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TOPIC HIGHLIGHT

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Hepatocellular carcinoma, human immunodeficiency virus and viral hepatitis in the HAART era

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Abstract

The incidence of hepatocellular carcinoma (HCC) in patients with human immunodeficiency virus (HIV) is rising. HCC in HIV almost invariably occurs in the context of hepatitis C virus (HCV) or hepatitis B virus (HBV) co-infection and, on account of shared modes of transmission, this occurs in more than 33% and 10% of patients with HIV worldwide respectively. It has yet to be clearly established whether HIV directly accelerates HCC pathogenesis or whether the rising incidence is an epiphenomenon of the highly active antiretroviral therapy (HAART) era, wherein the increased longevity of patients with HIV allows long-term complications of viral hepatitis and cirrhosis to develop. Answering this question will have implications for HCC surveillance and the timing of HCV/HBV therapy, which in HIV co-infection presents unique challenges. Once HCC develops, there is growing evidence that HIV co-infection should not preclude conventional therapeutic strategies, including liver transplantation.

Key words: Hepatocellular carcinoma; Human immunodeficiency virus; hepatitis; Hepatitis B virus; Hepatitis C virus; Co-infection; Incidence; Transplant; Pathogenesis

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INTRODUCTION

With the increased survival of human immunodeficiency virus (HIV) patients with access to highly active antiretroviral therapy (HAART), it is unsurprising that conditions with a typically long latency are now being observed more frequently. Hepatocellular carcinoma (HCC) is such a disease, usually occurring several decades after the initial infection with hepatitis C virus (HCV) or hepatitis B virus (HBV). While few suspect that HIV infection alone is a risk-factor for HCC (indeed, this has been excluded in large retrospective cohort studies[1]), associated infection with HCV or HBV is common and the significantly increased risk of HCC with viral hepatitis is well-documented. More is now known of the interaction between HIV and HBV and/or HCV over the long-term. Broadly speaking, HIV co-infection seems to accelerate disease progression and reduces the efficacy of anti-HCV and anti-HBV therapy. However, it is unclear whether HIV infection directly increases the likelihood of HCC in viral hepatitis.

Some other key questions are as follows:

What is the true prevalence of HIV and HBV and/or HCV co-infection worldwide?

How should HIV status affect screening and treatment for HCC?

How should HIV infection influence therapy for viral hepatitis?

Answering these questions is essential to planning effective strategies for the prevention, screening and treatment of HCC in HIV-positive patients in the future. Here we review recent attempts to address these challenges.

THE WORLDWIDE AT-RISK POPULATION-WHAT IS THE TRUE PREVALENCE OF HIV AND VIRAL HEPATITIS CO-INFECTION?

HBV and HCV infection have distinct epidemiological and geographical profiles due to different modes of transmission. In broad terms, HCV transmission is predominantly due to intravenous drug use in Western societies and a mix of IV drug use and iatrogenic transmission in developing countries. These modes of transmission also apply to HBV but in endemic areas the primary route is through sexual contact and vertical transmission. HIV shares modes of transfection

Table 1 Examples of internationally diverse prevalences of HBV and HCV co-infection in HIV populations.

Country	Germany, Ockenga *et al* 1997[45]	Greece, Dimitrakopoulos *et al* 2000[45]	Thailand, Sungkanuparph *et al* 2004[45]	TREAT Asia HIV Observational Database (TAHOD)[45]	Spain, Gonzalez-Garcia *et al* 2002[45]	Australia, Lincoln *et al*[45]	Ivory coast, Rouet *et al* 2004[45]
n	232	181	529	1498	2820	3309	501
HCV + ve	23%	13.80%	7.80%	10%	-88%	10.70%	1%
HBV + ve	9%	67.40%	8.70%	10%	-5%	4.80%	26%

with both diseases and therefore its geographical and demographic distribution encompasses that of both HBV and HCV. There are many exceptions to this broad rule, however. In the Far East, for example, the HCV burden is predominantly found in the elderly population and probably represents iatrogenic exposure from poorly sterilized medical equipment in the 1920s[1]. Rates of HIV co-infection are predictably low in this cohort.

Between HIV positive populations in different countries, relative proportions of HCV and HBV co-infection vary widely according to the prevalence of different high-risk behaviours in the populations tested. Examples of these diverse prevalences are given in Table 1.

