

# HIV and viral hepatitis coinfections: advances and challenges

Karine Lacombe,<sup>1</sup> Juergen Rockstroh<sup>2</sup>

<sup>1</sup>Department of Infectious Diseases, Hôpital Saint-Antoine, Université Pierre et Marie Curie, Inserm UNR-S 707, Paris, France

<sup>2</sup>Department of Medicine I, University of Bonn, Bonn, Germany

## Correspondence to

Dr K Lacombe, Service de maladies infectieuses et tropicales, Hôpital Saint-Antoine, 184 rue du Faubourg Saint-Antoine, Paris 75012, France; [karine.lacombe@sat.aphp.fr](mailto:karine.lacombe@sat.aphp.fr)

## ABSTRACT

With a prevalence affecting over 30% of HIV infected patients, coinfection with hepatitis B (HBV) or C (HCV) virus remains one of the most frequent comorbidities in this population, with a significant impact in terms of morbidity and mortality associated with liver disease. Recent findings in the physiopathology of HIV in the liver have confirmed that it may contribute, along with hepatotoxicity of antiretrovirals and the burden of metabolic diseases, to a more rapid progression of liver fibrosis, especially when there is underlying chronic hepatitis coinfection. Both fields of research and clinical appraisal of HBV and HCV coinfection are rapidly evolving and prompt a change in the former paradigms of clinical care and management of chronic hepatic coinfection in the context of HIV. The advent of anti-HCV direct antiviral agents has indeed completely shaken up the treatment guidelines for HCV, and the tricky management of these new agents with antiretrovirals means referring patients to specialised centres. In HBV coinfection, therapeutic options have not changed recently but new challenges have emerged regarding the management of low replicating HBV-DNA in optimally treated patients and long term exposure to antivirals. Finally, the global increase in life expectancy in HIV infected patients has been accompanied in coinfecting patients by a higher risk of emergence of end stage liver diseases for which access to orthotopic liver transplantation and innovative procedures such as targeted hepatocellular carcinoma therapies should be facilitated.

## HIV, HBV, HCV: A MOVING EPIDEMIOLOGY

Because of the shared routes of transmission, hepatitis B (HBV) or hepatitis C (HCV) virus coinfection is common among HIV positive patients. The average estimated risk of transmission for HBV and HCV C in HIV based on mode of transmission is depicted in table 1.

## Hepatitis B

Of the 33.3 million HIV infected persons worldwide in 2009, it is estimated that up to 5 million have concomitant HCV, and 4 million HBV, coinfection. The prevalence and transmission route of HBV in the HIV infected population varies substantially across geographic regions.<sup>1 2</sup> In HBV endemic regions of Africa and Asia, the majority of HBV infections are vertically transmitted at birth or before the age of 5 years through close contact within households, medical procedures and traditional scarification.<sup>3</sup> In the USA and Europe, the

majority of HBV infections can be found in men who have sex with men, most of whom have evidence of past HBV infection and 5–10% exhibit markers of chronic HBV infection.<sup>2 4</sup>

Overall, rates of HBV–HIV coinfection are slightly lower among intravenous drug users compared with homosexual men and much lower among people infected through heterosexual contact.<sup>5</sup> With increased HBV vaccination rates, a decrease in new HBV infections can be observed, particularly in younger patient populations where national vaccination programmes have been implemented.<sup>6</sup>

## Hepatitis C

As HCV is transmitted with high efficacy via direct blood to blood contact, the prevalence of HCV coinfection within different countries, regions and populations is closely related to the prevalence of blood borne (mainly intravenous drug use) HIV infection. Among all HIV infected patients from Europe, Australia and the USA, at least one in four is infected with concomitant HCV.<sup>7</sup> HCV coinfection rates as high as 70% are observed in Eastern European countries such as Ukraine and Russia where intravenous drug use is the main route of HIV transmission.<sup>8</sup>

In contrast, in Central European countries such as Belgium, Austria and Germany, where sexual intercourse dominates as the mode of HIV transmission, HCV coinfection rates are rather low (10–15%).<sup>9</sup> In the USA, higher rates of HCV coinfection, ranging from 25% to 35% of patients with HIV, have been reported. Particularly high rates of HCV coinfection have been documented in intravenous drug users and prisoners.<sup>10 11</sup> In Asia, coinfection rates of up to 85% have been observed among Chinese plasma donors.<sup>12</sup> However, in countries with predominantly heterosexual HIV transmission, such as Thailand, or other regions of the world such as sub-Saharan Africa, coinfection rates are mostly below 10%.<sup>13</sup>

In the past 10 years epidemic HCV outbreaks among HIV positive men who have sex with men from several major European cities, such as London, Paris, Amsterdam and Berlin, as well as from Australia and more recently from the USA, Canada and Taiwan, have been reported, suggesting that HCV may well be sexually transmitted and should therefore also be taken into account on regular sexually transmitted disease screening.<sup>14–16</sup>

HCV is detected in 4–8% of infants born to HCV infected mothers.<sup>17</sup> Dual HIV–HCV infection increases the risk for transmission of both viruses and is closely linked to high maternal viral load.<sup>18 19</sup>

**Table 1** Average estimated risk of transmission for HIV, hepatitis B virus, hepatitis C virus and hepatitis B virus or hepatitis C virus in HIV coinfection

Mode of transmission	Average transmission risk (%)				
	HIV	HBV	HCV	HBV–HIV	HCV–HIV
Perinatal	10–20	10–90*	<2–7	10–90*	10–20
Sexual contact	<1	Up to 90†	<1	Up to 90†	<1–3‡
Needle stick injury with cannula	0.3	30	0.3	Unknown	Unknown

\*Transmission risk 10–40% in HBsAg positive but HBeAg negative mothers; risk significantly higher (up to 80%) in HBsAg and HBeAg positive mothers.

†Dependant on the level of HBV-DNA.

