BHIVA GUIDELINES - HIV AND CHRONIC HEPATITIS: CO-INFECTION WITH HIV AND HEPATITIS C VIRUS INFECTION

Updated October 2004

BHIVA Hepatitis Coinfection Guideline Committee on behalf of the British HIV Association.

Contents

1.0 Key recommendations

Levels of evidence:

I = Meta-analysis or RCT
II = Other good quality trial
III = Observational studies/ Case Reports
IV = Expert Opinion

1.1 Assessment of all HIV+ patients

1. Screen all HIV-positive patients for HCV infection, at first HIV diagnosis and subsequently according to risk, by antibody test and confirm viraemia with HCV PCR [II].
2. Perform PCR test even if HCV-antibody negative in patients with unexplained liver disease [III].

1.2 Assessment and management of HIV/HCV co-infected patients

3. All HIV/HCV co-infected patients should have a thorough assessment of disease status and risk of progression which includes a detailed clinical history, examination and blood tests including LFT, PT and HCV-RNA [IV].
4. Consider liver biopsy (if no contra-indications) to assess disease severity and exclude other causes of chronic liver disease [III].
5. Exclude co-infection with Hepatitis B and vaccinate for Hepatitis B and Hepatitis A if non immune (I). Vaccination success is related to CD4 count and re-vaccination should be attempted in vaccine failures who have a CD4 count response to HAART [II].
6. Counsel regarding risks of transmission [III].
7. Advise abstinence from alcohol [III].
8. Check HCV genotype as a predictor of treatment response [1].
9. All HCV-PCR positive patients without histological evidence of cirrhosis should be screened annually with AFP and USS. Patients with confirmed End Stage Liver Disease (ESLD) should have 6-monthly AFP and USS scans performed [III].
10. Patients with confirmed ESLD and hepatic decompensation should be considered for liver transplantation [III].
11. The presence of hepatitis C co-infection increases the risk of developing hepatotoxicity on HAART by roughly 2-3 fold and clinicians must be alert to this possibility [II]. The majority of patients with HCV are able to take HAART without problems and therefore HCV infection should not prejudice the decision to initiate treatment [II].
12. There should be close liaison between the HIV physician and local hepatology team with clear links to a transplant centre to ensure equity of access to hepatitis therapy irrespective of the patient's main site of care [IV].

1.3 Anti-HCV therapy in HIV/HCV co-infection

13. Assessment for anti-HCV therapy should ideally be at a centre with expertise in the management of both HIV and HCV [IV].
14. Consider treatment with pegylated interferon + ribavirin or enter into a clinical trial [I].
15. Patients with moderate disease (on the Ishak histological scoring system) are most suitable for anti-HCV therapy. Patients with mild disease may wish to defer therapy although should have regular monitoring which may include three-yearly liver

biopsies. Patients with compensated cirrhosis may also benefit but tend to tolerate therapy less well [II].

16. Treat patients who have a CD4 count >200 cells/mm^3 before commencing HAART ifpossible. Pre-treatment of HCV in co-infected individuals reduces the risk of liver toxicity associated with concurrent HIV therapy [II].
17. In patients who are already on HAART, delay their HCV therapy until the CD4 count sis >200 cells/mm^3 [II].
18. Monitor transaminases carefully if HAART is initiated and observe serum lactate for nucleoside analogue toxicity in those on ribavirin [II].
19. AZT and ddI should be ideally avoided in patients receiving ribavirin [II].
20. If treatment leads to successful eradication of HCV-RNA, these individuals should subsequently have PCR performed yearly to detect late relapse or re-infection [III].
21. Patients diagnosed with acute hepatitis C should be considered for treatment with pegylated interferon and ribavirin (III). As the treatment success rates with acute hepatitis C appear to be less than in the HIV negative population, individuals should be closely monitored after presentation and only those who fail to clear HCV or have no drop in HCV viral load on 4-weekly monitoring should be treated [III].

