Improved antiretroviral therapy (ART) has reduced HIV-related morbidity and improved survival. Such improvements have led to an increasing contribution of non-HIV related disease to overall morbidity among people with HIV. HIV/HCV co-infection and its associated liver disease is an emerging clinical management issue, particularly in settings of high co-infection prevalence. Treatment for HCV infection in HIV infected individuals is with pegylated interferon and ribavirin therapy. Sustained virological response to therapy is achieved in around 40%, which is 10-20% lower than in HCV mono-infection and therapy may be complicated by issues of drug interactions and significant toxicity. However, greater understanding of baseline factors can contribute to better prediction of treatment outcome, and monitoring of on-treatment virological responses increasingly allows individualisation of therapy. Where possible, treatment of HCV is often advisable before HAART is required to avoid the issues of drug interactions on HCV therapy and the risk of HAART related hepatotoxicity. Early diagnosis of both HIV and HCV-infection is essential to most effectively manage HIV-HCV co-infected individuals.

New therapies, including HCV protease and polymerase inhibitors, are in development and may widen therapeutic options for HIV/HCV co-infected individuals in the future.

**Keywords:** antiretroviral therapy, hepatitis, natural history, regylated interferon.

The population prevalence of HIV/HCV co-infection varies considerably between countries [1-3], dependant on rates of high-risk behaviour such as injecting drug use (IDU) and presence of harm reduction strategies. The prevalence of HIV/HCV co-infection has not been comprehensively estimated for the Asia-Pacific region. However, a recent study involving 12 countries in the TREAT Asia Network, a collaboration of HIV clinical sites, examined HCV prevalence in the TREAT Asia HIV Observational Database (TAHOD) [1]. Approximately 50% of 2979 HIV positive subjects had undergone HCV antibody testing, and in this group HCV antibody prevalence was estimated at 10.4%. The HIV/HCV prevalence within TAHOD is likely to provide an underestimate for the Asian region, as the marginalized nature of IDU populations means that many will not be receiving regular HIV clinical management.

Given an estimated 750,000 HIV positive IDU in the Asia-Pacific region [2], the vast majority of whom would be HIV/HCV co-infected, a growing burden of liver-disease morbidity is anticipated.

**Natural history of HCV in HIV co-infection**

Although the introduction of highly active antiretroviral therapy (HAART) has markedly reduced HIV-related morbidity and mortality, non-HIV-related conditions, particularly liver disease, now constitute an increasingly high proportion of causes of death among people with HIV [3].

After acute HCV infection, progression to chronic HCV infection is increased from 70-80% in those not infected with HIV to 90% in HIV infected individuals [4, 5]. Individuals with HIV/HCV co-infection have higher HCV RNA levels in plasma [6-8], which may translate to greater risk of transmission. For example, HCV viral loads are significantly higher in pregnant women who are HIV co-infected and the risk of perinatal transmission is three-fold higher (5% versus 15%) [9].
Effect of HIV on HCV disease progression

There is convincing evidence that co-infection with HIV worsens the prognosis of HCV-related liver disease. In addition to chronic hepatitis, chronic HCV infection may result in cirrhosis, liver failure (end stage liver disease - ESLD) and hepatocellular carcinoma (HCC), all of which are associated with high morbidity and mortality. A meta-analysis of eight studies examined the risk of cirrhosis and ESLD in HIV/HCV co-infected compared with HCV mono-infected individuals, with a two-fold and six-fold higher risk of progression to cirrhosis and liver failure, respectively. [10] Risk factors for liver disease progression in HIV/HCV co-infected individuals include heavy alcohol intake, older age (>25 years) at HCV acquisition, and more advanced HIV disease (CD4 count <200-250 cells/mm³) [11, 12].

HCC risk is higher among HIV/HCV co-infected individuals with cirrhosis, and is associated with shorter duration of HCV infection, younger mean age at diagnosis (cases in the fourth decade of life are not unusual), and a more aggressive clinical course than in HCV mono-infected individuals [13, 14].