‡Values are based on data from HCV serodiscordant heterosexual couples; it has to be speculated that within the current outbreak of HCV in men who have sex with men, traumatic mucosal damage through unprotected anal sex or fisting with a high risk of blood–blood contact, the risk for acquisition of HCV is much higher. HBV, hepatitis B virus; HCV, hepatitis C virus; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen.

The majority of HCV infections in the HIV coinfecting population are HCV genotype 1 infections (53% in the EuroSIDA cohort<sup>8</sup>). In the past decade in particular, a shift to an increase in HCV genotype 4 infections has been noted in HIV–HCV coinfecting patients resulting in part from increased migration, whereas conversely it has declined for HCV genotype 3, in association with the wider use of HCV therapy in this population along with higher response rates.<sup>20</sup> The increasing number of difficult to treat HCV genotypes underlines the need for developing improved treatment strategies for these particular patient groups.

### Multiple coinfections

Coinfection with HIV and HCV and/or HBV is highly prevalent in intravenous drug users. Indeed, triple infection with HIV–HCV–HBV reached almost 20% in a recent study in Chinese drug users.<sup>21</sup> Studies evaluating the viral interactions in multiple hepatitis coinfections identified many different viral patterns. In treated coinfecting patients, hepatitis delta virus expressed continuous suppression over HCV and HBV replications and an accelerated course of liver fibrosis.<sup>22–24</sup> Peaks and rebounds from undetectable hepatitis B, C and/or D viraemias warrant closer follow-up in this patient population.

### Natural history of hepatitis coinfection in HIV

HIV accelerates HBV and HCV liver disease, especially when HIV associated immunodeficiency progresses, and leads to an increase in morbidity and mortality.<sup>25</sup> Administration of successful antiretroviral therapy has been demonstrated to slow down fibrosis progression and to decrease liver disease associated mortality.<sup>26 27</sup> This explains why in most guidelines HBV or HCV coinfection represents a comorbidity in which earlier HIV treatment initiation is recommended.

Recent data suggest that HBV coinfection might impact on the natural history of HIV, in terms of increased all cause mortality<sup>28</sup> and AIDS events.<sup>29</sup> In patients treated with HIV–HBV dual active drugs, treatment interruption was associated with a greater decrease in CD4T cells and faster treatment reinitiation than in HIV seropositive patients without chronic hepatitis undergoing treatment

interruption.<sup>30</sup> HCV coinfection in contrast does not seem to unfavourably impact on the course of HIV in the era of combined antiretroviral therapy (cART).<sup>2 9</sup> Hepatitis coinfection, however, is associated with an independently increased risk for hepatotoxicity once cART is started, thereby limiting the potential benefits of cART therapy. This risk however declines once patients have achieved sustained virological response (SVR) under HCV therapy.<sup>31</sup>

Therefore, control or even better cure of hepatitis coinfection remains the most desirable goal in the management of coinfecting individuals.

### RECENT FINDINGS IN THE PHYSIOPATHOLOGY OF HIV AND HEPATITIS COINFECTION

Recent findings have shed new light on the process of liver fibrosis in the context of HIV induced immunosuppression, disentangling the profibrogenic effects of HIV itself as well as various aspects of the altered innate and adaptive immune responses.

HIV evinces a strong tropism for hepatic stellate cells and hepatocytes through chemokine (C-X-C motif) coreceptor 4 (CXCR4) and chemokine (C-C motif) coreceptor 5 (CCR5), which in turn exerts a direct cytopathic effect on liver tissue. When HIV envelop glycoprotein 120 ligates to CXCR4 coreceptors of liver cells, expression of tumour necrosis factor related apoptosis inducing ligand is upregulated, resulting in cellular apoptosis.<sup>32</sup> Based on these experimental results, the authors further suggest that HIV infection renders hepatocytes more susceptible to liver injury, particularly during disease states associated with enhanced tumour necrosis factor related apoptosis inducing ligand production, such as HBV and HCV. On entry into hepatocytes and hepatic stellate cells, HIV also triggers a proinflammatory cascade, leading to myofibroblastic differentiation via enhanced production of  $\alpha$ -smooth muscle actin, collagen and monocyte chemoattractant protein 1.<sup>33</sup>

Furthermore, the role of HIV on exhausted innate immune responses, indirectly facilitating HCV and HBV clearance, is a newly developing factor for liver fibrosis. One consequence of such an alteration is the modified expression of Toll-like receptors (known for pathogen recognition), which trigger proinflammatory signalling cascades and enables liver fibrogenesis.<sup>34</sup> HBV itself has also been shown to suppress toll-like receptor mediated innate immune responses, eliciting activation and expression of proinflammatory transcription factors and cytokines.<sup>35</sup> Finally, HCV can also alter the expression of some Toll-like receptor pathway inhibitors—namely SHIP—with the consequences affecting the severity of liver fibrosis.<sup>36</sup>

### HEPATITIS B: REMAINING CHALLENGES IN DIAGNOSIS, TREATMENT AND FOLLOW-UP

In the past 10 years, unprecedented progress has been made in the clinical and therapeutic management, as well as the prevention, of chronic HBV. Firstly, recently published results on the increase in

anti-HBV immunisation efficacy by administering an additional double dose vaccine booster is an encouraging step towards better prevention of HBV transmission in HIV infected patients.<sup>37</sup>

At the same time as HIV diagnosis, HBV screening is now routinely performed on a large scale, and this observed trend in developed countries will soon apply to developing countries where the WHO is advocating systematic screening for chronic hepatitis before antiretroviral treatment initiation. A recent rise in the proportion of patients with liver staging and grading, by means of liver biopsy or non-invasive liver markers, has been observed before discussing treatment options.<sup>38 39</sup>

Finally, treatment efficacy has considerably increased with the large scale use of tenofovir disoproxil fumarate (TDF), a very potent reverse transcriptase nucleotide analogue.<sup>40</sup> As a consequence, HBV as an attributable cause of end stage liver disease in HIV infected patients remains marginal.<sup>41</sup>

