Prevention of viral hepatitis in HIV co-infection

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Co-infection of HIV-positive patients with hepatitis viruses worsens the long-term prognosis and this is summative for each new infection in any individual. Vaccination against hepatitis A or B may be effective but response rates are reduced in HIV infected patients. Improvement in response can be induced through extra doses, higher doses and HAART-induced increase in the CD4 count. Hepatitis B and C may also be prevented through counselling about safer sex, particularly condom use. In intravenous drug users, harm reduction, counselling and the use of needle/syringe exchange schemes may be helpful.

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1. Introduction

In patients already infected with HIV and either hepatitis B or C, the prognosis is made much worse with additional infection by other hepatotropic viruses [1–3]. Evidence from HIV-negative patients shows a rate of acute fulminant hepatitis of up to 40% when a chronic hepatitis C carrier subsequently gets hepatitis A or B [4–6]. Similarly, the rate of progression to cirrhosis and liver cancer is higher in dual chronic hepatitis B and C compared to either alone [7,8]. There is, therefore, a need to prevent all of these infections in the HIV-positive patient and even more need when a patient already has HIV/hepatitis co-infection. Prevention strategies include vaccination, safer sex and harm-reduction for intravenous drug users. Safer blood and blood products and medical practices are also important but beyond the scope of this article.

2. Vaccination

There are no published, clinical end-point trials for the efficacy of vaccination in co-infected patients, nor indeed in HIV mono-infected people. Therefore, evidence for efficacy comes from surrogate markers in the form of antibody responses. As prevention of infection with hepatitis A and B by vaccination correlates with post-vaccine antibody production in HIV-negative people, it is assumed that the same applies to HIV-positive people [9–13]. We also have precedence from immunisation of other immuno-compromised groups such as dialysis patients. It is generally accepted that adequate response to hepatitis B vaccine is the production of serum anti-HBs antibodies at levels > 10 IU/l [9–11]. Studies on vaccination in HIV have used the 0, 1, 6 month or 0, 1, 2, 12 month hepatitis B schedule and the 0, 6 month hepatitis A schedule [14–17]. Currently, there is no published information on the efficacy of the 0, 1, 3 week, 12 month hepatitis B schedule.

Compared to HIV-negative patients, those who are HIV-positive are less likely to respond to HBV vaccine, have lower mean antibody titres (by a factor of about 30), and lose 'protective' antibody levels more quickly (40% loss in 1 year vs 5% loss in HIV negative) [14–18]. Hepatitis B vaccine response correlates with the CD4 count (Table 1) [16,17,19]. The situation with hepatitis A vaccine response is the same as that for hepatitis B—the response rate is reduced and this correlates with CD4 count [20]. Mean anti-HAV antibody titres in responders is about 10-fold less in HIV-positive patients compared to those who are HIV-negative [20].

3. Improving vaccine response

This may be attempted in any of three ways—increasing the number and size of vaccine doses, using immune

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Table 1
Hepatitis B vaccine response at differing CD4 counts

CD4 count (cells/µl)	Proportion of patients achieving anti-HBs >10 IU/l (%)
>500	87
200–500	33
<200	25

stimulants/vaccine adjuvents and raising the CD4 count. Increasing the number of hepatitis B vaccine doses from three to six increased the vaccine response rate from 55 to 95% in one study of HIV-positive patients [17]. There is evidence from other immunocompromised groups that giving a double dose of vaccine will also improve response although there are no good quality published studies in HIV. There is no such data for hepatitis A vaccine. Attempts have been made to increase response using adjuvant granulocyte-macrophage colony stimulating factor (GMCSF) and interleukin-2 (IL-2) [21,22]. GMCSF has been used to improve hepatitis B vaccine response with some success in haemodialysis patients [23]. There is some evidence of efficacy for GMCSF in one study in HIV-positive people, which showed an earlier response to vaccine by doubling the proportion of anti-HBs seroconverters after the second dose from 30 to 62% and increasing the mean anti-HBs antibody titres from 375 to 644 IU/l, compared to those not receiving GMCSF. However, the response rates after the third vaccine dose equalised [21]. The effect of IL-2 has also been studied in patients vaccinated for hepatitis A or B during HIV treatment trials [22]. Although the CD4 count went up substantially in those patients given IL-2, the immune responses to vaccine were not improved when comparing IL-2 plus HAART treated patients with those given HAART alone. Indeed, the hepatitis A vaccine response was blunted in this study. There are no studies looking at the effect of giving HAART to vaccine non-responders and then repeating vaccination after a rise in CD4 count. However, studies of vaccine response clearly shows an association with CD4 count and, therefore, it is likely that response to HAART will improve vaccine response when the CD4 count rises to levels above 500 cells/µl [16,17,19].