Among the 10-20% of HIV-HCV co-infected individuals who have normal transaminases [15], a proportion (up to 30%) may have significant liver fibrosis on biopsy. Thus, a normal ALT level in HIV/HCV co-infection should not provide reassurance that liver fibrosis progression is unlikely.

The effect of HAART on HCV-related liver disease progression

Studies examining the impact of HAART on liver disease morbidity and mortality in people with HIV/HCV co-infection generally find a protective effect on fibrosis progression [16-19]. The potential for antiretroviral therapy to impact protectively on liver disease indicates that earlier introduction of HAART may be a beneficial strategy in HIV/HCV co-infected individuals. On the other hand, HAART may enhance liver damage in some HIV/HCV co-infected individuals through drug-related hepatotoxicity. Most episodes of mild-moderate hepatotoxicity are asymptomatic, short-term, and manageable with either switching of specific antiretroviral therapy agents (e.g. nevirapine) or a period of treatment cessation.

Effect of HCV on HIV disease progression

The majority of studies have found no association between HIV/HCV co-infection and poorer HIV disease outcomes. In 2002, a US study of more than 1900 HIV-infected individuals demonstrated no differences between HIV mono-infected and HIV/HCV co-infected populations with regard to incidence of AIDS, death or decline of CD4 count [20]. Survival was also examined in a European cohort study, EuroSIDA, together with HIV disease progression, virological and immunological response in almost 6000 individuals, of whom 33% were HIV/HCV co-infected. [21] HIV/HCV co-infected individuals had an expected much higher rate of liver-related mortality, but there was no increased risk of AIDS, and overall mortality rates were similar to HIV mono-infected individuals. HIV virological suppression and CD4 count responses following HAART were not affected by HCV co-infection. Similar findings have been reported from Asia-Pacific countries such as Thailand and Taiwan [22, 23].

Diagnosis and monitoring of HCV in HIV infection

Due to increased HCV prevalence in HIV infected individuals, and the implications of HIV/HCV co-infection on disease progression, all HIV infected individuals should be tested for the presence of HCV antibody. It is important to note that HCV antibody may be negative, despite active HCV viraemia, in 10-15% of immune suppressed patients. Consideration should therefore be given to HCV RNA testing despite negative HCV antibody in cases of unexplained transaminase elevation in patients with CD4 counts <200/mm³ and when acute hepatitis C is suspected. HIV positive individuals who are found to be HCV co-infected should undergo a similar work-up as HCV mono-infected patients, with assessment of HCV genotype, quantitative HCV RNA (viral load) determination, HBV serology, HBV and HAV vaccination status and laboratory and clinical assessment of liver disease stage.

The role of liver biopsy in HIV/HCV co-infected individuals is under re-evaluation, as it is in HCV monoinfected individuals. The decision to biopsy is made on an individual basis; it is most often performed when the risk-benefit ratio with treatment is unclear, for example in patients with liver disease associated with HCV genotype 1 and high viral load. Non-invasive methods of diagnosing and staging liver disease, such as transient elastography (Fibroscan) and algorithms involving serum biochemical markers (e.g. Fibrotest, Hepascore) are increasingly being used as alternatives to liver biopsy [24-26].
All HIV/HCV co-infected individuals with confirmed or suspected cirrhosis should undergo regular (every 6-12 months) monitoring with alpha-fetoprotein and liver ultrasound for HCC, as well as screening for the complications of cirrhosis, such as oesophageal varices.

**Treatment of HIV/HCV co-infection**

All HIV infected individuals who are identified as HCV RNA positive should undergo further investigation to assess their suitability for HCV antiviral therapy. Factors to be considered prior to treatment include those that are HCV related, those that are HIV related, and those related to other psycho/social issues (Table 1).