Most of these studies are disadvantaged by a small sample size (especially in developing countries) or are limited to one particular at-risk group (e.g. haemophiliacs or IV drug users). Thus wide variation is often seen between studies in the same geographical region. For example, in Greece a recent study of 737 HIV infected individuals found a prevalence of 48.1% and 12.1% of HCV and HBV co-infection respectively[3], a marked contrast to a study only 6 years earlier in the same country (13.8% and 67.4% respectively[4]).

The recorded prevalence is likely to be inaccurate for other reasons. Around 30% of HCV antibody-positive patients will have undetectable HCV RNA (i.e. have cleared the virus) and yet most studies of prevalence use the antibody test alone. Hepatitis B surface antigen (HBsAg) is almost universally used as a surrogate of HBV co-infection, yet there is growing recognition for a significant subset of patients who are HBsAg-negative but have detectable HBV DNA on quantitative PCR and/or positive anti-HB core antibodies. So-called "occult" hepatitis B infection is frequently detected in patients with HCV infection, HIV and HCC of non-HCV aetiology. The prevalence of occult HBV co-infection in HCV may be as high as 80% in HCV endemic areas such as Japan[4]. Occult HBV infection is also more common in HIV-positive than HIV negative patients in HBV endemic areas (22.1% *vs* 2.4%)[5]. This is especially relevant to studies of HCC in HIV infection, since occult HBV infection seems to maintain its oncogenic potential despite lower viral titres. In a recent Italian study, HBV DNA was detected in 68 of 107 cases of HBsAg-negative HCC (63.5%)[6] and occult HBV infection has been demonstrated in up to 70% of patients with HBsAg-negative HCC in Japan[7].

It thus seems that larger prevalence studies using RNA and DNA titres are needed to achieve a more accurate estimate of the true burden of viral hepatitis in HIV, particularly in developing countries where the largest reservoirs of infection exist.

HIV CO-INFECTION AND PROGRESSION TO HCC IN VIRAL HEPATITIS

The pathogenesis of HCC in viral hepatitis

Up to 75% of cases of HCC worldwide are thought to be associated with hepatitis B or C[8]. While the continual inflammation and repair of cirrhosis is an important pathogenic factor in both diseases, the degree of viral replication is more closely related to HCC risk in HBV than in HCV infection. The risk of HCC in active chronic hepatitis B is some 90-fold greater than age-matched healthy controls but only 9-fold greater in inactive carriers of HBV where viral load is low. Also, viral titres seem to correlate directly with the risk of HCC in hepatitis B[9].

In hepatitis C, the presence of cirrhosis is a prerequisite to the development of HCC, which occurs in between 1%-4% of patients per annum once cirrhosis is established. Indeed, the increased risk of HCC in cirrhotic patients persists in the absence of the virus after successful eradication with IFN therapy[10].

These differences probably represent the different underlying pathogeneses of HCC in HBV *versus* HCV[11]. In the former, the random integration of viral DNA into the host chromosomes (an incidental process not necessary for viral replication) leads to secondary chromosomal rearrangement and genomic instability. The HBV DNA product protein HBx (crucial to replication) transactivates genes involved in cell-cycle control (c-jun and c-myc for example). *In vitro* HBx has been shown to disrupt cell-cycle control and inhibit DNA repair and apoptosis all of which have oncogenic potential in their own right[12].

By contrast, the HCV does not integrate into host cell DNA. Some HCV core proteins do enter the nucleus and modify a variety of signal transduction pathways. Additionally, oxidative cellular injury occurs as a direct result of HCV core protein expression both *in vitro* and *in vivo*[13]. Although this may participate in the carcinogenic process to a small degree, the principal oncogenic effect of HCV is mediated indirectly through activation of the immune-mediated inflammation and its downstream effects on cell proliferation and apoptosis.

The incidence of HCC in the HIV positive cohort

The 2001 French Mortavic study[14] was a prospective 1-year cohort study of 25178 HIV positive patients across 65 national centres comparing the incidence and causes of death to similar cohorts in 1995 and 1997. Deaths from end-stage liver disease (ESLD) rose significantly from 1995 to 2001 (1.5% to 14.3%) and the proportion of those deaths due to HCC also rose 5-fold (4.7% to 25%). Nearly all deaths from HCC were in patients

with HCV co-infection. Deaths from AIDS during this period fell from 91.6% to 48.7% and overall mortality from 8.15% to 1.05%. The authors thus concluded that increased longevity in the HAART era is the principle reason for increased ESLD and HCC in the 2001 cohort. A large retrospective cohort study of US veterans (following 14018 male veterans from 1997 to 2004) has also confirmed a much higher risk of HCC in the HIV population, nearly exclusively in association with HCV (and to a lesser extent HBV) co-infection[15]. A third retrospective cohort-spanning the pre-HAART and HAART eras-revealed a much higher incidence of HCC in patients with HIV/HCV co-infection than average and the difference was much more marked in the HAART era (only 5 diagnosis of HCC were made in the entire cohort of 11678 patients in the pre-HAART era, *versus* 22 in the HAART era)[1]. Smaller, retrospective cohort studies in Europe have yielded similar results. One study of 2383 HIV positive patients found a higher-than-expected incidence of HCC (6 cases in total, four of which had HCV co-infection) compared with the population average[16].

