significantly prolonged survival in patients with unresectable HCC, with an overall survival (OS) of 10.7 months compared to 7.9 months for placebo, with a 31% reduction of risk of death [96]. The favorable effect of sorafenib in improving survival and delaying tumor progression was also confirmed within the phase III Sorafenib Asia–Pacific trial, performed in China, South Korea, and Taiwan [28]. Jointly, these two trials proved the effectiveness and activity of sorafenib throughout different disease etiologies, leading to its approval as first-line systemic therapy for patients with advanced HCC [20,114,56,72] (Table 1).

Sorafenib is an oral multikinase inhibitor that, among the others, targets rapidly accelerated fibrosarcoma (Raf) kinases, vascular endothelial growth factor receptor (VEGFR), c-Kit and platelet-derived growth factor receptor (PDGFR), thus inhibiting both tumor-cell proliferation and angiogenesis [26,137]. The main molecular mechanisms by which sorafenib exerts its antitumor activity in different malignancies have not been completely clarified [131]; in HCC in particular, both Raf/MEK/ERK-dependent or -independent mechanisms have been reported [136,167,159]. At present, no validated biomarker of response to sorafenib has been identified [182].

Sorafenib is usually administered at a dose of 800 mg/day; however, dosage may vary based on physician decision, Child-Pugh class, performance status, and comorbidities [21,3].

Data about sorafenib effectiveness and safety in HIV-infected patients are limited, especially for patients who are on HAART, and could be at increased risk of developing drug–drug interactions [11,27,123,118,42,130,148]. Real life data [106] have suggested that sorafenib efficacy in HIV-infected patients may be inferior compared to registration trials, while the frequency and type of adverse events are similar to those described in other cohorts [100,154,79,129]. These findings are not unexpected when one considers the outcomes of a randomized controlled trial in which a toxic therapy is delivered to fit patients, as compared with the everyday treatment of patients with more advanced liver impairment. The Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib (GIDEON) trial, a non-interventional, international study undertaken to fulfill *post approval commitments* to the European Medicines Agency (EMA), showed that although median time to progression (TTP) was similar (4.7 vs. 4.4 months, respectively), median OS was longer for Child-Pugh A patients (13.6 months) compared to Child-Pugh B patients (5.2 months) [35,90,100].

Another concern is about potential overlapping toxicities and pharmacokinetic interactions between molecularly targeted agents as a whole, and sorafenib in particular, and HAART. Again, most studies of novel agents for the treatment of HCC (and not only) did not include patients with HIV, leading to the paucity of available data on the use of antineoplastic drugs for the treatment of this peculiar patient population. The potential drug interactions of HAART are well established [130,148]. Likewise, the risk of incremental toxicities and associated costs of new anticancer drugs approved for use by regulatory agencies are expected to be higher with less specific agents, and in less selected patients. The therapeutic index (defined as a ratio of a measure of therapeutic benefit to a measure of toxicity) for new drugs is likely to be lower for patients treated within routine clinical practice, compared with that reported in controlled clinical trials, highlighting the need for translational studies addressing potential interactions between anticancer agents and HAART [115]. Results from two meta-analyses didn't show any improvement in OS for patients receiving sorafenib who were positive for HBV and negative for HCV, which is informative when using

Table 1
Targeted therapies evaluated in phase III – overall survival results.