2.0 Audit standards

1. All HIV+ patients should be HCV tested.
2. All HCV-positive patients non-immune to HBV or HAV should be vaccinated.
3. All patients with abnormal ALT/AST levels of unknown cause who are anti-HCV negative should have a serum HCV-RNA PCR measured.
4. All patients should have their HCV status checked before commencement of antiretroviral therapy
5. All HCV-infected patients should have documented evidence in their case-notes of a discussion on alcohol avoidance and how to reduce the risks of transmission.
6. Case-notes should contain clear evidence of an attempt to notify parenteral and sexual contacts and offer them a test if their HCV status was previously negative/unknown.
7. All patients who are HCV-positive should have a clear management plan written in their notes and there should be effective and rapid communication between all parties involved in their care.

3.0 Background

3.1 Prevalence

- There is now widespread recognition of the potential morbidity and mortality associated with HIV and hepatitis C co-infection. Overall, the prevalence of HCV in the general UK population is estimated to be approximately 0.4% [1] but the rate varies by area and population and should be considered as a minimum.
- The highest risk groups for HCV infection are injecting drug users and people with bleeding disorders such as haemophilia. Other risk groups include sexual partners of injectors, prisoners, sex workers and children of HCV-infected mothers. There may also be an increased rate in people who have had treatment abroad and healthcare workers subject to sharps injury.
- Although heterosexual transmission of HCV is uncommon the higher levels of HCV RNA seen in the setting of HIV infection may facilitate transmission [2-4], particularly

in the presence of other sexually transmitted infections such as infectious syphilis. This is of particular concern in the light of the recent rise of syphilis cases within the HIV community [5-7]. HCV transmission may also be linked to other, as yet poorly defined, risks such as non-injecting recreational drug use, particularly snorting cocaine.

- The prevalence of HCV infection in HIV positive individuals is higher than in the general population but varies between clinics according to risk factors for HIV acquisition. Since shared risk factors for both infections are common and co-infection has important implications for treatment and prognosis, all HIV positive patients should be screened for the presence of anti-HCV antibodies [8,9]. Repeat screening should take place at yearly or less intervals depending on the presence of risk factors for acquisition (see above) and in all patients with abnormal liver function tests. This is especially important given the recent increase in new diagnoses of acute infection in homosexual men [7,10].
- Since the heat treatment of clotting factor concentrates in 1985, it is unlikely that individuals with haemophilia will become infected with HCV as a result of treatment with blood products and clotting factors so there is less value in re-testing these patients unless other risk factors are present.

3.2 Natural History

3.2.1 The Influence of HCV on HIV infection

- HCV may have a deleterious effect on HIV progression. The Swiss HIV Cohort study and others have demonstrated that HCV infection was independently associated with an increased risk of progression to AIDS or death, despite a similar use of antiretroviral therapies within the co-infected group as those with HIV alone [11-13]. The Swiss study also suggested that those patients with dual infection may be less likely to achieve a CD4 count rise of at least 50 cells mm3 within 1 year than those with monoinfection. The HIV viral load response to therapy was similar, however, in patients with and without HCV. This deleterious effect is confirmed in some, [14] but not all [15, 16] other studies.

3.2.2 The Influence of HIV on HCV infection

- Only 20-30% of immunocompetent individuals with HCV will progress to cirrhosis over an average of 15-30 years. Evidence suggests that in HIV positive individuals progression is likely to occur more frequently and at a faster rate [17-22]. One study estimated the median time to cirrhosis as 32 years and 23 years from time of acquisition in HCV and HCV/HIV co-infected individuals respectively. This is now manifest as a proportional increase in deaths from end stage liver disease (ESLD) throughout the HIV infected population such that HCV infection is one of the major causes of death in people with HIV [23, 24].
- In contrast, studies that have considered absolute numbers of deaths (rather than proportions of deaths due to different causes) have often reported no increase in the number of deaths from liver failure [25]. It is therefore uncertain if there has been a true increase in deaths from liver failure, or whether the apparent increase is simply a consequence of the longer HIV survival.
- It should also be noted that haemophilic men and intravenous drug users, in whom many of these studies have been carried out, have generally been infected with HCV

for some time before becoming infected with HIV. The impact of HCV seroconversion after HIV seroconversion is unclear .

