Hepatitis B co-infection among people living with HIV/AIDS in rural Tanzania

Caroline Hvitmyhr
Norunn Otterstrøm

Prosjektoppgaven i medisinstudiet
Medisinsk fakultet

UNIVERSITETET I OSLO

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Abstract

Background: Both human immunodeficiency virus (HIV) and hepatitis B virus (HBV) infection are highly prevalent in sub-Saharan Africa, and co-infection is likely to occur. Co-infection raises several challenges: there are changes to the natural history of HBV infection, resistance may emerge in HBV as a result of HIV treatment, and changes should be made to the treatment regimens to take both infections into account. Epidemiological data on this problem is therefore needed.

Methods: This study was conducted in Haydom hospital in rural Tanzania. The HIV Care and Treatment Clinic (CTC) at this hospital provides free HIV treatment according to national Tanzanian guidelines. The patients included in the study were HIV infected attending this clinic. 120 patients were tested for HBV infection and evidence of previous HBV exposure, using a five parameter HBV rapid test (OnSite HBV 5-Parameter Rapid Test). The parameters used were HBsAg, HBeAg, anti-HBs, anti-HBc and anti-HBe. Patient files were studied for information about HIV treatment and most recent lab results, including CD4, platelets and ALT. The association between lab results and HBV infection was calculated using a two sample independent t-test.

Results: 11 (9%) of the 120 participants tested positive for HBsAg, as a marker of HBV infection. 47 (39 %) patients showed serological evidence of HBV exposure. 62 (52 %) patients tested negative for all parameters. There were no significant difference in ALT, platelets and CD4 between HBsAg-positives and HBsAg-negatives.

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1. Introduction

1.1 Epidemiology

40-58 million people are living with HBV infection in sub-Saharan Africa (1). This is an area where HIV/AIDS is highly prevalent; approximately 23.5 million are HIV positive (2). A systematic review from 2010 reports the mean prevalence of HBV infection among HIV infected to be 14,9 % in sub-Saharan Africa and 5-17 % in Tanzania (3).

1.2 Routes of transmission

HBV is present in blood and other body fluids, such as saliva, semen and vaginal fluid (4). Exposure to infected fluids may transmit virus. Therefore, routes of transmission may be vertical or horizontal. Horizontal routes include transmission among family members, between children, sexually, contaminated needles and by blood transfusions. The most common route of transmission in sub-Saharan Africa seems to be horizontal transmission in childhood (1).

HIV is present in blood, semen, vaginal fluid and breast milk. The virus may be transmitted sexually, through contaminated needles or blood products and mother to child during pregnancy, and breastfeeding (5).

Because of shared routes of transmission, HIV/HBV co-infection is likely to occur.

1.3 Natural history of hepatitis B infection

1.3.1 Acute infection and risk of developing chronic infection

Infection with HBV has a variable course. Acute infection can proceed asymptomatically or lead to acute hepatitis, which in the worst case may lead to acute liver failure and death (6).

An acute infection can resolve spontaneously or progress to chronic infection. Approximately 5 % of previously healthy adults develop chronic hepatits B (CHB) following an acute infection. Young age at the time of infection correlates with a higher risk of developing CHB, highest among children infected perinatally, where the risk is up to 90 % (7).

1.3.2 Serology

Hepatits B surface antigen (HBsAg), and possibly hepatitis B e antigen (HBeAg), can be detected in the serum of HBV infected individuals. HBsAg is routinely used as a diagnostic marker for HBV infection, while HBeAg is a marker of viral replication (8).

Antibodies against HBV start developing approximately eight weeks after infection. Hepatitis B core antibody (anti-HBc) appears first, secondly hepatitis B envelope antibody (anti-HBe) is detectable. Hepatitis B surface antibody (anti-HBs) is developed approximately six months after infection (6).

1.3.3 Chronic hepatitis B

CHB is defined by the presence of HBsAg in serum for more than 6 months. Common complications of the disease are cirrhosis and hepatocellular carcinoma (HCC) (9).

