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CO-INFECTIONS AND COMORBIDITY (S NAGGIE, SECTION EDITOR)

Screening for Hepatocellular Carcinoma in HIV-Infected Patients: Current Evidence and Controversies

N. Merchante[1] · M. Rodríguez-Fernández[1] · J. A. Pineda[1]

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Abstract

Purpose of Review This review aims to summarize evidence regarding hepatocellular carcinoma (HCC) screening in the specific context of HIV infection and discuss areas of uncertainty.

Recent Findings It has not been definitely established if HCC incidence in HIV/HCV-coinfected patients with cirrhosis is above the 1.5%/year threshold that makes screening cost-effective. Outside cirrhosis or HBV infection, available data do not support surveillance. The performance of currently recommended ultrasound (US) screening strategy is poor in HIV-infected patients, as rates of early-stage HCC detection are low. Magnetic resonance imaging–based surveillance strategies or liquid biopsy are innovative approaches that should be specifically tested in this setting.

Summary HIV-infected patients with cirrhosis are at risk of HCC. US surveillance identifies patients with early-stage HCC who will benefit of curative therapies, although the quality of the evidence supporting screening remains limited. The HIV population should be a priority group to assess and validate new surveillance strategies.

Keywords Hepatitis C virus · Cirrhosis · Hepatocellular carcinoma · HIV · Screening · Surveillance

Introduction

Liver cancer is one of the most incident neoplasms worldwide, ranking fourth in terms of cancer-related mortality [1]. Hepatocellular carcinoma (HCC), which accounts for the majority of primary liver cancers, is a leading cause of death among patients with cirrhosis [2]. HCC is one of the most lethal tumors with a 5-year survival rate of 10% to 15% [3]. As with other tumors, cancer stage at diagnosis is one of the main prognostic factors. Thus, a 5-year survival rate of 70% can be achieved in patients diagnosed at early stage and treated, whereas expected survival of those with advanced HCC is less than 1 year [2]. Since the cornerstone for improving survival of HCC is the application of curative therapies [2], an early diagnosis is essential to achieve this goal and it has been the rationale for recommending HCC surveillance in high-risk patients [2, 4, 5].

Individuals living with HIV are a high-risk population for developing HCC, mostly as a consequence of hepatitis C virus (HCV) coinfection [6–9, 10••]. Worldwide data indicate that HCC has become a major clinical problem for HIV-infected patients. Our group showed that the incidence of HCC had risen in HIV-infected patients between 2000 and 2009 in Spain [6]. In keeping with this, an increase of HCC-related mortality in HIV-infected patients has been reported in France [7], and the prevalence of HCC is on the rise in the HIV population in the USA [8]. As a result, HCC is the second cause of death in HIV/HCV-coinfected patients with cirrhosis in Spain [11••]. Although the arrival of the highly effective direct-acting antiviral agents (DAA) is expected to result in a future decline of HCC incidence due to the protective effect of sustained virological response (SVR) on the risk of HCC [11••, 12–18], new cases will continue to emerge in the near term. Consequently, clinicians caring for HIV-infected individuals should be aware of the appropriate management, including surveillance for HCC, with the goal of early diagnosis.

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✉ J. A. Pineda
japineda@telefonica.net

N. Merchante
nicolasmerchante@gmail.com

M. Rodríguez-Fernández
migrodfer92@gmail.com

[1] Unit of Infectious Diseases and Microbiology, Hospital Universitario de Valme, Avenida de Bellavista s/n, 41014 Seville, Spain

This review summarizes the scientific evidence regarding HCC screening, with an emphasis on the available data in the specific context of HIV infection, and discusses areas of uncertainty, where more research is needed.

