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Influence of viral hepatitis on HIV infection

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The natural history of HBV is known to be complicated by HIV-co-infection. In contrast, the effect of HBV on the outcome of patients infected with HIV-1 is controversial. Some cohort studies from the pre-HAART era described a more rapid progression to AIDS in patients carrying antibodies to the core-antigen or having chronic HBV infection, but post-HAART studies did not detect any impact of HBV co-infection on HIV-disease progression. Similarly, studies assessing the impact of HCV on progression of HIV-disease delivered conflicting results. In the Swiss cohort study, the presence of HCV was independently associated with an increased risk of progression to AIDS and death. Subsequent studies, however, did not find any difference in survival. Most interestingly, the EuroSIDA cohort analysis found no difference between HCV-positive and HCV-negative HIV-patients starting HAART in the time needed to decrease viral loads to less than 400 copies as well as in the time needed to increase CD4-counts by 50%. In summary, there are no major differences in HIV-related mortality between hepatitis B or C co-infected individuals and patients infected with HIV alone, particularly if antiretroviral treatment is given. There is, however, an increased risk of liver disease related morbidity and mortality as well as more hepatoxicity under antiretroviral treatment regimens.

Keywords: **Hepatitis C; Hepatitis B; HIV; Co-infection**

1. Introduction

Since the decline in HIV-related morbidity and mortality after the introduction of highly active antiretroviral therapy (HAART) in 1996, liver disease caused by chronic infection with hepatitis B or C virus has become an increasingly important cause of morbidity and mortality among HIV-infected patients. One third of HIV-infected individuals in Europe and the USA have HCV-co-infection, and up to 10% have HBV-co-infection. HIV accelerates HBV and HCV liver disease especially when HIV-associated immunodeficiency progresses. Studies on the influence of hepatitis on progression of HIV-disease, however, have delivered conflicting results. In the following review, the findings and results from trials examining the impact of hepatitis co-infection on the course of HIV are summarized and discussed.

2. Is HBV a co-factor for HIV-disease progression?

In the setting of chronic hepatitis B, a persistent state of immune activation has been described in patients with chronic HBV replication possibly upregulating HIV-replication. Moreover, it has been suggested that the HBV X-protein (HBx) superinduces ongoing HIV-1 replication and HIV-1 long-term repeated transcription by synergizing with tat-protein and with T-cell activation signals [1]. These findings indicate that HBx could contribute to a faster progression to AIDS in HBV/HIV-co-infected individuals. Indeed some of the early cohort studies from the pre-HAART-era described a more rapid progression to AIDS in patients carrying antibodies to the core-antigen or having chronic HBV infection [2,3]. Within one of these studies 232 HIV-infected patients (age 37 + 8 years; CD4-count 167 + 167/μl; 46% had AIDS) were investigated. Blood samples of the patients were investigated for markers of HBV and HCV infection (HBs-Ag, HBe-Ag, HBV-RNA, anti-HBs, anti-HBC, anti-HCV, HCV-RNA). Overall, 60 of 232 patients (23%) were anti-HCV-positive, 28% of these seropositive for HCV-RNA. 22/232 (9%) suffered from chronic HBV-infection (HBs-Ag positive), 18/22 (82%) of these had detectable HBe-Ag and

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19/22 (86%) HBV-DNA. Presence of HCV-RNA, HBe-Ag and amount of HBV-RNA were related to the degree of immune deficiency. In contrast to the control group without HBV- or HCV-infection patients infected with HIV and either HBV or HCV showed a direct correlation between the reduction of CD4-counts and decreased cholinesterase activity. In patients with AIDS, co-infection with HBV or HCV was associated with a reduced survival compared to controls (HBV: 212 days, 95% CI: 106–317; HCV: 267 days, 95% CI: 112–396; controls: 439 days, 95% CI: 364–513).

As liver disease associated with HBV- or HCV-co-infection progresses especially in the setting of progressive immune deficiency some of the deaths may be attributed to liver-related disease rather than deriving from a more rapid HIV-disease.

Other studies from the pre-HAART era, however, were not able to demonstrate a significant impact of HBV carriage on HIV-disease progression [4–7]. In a study on 4498 homosexual participants from the Multicenter AIDS Cohort Study men were classified according to previous infection with HBV and prevalent or incident infection with HIV-1 [7]. Positivity for HBV-infection on entry was not related to initially low or more rapid subsequent decline in T-helper lymphocyte counts and was not associated with an increased incidence of AIDS during 2.5 years of follow-up. Indeed the authors concluded that prior HBV-infection in their study was unrelated to more rapid progression of HIV-1 induced immune deficiency. More recent data from the EuroSIDA cohort found the incidence of a new AIDS-defining event to be similar between HBs-Ag positive patients and negative patients [7,8]. After adjustment for confounding factors (use of HAART, baseline viral loads, CD4-cell counts, age, race, and risk factor for transmission of HIV) in a multivariate analysis, the incidence rate ratio of developing new AIDS events was again similar for the HBs-Ag positive group compared with the negative group. Interestingly, the time for patients to reach undetectable viral loads ($<$400 copies/ml) or a 50% increase in CD4-counts after 6–12 months of HAART were the same in both, HBs-Ag positive and negative groups [7,8]. In contrast, all cause mortality was higher for HBs-Ag positive patients compared to HBs-Ag negative patients. HBs-Ag positive individuals were also more likely to die from liver-related disease than HBs-Ag negative patients.

