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Management of HIV and hepatitis B or C co-infection in resource-limited settings

By Theo Smart

In January we introduced the topic of HIV and hepatitis coinfection in resource-limited settings. The article covered what is known about the prevalence of hepatitis B and C around the world, the extent of coinfection with HIV and hepatitis viruses, the natural history of hepatitis in coinfecting people and the potential treatments for hepatitis infection in HIV-positive people.

This edition of *HIV & AIDS Treatment in Practice* covers the practical clinical management of HIV and hepatitis coinfection, through comments from our advisory panel.

What is particularly telling is just how little clinical experience exists in the treatment of hepatitis B or C in resource-limited settings, despite the high prevalence of these infections among the HIV-positive population (especially where the epidemic is driven by injecting drug use, but also, surprisingly, in some African countries where injecting drug use is not considered a contributor to the HIV epidemic).

When antiretroviral treatment was introduced in wealthy countries after 1996, few people anticipated how important the long-term management of HIV and hepatitis coinfection would turn out to be, or that liver disease would become one of the most important causes of death amongst people living with HIV.

What is also striking from our research is the lack of information from countries in Eastern Europe. This may be due to the early stages of treatment scale-up in the region, but it may also reflect the strong bias against treatment of injecting drug users reported in the region (see for example a recent report by Human Rights Watch, <http://www.aidsmap.com/en/news/A4501801-252B-478D-ACE0-9E32CE259F09.asp>). However, as we reported in our previous coverage of hepatitis C, up to two thirds of HIV-positive people in some locations in Russia are coinfecting with hepatitis C, so treatment in the region must eventually take account of the importance of coinfection if CIS countries are to reach ambitious targets for treatment-scale up.

Discussion on co-management of HIV and hepatitis B or C

We requested comments from HATIP's advisory panel focusing on their experience in the field caring for patients co-infected with hepatitis and HIV.

We asked the following questions:

- 1 **Do you routinely screen for HBV or HCV or both? What tests do you use?**
- 2 **How closely (frequently) do you monitor liver enzymes in your patients? What do you do when liver function tests (LFTs) hit 3 x upper limit of normal (ULN) in a patient on ART?**

[Note: In our previous article we quoted textbook figures of the normal range for ALT and AST as 5-40 IU/l. However, Chris Green, of the Spiritia Foundation in Indonesia wrote us pointing out that "normal ranges for LFTs seem to vary very greatly" between labs and for men and women. "Depending on the lab, 3 x ULN ALT can be anything from 69 to 165! It is

clear that we MUST quote the reference range every time we quote absolute figures for LFTs."]

- 3 **Do you manage patients on nevirapine differently?**
- 4 **Otherwise, does chronic HBV or HCV influence how you use ART in your patients?**
- 5 **Do any of you treat HCV in your patients? Is alpha interferon/ribavirin available at referral hospitals for patients with advanced HCV?**
- 6 **Have any of you had to manage patients who were doing well on ART but whose liver disease is progressing? How do you manage their liver disease?**
- 7 **How do you manage cirrhosis and end stage liver disease (EDSL)? Are there any special considerations for palliative care?**

Comments

In resource-rich settings

Professor Brian Gazzard, of Chelsea & Westminster Hospital in London, addressed first what the practice is in the developed world.

"We routinely screen for both HBV and HCV at least annually by all the tests available and every time there is a significant change in LFTs." For patients on ART, "we do liver function tests every three months. If it is three times normal, we would repeat in two weeks depending on the background data. We don't manage patients on nevirapine differently.."

He said that pre-existing liver disease has no influence on how ART is used in his patients.

As for management of hepatitis C, "we use Interferon/Ribavirin, which is available for advanced disease." He said that patients whose liver disease progresses to cirrhosis and end stage liver disease (EDSL) are usually referred for liver transplantation.

In resource-limited settings

Clearly, however, liver transplantation is not an option in more resource-constrained settings. Only a handful of the middle income countries perform liver transplants, but the procedure is not yet being performed in people with HIV in those countries, although it is under consideration in Brazil.

Likewise Prof. Gazzard, who also trains healthcare workers in Botswana, noted that other resources constrain hepatitis C treatment options there. "Obviously drug availability is the issue in Botswana," he said.