It is noteworthy that studies examining cohorts in the pre-HAART era or in countries where HAART is not readily available, have frequently found the incidence of HCC to be lower or equal to average population rates[17,18]. The more recent studies, however, proffer convincing evidence that HCC incidence is higher than the population average and rising amongst the HIV-positive population receiving HAART-nearly exclusively in association with HCV or HBV infection- and cite increased longevity as the principal cause of this phenomenon.

However, none of the above studies indicates that there is a higher incidence of HCC in HIV and viral hepatitis co-infection compared to isolated HCV or HBV infection- as one might expect if HIV accelerates the disease progression of viral hepatitis towards HCC.

HCC oncogenesis in viral hepatitis-is HIV a true additional risk factor?

While the HIV virus itself is not considered to be particularly oncogenic in its own right, a number of cancers are well known to occur with increased frequency in people with HIV infection. For the most part this is a consequence of impaired immunity and failure to clear several common oncogenic viruses such as HHV8 in Kaposi sarcoma (KS), EBV in non-Hodgkin's (NHL) and HPV in anal and cervical cancer.

In vivo studies in murine models have revealed a potential role for the HIV Tat gene in liver tumorigenesis. Transgenic mice expressing this gene have a greater incidence of hepatocellular carcinoma. This is thought to be mediated by extra-hepatic growth signals rather than by direct disruption of the hepatocyte cell cycle by the Tat product and the effect is not specific for hepatocarcinoma; these animals suffer a higher incidence of other extra-hepatic tumours (leiomyosarcomas, squamous cell papillomas and carcinomas, adenocarcinomas of skin adnexa and B-cell lymphomas). In humans, however, large retrospective cohort studies in the HAART era have shown no increased incidence of HCC in HIV monoinfection[1].

There is clearer evidence that HIV can accelerate disease progression of both HBV and HCV and thus indirectly increase the chance of subsequent HCC. HIV affects the natural history of HCV infection in two important ways: firstly, it increases the likelihood of chronic infection following the acute episode[19] and secondly, it hastens the development of cirrhosis once chronic infection is established[20,21]. This has important implications for the subsequent development of HCC and any screening strategy. HIV co-infection has also been shown to accelerate the progression of HBV infection[22], with patients suffering from more severe disease at an earlier stage. Increased liver injury in viral hepatitis may also be mediated indirectly in HIV by antiretroviral therapy-related hepatotoxicity and by immune reconstitution syndrome. Indeed, HCV infection seems to increase the risk of HAART-related hepatotoxicity[23]. It must also be considered that once HCC has developed, a putatively weaker anti-tumour response due to chronically low CD4+ and CD8+ lymphocyte counts may result in more rapid growth and spread of disease.

Despite evidence for acceleration of cirrhosis in viral hepatitis with HIV co-infection, attempts to demonstrate a specific increase in HCC in this context-over and above that observed in HCV or HBV monoinfection- have so far yielded variable results.

In the US veterans studies mentioned above, direct comparisons were made between HCV mono-infected subjects and groups with HIV/HCV co-infection.

Mcguinnis *et al* (2001)[15] compared the incidence of HCC between 14018 HIV positive and 28036 age-, sex- and location-matched HIV-negative controls in a large retrospective cohort study from 1997 to 2004. A higher age-matched incidence of HCC was clearly demonstrated in the HIV positive group (incidence rate ratio 1.68) but when adjusted for HCV infection and/or alcohol consumption the incidence rate rations were similar, suggesting HIV co-infection confers no additional risk of HCC compared to HCV infection alone.

A precursor of this study (another retrospective cohort of US veterans) compared the incidence of cirrhosis and HCC in 26641 HCV-only with 4761 HCV/HIV co-infected subjects between 1991 and 2000[24]. The incidence of HCC in both groups was found to be the same in the HAART era and lower in the HIV/HCV co-infection group in the pre-HAART era. This would corroborate the premise that HIV patients did not survive sufficiently long in the pre-HAART era to develop HCC, but also suggests that in the HAART era HIV status does not seem to alter the likelihood of progression to HCC in HCV infection.