- Co-infected patients have comparably higher levels of HCV viraemia and HCV in other body fluids[26] and these are inversely correlated with the CD4 count and degree of immunosuppression present. Other variables that negatively influence HCV progression have been shown to be alcohol, increasing age at acquisition and the presence of hepatitis B infection [17].
- Hepatocellular carcinoma (HCC) is estimated to occur at a rate of 1-4% per annum in patients with HCV-related cirrhosis; in patients who also have HIV infection it tends to occur at a younger age and within a shorter time period [27].

3.3 HAART and hepatotoxicity

- Most antiretroviral agents have the potential to cause hepatotoxicity, although the rate at which this may occur varies both between classes of drugs and between individual drugs within classes.
- The presence of hepatitis C co-infection increases the risk of developing hepatotoxicity on HAART by roughly 2-3 fold and clinicians must be alert to this possibility. [28-30]. However, it is also the case that the majority of patients with HCV (88% in one study) are able to take HAART without problems and therefore HCV infection should not prejudice the decision to initiate treatment. Pre-treatment of HCV in co-infected individuals reduces the risk of severe liver toxicity associated with subsequent HIV therapy. [31]
- The mechanisms behind the increased risk for hepatotoxicity are as yet unclear and may be multifactorial. It has been postulated that the presence of hepatitis C infection may result in enhanced antiretroviral toxicity through altered drug metabolism and higher drug levels [32,33]. It has also been suggested that the flare in transaminases may represent an enhanced immune response to HCV itself (similar to immune reconstitution syndromes) [34].
- Other causes of abnormal liver function tests after HAART initiation include the potentially lethal hypersensitivity reaction to nevirapine and the lactic acidosis/metabolic syndrome with NRTIs. The proportional risk for individual drugs is unclear. Den Brinker *et al* found no predictive risk for specific antiretroviral therapies [28] whereas both ritonavir [31] and nevirapine [32] have been specifically associated with a higher risk of toxicity.
- Many of the studies on which these associations are based, however, are often observational and the populations studied may not be representative of the clinic population. Thus the true impact of specific drug combinations remains unclear.
- A history of herbal remedy use should be taken as HAART will interact with Milk Thistle, St John's Wort and others.
- **In summary,** although liver enzymes should be carefully monitored after HAART initiation in a patient co-infected with either hepatitis C or B, in the majority of cases mild to moderate transaminase elevation can and should be managed without drug cessation [28,35]. Clinicians should remain alert however to the possibility of nevirapine-related hypersensitivity or severe lactic acidosis syndromes, and in these situations drugs should be discontinued.
  Nevirapine treatment may be associated with an increased risk of fibrosis [36] and until further information is available, it is recommended that nevirapine is only used where necessary in co-infected individuals

4.0 Assessment and investigations

4.1 Diagnosis of HCV infection in HIV infected individuals

- The majority of individuals (60-80%) who are infected with hepatitis C are likely to become chronic carriers with detectable HCV viraemia. Diagnosis of HCV is typically made on the basis of a positive anti-HCV antibody test (ELISA +/- RIBA) often associated with abnormal liver function tests [37]. However, a proportion of patients will have normal liver function tests or a negative antibody test in the presence of chronic HCV viraemia [38-40]. If present, HCV viraemia is confirmed by a qualitative or quantitative HCV RNA test (polymerase chain reaction, PCR) [38-40]. Qualitative tests are generally more sensitive with a lower limit of detection of around 200 copies/ml. There are now a number of commercial assays available which give widely differing values, but there are attempts to standardise measurements.
- False negative antibody tests are less common with newer assays in the setting of HIV infection and may relate to the degree of immunosuppression present [41]. False positives are also less common with the use of more sensitive, third-generation antibody assays, although a small proportion of individuals appear to spontaneously clear HCV infection, becoming HCV-RNA negative [42]. Consideration should be given to HCV RNA testing of HCV-antibody negative HIV positive individuals where acute HCV infection is suspected where the antibody response may not be evident for several months (jaundice and/or acute hepatitis) or in the setting of otherwise unexplained abnormal liver function tests.