Elsewhere, co-management of HIV and chronic hepatitis varies significantly, sometimes even within the same country.

HBV/HCV screening

Dr Francois Venter, Clinical Director, Essalen Street Project in Johannesburg, South Africa said "we don't routinely screen for HBV or HCV, but we monitor LFTs in patients with chronic hepatitis." In contrast, Dr Halima Dawood of King Edward's Hospital in Durban said "we screen routinely for hepatitis B. We screen for hepatitis C when investigating abnormal LFTs or if there is a risk factor."

In Senegal, Dr Adama Ndir of the National AIDS Programme, said that the current practice is not to routinely screen for HBV or HCV or both because patients have to pay for those tests. "But we systematically propose them," because he said, "in Senegal, about 90% of people are living with HBV but only 10% will develop the disease and then its complications. For hepatitis C, we have no data on the population but some data available on patient monitoring in some hospitals suggest that prevalence is about 5%."

In Indonesia, Chris Green said: "It seems to be general practice to screen those with an IDU background for HCV with antibody test only; for most a confirmation with viral load is unaffordable. For some reason I have been unable to unearth, it is not common practice to screen for HBV."

Monitoring LFTs on ART or nevirapine-based ART

The monitoring of liver function for nevirapine is recommended, ideally every two weeks for the first six weeks and monthly thereafter for the first 18 months of treatment. The monitoring of liver function in people receiving other drug combinations is less clearly defined.

All patients should be informed about the symptoms of liver toxicity if they are receiving nevirapine. Nausea, loss of appetite, fatigue, tenderness or swelling in the liver region, jaundice and malaise should be reported to the doctor immediately, since liver toxicity related to nevirapine can progress very rapidly. (

<http://www.aidsmap.com/en/docs/5416032E-A9FB-4351-9863-5D7F04ED8E07.asp>)

In South Africa LFT monitoring "depends on the regimen used," said Dr Dawood. In patients on nevirapine, Dr Dawood monitors liver enzymes very closely "initially weekly, then every two weeks, then monthly. With other regimens initially monthly and then every third month."

Dr Venter on the other hand said: "I only monitor liver enzymes if clinically indicated or on nevirapine. On nevirapine, we monitor ALT regularly."

Chris Green said that in Indonesia, "there are no clear national guidelines for monitoring LFTs. However, an increasing number of doctors are doing so with some sort of regularity, especially for those with an IDU background, and thus likely to be infected with HBV or HCV."

However, in Senegal, there are clear guidelines, said Dr Adama Ndir: "We routinely use lab tests every six months for HIV/AIDS patient monitoring and LFTs are some of the tests used. We use both AST and ALT. We use WHO classification for toxicity. If a patient is between 3 and 4, we treat clinical side effects and switch (or stop treatment) when LFTs go >5 ULN." However, Dr Ndir noted that nevirapine/AZT/3TC is the standard first line regimen.

When LFTs hit more than 3 x ULN in a patient on ART, Dr Dawood said that, depending on baseline LFTs, "I just monitor closely, do preliminary screens such as hepatitis, CMV, EBV, enquire about other drug use, especially alternative meds and alcohol use."

In Indonesia, Chris Green said that most patients are started on NVP unless they are known to have high LFTs at baseline. "Thus all are managed similarly." But he noted that "in cases of elevated LFTs (sometimes even less than 3 x ULN), there is often 'panic', even in asymptomatic cases.

"Nevirapine (NVP) or all ART is stopped and (sometimes later) changed to efavirenz (EFV) — with the result that use of EFV is significantly exceeding forecasts, resulting in stock-outs and over-expenditure, because EFV is much more expensive than NVP. In one case recently, the doctor decided to change immediately to EFV (LFTs were more than 5 x ULN in this case), but started EFV at 200mg daily, rising to 400mg after a week and then full dose a week later. The logic was that the impaired liver function and thus lower metabolism would result in a higher level of EFV in the blood, while the lower dose would allow the liver to recover. I have been unable to find any support for this approach!"

"Regarding elevated LFTs, we need to do a much better job of educating doctors regarding the risks. The picture I get is that even

very high LFTs do not need to be a concern if this is asymptomatic. Yet as I say, doctors tend to 'panic' when they exceed even 2 x ULN. We need continual and careful monitoring, plus advice to patients on what symptoms to look out for. But stopping everything may be more dangerous than continuing with observation."