Rationale and Evidence for HCC Surveillance

As in other cancers, HCC surveillance aims to reduce disease-related mortality by diagnosing the malignancy earlier in the course disease. Regrettably, most current evidence of the effectiveness of HCC surveillance derives from non-randomized studies showing earlier diagnosis, higher rates of treatments, and better overall survival in patients enrolled in surveillance programs when compared to those not screened [19]. However, these studies suffer from the potential of several biases described for other cancer screening studies [20]. There is only one randomized controlled clinical trial of HCC surveillance, which was done in a Chinese population of HBV-infected patients. In this study, subjects were allocated to a surveillance strategy based on an ultrasound (US) examination plus alfa-fetoprotein (AFP) determination every 6 months versus no screening [21]. Patients who were screened benefited from a 37% reduction in HCC-related mortality despite a suboptimal 60% adherence to surveillance. Extrapolating these data to the population from Western countries, most of which have cirrhosis from etiologies other than HBV, such as HCV, alcohol or non-alcoholic fatty liver disease (NAFLD), is problematic. Patients not represented in the study are likely older, may have comorbidities, and a have lower probability to undergo aggressive surgical resections. In addition, survival rates are poorer despite treatment due to impaired liver function when compared to younger Asian HBV patients. No validation trial has been conducted and is unlikely to occur [22]. The lack of equipoise on the benefit of HCC surveillance means it is not feasible to conduct a randomized trial without a surveillance arm in Western countries. Perceived benefits of surveillance by most providers and the fact that US surveillance is part of the routine of care of these patients would make enrollment difficult. Mathematical models [23••] and meta-analyses of cohort studies [24] suggest a survival benefit from HCC surveillance in high-risk patients. A systematic review of 47 studies concluded that surveillance was associated with higher rates of early diagnosis, curative treatment, and 3-year survival [24]. Despite limitations of cohort studies, the consistent message from available evidence is that HCC surveillance is likely beneficial in patients with cirrhosis, a recommendation that is also endorsed by recent practice clinical guidelines [5, 25]. By contrast, in a recent case–control study, previous screening receipt was not different between cirrhotic patients who died from HCC and a matched control population with cirrhosis without HCC [26], but the low uptake of curative therapy and the lack of a control population of patients who survived HCC limit its conclusions.

Potential Harms of HCC Surveillance

As in other cancer screening strategies, the potential harms associated with surveillance should be carefully evaluated before implementing a systematic surveillance program. These includes among others (1) physical harms, as a result of false-positive results, which can lead to unnecessary invasive procedures [27], and have been reported in 27% of patients in one study [28]; (2) financial costs due to the need of clinical visits and diagnostic evaluations, plus indirect costs such as days of work missed; and, finally, (3) psychological harmful consequences as fear, worries, or anxiety develop during the process.

Indications for HCC Screening: Who to Test?

Due to the lack of robust clinical trial data, most experts and policy-makers recommend decision-making of entering a patient into a surveillance program be based on available cost-effectiveness analyses. These analyses mainly rely on the estimated HCC incidence, the expected patient survival, and the economic costs. According to these models, HCC surveillance is considered to be cost-effective in certain scenarios, with HCC incidence being the cornerstone of these strategies. In the case of cirrhosis, an annual incidence of HCC higher than 1.5% is argued to justify screening from a cost-effective point of view [29]. On the basis of this, it has been assumed that patients with cirrhosis, irrespective of its etiology, should undergo screening. Notably, surveillance is not justified in cirrhotic patients with severe liver dysfunction (Child–Pugh stage C) who are not candidates to liver transplantation, as these patients will not receive specific treatment in the case of HCC diagnosis, which would be classified as BCLC stage D and allocated to receive only best supportive care.