	Trial	Clinical trial design	Arms	Schedule	Overall survival, months	HR (95% CI)
First-line	SHARP [96]	Multicenter, randomized, double-blind, placebo-controlled, phase 3 trial	Sorafenib Placebo	Sorafenib 400 mg orally twice daily or matching placebo	10.7 7.9	0.69 (0.55–0.87)
	Asia-Pacific [28]	Multicenter, randomized, double-blind, placebo-controlled, phase 3 trial	Sorafenib Placebo	Sorafenib 400 mg orally twice daily or matching placebo in 6-week cycles	6.5 4.2	0.68 (0.50–0.93)
	REFLECT [84]	Multicenter, randomized, open-label, phase 3, noninferiority trial	Lenvatinib Sorafenib	Lenvatinib 12 mg/day (for body weight ≥60 kg) or 8 mg/day (for body weight <60 kg) or sorafenib 400 mg orally twice daily	13.6 12.3	0.92 (0.79–1.06)
	IMBRAVE150 [57]	Multicenter, randomized, open-label, phase 3, superiority trial	Atezolizumab +bevacizumabSorafenib	Atezolizumab 1200 mg plus bevacizumab 15 mg/kg body weight intravenously every 3 weeks or sorafenib 400 mg orally twice daily	NE 13.2	0.58 (0.42–0.79)
Second-line	RESORCE [22]	Multicenter, randomised, double-blind, parallel-group, phase 3 trial	Regorafenib Placebo	Regorafenib orally 160 mg or placebo once daily during weeks 1–3 of each 4-week cycle	10.6 7.8	0.63 (0.50–0.79)
	CELESTIAL [1]	Multicentre, randomised, double-blind, placebo-controlled, phase 3 trial	Cabozantinib Placebo	Cabozantinib orally 60 mg once daily or matching placebo	10.2 8.0	0.76 (0.63–0.92)
	REACH-2 [183]	Multicentre, randomised, double-blind, placebo-controlled, phase 3 trial	Ramucirumab Placebo	Ramucirumab 8 mg/kg intravenous every 2 weeks or placebo	8.5 7.3	0.71 (0.53–0.95)

CI, confidence interval; HR, hazard ratio; NE, could not be evaluated.

a drug with a poor therapeutic index [105,71].

Currently, there are no published pharmacokinetic data about the combined usage of sorafenib or other multikinase inhibitors and HAART, as well as a guidance for dose adjustments when they are used concomitantly. However, sorafenib is not reported to modify the efficacy of HAART. In fact, CD4 cell count did not vary during sorafenib treatment, and HIV viral load remained undetectable in the majority of patients [106]. Moreover, during sorafenib treatment there were no modifications or discontinuation of HAART. These data suggest that HIV infection should not be a cause to prevent the access to sorafenib therapy, which should thus be used on the same basis as in the general population. However, concurrent administration of sorafenib with cytochrome P450 3A4 (CYP3A4) inhibitors or inducers may alter sorafenib concentrations [155], which is mainly metabolized in the liver via cytochrome P450 (CYP) 3A4 [143]. For example, fosemprenavir and ritonavir, both CYP450 inhibitors, could result in sorafenib accumulation, and possible toxicity. Among antiretroviral drugs, atazanavir and indinavir have been associated with unconjugated hyperbilirubinemia secondary to glucuronidation by uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1) inhibition, similarly to Gilbert's syndrome [143,85,142,156], and bilirubin is one of the parameter used for dose adjustment for sorafenib [108]. To address some of these issues, the AIDS Malignancy Consortium, a National Cancer Institute-supported clinical trials group, conducted a phase 1/pharmacokinetic study of the tyrosine kinase inhibitor sunitinib in combination with HAART in HIV-positive patients with cancer (AIDS Malignancy Consortium trial AMC 061) [144]. The results of the study showed how the inhibitory influence of HIV-protease inhibitors on cytochrome P450 worsen the clearance of sunitinib; this produced greater side effects in patients receiving ritonavir-based treated with sunitinib at standard dose [144].

More recently, other drugs have shown clinical benefits in advanced HCC patients, and have been approved as first-line (i.e. lenvatinib and atezolizumab plus bevacizumab) [84,57], or second-line, therapies (i.e. regorafenib [22], cabozantinib in patients with baseline AFP ≥400 ng/mL [1], nivolumab [51] and ramucirumab [183]) (Table 1). Data about effectiveness and safety in HIV infected patients of these novel agents for HCC are even more sparse [98].