In an individual in whom HCV treatment is not considered an option, ongoing HCV monitoring and modification of factors which may negatively affect liver disease progression (e.g. drug toxicities, alcohol use, obesity and insulin resistance, uncontrolled HIV infection) should continue.

**Antiviral therapy for HCV in HIV infected individuals**

The goals of HCV therapy in HIV/HCV co-infected individuals are similar to those in HCV mono-infected persons. Treatment success is defined as sustained virological response (SVR), indicated by a negative HCV RNA by qualitative PCR 6 months after completion of therapy. The durability of SVR in co-infected patients appears similar to HCV mono-infected patients; there is no evidence of late relapse [27]. SVR in HIV-HCV co-infected individuals results in fibrosis regression and histological improvement [28], potentially reducing the rate of progression to end-stage liver disease (ESLD) and the development of hepatocellular carcinoma (HCC).

**Table 1. Variables to consider in pre-treatment assessment.**

<table>
<thead>
<tr>
<th>HCV:</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
<td>1 vs non-1 (2, 3 and 4)</td>
</tr>
<tr>
<td></td>
<td>Most important predictor of SVR</td>
</tr>
<tr>
<td>Baseline HCV viral load</td>
<td>HCV viral load (greater or less than 400,000 IU/mL)</td>
</tr>
<tr>
<td></td>
<td>Predicts SVR, particularly in genotype 1</td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>Not required in all cases.</td>
</tr>
<tr>
<td></td>
<td>Recommended if risk/benefit of treatment unclear</td>
</tr>
<tr>
<td>Non-invasive markers</td>
<td>Role in assessment of liver fibrosis still unclear. Not routinely available in many countries.</td>
</tr>
<tr>
<td>ALT</td>
<td>Normal ALT does not preclude significant fibrosis, and does not constitute a contraindication for treatment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIV</th>
<th>Consider HIV treatment first if CD4 &lt;350 cells/μL</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4</td>
<td>Should be stable</td>
</tr>
<tr>
<td>Antiretroviral therapy</td>
<td>Avoid DDI - absolute contra-indication</td>
</tr>
<tr>
<td></td>
<td>AZT/D4T - relative contra-indications</td>
</tr>
<tr>
<td></td>
<td>If initiating HAART choose “liver-friendly” regimen</td>
</tr>
<tr>
<td>Lipids</td>
<td>Insulin resistance may be associated with poor treatment response</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other factors:</th>
<th>Advise abstinence from alcohol during therapy to maximise treatment response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol intake</td>
<td>Not a contra-indication to therapy providing drug use stable</td>
</tr>
<tr>
<td>Recreational drugs</td>
<td>Advise re potential for re-infection</td>
</tr>
<tr>
<td>Injecting behaviour</td>
<td>Not a contra-indication to therapy</td>
</tr>
<tr>
<td>Opioid substitution therapy</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Social/psychological</th>
<th>Important for patient support through treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social support/networks</td>
<td>History of severe or current depression may be a contra-indication to treatment</td>
</tr>
<tr>
<td>Psychiatric history</td>
<td>Consider role of prophylactic antidepressant in selected patients.</td>
</tr>
</tbody>
</table>

a DDI didanosine, AZT zidovudine, D4T stavudine.
Standard HCV therapy in HIV/HCV co-infected individuals is with pegylated interferon (PEG-IFN) (alfa-2a or alfa-2b) plus ribavirin [29]. Both forms of PEG-IFN have been studied in large trials in HIV/HCV co-infected populations [30-33] and, although no head-to-head comparison has been performed, their efficacy appears similar, with SVR rates of between 27 and 44% overall (Table 2). Treatment response rates (SVR) in these four studies involving over 1500 HIV/HCV co-infected individuals have been 10-20% lower than similar large-scale trials in HCV mono-infected populations (for HCV genotype 1 or 4, 14-38%; for genotypes 2 or 3, 44-73%).