These general recommendations have also been applied in HIV-infected patients, but only based on extrapolated data from non-HIV populations. Although scarce, there are some data regarding HCC incidence in HIV-infected patients with cirrhosis which deserve consideration. A large retrospective study conducted in HIV-infected patients with or without HCV coinfection hospitalized in the national Veterans Health administration between 1991 and 2000 reported an incidence rate of HCC of 0.20 and 1.32 per 1000 person-years in HIV only and HIV/HCV-coinfected patients, respectively. Incidence rates were 0.42 and 2.18 per 1000 person-years, respectively, when considering only patients diagnosed of HIV during the HAART era. Notably, 3-year risk of HCC in the HAART era was 0.4% in HIV/HCV-coinfected patients. Although analyses were not adjusted for baseline cirrhosis, overall rates reported here would be lower than those suggested for surveillance purposes [30]. In a cohort of HIV-infected patients with cirrhosis (95% due to HCV and 25% previously decompensated), the HCC incidence was 2.7%

after a median follow-up of 5 years [31]. Recently, it has been reported that the probability of HCC increases 1% every year in the HEPAVIR cohort, a prospective multicenter cohort of 495 HIV/HCV-coinfected patients with compensated cirrhosis [11••]. Of note, 61% of patients were cured from HCV during follow-up. Similarly, HCC was diagnosed in 0.87% of 916 HIV/HCV-coinfected cirrhotics achieving SVR with DAA in the GEHEP-002 cohort during the first year after therapy [10••]. In the Veterans Affairs HIV Clinical Case Registry in the USA, 0.41% of HIV/HCV-coinfected patients with cirrhosis, as indicated by FIB-4 score, developed HCC during a mean follow-up of 10.6 years [32]. Finally, HCC incidence rate was 0.3 per 100 person-years in 640 HIV/HCV-coinfected patients with F3–F4 fibrosis achieving SVR with DAA in Spain [33]. Although disparity of criteria used across these studies for cirrhosis diagnosis (liver biopsy, FIB-4, liver stiffness) limits comparisons of observed rates, all the HCC incidence rates reported in contemporary studies are slightly lower than the threshold proposed for surveillance to be cost-effective in the general population and generate doubts whether HCC incidence in HIV-infected patients with HCV cirrhosis justify a systematic surveillance of HCC in these individuals. Despite this, recently updated clinical practical guidelines of care of HIV-infected patients in Spain still recommend surveillance of HCC in those with cirrhosis [34].

Some patients without cirrhosis but at a high risk for HCC are also candidates for surveillance. This is the case of patients with HBV infection for whom HCC surveillance has been estimated to be cost-effective if the estimated risk is greater than 0.2% per year [4]. Although the risk of HCC increases markedly with the development of cirrhosis, it is well known that HCC can emerge without pre-existing cirrhosis in HBV-infected patients. Risk factors are, among others, ethnicity, male sex, age, and a family history of HCC. Based on this, surveillance is recommended in HBV-infected Asian males over 40 years old without cirrhosis and Asian females over 50 years as well as in HBV carriers with African origin or those with a family history of HCC. Several risk scores have been proposed for HCC prediction in patients chronically infected by HBV, but most of them have only been validated in untreated Asian patients. The PAGE-B score, which is based on age, platelets, and gender, has been shown to predict HCC development at 5 years in Caucasian HBV-infected patients treated with tenofovir (TDF) or entecavir [35••]. Patients with a PAGE-B score <10 had a 0% HCC incidence both in the derivation and validation datasets. A modified PAGE-B score, which also includes albumin, has been shown to predict HCC emergence in Asians on HBV antiviral therapy [36]. A recent analysis of a large prospective multi-ethnic European cohort of HIV/HBV-coinfected patients found that the main predictors of HCC were the presence of cirrhosis and, as a protective factor, TDF treatment [37••]. Interestingly, among patients without cirrhosis treated with TDF, starting TDF at younger age was associated with an HCC incidence lower than the 0.2%/year threshold warranting screening. To date, no predictive HBV-related HCC scores have been validated in patients living with HIV.