### Diagnosis: how to maximise evaluation of liver disease severity

Because of impaired immune control from HIV infection, the rate of acute infections evolving into chronic HBV after infection is five times higher in HIV than in non-HIV infected adults.<sup>42</sup> Furthermore, the rate of hepatitis B e antigen, and ultimately hepatitis B surface antigen, seroclearance is strongly linked to the level of immunosuppression,<sup>43</sup> which can be eventually restored with the use of antiretrovirals.<sup>44</sup> The intertwined natural histories of these two viruses have been proven to be particularly deleterious—coinfected patients have an excess risk of all cause mortality (while not including AIDS) as high as 36% compared with HIV monoinfected patients<sup>28</sup> and 10 times higher risk of dying from liver related causes compared

with HIV or HBV monoinfected patients.<sup>45</sup> This higher risk of death is driven by the oncogenic nature of HBV (which can directly induce hepatocellular carcinoma (HCC)) and the profibrogenic effect of both HIV and HBV. It is therefore essential to appropriately and repeatedly evaluate liver disease severity in this population.

In view of this, liver biopsy still remains an important tool because of its ability not only to accurately provide staging and grading of liver fibrosis/activity<sup>46</sup> but also to provide information on overlapping comorbidities that may alter liver prognosis and compromise treatment efficacy and tolerance (non-alcoholic steatohepatitis,<sup>47</sup> occlusive venopathy,<sup>48</sup> granulomatous disease<sup>49</sup>). However, the need for more practical tools, whose use could be repeated and help longitudinal fibrosis screening, has urged the development on non-invasive markers of fibrosis.

Elastometry is being widely used in various liver conditions with a very satisfying performance, but has seldom been evaluated in the setting of HIV–HBV infection as only one study performed on a relatively small number of patients is available.<sup>50</sup> However, the peculiarities of HIV–HBV infection are clearly underlined with the differing cut-offs for extended fibrosis and cirrhosis than those reported for HIV–HCV infection or HBV monoinfection (see table 2), thereby increasing the risk of inaccurately estimating liver fibrosis when using only elastometry.

Many biochemical markers have also been developed which include direct and indirect markers of degradation in the extracellular matrix. Eleven have been specifically studied in the context of HIV–HBV infection<sup>51</sup> and three (Fibrotest, Fibrometer and Hepascore) have proven to be accurately associated with levels of liver fibrosis, again with thresholds differing from

**Table 2** Thresholds for liver fibrosis stages with non-invasive tools

	Thresholds		AUROC		PPV (%)		NPV (%)	
	HCV	HBV	HCV	HBV	HCV	HBV	HCV	HBV
Fibrotest*†								
≥F2	0.49	0.43	0.64			80		61
≥F3	0.59	0.59	0.72	0.77		67		83
F4	0.75	0.74	0.81	0.87		50		94
Fibrometre*†								
≥F2	0.5	0.46	0.70			78		62
≥F3		0.69	0.78	0.75		74		84
F4		0.83	0.84	0.90		52		96
Hepascore*†								
≥F2	0.5	0.48	0.69			77		57
≥F3		0.76	0.76	0.74		76		84
F4	0.84	0.90	0.83	0.91		60		96
Fibroscan‡§								
≥F2	7.0	5.9	0.72	0.85	70.2	91	81.1	74
≥F3	11.0	7.6	0.91	0.92	60	77	96.3	92
F4	14.0	9.4	0.97	0.96	57.1	79	100	98

Adapted from: \*Bottero J *et al.*,<sup>51</sup> †Cacoub P *et al.*,<sup>52</sup> ‡Sanchez-Conde *et al.*,<sup>53</sup> §Mialhes *et al.*,<sup>50</sup>

METAVIR fibrosis score: F0=no fibrosis; F1=portal fibrosis, no septae; F2=portal fibrosis, few septae; F3=bridging fibrosis; F4=cirrhosis.

AUROC, area under the curve of operational receiver; HBV, hepatitis B virus; HCV, hepatitis C virus; NPV, negative predictive value; PPV, positive predictive value.

those established for other liver conditions (see table 2).

### Treatment: optimising control of HBV-DNA replication

In the early years of 2000, the availability of TDF, a HBV and HIV reverse transcriptase nucleotide analogue, triggered a shift in the paradigm of HIV–HBV treatment in both HBV naive<sup>54</sup> and pretreated patients with lamivudine (LAM) or adefovir.<sup>55</sup> Until then, LAM had been extensively used in developed countries, with the main drawback of rapidly inducing polymerase gene mutations (20% per year of exposure, with a peak of 90% at 5 years).<sup>56</sup> Subsequent viral breakthroughs have been observed, leading to a risk of cytolysis and fulminant hepatitis.<sup>57, 58</sup>

The efficacy of interferon (IFN) and Peg-interferon (Peg-IFN) has also been questioned in this setting, but no convincing results have ever been obtained during monotherapy<sup>59</sup> or when combined with reverse transcriptase nucleotide analogues.<sup>60, 61</sup> Other oral drugs have been evaluated in the context of HIV–HBV coinfection with mixed results so far.