4.2 Assessment and Treatment of HCV in HIV infected individuals

- Although there are previous treatment guidelines for men with haemophilia [43], these BHIVA guidelines can be applied equally to this group of patients.
- As a result of the fall in HIV-related mortality and morbidity, all patients with HIV/HCV co-infection should at least undergo assessment for potential treatment of hepatitis C. In addition to the usual clinical history, in an HIV infected person, it is also useful to have detailed information on the patients' family history of liver disease and a personal history of the following:
  - Any intravenous drug use
  - Previous and current alcohol consumption
  - Psychiatric illnesses
  - Previous tests for HCV
  - Any indication of the possible time of first infection e.g. jaundice, tattooing or piercings, major operations, blood transfusions, date of first injected drug use.
  - Sex with a HCV-positive partner.
- Examine the patient for clinical stigmata of chronic liver disease.

4.2.1 Initial work-up

The following tests should be performed:

- HBsAg, anti-HBs and anti-HAV IgG.; FBC and clotting studies; liver function tests (including albumin and _-GT), TFT serum Fe, liver autoantibodies and liver ultrasound.

- HCV genotype and HCV viral load: If repeated exposure to HCV is suspected, as in injecting drug users, then the predominant HCV genotype may change over time and thus might need to be measured again later [44].
- It is not necessary, outwith an antiviral regimen, to repeat the HCV viral load on a routine basis.
- Counselling should also take place including discussion of routes of transmission, complications of disease, treatment options and advice regarding alcohol intake.

4.2.2 Additional tests

- Patients who are known to have cirrhosis or transition to cirrhosis should be considered for regular screening with biannual or more frequent ultrasound and alpha-fetoprotein (AFP) measurements to enable the early detection of hepatocellular carcinoma (HCC). It should be recognised that even with frequent screening a treatable HCC may not be detected [45].

4.2.3 Liver biopsy

- The risks versus benefits should be carefully weighed for each individual. Many centres feel that the risk of a liver biopsy outweighs the benefit in haemophilic men and there remains debate on the value of biopsies in HIV infection, even in those without haemophilia [46, 47].
- On the basis of a biopsy, liver damage can be categorized as mild, moderate or severe (Table 1) [48].
  - Mild liver damage is classified as a modified Ishak score of 3 or less and a fibrosis score of 2 or less.
  - Moderate liver damage has an inflammatory score of 4 or more and/or a fibrosis score of 3 to 5.
  - The clinical severity of advanced liver disease can also be graded by scores such as the Child-Pugh system [49]. A combination of biochemical markers or innovative imaging techniques may in the future allow an indirect assessment of fibrosis without the need for invasive liver biopsy but as yet this method remains unvalidated in co-infected patients [50].
- With the improved results of treatment with pegylated interferon for genotypes 2 and 3 [51-53] many physicians may consider treatment without liver biopsy for those infected with these genotypes.

4.2.4 Networks

- There should be close liaison with the local hepatology team (gastroenterologist specialising in hepatology or hepatologist), virologist, and established contacts with the regional transplant centre. This is particularly important for patients with advanced disease. It is expected that in the developing HIV service networks, protocols detailing clear referral pathways will be developed so that all patients with HIV/HCV co-infection with have equity of access to specialist care by teams of doctors and Nurse Specialists, irrespective of their main site of HIV care.