There is some controversy on the need for screening patients with chronic hepatitis C and F3 fibrosis. Arguments favoring surveillance are, on the one hand, the risk that these patients are erroneously under-staged and actually at a significant risk of HCC [38] and, on the other hand, a non-negligible risk for HCC for F3 stage [38]. HCC incidence at 3 years in patients with F3 fibrosis and active HCV infection in the placebo arm of the HALT-C trial was 1.4% [38], lower than the 1.5%/year threshold claimed to justify screening. In the GEHEP-002 cohort, a multicenter nationwide cohort recruiting 373 HCC cases in HIV-infected individuals from 32 centers in Spain, less than 1% of cases emerged in individuals without cirrhosis (Merchante N., unpublished data). In addition, HCC incidence after HCV cure with DAA in HIV/HCV-coinfected patients with F3–F4 fibrosis was 0.3 per 100 person-years [33], with no case in subjects with liver stiffness under 14 kPa. These data reflect that HCC incidence in those with F3 is low. Due to these, we believe that systematic surveillance for F3 patients is not justified, although individual patients harboring F3 fibrosis and risk factors for ongoing liver injury, i.e., excessive alcohol intake or NAFLD, might benefit from such a strategy. Table 1 summarizes populations who clearly benefit of HCC surveillance and other situations in which the decision to screen is more controversial.

Surveillance Tools

Ultrasonography

Ultrasound (US) is the recommended imaging modality for the surveillance of HCC in high-risk patients [4, 5, 39–41]. A previous meta-analysis reported a pooled sensitivity of US to detect HCC at any stage of 94% [42]. Drawbacks of US surveillance are its operator dependency and poorer performance in obese patients [43, 44]. It has been estimated that 20% of US are inadequate for surveillance purposes [44]. Standardized guidelines for US performance and interpretation when done for HCC screening have been developed [45].

The ideal interval between US examinations has been assumed on the basis of expected tumor doubling times, the results of retrospective studies and of a single clinical trial [21], all conducted in HIV-uninfected patients. Consequently, US screening every 6 months is recommended. When compared to yearly interval, the 6-month scheme was superior in terms of detection and survival [46]. Conversely, a 3-month interval increased the detection of small nodules but had no impact on survival in a previous randomized clinical trial [47]. Given that no definite data support the notion that higher risk correlates with faster tumor growth, shortening to a

Table 1 High-risk groups of HIV-infected patients for hepatocellular carcinoma surveillance

Cirrhosis:	
Chronic hepatitis B (including patients with viral suppression) Chronic hepatitis C (including patients post-SVR) Alcohol-related Genetic hemochromatosis Primary biliary cirrhosis Non-alcoholic steatohepatitis Autoimmune hepatitis Cirrhosis from other etiologies	Surveillance in the general population with cirrhosis is considered cost-effective if HCC incidence exceeds 1.5%/year Cost-effectiveness of long-term surveillance in HIV-infected patients is not known Cumulative incidence of HCC in HCV-related cirrhosis, especially if SVR seems lower than 1.5%/year Risk stratification and individualized strategies needed in this population
Non-cirrhotic patients:	
HBV: Asian males ≥40 years Asian females ≥50 years Family history of HCC African persons ≥20 years PAGE-B score[1] >10	Surveillance has been estimated to be cost-effective if the estimated risk of HBV-associated HCC is greater than 0.2% per year Scarce data in HIV. Non-cirrhotic HIV-infected patients starting tenofovir under 46 years had an HCC incidence lower than 0.2%/year in one study PAGE-B score needs validation in the specific HIV context
HCV-related F3 fibrosis	Exact incidence unknown but probably lower than the cost-effective threshold. Consider in individual patients with additional risk factors such as heavy alcohol intake or features of NAFLD
NAFLD-related F3 fibrosis	No data. Probably not cost-effective

SVR sustained virologic response, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *NAFLD* non-alcoholic fatty liver disease

[1] PAGE-B score is based on baseline patients' age, gender, and platelets

3-month interval in individuals at high risk has been discouraged [39].

Performance of US Surveillance in HIV-Infected Patients

Until very recently, there was a lack of information regarding the performance of US in HIV-infected patients. Due to a concern that HCC may have a more aggressive course in the HIV-infected patient, there is a need for testing the effectiveness of US in the specific setting of HIV infection [48–50], which, in turn, might affect surveillance efficacy.