Lower HCV treatment response rates in HIV-HCV co-infected populations are probably related to multiple factors, including higher HCV viral load, immunosuppression, increased toxicity/poorer treatment adherence, and suboptimal dosing of ribavirin. Initially, ribavirin was administered at the lower dose of 800 mg/day, regardless of genotype, largely due to concerns about anaemia. This lower dose may have been partly responsible for the particularly poor responses to therapy in genotype 1 high viral load co-infected patients seen in the APRICOT study, where the SVR was only 18% [30]. Subsequent studies have demonstrated that higher doses of ribavirin, based on body weight, can be used safely and are associated with an improvement in SVR [34]. The current recommendation for ribavirin dosing is therefore weight based: <75 kg 1000mg, >75 kg 1200 mg [35]. Treatment doses for PEG-IFN are the same as those in HCV mono-infection (PEG-IFN alfa2a 180 mcg/week, PEG-IFN alfa2b 1.5 mcg/kg/week).

The optimum duration of treatment for HIV-HCV co-infected patients is still unclear. Based on published trials that used 48 weeks of therapy for all genotypes, guidelines have recommended 48 weeks of treatment for genotypes 1 and 4 and 2 and 3. [29] However, more recent data from non-randomised studies indicate that in patients with genotypes 2 or 3 who achieve undetectable HCV RNA at week 4 (rapid viral response, or RVR) and have other associated favourable factors (low baseline HCV viral load, no advanced fibrosis) therapy can be shortened to 24 weeks without reducing SVR [36].

HIV/HCV co-infected individuals require careful monitoring during antiviral therapy. Discontinuation and toxicity rates from earlier trials were higher than those seen with HCV mono-infection (the serious adverse event rate in RIBAVIC was 35%), but this may have been partly related to lack of experience in managing side effects. Drug interactions are a particular concern in HIV/HCV co-infected individuals on antiretroviral therapy. Mitochondrial toxicity, lactic acidosis and hepatic decompensation have been reported in several individuals on the combination of ribavirin and didanosine (DDI) [37, 38]. This interaction is thought to arise due to the inhibition of inosine monophosphate dehydrogenase (IMPDH) by ribavirin and a resultant increase in the intracellular concentration, and therefore toxicity, of DDI. This drug

Table 2. Results of large randomised clinical trials of PEG-IFN in HIV/HCV co-infected patients.

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Number</td>
<td>868</td>
<td>412</td>
<td>133</td>
<td>95</td>
</tr>
<tr>
<td>Location</td>
<td>International</td>
<td>France</td>
<td>USA</td>
<td>Spain</td>
</tr>
<tr>
<td>PEG-IFN</td>
<td>Alfa-2a</td>
<td>Alfa-2b</td>
<td>Alfa-2a</td>
<td>Alfa-2b</td>
</tr>
<tr>
<td>Ribavirin dose (mg)</td>
<td>800</td>
<td>800</td>
<td>600-1000 (escalation over 12 weeks)</td>
<td>800-1200 (weight-based)</td>
</tr>
<tr>
<td>Treatment duration (weeks)</td>
<td>48</td>
<td>48</td>
<td>48</td>
<td>48 GT1/4 and GT2/3 (HCV VL &gt;800,000 IU/mL)</td>
</tr>
<tr>
<td>Mean baseline CD4 cells/mL</td>
<td>530</td>
<td>482</td>
<td>474</td>
<td>24 GT2/3 (HCV VL &lt;800,000 IU/mL)</td>
</tr>
<tr>
<td>SVR—overall (%)</td>
<td>40</td>
<td>27</td>
<td>27</td>
<td>44</td>
</tr>
<tr>
<td>GT1/4 (%)</td>
<td>29</td>
<td>17</td>
<td>14</td>
<td>38</td>
</tr>
<tr>
<td>GT2/3 (%)</td>
<td>62</td>
<td>44</td>
<td>73</td>
<td>53</td>
</tr>
<tr>
<td>Dose modification for anaemia (%)</td>
<td>16</td>
<td>11</td>
<td>5</td>
<td>13</td>
</tr>
</tbody>
</table>
combination is therefore contra-indicated and DDI should be switched to alternative nucleoside analogues before commencing HCV therapy.