CHB may be divided into four phases: immune tolerant phase, immune active phase, inactive phase and resolution phase. Immune tolerant phase is characterised by high levels of HBV-DNA, normal liver enzymes and low hepatic inflammation, and is usually asymptomatic (10). This phase predominantly occurs in individuals infected perinatally or in early childhood and may last several decades (7).

Immune tolerant phase eventually develops into immune active phase, when the immune system starts recognizing the infection. In this phase levels of HBV-DNA are high, but lower than in the immune tolerant phase. There is mild to severe inflammation on liver biopsy and liver enzymes are elevated (10). Persisting inflammation leads to fibrosis. HBeAg may be present (7).

Immune active phase may proceed into the inactive phase by seroconversion from HBeAg-positivity to HBeAg-negativity. Antibodies against HBeAg (anti-HBe) may develop. Levels of HBV-DNA are reduced or absent, liver enzymes are normal and there is low inflammation in liver biopsy. Reactivation into immune active phase may occur, and lead to repeated cycles of inflammation and regeneration (7).

Some individuals will eventually become HBsAg-negative, which occurs at a rate of 0,5-0,8 % per year. This phase is called the resolution phase. HBV-DNA is not detectable, liver enzymes are normal and many develop anti-HBs (10).

There may be an additional phase; the occult phase, where HBsAg is negative, and HBV-DNA levels are low but measurable by sensitive PCR techniques. Different theories on why HBsAg is undetectable include, among others, mutations in HBV, immune suppression and immune complexes masking HBsAg. Occult HBV may cause acute exacerbations of CHB and development of HCC (11).

1.3.4 Changes to natural history in the setting of HIV co-infection

In the setting of HBV/HIV co-infection the course of chronic HBV infection may be different. Progression to CHB after transmission of the virus is five times higher among HIV infected. Risk of developing complications from chronic HBV infection, such as cirrhosis and HCC, is also increased. In the immune active phase levels of liver enzymes are lower than in HIV uninfected individuals, and seroconversion from HBeAg to anti-HBe is less frequent. In the inactive carrier phase, there is an increased prevalence of reactivation of HBV due to HIV related immune suppression (9).

1.4 Natural history of HIV

2-6 weeks following transmission of HIV, there might be symptoms of primary infection. Clinical features may be fever, rash, pharyngitis, muscle and joint pain, headache and lymphadenopathy. However, this may be mild and not recognised by the patient. In this phase there are high plasma levels of HIV-RNA and a fall in the CD4-count.

The primary infection is followed by an asymptomatic phase, although there may be persistent generalised lymphadenopathy. There is a gradual fall in CD4-count. This phase may last many years.

As CD4-count falls, mild symptomatic disease develops. This includes, among others, oropharyngeal and vaginal candidiasis, oral hairy leukoplakia, herpes zoster, chronic diarrhoea and weight loss.

AIDS is defined by a number of AIDS defining illnesses. These may be recurrent or opportunistic infections, such as toxoplasmosis and pneumocystis jirovecii, malignancy, such as Kaposi's sarcoma and lymphomas, and other diseases such as HIV associated dementia and HIV wasting syndrome (12).

1.5 Treament

1.5.1 Hepatitis B

Chronic HBV infection may be treated with either interferon or nucleoside analogs. Indication for treatment is active viral replication, represented by HBV-DNA > 2000 IU/ml for HBeAg-negative and > 20 000 IU/ml for HBeAg-positive, plus evidence of active liver inflammation: elevated transaminases (ALT/AST) and/or moderate or severe fibrosis or inflammation on biopsy.

According to Swedish recommendations, first line treatment is pegylated interferon alpha-2a (Peg-IFN), but its use is limited by its side effects and cannot be used in patients with cirrhosis.

If Peg-IFN cannot be used, entecavir is recommended. Adefovir and tenofovir are alternatives. Telbivudine may be used in selected patients.

For patients with cirrhosis, a combination of nucleoside analogs, adefovir and either lamivudin or entecavir, is recommended.