The performance of US surveillance in 346 HIV/HCV-coinfected patients has been assessed in the Spanish GEHEP-002 cohort and in a control group of HCV-monoinfected patients with HCC diagnosed at a single institution during the same study period [51••]. The main findings are summarized in Fig. 1. Surveillance uptake was suboptimal, as only 54% of cases were diagnosed within a surveillance program. However, this figure is line with the published uptake of surveillance in real-life settings [26, 44] and similar to what has been reported in the general population with HCC in Spain [52]. Sensitivity of US to detect any stage HCC was not affected by presence of HIV-infection. US lack of detection, defined as an HCC diagnosed within 3 months after a previous surveillance examination not showing suspicious nodules, was seen in 8.6% of patients. This percentage, which was identical to that observed in the control HIV-negative group, is in the range of 90% sensitivity that is expected for US [42]. Interestingly, cases observed after US lack of detection in our study showed higher frequencies of portal thrombosis and Child–Pugh stage C cirrhosis, being the latter one of the predictors of inadequate ultrasound quality for HCC surveillance in one study [53••]. The performance of US to detect HCC at early stage was also assessed. US surveillance failure, defined as HCC diagnosis at Barcelona Clinic Liver Cancer stage ≥B, occurred in 57% of cases in HIV-infected patients versus 29% of the HIV-negative control group [51••]. Despite this, HCC mortality was lower in HIV-infected patients diagnosed by screening than in those not screened. However, the worst performance of US surveillance in HIV-infected patients translated into lower survival rates when compared to the HIV negative group. Taken all these findings together, our study shows that US surveillance has a low performance for HCC surveillance in HIV-infected patients, with a suboptimal 43% rate of early stage diagnosis, far from the 63%–71% rate found in studies conducted in non-HIV-infected patients [42, 52].

As the lack of effectiveness of US does not seem to be explained by a lower uptake or lower sensitivity of US, our study raises the question if there are distinct biological processes in the HIV-infected patient. The incidence of several non-AIDS defining neoplasms seems higher in persons living with

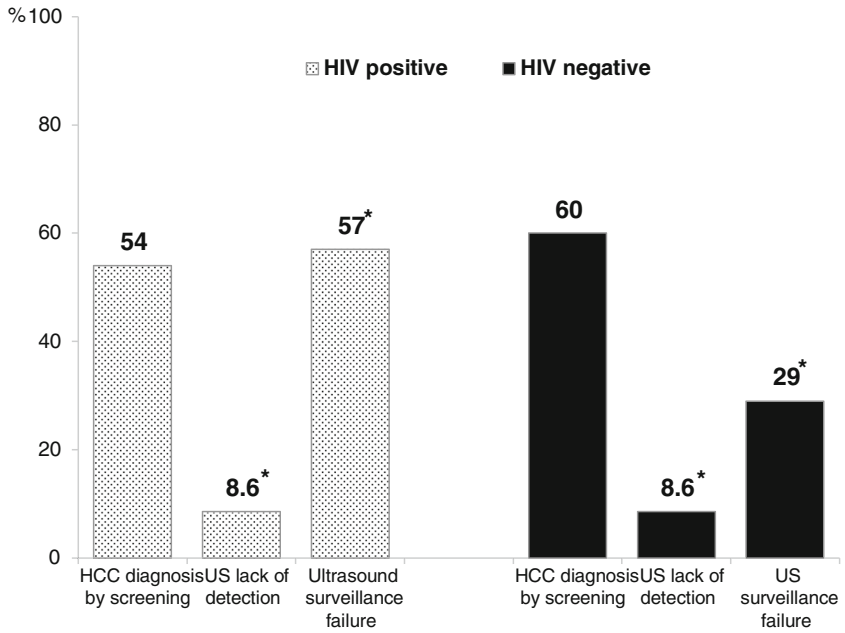

Fig. 1 Performance of hepatocellular carcinoma (HCC) ultrasound (US) surveillance according to HIV status (adapted from [49]). Screening of HCC was done by the performance of an abdominal US every 6 months. US lack of detection is defined as HCC diagnosis in the first 3 months after a normal surveillance US examination. US surveillance failure is defined as HCC diagnosis made by screening at a Barcelona Clinic Liver Cancer stage equal or greater than B. (*) Rates of US lack of detection and US surveillance failures are referred as the percentage from the total of HCC cases diagnosed within a screening program