Adefovir dipivoxil has proved to be partially efficacious in LAM pretreated patients, with 25% of patients achieving an HBV-DNA level  $>2.3$  log<sub>10</sub> copies/ml after 144 weeks of treatment.<sup>62</sup> However, the emergence of specific polymerase gene mutations (such as rtA181T, first described in HIV infected patients<sup>63</sup>) and subsequent ongoing viral replication has precluded its use in this population. Moreover, adefovir dipivoxil has been shown to be inferior to TDF in terms of virological response.<sup>64, 65</sup> Entecavir (ETV) was initially prescribed in HIV–HBV coinfecting patients as monotherapy but has been associated with the emergence of HIV reverse transcriptase mutation (L184V) conferring resistance to LAM *in vitro* and *in vivo*.<sup>66, 67</sup>

Finally, telbivudine (LdT) has been examined recently in a similar context. Although a slight decrease in HIV-RNA was observed,<sup>68</sup> no HIV mutation was found *in vitro*,<sup>69</sup> suggesting that the supposed ‘anti-HIV activity of LdT’ might proceed from the consequence of HBV suppression and a direct immune modulating effect of LdT.<sup>70</sup>

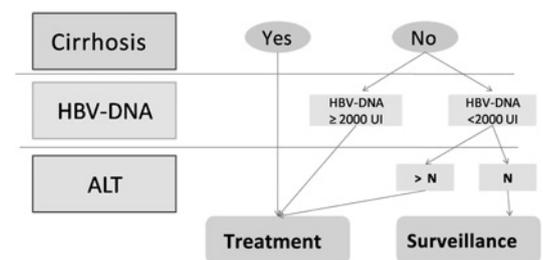
TDF associated with a potent anti-HIV combination is presently the most effective option for patients in need of dual HIV and HBV treatment.<sup>71</sup> More than 95% of patients are still virologically suppressed after 5 years of treatment<sup>40</sup> and no convincing mutations conferring phenotypic resistance have been described to date.<sup>72</sup> Of note, the A194T polymerase mutation described in patients treated with tenofovir under suboptimal viral control may confer a decrease in phenotypic sensitivity,<sup>73</sup> yet these results need to be confirmed in larger studies.<sup>74</sup> Hepatitis B e antigen loss occurs in 35% and 46%, and hepatitis B surface antigen loss in 3.6% and 12% of patients at 3 and 5 years of treatment, respectively.<sup>40, 72</sup> Significant histological improvement has also been noted,<sup>75</sup> even in cirrhotic patients.<sup>76</sup> In parallel with what has been

observed in HIV monoinfected patients, renal and bone tolerance during long term TDF use has been examined in coinfecting patients but a higher risk of renal dysfunction has not been observed thus far.<sup>77</sup> In the case of renal impairment, TDF dose should be adapted to creatinine clearance.<sup>71</sup> Because of the lack of other therapeutically effective options in the meantime and the high risk of viral breakthrough resulting in deleterious consequences, interruption of TDF must be avoided.

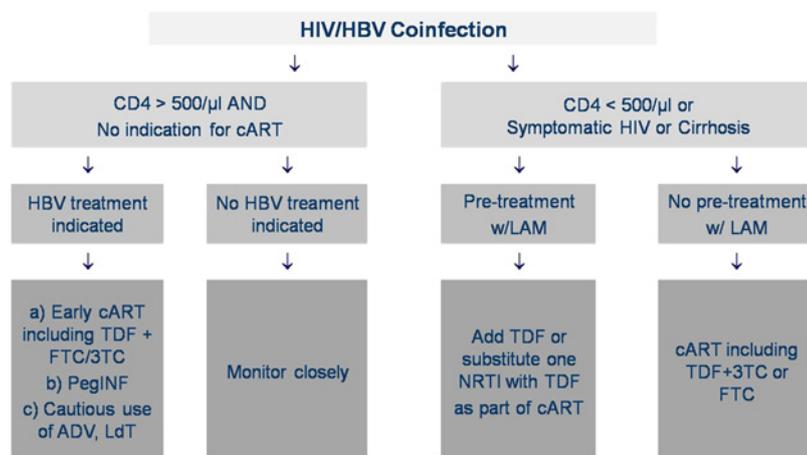
Three important issues of HBV management during HIV infection are of interest to clinicians. Firstly, when is the optimal time for HBV treatment initiation in the context of HIV? The European AIDS Clinical Society in its recently updated guidelines suggested proceeding in a hierarchical manner (see figure 1): starting with an evaluation of cirrhosis status, the level of HBV-DNA (with a threshold of 2000 IU/ml), then the level of alanine aminotransferase. The opportunity and/or necessity of antiretroviral treatment is assessed based on the level of CD4+ T cells (see figure 2).

However, the second residual issue is the timing of antiviral initiation among patients with no indication for HIV treatment. Neither TDF nor ETV as monotherapy should be prescribed because of their anti-HIV activity. The therapeutic option with the least amount of virological complications may be early introduction of cART, including TDF, associated with either LAM or emtricitabine (although no study has reported the superior efficacy of dual therapy over TDF monotherapy with regards to HBV<sup>78</sup>). However, it is strongly recommended to opt for dual therapy in pretreated patients with advanced liver fibrosis (F3–F4).<sup>71</sup> In patients with favourable determinants to IFN response (ie, HBV genotype A, high alanine aminotransferase level and low HBV-DNA level), it is suggested that a 48 week course of IFN could be attempted. Otherwise, the remaining options include the use of LdT or adefovir as monotherapy or in combination, but no data are currently available supporting their long term use.

The last, but certainly not the least, therapeutic concern is which attitude to adopt in the face of low but persistent replicating HBV-DNA under long term TDF. The clinical impact of persistent viral replication under treatment is not known,



**Figure 1** When to treat hepatitis B virus infection in HIV infected patients? ALT, alanine aminotransferase; HBV-DNA, hepatitis B virus DNA; N, normal threshold. (Adapted from European AIDS Clinical Society guidelines.<sup>71</sup>)



**Figure 2** How to treat hepatitis B virus infection in HIV infected patients? 3TC, ; ADV, adefovir dipivoxil; CD4, CD4+ T lymphocytes; cART, combined antiretroviral therapy, FTC, emtricitabine; HBV, hepatitis B virus; LAM, lamivudine; LdT, telbivudine; NRTI, HIV nucleos(t)ide reverse transcriptase inhibitor; Peg-IFN, pegylated interferon; TDF, tenofovir dipivoxil fumarate. 3TC; lamivudine. (Adapted from European AIDS Clinical Society guidelines.<sup>71</sup>)

neither are their pathophysiological pathways; suboptimal adherence or the presence of supposedly TDF resistant strains having been ruled out.<sup>72–79</sup> One clue might be the persistence of a severe deficiency in T cell proliferation and activation from HIV infection, with the increased exhaustion of CD8+ T cells, which is not fully restored under antiviral therapy.<sup>80</sup> Intensification strategies with ETV have been proposed with promising results which need to be confirmed on a larger scale.<sup>81</sup> Stronger evidence would be needed before advocating the use of the expensive TDF–ETV combination in low replicating patients.