5.0 Management

5.1 General principles of Hepatitis C therapy

- Prior to treatment all coinfected individuals ideally require a CD4 count over 200 cells/mm^3 as counts lower than this are associated with a poorer response [54]. However, results of the APRICOT study suggests that CD4 count was not a predictor of treatment success [51]. In individuals with a CD4 count <200 cells/mm^3, the risk of HIV disease progression is probably greater than hepatitis C progression and apart from in exceptional circumstances HIV treatment should begin prior to hepatitis C therapy.
  Patients should be advised to abstain from alcohol, with relevant support where necessary, and should be screened and vaccinated for hepatitis A and B if non-immune. [55,56].
- Rates of success of vaccination are related to CD4 count, and re-vaccination should be considered in those failing to respond to vaccine, who subsequently respond to HIV antiviral therapy.
- Criteria for treating patients with HIV/HCV co-infection are similar to those in immunocompetent patients and should ideally include information on histology obtained from liver biopsy, thus allowing accurate assessment of the stage and severity of disease. However many physicians will now treat hepatitis C genotypes 2 and 3 without biopsy because of the relatively high degrees of success. By contrast, in genotype 1 infections where rates of treatment success are much less, biopsy should probably be performed in all so that only those in whom treatment is deemed essential should undergo therapy [51-53].
- The primary goal of therapy is viral eradication (sustained viral response (SVR) defined as a negative HCV PCR 6 months post therapy cessation). Late relapse or re-infection may occur and individuals who undergo a SVR should have PCR performed yearly post successful therapy. Other aims of therapy may include the treatment of extrahepatic manifestations of HCV (cryoglobulinaemia etc), a potential reduction in the likelihood of transmission and, in those patients not eradicating virus, a regression in the degree of fibrosis present.

5.2 Who to treat (See Fig. 1)

- Moderate to severe disease without cirrhosis: This is the main indication for therapy.
- Mild disease: Available treatment options should be discussed with the patient. - Depending on HIV stage patients may wish to defer treatment. If so, they should be encouraged to consider a repeat biopsy in 2-3 years to assess disease progression. This is slightly earlier than the 5 years recommended for those with monoinfection but takes into account the faster rate of HCV progression in HIV patients
  - There is an argument for treating mild disease in patients with early HIV infection and a reasonable CD4 count in the hope that they will have a better response with a higher CD4 count and that, if HIV treatment naïve, will be less at risk of drug interactions. The results of clinical trials are awaited. Other treatment considerations include presence of extra-hepatic disease or a desire to reduce infectivity (see above).
- Cirrhosis: Options are limited for decompensated disease. A patient with decompensated disease may be a candidate for transplantation if the HIV prognosis is reasonably good. All forms of Interferon are generally contraindicated in patients

with hepatic decompensation. In the case of compensated disease pegylated interferon + ribavirin may be considered, although the patient may not tolerate the full interferon dose and will require frequent monitoring.

- A trial of PEG-IFN alone (180 mcg/wk) in 271 HIV negative patients with either bridging fibrosis or cirrhosis produced an overall SVR of 30% (12% genotype 1 and 51% genotype non-1) [57].
- A study performed in HIV positive patients with cirrhosis confirmed a protective effect for the use of IFN plus ribavirin in progression to decompensation. [58].

If portal hypertension is present, a beta-blocker should be considered in patients with compensated disease. Ultrasound and _FP surveillance for HCC should be considered

5.3 When to start treatment

- If treatment is warranted then careful consideration should be given to the timing of initiation of therapy. This should be related to the status of both HCV and HIV infection in the individual patient.
- HCV disease should be treated first if the HIV infection is felt to be stable and not requiring treatment, whereas HIV disease should be treated prior to hepatitis C if the CD4 count is low or the patient deemed to be at risk of HIV progression, although as yet, there are no data from randomised trials to assess whether this treatment approach is valid.
- Assessment and treatment of HCV in HIV infection should ideally be carried out in a unit with experience of treating both conditions and where specialized support is available. The management of a patient with mild HCV and advanced HIV is likely to be different from the patient with end-stage liver disease and a CD4 count of 800 cells/mm^3. To optimize care, it is therefore important that there is close liaison with the local hepatology team, and, if necessary, the regional transplant centre.

5.4 Treatment Options

5.4.1 Interferon

Following the results of three large randomised trials, treatment with standard interferon is not recommended. All patients requiring therapy should receive pegylated interferon plus ribavirin unless contraindicated. [51-53]

5.4.2 Pegylated Interferon and Ribavirin (Fig. 1)

- Compared with non-pegylated interferon, the improved response rate in HIV negative patients given pegylated interferon is mainly in those with genotype 1 infection.
- Sustained virological response rates in non-cirrhotics reach up to 46% for genotype 1 and 82% for genotypes 2 and 3 in the non-HIV infected.[59-67].
- In patients with HCV monoinfection, pegylated interferon (PEG-IFN) plus ribavirin has become the treatment of choice following studies demonstrating its greater efficacy over standard interferon/ribavirin, both in patients with and without cirrhosis [57,68,69]
- Pegylated interferon also has an anti HIV effect (approximately 0.5 log fall in HIV viral load) and although associated with a fall in absolute CD4 count, CD4

percentage increases suggesting the absolute fall is part of the generalized lymphopaenia associated with therapy[70].