The goal for treatment is to prevent complications of HBV infection, such as HCC, cirrhosis and liver failure (13).

Peg-IFN is not available in resource limited settings. Lamivudine is widely available in sub-Saharan Africa, and tenofovir is becoming more available due to antiretroviral treatment of HIV. Adefovir has limited availability (9).

1.5.2 HIV

HIV infection may be treated with antiretroviral drugs. Indications for treatment, according to WHO guidelines, are CD4-count ≤ 350 cells/mm^3 or WHO clinical stage 3 or 4 irrespective of CD4-count. WHO recommends that first line treatment should include two nucleoside reverse transcriptase inhibitors (NRTIs), lamivudine and either zidovudine or tenofovir, and one non-nucleoside reverse transcriptase inhibitor (NNRTI), either efavirenz or nevirapine.

Second line treatment should include two NRTIs and a boosted protease inhibitor (PI), preferably atazanavir/ritonavir or lopinavir/ritonavir. Choice of NRTIs should be different from what the patient received as first line treatment (14).

1.5.3 HIV/HBV co-infection

In the setting of HBV/HIV co-infection, indication for HBV treatment is the same as for patients without HIV, according to Swedish recommendations. Nucleoside analogs for treatment of HBV, should not be given to HIV positive patients, unless on an effective HIV treatment regimen, to avoid development of resistance (13).

Patients without indication for HIV treatment should receive Peg-IFN. However, WHO recommends initiation of HIV treatment in all patients with co-infection (14).

Patients with indication for HIV treatment, should be treated with an antiretroviral regimen including two NRTIs effective against HBV, tenofovir and either lamivudine or emtricitabine (14). If tenofovir is not suitable, entecavir or adefovir are alternatives (13).

For second line antiretroviral therapy (ART) in co-infection, zidovudine and a protease inhibitor should be added (14).

1.6 Resistance to lamivudine

Lamivudine is a nucleoside analogue which is effective against both HBV and HIV, by inhibiting HBV-DNA polymerase and HIV reverse transcriptase (15). Resistance to lamivudine occurs frequently in both viruses (16). The incidence of resistance in HBV is reported to be approximately 20-25 % per year in co-infected individuals (9;15). Emergence of resistance is characterised by an increase in HBV-DNA and ALT levels (16). Resistance in HBV may be caused by lamivudine as a part of an ART regimen. ART should therefore include two drugs with activity against HBV, in the setting of co-infection (14;15), as mentioned above.

1.7 Hepatotoxicity of antiretrovirals

Hepatotoxicity is an adverse effect of antiretrovirals, which may lead to increased morbidity and mortality in HIV infected patients on ART, and may also aggravate prior liver disease. Incidence of severe hepatotoxicity is 2-18 %, according to a review (17). Severity ranges from asymptomatic elevation of transaminase levels to acute fulminant hepatitis and liver failure, and outcome ranges from spontaneous resolution to death.

Risk factors for development of hepatotoxicity of antiretrovirals are infection with HBV or hepatitis C virus (HCV) and alcohol abuse. In addition, some antiretrovirals seem to have more potential for hepatotoxic reactions than others. However, these results are conflicting. It is also difficult to identify which component of the ART regimen is causing the hepatotoxicity.

There are several pathogenic mechanisms of hepatotoxcity, although these are not well understood, and more than one mechanism may occur simultaneously. The mechanisms are, among others, direct dose-dependent toxicity, mitochondrial toxicity, hypersensitivity reactions, and immune reconstitution in patients with chronic viral hepatitis. Mitochondrial toxicity may be caused by most NRTIs. Didanosine, stavudine and zidovudine seem to have most potential for toxicity. Hypersensitivity reactions are mostly caused by NNRTIs, especially nevirapine. Reconstitution of the immune system following ART may lead to increased inflammatory response to the viral infection, thus leading to immune mediated liver damage.

Low grade liver toxicity often resolves spontaneously. ART should be discontinued if there is severe toxicity. Following resolution, a new ART regimen, with less potential for hepatotoxicity, should be initiated (17).