#### Follow-up: tools and indications

The follow-up of treatment efficacy relies on regular monitoring of HBV-DNA (every 6 months) and repeated HBV serology (every year), with the aim of identifying those patients with viral breakthrough and hepatitis B e antigen/hepatitis B surface antigen clearance. However, most patients are perfectly virologically controlled under TDF and do not lose hepatitis B e antigen or hepatitis B surface antigen. New markers of treatment efficacy have therefore been explored to circumvent the problem of HBV-DNA as a poor predictor of hepatitis B e antigen or hepatitis B surface antigen clearance. Hepatitis B e antigen ratio at 12 months has been shown to accurately predict hepatitis B e antigen loss at 36 months, whereas a baseline level of hepatitis B surface antigen <400 UI/ml was highly predictive of hepatitis B surface antigen loss, yet in rare circumstances.<sup>82</sup>

However, their clinical pertinence in everyday practice is still questionable as it is not designed, unlike in HBV mono-infection, to anticipate treatment interruption during hepatitis B e antigen or hepatitis B surface antigen clearance. This tool might be more useful in the case of IFN use (where it has been proven to accurately predict loss of hepatitis B surface antigen in HBV mono-infect

patients) but data in the context of HIV are still lacking. Treatment efficacy should also be evaluated on the basis of liver fibrosis regression under treatment. Two studies based on repeated liver biopsies have reported regression of extensive fibrosis and even cirrhosis under TDF,<sup>75–76</sup> also seen by means of non-invasive markers.<sup>75–83–84</sup>

#### HEPATITIS C: ADVANCES IN THERAPEUTIC MANAGEMENT

The unfavourable course of HCV in HIV coinfecting individuals with an increased risk of fibrosis progression and development of HCC at younger ages<sup>85</sup> has been the underlying rationale for treating chronic HCV in HIV. With the previous gold standard of Peg-IFN and ribavirin (RBV), SVR rates between 27% and 50% were achieved.<sup>86–90</sup> Clearly response rates were highest in genotype 2 and 3 patients with 44–73% versus only 17–35% in genotype 1 and 4 patients. The recent introduction of the first oral HCV protease inhibitors (PIs) however has dramatically improved treatment options for HCV mono-infecting genotype 1 patients. First results from ongoing pilot trials in coinfecting patients have shown similarly improved HCV suppression rates in patients receiving triple therapy over patients in the control arm receiving combined Peg-IFN/RBV therapy (74% and 60.7% HCV undetectable at 12 weeks after end of treatment with triple therapy containing telaprevir (TVR) or boceprevir (BOC), respectively, versus 45% and 26.5% in the control arms).<sup>91–92</sup>

Despite these recent advances however, treatment of HCV infection is expected to further evolve rapidly, with promising molecules with improved antiviral activity, safety profile and once daily dosing. This will also include new drugs with broad genotype activity, suggesting changes in the treatment paradigms not only for HCV genotype 1 patients but also for all other genotypes, possibly with shorter treatment durations and also, at best, interferon free.<sup>93</sup>

#### Individualised treatment strategy for non-HCV genotype 1 patients

Information on liver fibrosis staging is important for making therapeutic decisions. Fibrosis staging can be done by liver biopsy or, where available, by licensed non-invasive techniques such as transient elastography.<sup>53</sup> Many serum biomarkers have also been validated, and Fibrotest, Hepascore and Fibrometer are especially useful tools in this setting<sup>52</sup> (table 2). Preferably, two methods should be combined for an accurate result. In the presence of the lower stages of liver fibrosis (F0–F1), regardless of HCV genotype, treatment can be deferred. This may also account for patients with low fibrosis stages and low chances of SVR under the current treatment options (ie, interleukin 28b (IL28b) genotype TT) for whom improved treatment options will become available within the coming years. In these cases, fibrosis assessment should be carried out at frequent intervals to monitor for

fibrosis progression. Based on four baseline variables (serum HCV-RNA, HCV genotype, liver fibrosis staging using elastometry and IL28B genotyping), the Prometheus Index can be used as a risk calculator for predicting the likelihood of SVR using Peg-IFN/RBV.<sup>94</sup> It is freely available on the web (<http://ideasydesarrollo.com/fundacion/prometheusindex.php>).