Concerns regarding the synergistic effect of zidovudine (AZT) and ribavirin in accelerating the onset of severe anemia have led to the recommendation that, where possible, AZT should also be substituted with an alternative antiretroviral agent. A recent study confirmed that anemia during HCV therapy in HIV/HCV was attributable to the AZT dose but not the dose of ribavirin [34].

Reduction in the absolute CD4 cell count by 10-15% is common during HCV antiviral treatment and has been attributed to IFN-induced myelosuppression. Providing the CD4 percentage remains unaffected and HIV RNA titres remain stable, reassurance can be given that the CD4 decline does not reflect deterioration in HIV control. In fact, PEG-IFN has documented anti-HIV activity and it is common to see HIV viraemia fall by approximately 0.5-1.0 log during HCV treatment.

Neuropsychiatric effects of PEG-IFN, in particular depression, are common in HIV/HCV co-infected patients. [39] Early and aggressive intervention with counselling, support and antidepressants, are often required and may be essential to maximise treatment completion and success.

PEG-IFN should be used cautiously in any HIV/HCV co-infected individual with cirrhosis and is contraindicated in decompensated cirrhosis. In the APRICOT trial (also observed in RIBA VIC) an unexpected number of cases of hepatic decompensation were observed among patients with compensated cirrhosis pre-treatment (approximately 10% of those with cirrhosis); these resulted in death from liver failure in six individuals, which is rarely observed when treating mono-infected patients with HCV-related compensated cirrhosis. In a multivariate analysis, factors predicting decompensation were markers of advanced liver disease and the use of DDI [40].

Predictors of treatment outcome-early virological response

Prediction of SVR through early virological testing has allowed treatment to become increasingly individualised in HCV mono-infection. Based on HCV genotype and HCV viral load reduction on treatment at week 4 (RVR) and/or week 12 (early virologic reponse, or EVR), therapy may either be shortened or discontinued, thereby minimising cost and toxicity. Alternatively, it may be extended in an attempt to improve otherwise suboptimal efficacy, although the evidence for the latter type of strategy is incomplete. Similar analyses of viral load data from HIV-HCV treatment trials have been performed. As with HCV mono-infection, the negative predictive value of an HCV viral load reduction <2 logs at week 12 (non-EVR) for eventual SVR is high (98-100%) in genotype 1 infection, [30] thus supporting cessation of treatment at this time point in non-EVR cases. The positive predictive value (PPV) of EVR is less precise at around 56-64%.

More recently attempts have been made to use a negative qualitative HCV RNA assessment at week 4 (RVR) to predict outcome and to further reduce the duration of treatment. RVR may be particularly useful in some subsets of HIV-HCV co-infected individuals. Data from a posthoc analysis of a Spanish trial involving HIV-HCV genotype 3 patients treated for 24 weeks demonstrated HCV RNA <600 IU/μL at 4 weeks to be the strongest predictor of SVR, with a No relationship in APRICOT was seen between baseline HIV RNA or baseline CD4 count and SVR. This is somewhat surprising but may reflect the small study populations with advanced HIV disease (in APRICOT individuals with CD4 <100 cells/μL were excluded and relatively few had counts of 100-200) cells/μL.