These studies, however, are subject to several sources of error. In one retrospective cohort the authors concede that up to 50% of the apparent HCV-only group were never tested for HIV (which would bias the study towards the null) and it was also subject to changes in disease reporting and coding during the study period which may have lead to significant acquisition bias. More importantly, a recurring confounding factor is the rising incidence of cirrhosis (and therefore HCC) throughout the study period in patients with isolated HCV infection. This may reflect earlier acquisition of HCV in this group (often in

the 1970s in the US) compared to their HIV co-infected counterparts and highlights a recurring deficiency in such retrospective cohort studies: they rarely include data on when infection was acquired. Although HCC rates may be similar in HIV/HCV and HCV-only groups in the immediate post-HAART era, the HIV/HCV co-infected cohort may well have acquired HCV more recently and thus the equal incidence may actually belie accelerated disease progression in this group.

The 2004 Italian cooperative group on AIDS and Tumours (GICAT) study examined 41 cases of HCC in HIV positive individuals (from a joint Italian and Spanish database) and compared them with 384 HIV-negative controls diagnosed over the same period (1995-1998)[25]. This is the largest study purporting to show an acceleration of liver disease towards HCC in HIV and viral hepatitis co-infection. The HIV group with HCC were much younger at presentation (age 40-46 *vs* 60-70) and had more advanced infiltrating disease. There was also a trend to more advanced cirrhosis at presentation in the HIV positive population. Accordingly, few of the HIV patients were offered active treatment and survival rates were poor. Again, HCV co-infection was clearly the main risk factor in both the HIV positive group and negative controls. In this study, the younger age at diagnosis and the limited data available on the timing of HCV infection in both HIV co-infected and HCV-only groups suggested HIV-HCV co-infected patients develop HCC some 10 years earlier than expected (compared with a previous series examining HCC in HIV-negative patients with post-transfusion HCV).

Three further studies have also described earlier development of HCC (and poorer outcome) in HIV co-infected subjects compared with HBV or HCV monoinfection, including one cohort of British haemophiliac men and boys[26], one of homosexual men in the United States[27] and a Spanish retrospective cohort of 2383 HIV positive subjects[28]. The total numbers of cases of HCC in each study were very low, however.

Convincing evidence for an HIV-induced acceleration of disease progression in viral hepatitis towards HCC thus remains lacking. Of note is a glaring lack of studies specifically addressing HBV and HIV co-infection-presumably because this is far less prevalent than HCV/HIV co-infection in the developed countries which have the advanced information infrastructure needed to carry out retrospective trawls of large databases.

If one postulates the ideal study to address whether HIV is a true additional risk factor for HCC in viral hepatitis, it would consist of a prospective cohort of HIV/HCV/HBV co-infected and HCV- and/or HBV-only subjects with all subjects cross-tested for co-infection before allocation to groups (and at regular intervals thereafter). It would also instigate screening for HCC on a regular basis. It might be reasonable to expect that even if HIV has an accelerative effect on HCC pathogenesis this might be countered viral suppression by HAART, therefore such a study would undertake regular monitoring of HIV viral load in the HIV co-infected group. Crucially, if the duration of HIV and HBV/HCV infection is known for each patient, fewer patients and years of follow-up would be necessary to detect an accelerative affect of HIV on progression to HCC.

It is telling that almost none of the studies mentioned above include any such parameters. On the basis of existing evidence, we can only conclude that if an additional risk of progression to HCC in viral hepatitis is conferred by HIV it is not large enough to be detected by relatively crude retrospective examination within the short space of time (relative to normal HCC pathogenesis) that has passed since the introduction of HAART.

SCREENING, PREVENTION AND TREATMENT OF HCC IN HIV

Treatment and outcome of HIV patients with HCC

In the HIV negative population, solitary or a small number of HCC lesions are resectable, and associated with a 5-year survival of 60%-70%[27]. In the presence of cirrhosis patients with operable lesions are offered transplantation resulting in equivalent survival data. Operability is determined by the Milan criteria (no evidence of extrahepatic tumour and unifocal tumour mass < 5 cm in diameter or multifocal tumours < 4 in number, each < 3 cm in diameter[29], although some large-volume centres now adopt the more aggressive University of California, San Francisco (UCSF) criteria which have extended tumour burden limits with similar outcomes[30]. Ethanol injection is another treatment option for patients with local disease who are not candidates for surgery and is associated with 5-year survival rates of approximately 50%[31]. Patients with more advanced disease are limited to palliative embolization. No chemotherapy or targeted therapy has been shown to offer a survival benefit for these patients.