Three large multicentre studies have been presented comparing pegylated interferon with ribavirin to standard interferon/ribavirin. Two (ACTG A5071 and APRICOT) have utilised pegylated interferon alpha 2a (Pegasys), and the third, RIBAVAC, utilised pegylated interferon alpha 2b (Viraferon peg) [51-53]. Due to differences in the patient populations recruited to these studies it is not possible to make a comparison between the two forms of pegylated interferon.

5.4.2.1. APRICOT study [51]

The APRICOT study randomised individuals to interferon alpha 2a (3 miu , 3 times a week plus ribavirin 800mg daily (n = 285) pegylated interferon alpha 2a plus ribavirin placebo (n = 286) or pegylated interferon alpha 2_ plus ribavirin 800mg daily (n = 289). Individuals were treated for 48 weeks and followed for a further 24 weekspost thaerapy. Results were reported as end of treatment (ET) and as sustained response (SR) –defined as hepatitis C PCR-negative 24 weeks post cessation of therapy.

The results of this study showed the SR to be superior in the pegylated interferon with ribavirin treated arm. 12% of the standard interferon arm, 20% of the pegylated interferon + placebo arm and 40% in the pegylated interferon + ribavirin arm achieved SR.

Response rates were greater in all arms for individuals with genotype 2 or 3. For those treated with pegylated interferon and ribavirin response rates for genotype 1 were 38% ET and 29% SR and in genotype 2 or 3 64 % ET and 62% SR. This study also showed that a poor early (12 week) virological response defined as failure to achieve a HCV RNA less than 50 iu, or less than a 2 log drop in HCV RNA was highly predictable of lack of treatment response. In individuals failing to achieve these responses at 12 weeks treatment should be stopped unless the aim is to achieve histological improvement rather than HCV eradication.

5.4.2.2 . ACTG A5071 [53]

ACTG A5071 randomised individuals to receive either pegylated interferon alpha 2a weekly with ribavirin at an escalating dose from 600mg to 1,000mg per day depending on toleration or interferon alpha 2 alpha 6 mega units three times a week for 12 weeks, reducing to 3 mega units 3 times a week for a further 36 weeks with the same escalating dosage of ribavirin. Individuals were treated for 48 weeks in total with 24 weeks of follow up. The end of treatment response rate was greater in the pegylated interferon arm (41% vs 12%) as was the sustained response (27% vs 12%). Individuls with genotype non-1 had a greater chance of both end of treatment response (80% vs 29%) and sustained virological response (73% vs 14%)

5.4.2.3. RIBAVIC [52]

The RIBAVIC study compared pegylated interferon alpha 2b (1.5 µg/kg/week) plus ribavirin 800mg per day with standard interferon 3 million units three times per week plus ribavirin 800mg per day. The results of this study are difficult to interpret due to a very high drop out rate. SR was achieved in 27% of the pegylated interferon arm and 19% of the

interferon arm. SR was higher in individuals with genotype non1 (43%) than genotype 1(11%) treated with pegylated interferon.

5.4.3 Further information on anti-viral treatment

- Recently published, smaller studies, have shown response rate with pegylated interferon alpha 2b and ribavirin comparable to the APRICOT study. [71-72]
- Although studies in HIV positive coinfected individuals have utilized relatively low doses of ribavirin, higher doses of ribavirin have been associated with higher rates of response in HIV negative monoinfected individuals particularly those infected with genotype 1. Individual physicians may therefore consider giving ribavirin at a dose of 1000mg/day if less than 75Kg and 1200mg per day if over this weight in the case of CoPegasys and if rebotol is utilized 800 mg/day if less than 65Kg, 1000mg/day if between 65 and 85Kg and 1200mg/day if greater than 85 Kg.
- Opthalmological review should take place prior to commencement of therapy and 3 monthly during drug treatment.
- The use of growth factors G-CSF/Erythropoietin should be utilized to continue full dosage of Pegylated interferon and ribavirin
- There are only limited cases where conventional interferon is the favoured option eg where the patient has baseline thrombocytopenia and the shorter half life of the standard interferon allows for more rapid dosage adjustment.
- In a constantly evolving field such as HIV/HCV co-infection it is important that all patients should be offered the chance to participate in clinical trials where possible.