HIV than in the general population [54, 55]. In the specific case of HCC, several reports have suggested an accelerated and aggressive pattern of presentation for HCC in the presence of HIV [48–50], which could explain why HIV-infected patients are more prone be diagnosed in a more advanced stage, despite adequate screening. Of note, HCC cases in which surveillance failed in our study [51••] showed lower rates of controlled HIV viral replication and a non-significant trend for lower CD4 cell counts. In line with this, chronic immunosuppression has been proposed as a relevant factor driving HIV contribution to carcinogenesis, as lower CD4 cell counts have been associated with an increased risk for HCC [56]. It is reasonable to speculate that the negative effects exerted by HIV on the immune system, which are not fully reversed by antiretroviral therapy, could affect tumor immunosurveillance, facilitating faster tumor growth and accelerated progression. As a result, a significant proportion of patients would progress between surveillance imaging examinations toward an advanced stage when the diagnosis of liver cancer is made. To confirm this hypothesis, future research should investigate the immunological features of both host and tumor in HIV-infected patients in which surveillance failed.

Other Imaging Techniques

Given the limited sensitivity of US and the high diagnostic yield of multi-phase contrast enhanced computed tomography (CT) and magnetic resonance imaging (MRI), its role in surveillance has been a matter of interest. However, concerns regarding repeated radiation exposure, contrast-induced nephrotoxicity, higher costs, and lack of cost-effective data limit its application as a surveillance tool [57]. Furthermore, data to support the use of these more expensive imaging modalities is limited. CT-based surveillance failed to improve detection rate of early HCC in a randomized controlled trial [58]. A recent observational study comparing the performance of liver-specific contrast MRI screening with that of US reported a high sensitivity with fewer false-positive results with the MRI-based strategy [59••]. Although encouraging, these approach needs further validation, as well as optimization with abbreviated MRI protocols in order to minimize contrast exposure, examination duration, and costs, as previous studies of conventional MRI did not prove cost-effectivity [60]. As it is unlikely that an MRI-based surveillance is applicable to all the spectrum of high-risk patients, best candidates for MRI-based screening should be defined. Importantly, screened patients with inadequate or inconclusive US examinations should undergo CT or MRI to definite exclude HCC.

Serum Markers

Serum tumor markers are an attractive approach for early cancer diagnosis, as they provide a non-invasive assessment. The most widely used serological test is AFP, which is considered normal for screening purposes if below 20 ng/dL. However, even using this threshold, only 60% sensitivity and 80% specificity is

expected [61, 62]. Combining AFP with US increases detection rates but also false-positive results and costs [42, 44, 61–63], as AFP may increase in patients with chronic viral hepatitis with or without cirrhosis in the absence of HCC [62]. Consequently, most clinical guidelines do not recommend its routine determination as a surveillance test. However, some still favor its use in combination with US [57], a strategy that continues to be the routine of many clinicians. Of note, the sensitivity of AFP in HIV-infected patients is also very low, as up to 25% HCC showed values below 10 ng/dL at diagnosis [51••].

A large number of alternative serum markers have been explored but none of them have shown enough accuracy [61, 62, 64, 65]. A promising score, called GALAD, which combines clinical data, such as sex and age, with three different tumor markers (α-fetoprotein, α-fetoprotein-L3, and des-γ carboxyprothrombin), has shown promising results [66] but still needs further validation. None of these tumor markers have been evaluated specifically in HIV-infected patients.