These findings were recently reinforced by a study examining the impact of viral hepatitis co-infection on HIV-disease outcomes following commencement of combination antiretroviral therapy in a developing country setting [9]. HIV-RNA suppression, CD4 cell count recovery, and HIV-disease progression were examined within a cohort of Thai HIV-infected patients enrolled in eight HIV-NAT randomized controlled trials of antiretroviral therapy ($n=692$). Prevalence of HBV, HCV and HBV/HCV-co-infection was 8.7, 7.2 and 0.4% of patients, respectively.

Interestingly, median HIV-RNA reductions ($\log_{10}$ copies/ml) were approximately 1.5 for HIV as well as for HIV–HBV subgroups from week 4 up to week 48. Mean increases in CD4 cell count were significantly lower among HIV–HBV subgroups at week 4 (HIV, 62 cells/μl; HIV–HBV, 29 cells/μl), however, by week 48 CD4 cell increases were similar (HIV, 115 cells/μl; HIV–HBV, 113 cells/μl). Estimated progression to AIDS event or death at week 48 was 3.3% (95% confidence interval, 2.0–5.1%) for HIV and 6.7% (2.5–14.6%) for HIV–HBV. The authors concluded that an early delayed CD4-count recovery among HIV/HBV co-infected patients was not sustained, and was not associated with increased HIV-disease progression.

There are some reports on an increased risk for virological failure, development of hepatitis and hepatic decompensation and death in HIV/HBV co-infected individuals after commencement of HAART therapy [10]. It was, however, noteworthy that immunological response (increase in CD4-count) as well as development of new AIDS-defining events was similar between HIV and HIV/HBV-co-infected individuals. The higher virological failure rate is most likely the result of a higher treatment interruption rate due to hepatotoxicity and flare of HBV. As the median CD4-count upon HAART initiation was $<$50 cells/μl this may explain why the rate of liver disease associated morbidity and mortality was so high within this study.

3. Is HCV a co-factor for HIV-disease progression?

The issue of whether HCV also effects progression of HIV-disease remains controversial [11–17]. In the Swiss Cohort, the presence of HCV was independently associated with an increased risk of progression to AIDS and death [9]. The increased risk was mainly attributable to lesser recovery in CD4-cell counts 1 year after the start of HAART in HIV/HCV-co-infected than in HCV-negative individuals. Similar results were also reported from some other smaller cohorts [12,13]. Subsequent studies from other cohorts, however, did not find any differences in survival when multivariate analysis was applied to correct for use of HAART, baseline viral loads, CD4-cell counts, age, race, and risk factor for transmission of HIV [7,15–17]. The EuroSIDA cohort found no difference between HCV-positive and HCV-negative HIV-infected patients responding to newly initiated HAART with regard to time to achieve an HIV-RNA $<$400 copies/ml or the time for CD4-cell counts to increase by 50%. Interestingly, recent 4-year follow-up data from the Swiss HIV Cohort Study could not find any significant differences with regard to recovery of CD4-cell counts between HCV-positive and HCV-negative patients [18].

Looking at the controversial results the question remains why different observations have been made and which factors may possibly contribute to these divergent findings. First of all, differences in adherence and the lack of tools to adequately measure adherence have to be taken into

consideration especially in this predominantly IVDU population. Moreover, in most studies, information on continuous drug abuse is missing. Furthermore, differences in the type of HAART being applied as well as treatment history may have had an impact (i.e. differences in the use of AZT, prior NRTI mono- or dual therapy). Also there are some differences with regard to death event analysis. Some cohorts have looked at overall death, others specifically at HIV-related deaths. Clearly, with ongoing duration of co-infection the risk for liver death increases thereby possibly having an effect on overall mortality but not necessarily on HIV-disease related mortality. Finally, cohorts have mainly looked at the increase in absolute CD4-count after initiation of HAART. In the co-infected individual, however, possibly the initially blunted recovery of CD4-counts may be due to the overall lower white blood cell count as a sequelae of more advanced liver disease and hypersplenism. Here, further analysis looking at the gain in relative percentage of CD4-counts are needed to see whether there is a true effect on CD4-cell recovery in HCV-co-infected versus non-co-infected patients.

4. Conclusions

In summary, extended follow-up in patients with HAART suggests that there do not exist any major differences in HIV-related mortality between hepatitis B or C co-infected individuals and patients infected with HIV alone, particularly if antiretroviral treatment is given. There is, however, an increased risk for liver disease related morbidity and mortality as well as global mortality in hepatitis co-infected HIV-patients as well as a higher risk for hepatoxicity under antiretroviral treatment regimens. The initial CD4-count recovery may be blunted in the early weeks after HAART initiation but becomes comparable over time between HIV and HIV/HCV-co-infected individuals.

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