1.8 Background for this study

The individual prevalence of HIV and HBV in sub-Saharan Africa is relatively well documented. However, there are few studies describing the prevalence of co-infection. There is a systematic review including 50 studies concerning co-infection in sub-Saharan Africa, but most of these are set in urban areas and are mainly including women (3). Therefore, little is known from rural areas, and more studies are needed.

Information about the prevalence of HBV/HIV co-infection is important because co-infection may have consequences for progression of HBV and management of HIV.

The natural history of HBV infection is changed in the setting of HIV co-infection, as described above. There is an increased risk of progression from acute to chronic infection and of developing complications from chronic infection.

HBV/HIV co-infection also has consequences for management of HIV. Changes should be made in the ART regimen, to include two antiretrovirals with activity against HBV, to avoid resistance in HBV, particularly to lamivudine. There is also a greater risk of hepatotoxicity of antiretrovirals in the setting of HBV/HIV co-infection, which may lead to discontinuation of ART and increased morbidity and mortality.

Therefore, we wanted to investigate the prevalence of HBV/HIV co-infection in a rural area in Tanzania. We also wanted to investigate the prevalence of HBeAg-positivity and serological evidence of past HBV exposure, and if there is any association between biochemical and hematological markers, such as transaminase levels, CD4-count and platelet count, and HBV infection.

2. Methods

2.1 Study setting

Tanzania is located in the sub-Saharan region of Africa. The population is approximately 43,2 million people (18). It is a low income country facing one of the largest HIV epidemics in the world. According to UNAIDS, approximately 1,6 million people are living with HIV in Tanzania (19). The ART coverage in Tanzania is rapidly increasing, with an 82 % increase from 2007 to 2009. Despite this rapid increase, ART coverage was still less than 40 % in 2009 (20).

The national ART program in Tanzania was initiated in 2004. First line treatment regimen is a combination of two NRTIs and one NNRTI. Second line treatment is a combination of two NRTIs and one boosted PI (21).

Haydom Lutheran Hospital is located in the Manyara region, a rural area in northern Tanzania. The hospital is owned by the Evangelical Lutheran Church in Tanzania and is funded by the Norwegian Government, the Tanzanian Government and private donors. The hospital serves a population of approximately 300 000 people, and has a capacity of 400 beds (22).

2.2 HIV treatment in Haydom

The HIV Care and Treatment Clinic (CTC) has provided free ART to HIV positive patients since 2003, and currently approximately 1500 patients have been enrolled in care. The patients attending CTC are of all ages and both sexes, and come to CTC for HIV testing, information, counseling and treatment. ART is initiated according to WHO guidelines and treatment is according to the national Tanzanian guidelines. Only first and second line treatments with a limited selection of agents are available at this clinic. The following agents are available as first line treatment; stavudine, zidovudine, tenofovir, lamivudine, emtricitabine, nevirapine and efavirenz. Abacavir, tenofovir, diadenosine and lopinavir/ritonavir are available for second line treatment.
The patients included in the ART program are tested for HBV before initiation of treatment, with a HBsAg rapid test. However, the availability of this test is limited and is therefore not performed on several patients.

Currently there is no systematic treatment of chronic HBV infection in this area. There are usually no changes made to the ART regimen in the setting of HBV/HIV co-infection.

2.3 Data collection

This study was conducted over four weeks in august 2011. The patients included were HIV infected attending CTC, from the age of 15 and up. Both patients on ART and ART naïve patients were included. Blood samples were collected from 120 patients. These were centrifuged, and serum was used for a five parameter HBV rapid test (OnSite HBV 5-Parameter Rapid Test, CTK Biotech, Inc.). The five parameters used were HBeAg, HBsAg, anti-HBs, anti-HBc and anti-HBe. Patient files were studied for age, sex, date when ART was started, current and past ART regimen, previous HBsAg test result and most recent lab results, including CD4, platelets and ALT.