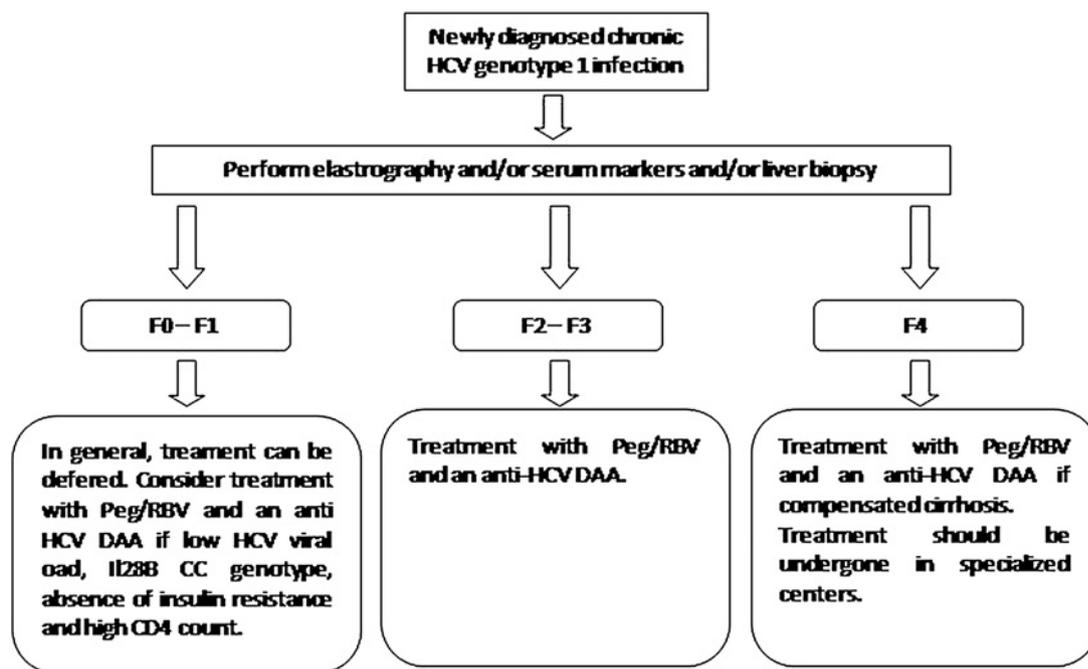
Current therapy is particularly recommended in patients with documented fibrosis (F2 and higher) and a high likelihood of achieving SVR: genotypes 2 or 3 and patients infected with genotype 4 if the viral load is low (<600,000 IU/ml) or if the IL28B-CC genotype is present. The combination of Peg-IFN/RBV remains the treatment of choice for these patients. The standard dose for Peg-IFN 2a is 180 µg once weekly, and for Peg-IFN 2b it is 1.5 µg/kg bodyweight once weekly. An initial weight adapted dose of RBV of 1000 (weight ≤75 kg) to 1200 (weight >75 kg) mg/day (administered twice a day) is recommended for all HCV genotypes in the HIV setting. In patients with rapid virological response (undetectable HCV-RNA at week 4 after HCV therapy initiation), 24 weeks of combination therapy are recommended for genotype 2/3 patients (if no cirrhosis at baseline and low HCV RNA) and 48 weeks for genotype 4 patients.<sup>71</sup> If an early virological response (decline of at least 2 log<sub>10</sub> reduction in HCV-RNA at week 12 compared with baseline) is not achieved, treatment should be stopped. Patients with early response and negative HCV-RNA at week 24, treatment duration for genotype 2/3 patients is recommended for 48 weeks and 72 weeks for genotype 4.<sup>71</sup>

### Individualised treatment strategy for HCV genotype 1

Again, fibrosis staging appears essential. An algorithm for the management of newly diagnosed genotype 1 patients is provided in figure 3. In patients with F0–F1 fibrosis, treatment can be deferred until better tolerated and easier to administer HCV drugs become available unless all treatment response prediction factors are favourable, suggesting a very high chance of SVR (includes IL28b-CC genotype, lack of insulin resistance and high CD4 count). In countries with restricted availability of the new HCV PIs or cost constraints, these patients could also be treated with Peg-IFN/RBV alone as treatment success is very likely. In patients with higher fibrosis stages, triple therapy including an HCV PI is recommended.

TVR can be added to Peg-IFN/RBV for 12 weeks at 750 mg (two pills) every 8 h with food (preferably high fat intake). In the case of successful treatment response (HCV-RNA <1000 IU at weeks 4 and 12), Peg-IFN/RBV can be continued for another 36 weeks (HCV-RNA should be negative at week 24 to continue therapy). Due to drug–drug interactions and limited drug interaction studies, TVR can currently only be safely combined with raltegravir, boosted atazanavir or efavirenz (with efavirenz, TVR doses need to be increased to 1125 mg every 8 h) in combination with TDF or abacavir and emtricitabine or LAM. A summary of the drug–drug interactions between HCV PIs and HIV antiretroviral drugs is provided in table 3.

BOC is added to Peg-IFN/RBV following a lead-in of biotherapy for 4 weeks. BOC is dosed orally with



**Figure 3** Management of newly diagnosed HIV–hepatitis C virus (HCV) coinfected genotype 1 patients. METAVIR fibrosis score: F0=no fibrosis; F1=portal fibrosis, no septae; F2=portal fibrosis, few septae, F3=bridging fibrosis, F4=cirrhosis. DAA, direct antiviral agent; IL28B, interleukin 28B; Peg, pegylated interferon; RBV, ribavirin. (Adapted from Ingiliz P, Rockstroh J. HIV-HCV co-infection facing HCV protease inhibitor licensing: implications for clinicians. *Liver Int* 2012, in press.)

**Table 3** Drug interaction data between hepatitis C virus protease inhibitors and antiretroviral drugs

HCV PI	ARD	PI AUC	PI C <sub>min</sub>	ARD AUC	ARD C <sub>min</sub>	Recommendation for combined use
Boceprevir 800 mg Q8 h	Tenofovir 300 mg QD	↑8%	NA	↑5%	?	Can be combined
Boceprevir 800 mg Q8 h	Efavirenz 600 mg QD	↓19%	↓44%	↑20%	?	Not recommended
Boceprevir 800 mg Q8 h	Ritonavir 100 mg QD	↓19%	NA	?	?	Can be combined
Boceprevir 800 mg Q8 h	Lopinavir/r	↓45%	Not reported	↓34–44%	↓43%	Not recommended
Boceprevir 800 mg Q8 h	Darunavir/r	↓32%	Not reported	↓34–44%	↓59%	Not recommended
Boceprevir 800 mg Q8 h	Atazanavir/r	↔	Not reported	↓34–44%	↓49%	Not recommended
Telaprevir 750 mg Q8 h	Tenofovir 300 mg QD	↔	↔	↑30%	↑41%	Can be combined
Telaprevir 750 mg Q8 h	Lopinavir/r	↓54%	↓52%	↔	↑14%	Not recommended
Telaprevir 750 mg Q8 h	Darunavir/r	↓35%	↓32%	↓40%	↓42%	Not recommended
Telaprevir 750 mg Q8 h	Atazanavir/r	↓20%	↓15%	↑17	↑85%	Can be combined
Telaprevir 750 mg Q8 h	Raltegravir	↑7%	↑14%	↑31%	↑78%	Can be combined
Telaprevir 1125 mg q8 h	Efavirenz + tenofovir	↓18%	↓25%	↓18%	↓10%	Dose adjustment of telaprevir