Data from other HIV positive non-AIDS defining cancers, such as lung cancer, suggest these patients are offered curative therapy less frequently than their HIV negative counterparts due to the advanced nature of their disease at presentation[32]. In the series described in the GICAT study[32] 15 of the 41 patients with HIV and HCC had disease within the Milan criteria that would be deemed curable with liver transplantation. However, none underwent liver transplantation and only two underwent surgical resection. Overall, HIV positive patients have a much worse outcome compared to their HIV negative counterparts with only a 28% 1 year survival.

Although HIV-positive status was previously an absolute contraindication to liver transplantation, this is now becoming more commonplace following several transplant series which have demonstrated similar survival outcomes in MELD-score matched HIV- positive and negative recipients[33-38]. There is no evidence, as previously feared, that the subsequent immunosuppressive therapy results in progression of HIV disease[39].

There is now data specifically addressing liver transplants in HIV positive patients with HCC. Di Benedetto *et al* recently reported a series of 7 patients with HIV and HCC who fulfilled Milan criteria and underwent liver transplantation[40]. After a mean follow-up of 232 d, the overall patient and graft survival was 85.7%. One patient died of a myocardial infarction with a functioning graft and no evidence of HCC recurrence.

Liver transplant patients with HIV, for any indication, clearly face specific problems post-transplant compared with HIV negative counterparts. These include more aggressive HCV re-infection, more common lamivudine resistance in HBV and a higher incidence of tacrolimus toxicity[41]. However, where an increased mortality has been observed it is frequently cited that late referral plays a role[42]. A greater proportion of HIV-positive patients seem to die on the waiting list for liver transplantation from liver-related causes. Two conclusions can therefore be drawn: firstly, patients with HIV and HCC should not be denied the opportunity for liver transplantation and secondly, detecting these cancers early is of paramount importance.

Preventative therapy in HIV and HBV/HCV co-infected patients

Patients with HIV-HCV co-infection benefit from HCV eradication for the same reasons as those with HCV alone. Sustained virological response rats (SVR) of between 27%-40% have been achieved with IFN and ribavirin therapy in HIV co-infected patients[43]. Not only is the risk of HCC reduced with HCV eradication but the resulting enhanced liver function increases tolerance to antiretroviral agents. Treatment of the HIV-HCV patient presents several challenges however, such as (1) more severe and frequent IFN related myelosupression, (2) more frequent haemolytic anaemias caused by ribavirin interaction with zidovudine, (3) antagonism of zidovudine phosphorylation (4) increased risk of lactic acidosis. Most significantly, patients with low CD4+ counts respond very poorly to HCV eradication therapy[44].

In HIV-HBV infection, there is every reason to suspect the risk of progression to HCC can be reduced by viral suppression just as it is in monoinfected HBV cases. Given that HAART and HBV suppression regimens share many common agents (lamivudine, for example) the principal problem encountered in this group is cross-resistance. Dual therapy for effective HBV suppression is frequently required (e.g. lamivudine plus tenofovir) but, as in HCV coinfection, response rates are poor in patients with low CD4+ counts.

Although anti-viral therapy in HIV and HBV and/or HCV is more complex and generates more potential adverse events, if early hepatological expertise is sought then the vast majority of patients should have the option of potentially curative therapy in HCV and effective long-term viral suppression in HBV.

Screening for HCC in patients with hepatitis and HIV co-infection

The European association for study of the liver (EASL) has released guidelines for screening HIV and HCV/HBV co-infected individuals. These are similar to HCV and HBV monoinfected patients with established cirrhosis and recommend screening every 6 mo with ultrasonography and alpha-fetoprotein levels. In the United States suggested screening of co-infected individuals incorporates the use of ultrasound as the primary screening modality. They suggest AFP should not be used alone unless ultrasonography is unavailable; screening should occur at 6-12 mo intervals and should include all those at elevated risk for HCC[32,38].

In our unit we currently do screen co-infected individuals with both α-fetoprotein (AFP) and ultrasound scans if the AFP is raised. This has not been validated and early unpublished results suggest these may be problems with sensitivity and specificity of AFP in this setting, especially as HAART can cause an increase in AFP levels[41]. Anecdotally our programme has revealed a low sensitivity and specificity. This may in part be due to patient selection and the potentially rapid development of the disease. More frequent imaging surveillance in very high-risk groups (such as those with persistently high HBV titres, for example) may prove to be the way forward. Data in this setting is urgently required.