5.5 The interaction between ribavirin and anti-retroviral agents

- Ribavirin has also been shown *in vitro* to inhibit the phosphorylation of the thymidine analogues (AZT/d4T) [73] although a theoretical risk exists that it may inhibit their effectiveness, a recent study demonstrated no significant pharmacokinetic interaction between these drugs. However, as AZT and ribavirin are both associated with anaemia, albeit by different mechanisms, where possible they should not be given concurrently
- Of more concern is the finding that ribavirin enhances the phosphorylation of didanosine (ddI) leading to higher concentrations of dideoxyadenosine triphosphate (ddATP). Whilst this may lead to a greater anti-HIV action, it also increases the risk of ddI-related toxicity through its' inhibitory action on mitochondrial DNA polymerase g.
- Amongst the nucleoside analogues, ddI is one of the commonest to be associated with mitochondrial toxicity syndromes and lactic acidosis, particularly when combined with stavudine (d4T) [74]. The combination of ribavirin and ddI is of concern in coinfected patients. Indeed, there have been increasing reports of cases of lactic acidosis with ribavirin in dual infected patients [75-77], the majority of whom have also been on ddI. For this reason, consideration should be given to avoiding the use of these two agents together.

5.6 Non-responders and relapsers

- Treatment options are limited in the above situations. HIV negative patients who have relapsed after a previous course of interferon monotherapy may respond to treatment with pegylated interferon/ribavirin but at a muchreduced rate than in naïve

to treatment individuals. There are limited data to suggest that non responders to PEG-IFN may have a continued benefit with maintenance therapy in terms of slower fibrosis progression and a delay in clinical outcomes such as cirrhosis, HCC and death [78]. This area of therapy is currently the subject of the NIH sponsored HALT-C clinical trial.
No data is available in the coinfected patient on the best strategy of care in those who have failed previous interferon based therapy.

5.7 Acute hepatitis C

- Since most cases of acute hepatitis C are asymptomatic, diagnosis of hepatitis C infection is usually made during the chronic phase. Some patients however will be diagnosed with acute HCV, either during a period of clinical illness with jaundice and nausea, or following screening and the finding of unexplained elevated transaminases.
- Clinical trials in this setting are difficult to perform but those that have been done suggest a good response to early treatment. Jaeckel et al treated 44 HIV-negative patients with acute hepatitis C using interferon-alfa at relatively high doses for 24 weeks and found a 98% sustained virological response rate [79].
- There is a relatively high spontaneous clearance of HCV within 12 weeks in those presenting with acute hepatitis C although this may not be the case in those presenting with asymptomatic disease. As the treatment success rates of acute hepatitis C appear to be less than in the HIV negative population, individuals should be closely monitored after presentation and only those who fail to clear HCV or have no drop in viral load on 4 weekly monitoring should be considered for treatment [80].
- Whether treatment should be with conventional or PEG-IFN and whether it should also include ribavirin remains unclear. Ribavirin is thought to have important immunomodulatory effects and although it enhances the treatment response in chronic infection the same may not be true in acute HCV. ie Trials are required.

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Table 1: Modified Ishak Score of Liver Histology [48]

Liver Damage	Inflammatory Score*	Fibrosis Score**
Mild	1-3	1-2
Moderate	4-18	3-5
Cirrhosis		6

* Portal/Periportal Inflammation Graded 1-18

** Fibrosis Graded 1-6

Fig. 1 MANAGEMENT ALGORTIHM FOR HIV POSITIVE PATIENTS WITH HCV INFECTION