Thus, decisions on HCV treatment should be determined predominantly by HCV-related rather than HIV-related variables, unless the CD4 count is particularly low. Most clinicians would advise treating HIV disease first if the CD4 count is below 250 cells/mm³ (especially as the CD4 count will decline on IFN) and many would prefer to treat HIV disease first if the CD4 count is less than 350 cells/mm³. However, for most patients with good CD4 counts it is preferable to treat HCV first to avoid issues of drug interactions and HAART-hepatotoxicity. There is no evidence that HCV treatment accelerates HIV disease progression.
ALT/AST ≥ 5xULN

Severe hepatotoxicity

Exclude other. Examine for causes of acute signs of drug hepatitis hypersensitivity HAV, HBV, HCV. Check serum alcohol lactate level other drugs

ALT/AST ≥ 10xULN, raised bilirubin, falling serum albumin, acidosis or symptoms of acute hepatitis

Cease antiretroviral therapy

ALT/AST > 10xULN or symptoms

Re-commence antiretroviral therapy when ALT/AST < 2-3xULN

ALT/AST 5-10xULN +
No symptoms

Monitor LFTs 3-4 weekly. Continue antiretroviral therapy

Refer for further investigation and possible liver biopsy if:
- lack of resolution of ALT/AST within 3-6 months
- underlying chronic viral hepatitis (HBV, HCV)

Fig. 1 Clinical management of severe HAART-related hepatotoxicity. ULN = upper limit than normal.
relapse rate of 50% in non-RVR patients compared to relapse in only one patient with RVR patients [36]. These data suggest that it may be possible to shorten treatment to 24 weeks in individuals with genotype 3 infection and RVR.

HAART treatment issues: hepatotoxicity and choice of antiretroviral agents

Severe hepatotoxicity (ACTG Grade 3 or 4 change in AST/ALT = 5 or 10 x upper limit of normal) after HAART initiation ranges in incidence from 2-18%, and is particularly important because it may result in the need to interrupt or discontinue HAART [42]. The majority of studies examining factors associated with hepatotoxicity have found co-infection with either HCV or HBV (and particularly both viruses) increases the risk 3-5 fold. Heavy alcohol use, older age, and female sex are additional factors [43-46]. Hepatotoxicity can occur with all antiretroviral agents, but is frequently linked to the use of non-nucleoside reverse transcriptase inhibitors (NNRTIs), and in particular nevirapine, as part of a hypersensitivity syndrome [46, 47]. In the protease inhibitor class hepatotoxicity has been linked to the use of full dose ritonavir (no longer commonly used) and tipranavir/ low dose ritonavir (r) combination [43, 45, 48], with other ritonavir boosted combinations such as lopinavir (LPV/r), fosampranavir (FOS/r) and atazanavir (ATZ/r) at much lower risk. This probably reflects the higher doses of ritonavir (400 mg) used with tipranavir than the other boosted PI regimens (200 mg). ATZ is associated with marked hyperbilirubinaemia in some individuals related to inhibition of UDP-glucuronosyltransferase, but this does not indicate underlying liver damage. In the NRTI-class, stavudine and didanosine are particularly linked to mitochondrial damage; cases of liver failure linked to hepatic steatosis, pancreatitis and severe metabolic acidosis (resembling Reye’s syndrome) have been described.

Suggested guidelines for the management of hepatotoxicity have been developed [49]. In most cases, HAART can be successfully continued with regular monitoring and/or drug substitution (Fig. 1).

Overall the benefits of HAART to the HIV-HCV co-infected individual outweigh potential disadvantages. It is particularly important to emphasise that HAART should never be withheld or delayed due to concerns over tolerability, particularly with the increasing number of available antiretrovirals. In many cases, HCV co-infection should be considered as an indication to consider earlier rather than later antiretroviral initiation. If immune function is relatively preserved (e.g. CD4 count above 350/mL), HCV treatment may be commenced prior to HAART as successful viral clearance will reduce risk of hepatotoxicity after HAART initiation, and potential drug interactions during HCV therapy are avoided. Unfortunately, many people with HIV, particularly those in developing countries, present late with advanced HIV disease. Earlier diagnosis of both HIV and HCV would improve management options for HIV-HCV co-infection.

The authors have no conflict of interest to report.

References