Other effects of chronic hepatitis on ART management

"We have different categories of patients, said Dr Ndir. "Some patients were able to support ARV treatment with a very slow progression of liver disease. We go on treating them with ARV even with hepatitis. But other patients who were doing well on ART have progression of liver disease. We manage patients with advanced liver disease conventionally. And management is not so easy if CD4 counts are low and viral load is climbing very fast."

According to Green "since most PLHAs in Indonesia now have an IDU background, and most IDUs are HCV-infected, there is no difference in management. But as noted, there is generally no way to know if the HCV infection is chronic. As noted, screening for HBV seems to be unusual. Even in cases where chronic infection is known, I have yet to hear of concern over effect of ART on the disease."

3TC and HBV

"If a patient has chronic hepatitis B, we use 3TC-based ARVs," said Dr Venter "but most end up on it anyway. 3TC is part of the first line — so you get two for one!"

This seems to be the case in most settings, although Green noted that in Indonesia "there seems little concern over HBV/HIV coinfection, and I know of no cases in which HIV treatment decisions are affected by HBV."

HCV treatment

Alpha interferon, with or without ribavirin is uncommonly used in our panel members' patients — or is limited to a select few who can afford it. "We don't treat advanced HCV, because it's very rare in South Africa," said Dr Venter. Dr Dawood added, however, that "treatment is available for select patients with motivation."

In Senegal, motivation means paying for the treatment. "We don't [usually] treat advanced HCV, because its very rare in Senegal," said Dr Ndir, adding that alpha interferon is available at two hospitals in Dakar. "But it's very expensive for patients."

In Indonesia, said Green "most doctors treating the 'haves' in Jakarta seem to advise HCV treatment. Schering [which manufactures interferon] has a strong sales team here. I can only seem to find anecdotal data on this, I have yet to meet someone who has actually been treated. But of course the vast majority of patients would not be able to afford such treatment, even if they wanted it."

Management of liver disease and palliative care

Everyone has had patients on ART whose liver disease continues to progress. In such cases, Dr. Dawood, "investigate fully, including liver biopsy +/- ERCP [endoscopic retrograde cholangiopancreatography] if indicated." She then treats symptomatically.

Green said that several members of their group have died of liver disease while on ART. He said that in addition to recommendations to avoid alcohol "Most doctors here will prescribe a herbal combination. Many of the local drug companies market such

products as 'hepaproducts'. One such, from a major local drug company, is called *Hepasil*, consisting of a mixture of silymarin (milk thistle), curcumin, xanthorrhizae, and echinacea. Others have different combinations. While these seem to be effective in that LFTs drop, they might have done this anyway. And the use of echinacea is questionable for PLHAs in the view of many experts including the WHO.

"The ethical drug industry does not seem to offer any solutions, while at least some of these herbs have some degree of evidence base supporting their use. We do need to validate the use of these herbal remedies. [But], there is an evidence base, even if it is weak."

Similar herbal medicines to support and detoxify the liver are commonly used in Eastern Europe, and well-conducted research that can investigate their usefulness is urgently needed.

Most of the clinicians on our panel offer symptomatic or palliative care for cirrhosis and end-stage disease.

Dr Dawood prescribes general treatments for cirrhosis, such as lactulose, thiamine and multivitamins. Lactulose (beta-galactosidofructose) is a laxative, that can help to absorb or bind toxins, such as ammonia, in the intestine and remove them from the body.

Acute thiamine deficiency is also typical in a cirrhotic liver. Supplementation with thiamine and multivitamins help to correct any nutrient deficiencies and promote healing of damaged liver tissue.

Dr Henry Ddungu of the African Palliative Care Association in Kampala Uganda (see <http://www.apca.co.ug/>) described what little is known about palliative care for coinfecting patients with end stage disease. He said that "there are virtually NO studies from Africa and/or Asia" on palliative care for liver disease.

"However, end-stage liver disease is very common in Africa. Liver cirrhosis is very common as well as hepatocellular carcinoma in Africa.

Morphine, the drug of choice for cancer patients with severe pain is 98% metabolised by the liver. There are concerns therefore that for patients with advanced liver disease, there might be problems of morphine metabolism. This is not actually a very big problem as morphine can be metabolised to the active metabolites even with just less than 1/8 of it remaining. Therefore, pain should be well controlled.