Implications of HCV Viral Eradication on Surveillance

DAA have revolutionized HCV care with cure rates higher than 95% in the vast majority of clinical scenarios [67]. Consequently, DAA are expected to modify the epidemiology of HCV-related HCC leading to a progressive decline of its incidence over time due to the protective effect of SVR [11••, 12–18, 68••, 69••, 70••]. However, it is well known that SVR does not completely eliminate the risk of HCC, especially if established cirrhosis was present before treatment [9]. Thus, new HCC cases are expected to emerge in the subsequent years after HCV cure, particularly in those patients who received DAA at advanced stages of fibrosis. Thus, one out of three new diagnoses of HCC in HIV/HCV-coinfected patients in Spain is being made in patients with SVR [10••].

The implications of risk reduction for HCC associated with HCV eradication on surveillance policies are a challenge. Initial studies [71••], including one conducted in HIV/HCV-coinfected patients [11••], suggested that the type of therapy leading to SVR, either IFN-based or not, does not have an influence on the HCC risk reduction, but longer follow-up after DAA-induced SVR is needed to definitely clarify this. Currently, most of the experts and clinical guidelines support continuing surveillance in those with cirrhosis prior DAA therapy [5, 25, 34, 39, 72, 73]. Supporting this, a large study conducted in the Veterans Health Administration has reported that the HCC incidence after SVR to DAA in those with previous cirrhosis ranges from 1.0% to 2.2% per year depending on other epidemiological and clinical factors [69••], which exceed the cut-off beyond which surveillance becomes cost-effective. Additionally, patients with cirrhosis and baseline FIB4 score ≥3.25 prior to therapy had an increased risk for HCC after SVR with DAA that reached 3.66%/year [74]. In a study of 640 HIV/HCV-coinfected patients with cirrhosis cured with DAA, and followed a median of 31.6 months after SVR, the incidence (95% CI) of HCC was 0.3 (0.1–0.7) cases per 100 person-years [33]. In this study, liver stiffness at SVR was associated with future risk of liver complications, including HCC, suggesting a predictive role for elastography in stratifying patients for surveillance. The ability of liver stiffness in this population to identify subjects who will not develop HCC after SVR seemed to be higher than for FIB-4 [33]. It is likely that a combination these two makers, perhaps along with other parameters, may help us to accurately identify subjects with residual risk of HCC in whom surveillance should be maintained after SVR.

HIV, HCC, and NAFLD: A Dangerous Triad?

The worldwide prevalence of NAFLD has been estimated to be around 25% [75] and it is expected to continue to increase in the future. In some regions, NAFLD has become a leading cause of chronic liver disease [73]. NAFLD is also frequently observed in HIV-infected individuals [76–79], as a consequence of a large number of factors, such as HCV coinfection, genetic factors [80, 81], or toxicity of antiretroviral therapy [82, 83], and based on recent evidence, a primary contributor to development and progression of steatosis in HIV are metabolic factors [78, 84, 85].

NAFLD-related cirrhosis is a major risk factor for HCC. In a large cohort of patients with NAFLD cirrhosis, the incidence of HCC was 1.06% per year [86••]. NAFLD is responsible for 10–14% of HCC cases in the USA [87, 88] and 6% in some European countries such as Spain [52], with differences probably reflecting the overall prevalence of obesity in the general population. Besides, NAFLD has become the fastest-growing cause of HCC-related transplantation in the USA [89]. The burden of HCC in NAFLD is mostly due to the enormous magnitude of the obesity epidemic, as HCC incidence seems lower in NAFLD than that seen in viral or alcoholic cirrhosis. Although NAFLD is a main etiology of chronic liver disease in the HIV-infected patient [78], its relative contribution to HCC development is not known. At present, almost all HCC cases in HIV individuals have developed in patients with HCV and/or HBV coinfection or with severe alcohol intake [51], but it is conceivable that concomitant steatosis may have played a role in some cases attributed exclusively to HCV. Notably, several retrospective reports have confirmed that HCC can emerge in the absence of cirrhosis in patients with NAFLD in a significant proportion of cases [90–92]. However, the incidence of NAFLD-related HCC in the absence of cirrhosis, which is not accurately known, is probably very low to warrant surveillance. Reliable diagnostic tests to differentiate steatosis from non-alcoholic steatohepatitis as well as predictive models of HCC emergence are needed in order to identify patients with NAFLD at high risk of HCC

who could benefit from screening. For now, only patients with cirrhosis should undergo screening.