Adapted from Van Heeswijk 2011,<sup>95</sup> Kasserra 2011,<sup>96</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Press\\_release/2012/02/WC500122880.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2012/02/WC500122880.pdf). ARD, antiretroviral drug; AUC, area under curve; C<sub>min</sub>, minimum plasma concentration; HCV, hepatitis C virus; NA, non-applicable; PI, protease inhibitor; Q8 h, administered every 8 h; QD, administered every 12 h.

800 mg (four 200 mg pills) three times a day with food. Treatment duration is 48 weeks but therapy needs to be stopped altogether in the case of non-response defined as HCV viral load >100 IU/ml at week 4 or detectable HCV-RNA at week 24. The stopping rules need to be strictly followed to minimise risk of development of HCV protease resistance. The metabolism of BOC seems to be complex as the drug is a substrate for the aldo-keto reductase, as well as a substrate and inhibitor of the cytochrome P450 3A system and a substrate and inhibitor of the P-glycoprotein membrane pumps. Pharmacokinetic studies did not show an impact on BOC when coadministered with low dose ritonavir. Therefore, all corresponding boosted PIs were allowed to be used in the ongoing phase II study in coinfecting patients. Most recently, however, significant interactions between BOC and various HIV PIs have been reported in a press release from EMEA, FDA and a Merck "Dear Health Care Provider" letter, dated 6 February 2012 (see table 3). Therefore, currently the combination of boosted PIs with BOC is not recommended. For patients currently on such a combination, close monitoring and contacting the treating physician is recommended. In addition, BOC trough levels have also been shown to decrease by over 40% in combination with efavirenz (see table 3). Therefore, coadministration of efavirenz with BOC is currently not recommended before further evaluation of this interaction has taken place. No relevant drug–drug interactions are expected between BOC and raltegravir or maraviroc and patients on these regimens were also allowed to be included in the ongoing pilot trial. Further pharmacokinetics study results are expected to be presented at CROI 2012 in Seattle.

#### Best time point for starting HCV therapy

If chronic HCV is detected early in the course of HIV infection (before initiation of cART is necessary), treatment for chronic HCV is advised. For patients with a CD4 count <500/μl however, cART initiation is recommended to optimise HCV treat-

ment outcome. If a patient has a significant immunodeficiency (CD4 count <350 cells/μl), the CD4 count should be improved using cART prior to commencing anti-HCV treatment. Patients with a CD4 relative percentage >25% are more likely to achieve SVR than patients with lower CD4 percentages.<sup>97</sup>

#### HCV therapy in HCV genotype 1 treatment experienced patients

In patients with HCV genotype 1 who have previously not been successfully treated with Peg-IFN/RBV, a treatment re-evaluation should be performed. A possible management algorithm for this particular patients group is depicted in figure 4. Clearly, the chances of successful HCV treatment are highest in previous relapsers and lowest in previous IFN null responders. Therefore, therapy can be deferred in earlier fibrosis stages in order to use more potent combination therapies in the near future. In more advanced fibrosis stages, the chances of SVR may be much lower but this needs to be weighed against missing a last possible treatment opportunity. Unfortunately, no data from coinfection trials are currently available to better define possible treatment outcome in HCV therapy experienced patients with more advanced liver disease.

#### HOW TO DEAL WITH END STAGE LIVER DISEASE IN COINFECTED PATIENTS?

##### Follow-up of end stage liver disease

As a result of faster fibrosis progression in HIV–HBV or HIV–HCV coinfecting patients, monitoring of fibrosis stage is of utmost clinical importance. Indeed, various studies have documented progression from early stages of fibrosis to more advanced stages in substantial numbers of patients within 2–3 years of observation time.<sup>98</sup> Once liver cirrhosis has been diagnosed, guidelines clearly recommend ultrasound and  $\alpha$ -fetoprotein for screening of HCC every 6 months. In addition, it should be emphasised that gastroscopy on

	naive	relapser	nonresponder
F0F1	Individual decision	Individual decision/triple therapy	defer
F2F3	Triple therapy	Triple therapy	defer*
F4	Triple therapy	Triple therapy	Triple therapy

\*monitor fibrosis stage annually, preferably with two established methods. Treat with triple therapy, if rapid progression.

**Figure 4** Algorithm for treatment decision according to fibrosis level and treatment history. Metavir fibrosis score: F0=no fibrosis; F1=portal fibrosis, no septae, F2=portal fibrosis, few septae, F3=bridging fibrosis, F4=cirrhosis.

diagnosis of cirrhosis is required to check for oesophageal varices and should be repeated every 1–2 years thereafter.

#### Access to orthotopic liver transplantation

For most patients with end stage liver disease, orthotopic liver transplantation (OLT) remains the only therapeutic option. As survival of HIV infected patients with end stage liver disease is shorter than in the non-HIV infected population, evaluation for OLT should be made after the first liver decompensation. Lower baseline CD4 counts, lack of therapy against HCV and higher Child Pugh scores have been associated with an increased risk of occurrence of clinical liver events.<sup>99</sup> However, further studies

have demonstrated that the baseline Model for End-Stage Liver Disease score was the only significant independent predictor of pre-transplantation mortality in HIV infected liver transplant candidates.<sup>100</sup> The current selection criteria for HIV positive transplant candidates includes: no history of opportunistic infections or HIV related neoplasms, CD4 cell count >100 cells/mm<sup>3</sup> and plasma HIV viral load suppressible with antiretroviral treatment. For drug users, a 2 year abstinence from heroin and cocaine is required, although patients can be in a methadone substitution programme.