On HAART side, more recent therapeutic schemes include integrase inhibitors in combination with one or two nucleoside reverse transcriptase inhibitors (NRTIs); these schemes have demonstrated to be highly efficacious and an excellent safety profile. In particular, raltegravir can be administered to patients with decompensated liver disease. Moreover, the pharmacokinetics of TKI seems not to be affected by the concomitant raltegravir-based HAART [97]. This suggests no interaction with TKIs like sorafenib and lenvatinib even though field practice experiences are lacking so far.

Immune checkpoint inhibitors (ICIs) in the challenging HIV population: T cell exhaustion and reversal of HIV latency

T-cell exhaustion, defined by poor effector function, sustained expression of inhibitory receptors (IRs) and a transcriptional state distinct from that of functional effector or memory T cells [174], is a main factor leading to flawed pathogen clearance in chronic viral infections [173,82] and reduced antitumor response.

Exhausted $CD8^+$ *T* cells are a distinct cell lineage that develop during chronic infections and cancers in both murine models as well as in humans [104]. The degree of $CD8^+$ *T* cells dysfunction varies according to viral burden, and the extent of infection. Additionally, during acute and chronic HIV-1 infection distinct phenotypes of the $CD8^+$ *T* cell response have been reported also in relation to the number of specific $CD4^+$ *T* cells [9,5].

Exhausted T cells are characterized by elevated expression of multiple IRs, an impaired response to homeostatic cytokines, altered transcriptional profiles, epigenetic features distinct from that of functional effector T cells and memory T cells [173,45,37,14,135,76,7,125,162,169,8,168] and are now the targets of immunotherapies in chronic infections and cancer [24,122]. In the last decade, various receptors have been recognized that can negatively regulate the activation and different properties of T lymphocytes and other leukocytes. The programmed death-1 (PD-1) molecule is one of the most relevant receptors for exhausted $CD8^+$ *T* cells. PD-1 is a member of the B7:CD28 family that has 2 ligands: programmed death ligand 1 (*PD-L1)* (B7-H1, CD274) and PD-L2 (B7-DC, CD273). PD-1 prevents T-cell activation by hampering T-cell receptor signaling [62,86,58] and by increasing the transcription factor BATF (Basic Leucine Zipper ATF-Like Transcription Factor) [134]. Studies in the murine lymphocytic meningitis virus (LCMV) model recognized PD-1 as a crucial element of immune deficiency [111,178]. T cell exhaustion can be in part reversed by blocking the interaction of PD-1 with its ligand PD-L1[6,74,69]. Seminal studies proved that blocking PD-1:PD-L1 interactions can recover specific subsets of exhausted T cells and significantly lower viral loads [6,74]. Studies of

exhausted HIV-specific $CD8^+$ *T* cells showed reacquisition of effector molecules production and increase of HIV-specific $CD8^+$ *T* cells following PD-1 blockade [37,125,162]. Low $CD4^+$ *T* cells count in HIV infection may also foster T cells exhaustion [102]. Studies in animal models and humans suggested that $CD4^+$ *T* cells are essential for immune regulation of HIV reproduction ([178,150,36,113]). PD-1 is up-regulated on HIV-specific $CD4^+$ *T* cells and its expression is driven by viral replication [47]. In fact, inhibition of the PD-1 pathway with a PD-L1–blocking antibody enhanced HIV-specific $CD4^+$ *T* cells proliferation [37,76,47]. Clinical trials to investigate PD-1 inhibitors in HIV patients have been conducted (NCT02028403), though results have yet to be established.