4. Other preventative methods

4.1. Condoms

The best evidence for condoms acting as an effective means of preventing hepatitis B comes from studies in female sex workers in high prevalence countries [24–26]. In one report from Peru, there was 40% lower prevalence and 66% reduction in incidence of serological evidence of hepatitis B in women reporting consistent condom use for vaginal sex, adjusted for other confounders, compared with women who did not use condoms regularly [24]. It would seem likely that given the evidence for condom use and the prevention of many other STIs, they will be effective for preventing hepatitis C and preventing transmission during other forms of penetrative sex such as penile/anal and penile/oral intercourse. Although hepatitis A is thought to be sexually transmitted in MSM, it is linked to fisting and oro-anal contact [27–29], in which case condoms will not be preventative.

4.2. Harm reduction in intravenous drug users

Although needle exchange schemes have been introduced in many parts of the world, the benefit seems to be greater for reducing HIV rather than HBV or HCV [30,31]. One study in Sweden showed an incidence of new HIV, HBV and HCV of 0, 11 and 26 cases/100 years at risk, in intravenous drug users (IVDUs) involved in a needle exchange scheme [30]. This reflects the greater infectivity and prevalence of HBV and HCV, but also the fact that sharing of 'works' other than the needle or syringe can still lead to transmission. Similarly, counselling of IVDUs on reducing risk seems to have some effect, but a greater impact on HIV than the hepatitis viruses. Comparing three programmes in Norway, Sweden and Denmark, the programmes that concentrated on counselling, rather than needle exchange, showed the greater fall in HIV incidence [31]. A further challenge in preventative work in IVDUs is engaging them in such schemes. One way that seems to work in HIV-negative clients is offering incentives. Linking vaccination to either monetary inducements or doses of methadone has been successful [32,33]. Vaccination completion was in the order of 65–70% in such programmes and in the case of offering money for adherence to vaccination, the vaccination schedule completion rate trebled.

5. Prevention better than cure?

Given the substantial rates of morbidity and mortality of HIV/hepatitis co-infection and the further worsening of prognosis with additional acute or chronic hepatitis infection and the very high cost of specific treatments such as pegylated interferon and the expense of management of decompensated liver disease compared with the low cost of many of the preventative interventions, then prevention is both a clinical imperative and cost effective.

6. Recommendations for prevention

All HIV-positive patients, and especially those who have co-infection with hepatitis B, should be tested for HAV, HBV and HCV infection/immunity. Where non-immune/non-infected with HAV or HBV, they should receive vaccination. Non-responders to HAV vaccine should have vaccination repeated once the CD4 count has risen, in response to

HAART, ideally above 500 cells/μl. HBV vaccine non-responders should receive up to three further doses at double strength. If there is still no response, then a further attempt at vaccination should be made after the CD4 count has risen in response to HAART (as with hepatitis A vaccine).

At the same time all patients should be counselled about safer sex and the use of condoms for penetrative sex. In the case of IVDUs, potentially effective strategies include counselling on harm reduction which will include attempts to stop injecting or safer injecting practices if stopping is not possible. Access to needle/syringe exchange schemes may also be of value as will incentives to complete vaccination schedules such as linkage to methadone replacement.

7. Future research needs

As this article shows, there is a need to improve methods of prevention. Better vaccines are required and the pre-S-containing vaccines or DNA vaccines are possible candidates [34,35]. GMCSF is the best candidate for an adjuvant that may improve vaccine response although further research is needed. Greater understanding of effective interventions such as education on safer sex and harm reduction in IVDUs is needed.

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