The concern will come in when hepatic-renal syndrome comes in. Morphine is excreted almost entirely by the kidneys and so if there is renal failure, then there is need to regulate the dose."

Nevertheless, by this point, the patient has very little time remaining.

Access to better information

Chris Green suggests that the greatest problem surrounding co-management of HIV and chronic hepatitis is the lack of clear and definitive information, both for patients and clinicians.

"For most of our members, their HIV infection is something they can understand. They can access clear information on the disease and on its treatment. But their HCV infection is a 'black hole'. Their HIV doctors don't seem to understand it, and even if they did, they've no time to explain it. Some doctors will only push the lucrative treatment. Most don't even know that they may be antibody-positive but not chronically infected; there is no clear information available on how to determine this; viral load tests are not offered, and are probably unaffordable anyway. While we do try to provide advice and information, our main focus is with HIV.

Hepatitis is a very complex and less-well explained topic. There are still few drugs available, and those that are don't yet seem amenable to activism for access as has been done with ART. I'd have a hard time advising someone to start the current treatment for hepatitis, especially with limited monitoring and doctors who are generally under-informed.

Update on antiretroviral drugs and liver toxicity

Since our previous article was published, a few studies presented at the Thirteenth Conference on Opportunistic Infections and Retroviruses in Denver in early February reached slightly different anomalous conclusions about whether antiretroviral drugs were more commonly associated with liver toxicity or liver damage in people coinfecting with HIV and hepatitis C.

For example, a French team, which conducted liver biopsies in 118 HIV/HCV coinfecting people with low or undetected HIV loads on antiretroviral therapy, reported finding hepatic steatosis (fatty liver) in 73 subjects. Steatosis was significantly associated with fibrosis ($p = 0.001$) and with HCV genotype 3. HCV type 3 was also associated with more severe steatosis. Looking at the role of antiretroviral therapy, in a univariate analysis, exposure to abacavir and nevirapine were associated with a decreased risk of liver degeneration (Martinez 2006).

Conversely, a Spanish study of 231 HIV/HCV coinfecting patients who underwent a liver biopsy, reported that, for a similar time on therapy with different antiretroviral drugs, a higher incidence of liver toxicity was observed in patients with cirrhosis receiving nevirapine than in those receiving lopinavir/ritonavir or efavirenz (12 vs 4.12 vs 2.75 episodes/100 patient-years, respectively; $p < 0.01$). However, liver toxicity in this study was defined as an increase in AST/ALT levels over 5 times the upper limit of normal, or a 3.5-fold increase if baseline levels were abnormal, with or without clinical symptoms of liver toxicity. There were no clear indications that time on antiretroviral therapy was associated with more cirrhosis. However, a low nadir for CD4 cell counts (156 vs 222 cells) when ART was initiated tended to be associated with more cirrhosis ($p = 0.06$) (Casado 2006).

Meanwhile, an analysis of the D:A:D study (Data collection on Adverse events of anti-HIV Drugs), which prospectively gathered data on over 23,000 individuals, could find no significant association between the longer term use of potent anti-HIV therapy and the death from liver disease. Yet when they adjusted these results for CD4 cell count at the time of death, a significant association did emerge ($p = 0.03$). The investigators cautioned, however that further data were required before firm conclusions could be drawn and concluded that in addition to chronic coinfection with hepatitis B or C, the main risk factors for liver-related death were age and low CD4 cell counts (Weber 2006). For more results of this study see <http://www.aidsmap.com/en/news/816C27F0-22D6-4AFD-B035-369FE8893110.asp>.

However, taken together, these studies suggest no reason to withhold ART from people who are coinfecting with chronic hepatitis B or C. Quite the opposite, delaying therapy until CD4 cell counts fall too low should be a far greater cause for concern.

Further information on hepatitis B or C

Visit the key topic guide on hepatitis C at www.aidsmap.com

<http://www.aidsmap.com/en/cats/07981BFE-2D6D-44E0-AE64-992E0FE3B277.asp>

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about HATiP

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The newsletter is edited by Theo Smart (Cape Town) and Keith Alcorn, NAM's Senior Editor (London).

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