T cell exhaustion has a key function also in immune dysfunction in cancer [122,180]. In the tumor microenvironment, many factors can modulate the existing activated antitumor T cells immune response, acting as an immune rheostat or "immunostat". PD-L1 is expressed on various cancer cells, as well as myeloid cells in the tumor microenvironment in response to inflammatory signals ([152];[46]). Also, tumor growth is usually sustained by aerobic glycolysis [104], and metabolic dysregulation promotes T cell exhaustion in the tumor microenvironment. Inhibition of the PD-1 pathway rises glucose availability in the tumor microenvironment thus enhancing tumor-infiltrating lymphocytes (TIL) function and tumor regression [81]. PD-1 pathway blockade has been shown to have antitumor effects both in vitro [69,66,77,34,157,15,70,161], and in vivo [179]. Notwithstanding the unique effectiveness of immune checkpoint inhibitors (ICIs), HCC patients embody a population with distinctive features. HCCs contain a combination of different cell types, involving cancer cells, immune cells, and endothelial cells within the extracellular matrix and stroma. This observation is consistent with prior evidence of the so-called "field effect" in the damaged liver secondary to chronic hepatitis and cirrhosis [63]. About one third of HCC patients with peritumoral immune profile displays immunosuppressive signals, for example TGF-ß activation and T-cell exhaustion.

Early data on the PD-1 inhibitor nivolumab in patients with advanced HCC (with a Child-Pugh score $\leq$B7) involved patients with chronic HBV or HCV infection. In patients with HCC who had disease progression or unacceptable adverse effects under sorafenib treatment, nivolumab showed a 10% rate of grade $\geq$3 liver enzyme elevation, but an overall manageable safety profile. Nivolumab achieved a median OS of 15.6 months [51], while the overall response rate was 14.3% according to Response Evaluation Criteria in Solid Tumors (RECIST); furthermore, in 55% of the treated patients the duration of the response was of more than 12 months [51] and responses to treatment were observed in both patients with HBV or HCV. The response data achieved in this single-group phase 2 trial prompted Food and Drug Administration (FDA) approval under accelerated program [117] (https://www.accessdata.fda.gov/drugsatfda_docs/label/). In patients with unresectable HCC, anti-PD-L1 atezolizumab combined with bevacizumab significantly improved survival outcomes compared with sorafenib in previously untreated patients [57].

Treatment with ICIs might potentially play a double action in HIV infected patients, acting on one side on cancer cells and on the other improving the eradication of HIV reservoirs that persist during HAART by enhancing the HIV-specific CD8 T-cell response. A likely assumption is that ICIs may induce a transient reactivation of HIV transcription within latently infected $CD4^+$ *T* cells and simultaneously decrease the exhausted $CD4^+$ and $CD8^+$ *T* cells displaying high PD-1 levels [38]. This hypothesis has not been proven yet. Nevertheless, a recent report showed for the first time a case of a drastic and sustained decrease of the HIV reservoir, together with the restoration of HIV-specific $CD8^+$ *T* cells function under anti-PD1 therapy in a patient affected with lung cancer [64]. Whether this promising effect is reproducible is presently the object of the French cohort study of HIV-infected patients treated with ICIs (ANRS-CO24, OncoVIHAC cohort; NCT03354936) and might open new treatment strategies on HIV cure. Moreover, preliminary data on safety profile in real-life case series of HIV patients treated with an anti-Cytotoxic T-lymphocyte Associated Protein 4 (CTLA-4) monoclonal antibody ipilimumab [175], or with nivolumab [88] (mainly for melanoma or lung cancer), indicated a tolerability and safety profile comparable with those observed in non-HIV patients [65,146]. The PD-1 inhibitor pembrolizumab has been also evaluated in patients with HIV and advanced cancers; this study allowed a variety of cancers and required a $CD4^+$ *T* cells count of $\geq$100 cells/mmc [166]. Pembrolizumab showed clinical benefit and an acceptable safety profile in cancer patients with HIV on HAART and >100 $CD4^+$ cells/μL [166], comparable to patients without HIV infection. Therefore, anti-PD1 inhibitors are proper for FDA-approved indications in this setting and HCC—HIV patients with appropriate eligibility criteria should be involved in immunotherapy-based clinical trials. Awaiting more mature data, HIV should not be considered a contraindication to treatment with anti-PD-1.