Future Directions

The treatment of HCC has evolved considerably and effective therapeutic options can now be offered in most stages of the disease with the aim of improving survival. As early diagnosis is a crucial step to accomplish this goal, surveillance strategies are of the paramount importance. However, improvement can still be made in this area. Uptake of US surveillance in real life is still suboptimal, with a high proportion of the target population not being screened and a significant fraction of those screened receiving inconsistent surveillance [93, 94]. Underuse of surveillance is determined by both failure of providers at several steps of the process [95–97] and failure of patients to adhere with recommendations [98], although some of these studies have been conducted in settings that could be not representative of the HIV-infected population. Interestingly, one study found that the strongest predictor of adequate surveillance was the number of visits to a specialist in the first year after cirrhosis diagnosis, whereas distance to the closest hospital and longer times between the date when US was ordered and the examination appointment were inversely associated [99]. To solve this, innovative initiatives such as electronic medical records with clinical reminders for clinicians [100] and mail/phone reminders for patients, which have been shown to improve surveillance rates [101••], should be considered. As discussed in this review, the yield of current tools is far from optimal. The detection of circulating tumor cells or its components in the blood, which is commonly known as *liquid biopsy*, is one of the major advances in the field of Medical Oncology in the last years [102]. Although initially developed for prognosis assessment, research has widened its role to diagnosis and treatment decisions, being an attractive strategy to anticipate HCC diagnosis in patients at high risk. A panel of six methylation markers found in the cell-free DNA has shown promising high sensitivity to identify patients with stage 0-A HCC [103••]. Besides, new biotechnologies such as next-generation sequencing and omics data, including, but not limited to, genomic, epigenomic, transcriptomic, proteomic, and metabolomic, have provided novel insights for HCC [104–106]. Multiple omics analyses for the diagnosis of HCC have also yielded promising results that could be useful for screening purposes [107]. Mass spectrometry–based metabolomic studies have identified biomarker panels of metabolites with better diagnostic value than AFP [108]. Although the potential of metabolomics is promising, current limitations are the lack of standardization of techniques, the absence of replication of studies, and the lack of data demonstrating higher rates of early diagnosis when compared to the current standard of imaging surveillance. Finally, the target population for surveillance strategies needs to be redefined, according to the changes in the epidemiology of chronic liver disease. At present, surveillance is currently recommended in all patients with cirrhosis, but the risk of HCC has a wide range among these patients and across etiologies. Unfortunately, reliable stratification tools are still lacking for the most relevant current scenarios as NAFLD or post-SVR follow-up. In this sense, predictive models of HCC risk after SVR are desperately needed to guide decisions.

Conclusions

HIV-infected patients with comorbidities leading to advanced chronic liver disease such as excessive alcohol intake, HBV or HCV infection, and/or NAFLD are at a high risk of HCC. Surveillance with bi-annual US, with or without AFP, identifies patients with early-stage HCC who will benefit of curative therapies, although the quality of the evidence supporting a benefit in terms of survival remains limited. Besides, the performance of US screening in the specific context of HIV is lower than that seen outside HIV infection, which may affect its cost-effectiveness. Future efforts should focus on improving surveillance uptake, refining risk stratification for a better selection of candidates, and the development and validation of novel imaging- and/or blood-based surveillance strategies for early detection of HCC. Finally, due to the considerable burden of HCC in HIV-infected individuals and the lack of effectiveness of US for the early diagnosis of HCC in these patients, we believe the HIV population is a priority risk group for which discovery and validation of surveillance strategies should be targeted.

Compliance with Ethical Standards

Conflict of Interest No potential conflicts of interest relevant to this article were reported.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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