2.4 Statistics

Results from measurements of CD4-count, platelet count and ALT in the HBsAg-positive group were compared to the results of the HBsAg-negative group, with a two sample independent t-test. Significance level was set to 0,05 and 95 % confidence interval was calculated. This was performed with Open Epi, version 2.3.1 (23).

3. Results

120 patiens were included in the study. 81 (67,5 %) of these were women. Age was ranging from 17 to 67 years, with a median age of 43 years.

Of the 120 patients included in the study, 91 had started ART, while 29 were ART naïve. 88 patients were currently on a regimen containing lamivudine, while all 91 had used lamivudine at some time in their treatment. Over 90 % of the patients were using lamivudine in combination of either stavudine or zidovudine, and either nevriapine or efavirenz. The most common ART regimen was lamivudine, stavudine and nevirapine, used by 37 of the patients.

11 (9 %) of the patients were found to be infected with HBV, as identified by detection of HBsAg in serum. Among these 11, 1 was HBeAg-positive and 6 were anti-HBe-positive. 47 (39 %) showed evidence of prior HBV infection by the presence of antibodies (anti-HBs and/or anti-HBc). In 62 (52 %) patients, all parameters for HBV were negative, thus they had never been exposed to HBV.

Among the 11 who tested positive for HBsAg, 9 had started ART, while 2 were ART-naïve. Among the ones who had been exposed to HBV, 36 had started ART, while 11 were naïve. 44 of the ones never exposed to HBV, were on ART, while 18 were naïve.
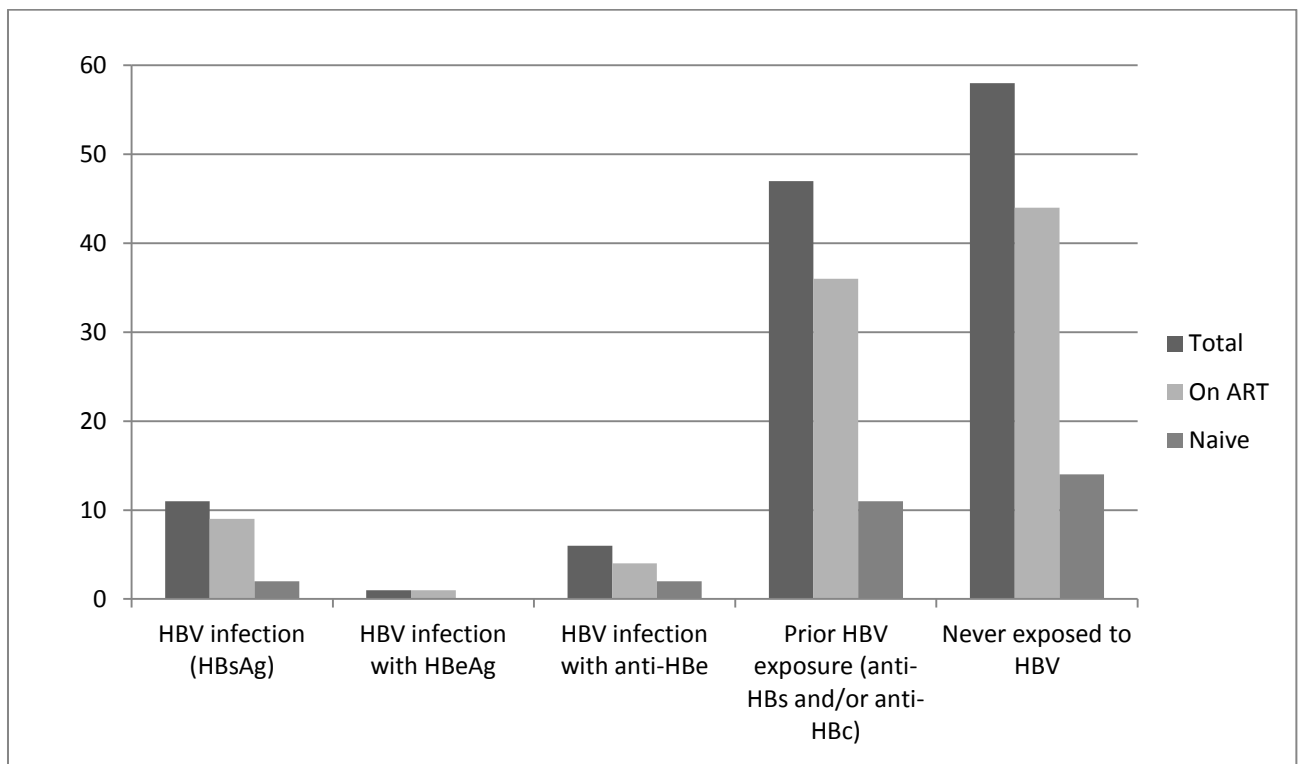
A rapid test for HBsAg had previously been performed in 65 of the 120 patients. 12 of these had tested positive for HBsAg at that time. 6 of these were still positive in our study, while the remaining 6 tested negative for HBsAg. 4 of these were now positive for anti-HBs, but negative for anti-HBc. 2 tested negative for all of our parameters.