HIV and inclusion in clinical trials

Notwithstanding the dramatic outcome improvement as a result of advances in the treatment of HIV over the past 20 years, and the increasing public health need to treat cancer in people with HIV, most oncology clinical trials still exclude people with HIV [165]. Lack of prospective data on therapies in HIV-infected patients limits evidence-based treatment decision and contributes to huge treatment disparities for this patient population [80]. Nevertheless, management of cancer in HIV-positive patients should converge on appropriate approaches for the malignancy. This normally comprises standard regimens combined with treatment of HIV and supportive care when required. In properly selected patients' treatment outcomes are comparable to those of HIV-uninfected individuals [164]. This has been confirmed for Burkitt's lymphoma [49], diffuse large B-cell lymphoma [48], classic Hodgkin lymphoma [110], as well as lung cancer [44].

In 2016, the HIV Working Group of the ASCO–Friends of Cancer Research engaged in several summits to revise the eligibility criteria related to HIV within oncology trials [165]. The Working Group established consensus recommendations based on an analysis of New Drug Applications from registration trials of single agents that conducted to FDA approval. HIV-related eligibility criteria from National Cancer Institute–sponsored studies were also examined. An FDA analysis of 2015 Investigational New Drug applications revealed that just five (1.7%) of 250 protocols allowed enrollment of HIV-infected patients with stable disease and adequate $CD4^+$ *T* cell count. Likewise, the working group noted that none of 46 studies examined contained inclusion criteria for patients with HIV, 30 studies contained specific HIV exclusion criteria, and nine studies considered exclusion of patients with active infection and likely HIV infection [165].

Modernization of eligibility criteria to comprise HIV-infected patients in cancer clinical studies is crucial to extend the generalizability of trial results to this patient population. Exclusion to clinical trial participation based on HIV infection alone is not validated, and eligibility criteria linked to HIV infection in adult patients with cancer ought to be established based on existing medical knowledge and scientific basis [124]. The HIV Working Group identified criteria to define patients with HIV as sufficiently healthy from the HIV perspective to be enrolled in oncology clinical trials [165]. For example, the HIV Working Group underlined that eligibility should be established through assessment of present and historic $CD4^+$ *T* cell counts, evaluation of any history of likely AIDS complications, and estimation of use of active HAART [165].

Personal perspectives

Still there is much concern about HCC patients co-infected with HIV and all issues related to HCC are even more amplified in this subgroup of patients. The main point for HCC—HIV patients is not only to select which drug to use but rather how to manage these patients and how to make all available drugs accessible. The main causes which could

negatively influence the number of HCC patients treated with targeted drugs are connected to difficult patient profiling in particular for possible drug-drug interactions and the lack of solid data on best treatment to offer. Therefore, a multidisciplinary approach is really necessary and require a constant cooperation between HIV and HCC experts. The ongoing phase IIIb AMETHISTA study (NCT04487067), designed to evaluate the safety and efficacy of atezolizumab in combination with bevacizumab in patients with unresectable HCC who have received no prior systemic treatment, includes HIV positive patients with a CD4+ *T* cell count ^{3} 200 cells/mmc and undetectable viral load. In our opinion this trial not only summarizes the correct approach requisite to assess the impact of new drugs in these patient population but also will provide the useful data that we are still missing. In any case we are confident that the improved safety profile of new drugs for people living with HIV will also benefit HCC treatments in the near future.

Conclusions

In addition to its role in triggering the pathogenesis of HCC, HIV infection augments complexity to the various process of treatment provision that differentiates the management of HCC.

With the improving of novel therapeutic options for both viral hepatitis and cancer therapy, including novel target-based drugs and ICIs for HCC, there is yet the necessity to gather further knowledge about the clinical outcome of patients with HIV-HCC after viral cure and intensive efforts to combine expertise across HIV treatment, hepatology and oncology. This is especially relevant in this niche of patients that has not been included in pivotal trials. HIV patients with cancer should not be treated differently with regards to clinical trials enrolment; consequently, we need to ensure their participation in clinical trials when appropriate.

Author contributions

FN, CP, and GM: conceptualization and writing original draft. FN, GM, ADA and CP: review and editing. All authors read and approved the final version of the manuscript.

Declaration of Competing Interest

All authors had nothing to disclose.

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