CONCLUSION

Retrospective cohort studies warn us that an increase in HCC in the HIV population is already underway in regions where HAART therapy is available. Increased access to HAART can be expected to have similar consequences in developing countries but the timing of this increase will be difficult to predict. Insufficient epidemiological data on HIV and HBV/HCV co-infection (especially in the developing countries which are most affected) makes the at-risk population very difficult to locate and quantify. Because the latency of HCC in HIV co-infection may be shorter than in isolated viral hepatitis, there may be less time than we might expect to prepare adequate screening, prevention and treatment services.

Such services are currently far from optimal. A recent US study of HIV clinic management of HBV co-infection found that HBV viral load was inadequately monitored in HIV co-infected patients despite regular measurements of HIV titres[45]. Other guidelines for HBV management were loosely adhered to. The applicability of current HCC screening techniques in viral hepatitis monoinfection remains untested in the context of HIV co-infection, and once HCC is diagnosed, patients are referred for potentially effective treatment less frequently and much later than their HIV-negative counterparts.

Although guidelines now exist on the management of viral hepatitis and HIV co-infection, there will always be unique scenarios not covered by these that present both opportunities (e.g. anti-viral cross-efficacy) and pitfalls (e.g. cross-resistance). As the HAART era takes us into uncharted waters, holding to the optimum course through prevention, screening and therapy for HCC will require both HIV physician and hepatologist at the helm.

REFERENCES

1 **Giordano TP**, Kramer JR, Souchek J, Richardson P, El-Serag HB. Cirrhosis and hepatocellular carcinoma in HIV-infected veterans with and without the hepatitis C virus: a cohort study, 1992-2001. *Arch Intern Med* 2004; **164**: 2349-2354

2 **Tanaka Y**, Kurbanov F, Mano S, Orito E, Vargas V, Esteban JI, Yuen MF, Lai CL, Kramvis A, Kew MC, Smuts HE, Netesov SV, Alter HJ, Mizokami M. Molecular tracing of the global hepatitis C virus epidemic predicts regional patterns of

hepatocellular carcinoma mortality. *Gastroenterology* 2006; **130**: 703-714

3 **Elefsiniotis S**, Paparizos V, Botsi C, Pantazis KD, Katsambas A. Serological profile and virological evaluation of hepatitis B and hepatitis C virus infection among HIV infected patients in Greece. *Cent Eur J Public Health* 2006; **14**: 22-24

4 **Chemin I**, Trepo C. Clinical impact of occult HBV infections. *J Clin Virol* 2005; **34**: S15-S21

5 **Mphahlele MJ**, Lukhwareni A, Burnett RJ, Moropeng LM, Ngobeni JM. High risk of occult hepatitis B virus infection in HIV-positive patients from South Africa. *J Clin Virol* 2006; **35**: 14-20

6 **Pollicino T**, Squadrito G, Cerenzia G, Cacciola I, Raffa G, Craxi A, Farinati F, Missale G, Smedile A, Tiribelli C, Villa E, Raimondo G. Hepatitis B virus maintains its pro-oncogenic properties in the case of occult HBV infection. *Gastroenterology* 2004; **126**: 102-110

7 **Shiota G**, Oyama K, Udagawa A, Tanaka K, Nomi T, Kitamura A, Tsutsumi A, Noguchi N, Takano Y, Yashima K, Kishimoto Y, Suou T, Kawasaki H. Occult hepatitis B virus infection in HBs antigen-negative hepatocellular carcinoma in a Japanese population: involvement of HBx and p53. *J Med Virol* 2000; **62**: 151-158

8 **Anthony PP**. Hepatocellular carcinoma: an overview. *Histopathology* 2001; **39**: 109-118

9 **Chen CJ**, Yang HI, Su J, Jen CL, You SL, Lu SN, Huang GT, Iloeje UH. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006; **295**: 65-73

10 **Toyoda H**, Kumada T, Tokuda A, Horiguchi Y, Nakano H, Honda T, Nakano S, Hayashi K, Katano Y, Nakano I, Hayakawa T, Nishimura D, Kato K, Imada K, Imoto M, Fukuda Y. Long-term follow-up of sustained responders to interferon therapy, in patients with chronic hepatitis C. *J Viral Hepat* 2000; **7**: 414-419