Despite additional immunosuppression caused by immunosuppressive drugs, the risk of opportunistic diseases remains low in the post-transplant period, as long as HIV infection remains suppressed below detectable levels. Most recently however, increased risk of infections was described in HIV infected liver transplant recipients with a history of AIDS, a high Model for End-Stage Liver Disease score or non-tacrolimus based immunosuppression.<sup>101</sup> Accumulated experience in North America and Europe in the past 5 years indicated that 1 and 3 year survival rates in selected HIV infected recipients of liver transplants were almost similar to that of HIV negative recipients.<sup>102–103</sup> Therefore, HIV infection by itself is not a contraindication to liver transplantation.

More recently, however, particularly with longer follow-up, it appears that HIV patients undergoing OLT because of HCV associated liver disease appear to have somewhat shorter long term survival rates than HCV monoinfected subjects due to the unfavourable course of HCV relapse in these patients.<sup>104</sup> Interestingly, HCV relapse frequently presents with a fibrosing cholestatic hepatitis.<sup>105</sup> Unfortunately, HCV relapse treatment in the HIV infected liver transplant recipient has mostly been associated with rather poor treatment responses. Possibly this will change with the advent of more potent HCV therapy, including oral direct antiviral agents. Long term survival rates in HIV–HBV coinfecting patients, in contrast, are comparable with HBV monoinfected patients as HBV reinfection of the transplant organ can be successfully prevented by hepatitis B immunoglobulin administration and HBV antiviral therapy.<sup>106</sup>

Additional problems in the post-transplant period are pharmacokinetic and pharmacodynamic interactions between antiretrovirals and immunosuppressive drugs which require close drug level monitoring and dose adaptations. Due to inhibition of cytochrome P 450 and P-glycoprotein, there are important pharmacokinetic interactions between antiretroviral drugs—for example, PIs and non-nucleoside reverse transcriptase inhibitors and the key immunosuppressive agents ciclosporin and tacrolimus.<sup>107–108</sup> These interactions fundamentally alter pharmacokinetic profiles of calcineurin inhibitors and require ciclosporin and tacrolimus to be either given in reduced doses or with prolonged dosing intervals, when PIs, particularly ritonavir boosted regimens, are part of the antiretroviral therapy after liver transplantation.<sup>109–110</sup> In

#### Key messages

- ▶ In Europe, Australia and North America at least 25% of HIV infected individuals have concomitant HCV; 5–10% are coinfecting with chronic HBV.
- ▶ The recently demonstrated profibrogenic effect of HIV coupled to the alteration of innate immune responses induced by HIV, HBV and HCV may be one key element of the progression of liver fibrosis in coinfecting patients, along with the relative hepatotoxicity of some antiretroviral drugs and other metabolic comorbidities, such as the metabolic syndrome.
- ▶ The advent of anti-HIV and anti-HBV dual activity oral drugs has induced a shift in the paradigm of HIV–HBV coinfection where complete and durable HBV-DNA suppression is the ultimate treatment goal.
- ▶ Understanding of the immunological and possibly virological determinants of continuous low level HBV replication under tenofovir might be one of the main treatment issues for the coming years.
- ▶ The recent introduction of the first oral HCV protease inhibitors has dramatically improved treatment options for HCV monoinfected genotype 1 patients. Improved HCV suppression rates in HIV–HCV coinfecting patients receiving triple therapy of up to 71% have been shown at week 24 in pilot trials.
- ▶ The main challenge in HCV therapy, including the new HCV protease inhibitors, is to check for clinically relevant drug–drug interactions between HIV and HCV drugs.
- ▶ Once liver cirrhosis has been diagnosed, ultrasound and  $\alpha$ -fetoprotein for screening of hepatocellular cancer is recommended every 6 months; evaluation for possible orthotopic liver transplantation needs to be considered.

contrast, non-nucleoside reverse transcriptase inhibitors may result in reduced levels of immunosuppressive drugs.

### Dealing with hepatocellular carcinoma

HCC is more common in persons living with HIV than in the general population. Overall, less treatable cases and lower survival rates have been described in HIV patients following HCC diagnosis.<sup>111</sup> New treatment strategies are available for advanced HCC but there are few data available on HIV infected patient<sup>112</sup> although first case reports suggest some benefit from sorafenib treatment in HIV seropositive individuals with newly diagnosed HCC.<sup>113–115</sup> Together with screening of patients at risk and an early diagnosis, aggressive treatment of neoplasia, including treatment of relapses and maintenance of HIV suppression, are the best management strategies for HCC in people living with HIV.

### CONCLUSION: BEYOND THE STATE OF THE ART

The coming years will eventually witness a decrease in chronic hepatitis associated mortality of HIV infected patients due to increased screening and improvement of treatment outcomes, with efficient HCV and HBV oral drugs becoming more widely available. However, many challenges still need to be examined, not only in the fields of fundamental and clinical science, but also in public health and policy.

From prevention of infection and screening to treatment and prevention of end stage liver disease, the continuum of care has to be the core of research, with the ultimate goal of improving the management of coinfecting patients. This especially resounds in resource constraint countries where the HIV epidemic and the endemic situation of HBV and HCV intersects to create a particularly dramatic situation.

Ineffective mother to child prevention of HBV transmission, thriving transmission of HCV among an increasing number of intravenous drugs users in the urban African setting,<sup>116</sup> unequal access to HIV or HBV treatment and no access to HCV treatment are all contributing factors to the uncontrolled increase in end stage liver diseases.<sup>117</sup> Political decisions have to be made on facilitating access to HBV screening and to TDF as a component of firstline HIV treatment, as advocated by the WHO.<sup>118</sup> Likewise, HCV care and management should no longer be neglected and more affordable access to anti-HCV drugs should be thoroughly advocated.

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