ALT had been measured in 64 of the 120 patients. The mean value was 27,2 IU/L. Among the HBsAg-positives, ALT had only been measured in 4 patients. The mean value in this group as 28,6 IU/L. Among the HBsAg-negatives the mean value was 30,6 IU/L. Mean values for HbsAg-positives and HbsAg-negatives are not significantly different, P-value 0,91 (mean difference 2, confidence interval -31,75 – 35,75).

Platelets had been measured in 118 patients with a mean value of $236,2*10^9$/L. Among HBsAg-positives (11 patients) it was $226,6*10^9$/L. Among the HBsAg-negatives the mean value was $234,8*10^9$/L. Mean values for HbsAg-positives and HbsAg-negatives are not significantly different, P-value 0,80 (mean difference 8,2, confidence interval -56,07 – 72,47).

CD4-count had been measured in all 120 patients. Mean CD4-result was 358,7 cells/mm^3. Among HBsAg-positives the number was 290,5 cells/mm^3. Among HBsAg-negatives the mean value was 365,6 cells/mm^3. Mean values for HbsAg-positives and HbsAg-negatives are not significantly different, P-value 0,39 (mean difference 75,1, confidence interval -98,14 – 248,34).

4. Discussion

We found a prevalence of HBV/HIV co-infection of 9 %, which correlates with the prevalance found in other studies. There were no statistically significant difference between HBsAg-positives and HBsAg-negatives, as regards to levels of platelets, ALT and CD4. However, the group of HBsAg-positives is small, and there are few values of ALT and platelets in this group, therefore the statistical power is low. There is a clear difference between the two groups as regards to CD4-count, where the value is markedly lower (approximately 20 %) in the HBsAg-positive group, even though this is not statistically significant.

There may have been several sources of error in our study. The information collected from the patient's file may be incorrect, as the results from analysis of blood samples may be inaccurate and the results may have been entered incorrectly into the file. The file was also handwritten, which opens up the possibility of misinterpretation.

The sensitivity and specificity of the five parameter HBV rapid test used in this study is unknown. Results may be inaccurate due to false positives and false negatives. The rapid test was at times difficult to interpret. It was difficult to distinguish weakly positive and negative reactions for antibodies, which may have lead to errors in our estimates of HBV exposure. Positive antigen reactions were always unmistakable. 4 of the samples tested positive for anti-HBe only, which seems unlikely. It is unclear whether these were false positives or weakly positive for other antibodies. These results were therefore included in the material as negative for all parameters.

There is a possibility of HBV infection without presence of HBsAg (occult hepatitis B), which will not have been detected in this study. This may lead to an underestimated prevalence of HBV infection.

5. Clinical implications

Before initiation of ART, all patients should be tested for HBV, for example with an HBsAg rapid test. In case of a positive test, ART should be modified to include two antiretrovirals with activity against HBV, to avoid resistance in HBV. In rural Tanzania, lamivudine and tenofovir would be an available choice for this treatment.

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