11 **Szabo E**, Paska C, Kaposi Novak P, Schaff Z, Kiss A. Similarities and differences in hepatitis B and C virus induced hepatocarcinogenesis. *Pathol Oncol Res* 2004; **10**: 5-11

12 Andrisani OM, Barnabas S. The transcriptional function of the hepatitis B virus X protein and its role in hepatocarcinogenesis (Review). *Int J Oncol* 1999; **15**: 373-379

13 **Okuda M**, Li K, Beard MR, Showalter LA, Scholle F, Lemon SM, Weinman SA. Mitochondrial injury, oxidative stress, and antioxidant gene expression are induced by hepatitis C virus core protein. *Gastroenterology* 2002; **122**: 366-375

14 **Rosenthal E**, Poiree M, Pradier C, Perronne C, Salmon-Ceron D, Geffray L, Myers RP, Morlat P, Pialoux G, Pol S, Cacoub P. Mortality due to hepatitis C-related liver disease in HIV-infected patients in France (Mortavic 2001 study). *AIDS* 2003; **17**: 1803-1809

15 **McGinnis KA**, Fultz SL, Skanderson M, Conigliaro J, Bryant K, Justice AC. Hepatocellular carcinoma and non-Hodgkin's lymphoma: the roles of HIV, hepatitis C infection, and alcohol abuse. *J Clin Oncol* 2006; **24**: 5005-5009

16 **Murillas J**, Del Rio M, Riera M, Vaquer P, Salas A, Leyes M, Angeles Ribas M, Penaranda Vera M, Villalonga C. Increased incidence of hepatocellular carcinoma (HCC) in HIV-1 infected patients. *Eur J Intern Med* 2005; **16**: 113-115

17 **Beral V**, Newton R. Overview of the epidemiology of immunodeficiency-associated cancers. *J Natl Cancer Inst Monogr* 1998; **23**: 1-6

18 **Mbulaiteye SM**, Parkin DM, Rabkin CS. Epidemiology of AIDS-related malignancies an international perspective. *Hematol Oncol Clin North Am* 2003; **17**: 673-696

19 **Thomas DL**, Astemborski J, Rai RM, Anania FA, Schaeffer M, Galai N, Nolt K, Nelson KE, Strathdee SA, Johnson L, Laeyendecker O, Boitnott J, Wilson LE, Vlahov D. The natural history of hepatitis C virus infection: host, viral, and environmental factors. *JAMA* 2000; **284**: 450-456

20 **Smukler AJ**, Ratner L. Hepatitis viruses and hepatocellular carcinoma in HIV-infected patients. *Curr Opin Oncol* 2002; **14**: 538-542

21 **Bruno R**, Gazzaruso C, Sacchi P, Zocchetti C, Giordanetti S, Garzaniti A, Ciappina V, Maffezzini E, Maserati R, Filice G. High prevalence of metabolic syndrome among HIV-infected patients: link with the cardiovascular risk. *J Acquir Immune Defic Syndr* 2002; **31**: 363-365

22 **Thio CL**, Seaberg EC, Skolasky R Jr, Phair J, Visscher B, Munoz A, Thomas DL. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet* 2002; **360**: 1921-1926

23 **Sauleda S**, Martorell M, Esteban JI, Tural C, Ruiz I, Puig L, Esteban R, Guardia J, Vargas V. Hepatotoxicity of antiretroviral drugs in HIV HCV patients with congenital coagulopathies followed at an Haemophilia Unit during a decade. *Haemophilia* 2006; **12**: 228-236

24 **Kramer JR**, Giordano TP, Souchek J, Richardson P, Hwang LY, El-Serag HB. The effect of HIV coinfection on the risk of cirrhosis and hepatocellular carcinoma in U.S. veterans with hepatitis C. *Am J Gastroenterol* 2005; **100**: 56-63

25 **Puoti M**, Bruno R, Soriano V, Donato F, Gaeta GB, Quinzan GP, Precone D, Gelatti U, Asensi V, Vaccher E. Hepatocellular carcinoma in HIV-infected patients: epidemiological features, clinical presentation and outcome. *AIDS* 2004; **18**: 2285-2293

26 **Darby SC**, Ewart DW, Giangrande PL, Spooner RJ, Rizza CR, Dusheiko GM, Lee CA, Ludlam CA, Preston FE. Mortality from liver cancer and liver disease in haemophilic men and boys in UK given blood products contaminated with hepatitis C. UK Haemophilia Centre Directors' Organisation. *Lancet* 1997; **350**: 1425-1431

27 **Llovet JM**, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet* 2003; **362**: 1907-1917

28 **Garcia-Samaniego J**, Rodriguez M, Berenguer J, Rodriguez-Rosado R, Carbo J, Asensi V, Soriano V. Hepatocellular carcinoma in HIV-infected patients with chronic hepatitis C. *Am J Gastroenterol* 2001; **96**: 179-183

29 **Mazzaferro V**, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693-699

30 **Yao FY**, Ferrell L, Bass NM, Bacchetti P, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: comparison of the proposed UCSF criteria with the Milan criteria and the Pittsburgh modified TNM criteria. *Liver Transpl* 2002; **8**: 765-774

31 **Bruix J**, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E, Pagliaro L, Colombo M, Rodes J. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 2001; **35**: 421-430

32 **Powles T**, Nelson M, Bower M. HIV-related lung cancer -- a growing concern? *Int J STD AIDS* 2003; **14**: 647-651

33 **Ragni MV**, Belle SH, Im K, Neff G, Roland M, Stock P, Heaton N, Humar A, Fung JF. Survival of human immunodeficiency virus-infected liver transplant recipients. *J Infect Dis* 2003; **188**: 1412-1420

34 **Fung J**, Eghtesad B, Patel-Tom K, DeVera M, Chapman H, Ragni M. Liver transplantation in patients with HIV infection. *Liver Transpl* 2004; **10**: S39-S53

35 **Stock PG**, Roland ME, Carlson L, Freise CE, Roberts JP, Hirose R, Terrault NA, Frassetto LA, Palefsky JM, Tomlanovich SJ, Ascher NL. Kidney and liver transplantation in human immunodeficiency virus-infected patients: a pilot safety and efficacy study. *Transplantation* 2003; **76**: 370-375

36 **Duclos-Vallee JC**, Vittecoq D, Teicher E, Feray C, Roque-Afonso AM, Lombes A, Jardel C, Gigou M, Dussaix E, Sebagh M, Guettier C, Azoulay D, Adam R, Ichai P, Saliba F, Roche B, Castaing D, Bismuth H, Samuel D. Hepatitis C virus viral recurrence and liver mitochondrial damage after liver transplantation in HIV-HCV co-infected patients. *J Hepatol* 2005; **42**: 341-349

37 **Neff GW**, Bonham A, Tzakis AG, Ragni M, Jayaweera D, Schiff ER, Shakil O, Fung JJ. Orthotopic liver transplantation in patients with human immunodeficiency virus and end-stage liver disease. *Liver Transpl* 2003; **9**: 239-247

38 **Prachalias AA**, Pozniak A, Taylor C, Srinivasan P, Muiesan P, Wendon J, Cramp M, Williams R, O'Grady J, Rela M, Heaton ND. Liver transplantation in adults coinfected with HIV. *Transplantation* 2001; **72**: 1684-1688
39 **Roland ME**, Stock PG. Liver transplantation in HIV-infected recipients. *Semin Liver Dis* 2006; **26**: 273-284
40 **Di Benedetto F**, De Ruvo N, Berretta M, Masetti M, Montalti R, Di Sandro S, Ballarin R, Codeluppi M, Guaraldi G, Gerunda GE. Hepatocellular carcinoma in HIV patients treated by liver transplantation. *Eur J Surg Oncol* 2007; (Epub ahead of print)
41 **Powles T**, Bower M, Daugaard G, Shamash J, De Ruiter A, Johnson M, Fisher M, Anderson J, Mandalia S, Stebbing J, Nelson M, Gazzard B, Oliver T. Multicenter study of human immunodeficiency virus-related germ cell tumors. *J Clin Oncol* 2003; **21**: 1922-1927
42 **Pache I**, Duclos-Valle JC, Teicher E, Bismuth H, Castaing D, Vittecoq D, Samuel D. Indications and timing for liver transplantation in HIV-coinfected patients. *Hepatology* 2004; **40**: 356A
43 **Hughes CA**, Shafran SD. Treatment of hepatitis C in HIV-coinfected patients. *Ann Pharmacother* 2006; **40**: 479-489; quiz 582-583
44 **Chung RT**. Hepatitis C and B viruses: the new opportunists in HIV infection. *Top HIV Med* 2006; **14**: 78-83
45 **Jain MK**, Opio CK, Osuagwu CC, Pillai R, Keiser P, Lee WM. Do HIV care providers appropriately manage hepatitis B in coinfected patients treated with antiretroviral therapy? *Clin Infect Dis* 2007; **44**: 996-1000

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