

**A survey to assess the prevalence of Hepatitis B
in the adult HIV positive population
of the TC Newman ARV centre, Paarl**

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Declaration

I, the undersigned, hereby declare that the work contained in this assignment is my original work and that I have not previously submitted it, in its entirety or in part, at any university for a degree.

Signature:

Date: 30/08/2011

Abstract / Summary:

Background: Hepatitis B Virus (HBV) and Human Immunodeficiency Virus (HIV) co-infection in South Africa is estimated between 5-17%; however research determining this prevalence is lacking. With co-infection there is increased risk of liver cirrhosis, end stage liver disease, death as well as higher rates of chronic Hepatitis B infection. Chronic HBV develops in 20% of HIV positive individuals when compared to less than 5% in HIV negative individuals. This also further complicates Highly Active AntiRetroviral Treatment (HAART).

Methods: A retrospective observational quantitative, cross-sectional, analytical study was done at the TC Newman Antiretroviral (ARV) centre in Paarl. All adult HIV positive patients that were started on antiretroviral therapy for the time period the new protocol was implemented were analyzed according to their Hepatitis B Antigen (HBsAg) result as well as for any association with gender, CD4 and age. The new protocol stated that all patients who were to start ARV's had to be tested for Hepatitis B by testing their HBsAg.

Results: A total of 498 participants were identified of which 40% were male and 60% were female. The HBsAg positivity rate was established at 7.6%. A higher prevalence was found among men as well as in the age group 50-59 years and those with a CD4 of 50/ μ L and less.

Conclusions: With a prevalence of almost 8% there should definitely be a recommendation towards routine testing of HIV positive patients for Hepatitis B. If not before commencing ART then at least when switching from a regimen containing Lamivudine (3TC) or Tenofovir (TDF) to a regimen not containing these drugs in order to prevent acute flare ups of hepatitis.

Introduction

Hepatitis B is the most serious type of viral hepatitis. It is 50-100 times more infective than HIV type 1.¹ Worldwide, Hepatitis B virus (HBV) infections account for 370 million chronic infections and HIV for an estimated 40 million of which 2-4 million are co-infected with HBV.² HBV-HIV co-infection commonly occur due to their endemicity in the same world regions and shared routes of transmission.^{3,4} There is evidence of prior HBV infection in approximately 90% of HIV infected persons whereas chronic HBV is detected in 5-15% of HIV infected persons globally. According to the WHO, 90% of infants infected with HBV within their first year of life and 30-50% of children infected between one to four years of age will become chronically infected. 25% of adults that have been chronically infected in childhood will die from HBV-related liver cancer or cirrhosis. In contrast 90% of healthy adults who are infected with HBV will recover and be rid of the virus within 6 months.¹ Co-infection is associated with a greater risk of developing chronic HBV infection, cirrhosis, end stage liver disease and death (especially in patients with a low CD4 or concomitant alcohol use).^{5,6,7} The risk of liver related mortality is 3 times higher in HIV-HBV co-infection.^{8,9} Chronic HBV may also complicate the administration of Highly Active AntiRetroviral Treatment (HAART) for HIV due to the 3-fold increase in the incidence of antiretroviral hepatotoxicity with HIV-HBV co-infection as well as the more complex selection of drugs to avoid resistances.^{9,10}

Lamivudine, Emtricitabine and Tenofovir display anti-HIV and anti-HBV properties.⁴ Dual efficacy has been found with Lamivudine in treating HIV-HBV co-infection. However, in HIV negative patients HBV resistance to Lamivudine reaches 70% after 5 years of mono therapy and this is accelerated in the setting of HIV-HBV co-infection, with resistance greater than 90% demonstrated after 4years^{10,11,12} Tenofovir has proven to be effective against Lamivudine resistant and Lamivudine naïve HBV infections with minimal resistance. Thus in patients with indications for both HBV and HIV treatment Tenofovir and either Lamivudine or Emtricitabine should be used in combination to avoid resistance.^{10,11,12,13,14}

How are we currently managing HBV-HIV co-infection in South Africa? In July 2008 a national policy was implemented by the Department of Health, in line with the ART guidelines published

by the South African HIV clinician's society, whereby all patients who were to start antiretroviral therapy were to be tested for Hepatitis B as part of baseline screening tests using the serum Hepatitis B surface antigen (HBsAg).⁶ Only those who tested HBsAg positive were then started on Tenofovir (instead of Stavudine or Ziduvudine) plus either Emtracitabine or Lamivudine.^{2,15,16} Those who tested HBsAg negative were to be vaccinated against hepatitis B once immune reconstitution had taken place ($CD4 > 200$). Those who were already on ARV's could continue on their current regimen and only be screened for Hepatitis B if clinically indicated or when switched from one regimen to another. After 2 years of implementing this policy, the South African Antiretroviral Treatment Guidelines were updated in 2010. Tenofovir now replaces Stavudine as first line treatment in all new patients that are started on antiretroviral treatment.¹⁷ As two HBV active substances now form part of the first line treatment, it was decided that Hepatitis B testing no longer would be part of baseline screening in new HIV positive patients. No guidance is given in these national guidelines with regards to HBV vaccination and neither are guidelines provided with regards to testing patients for HBV before switching them from a HBV-active ARV regimen to another, which may lead to hepatitis B flare-ups.¹⁵ Should this policy be reconsidered in light of the prevalence of HBV-HIV co-infection?

The prevalence of chronic HBV-HIV co-infection has been found to be between 6-14% in several studies done in the United States, Europe, Israel and the Americas, mostly differing in prevalence by geographical areas, with a prevalence of 17.8% in Argentina and less than 10% in the United States and Europe.^{2,9,18} In Asia and sub-Saharan Africa, the prevalence of HBV-HIV co-infection vary from 1.7% in rural Equatorial Guinea to 17.4 % in Ghanaian prisoners and 20.4% in Malawi.¹⁹ In South Africa, co-infection is estimated in approximately 5 to 17% of the HIV positive population with a mean prevalence of chronic HBV infection approximately 10%. In the past, comprehensive studies to determine the prevalence of HBV-HIV co-infection in South Africa have been lacking. In line of the global HBV-HIV problem, it is to be asked whether our national policy should not be revised, and whether we have enough prevalence studies to make an informed decision on such a change. At the time of initiating this study, the only study available was one which enrolled patients from several work place HIV programs in

the rural mining and industrial sector, and a prevalence of 20% was found.²⁰ However newer studies have since been published which demonstrated a prevalence of between 4.8% to 7.1%.^{21,22}

Aims and Objectives:

AIMS:

The aim of this study was to examine the prevalence of co-infection with Hepatitis B in our local HIV positive population.

The results of this study can be used to promote awareness of Hepatitis B amongst health workers and amongst the general population as well as to motivate for a review of the current guidelines with regards to the management of HBV-HIV co-infection.

OBJECTIVES:

1. To establish the HBsAg positivity rate amongst the HIV positive patients that were started on treatment at the TC Newman ARV center since October 2008, when the initial policy change introducing the HBsAg test was implemented, and thereby to estimate the prevalence of active Hepatitis B in this population.
2. To assess the compliance with the above mentioned policy, i.e. to determine coverage (the percentage) of patients that actually did receive HBsAg testing during the period when the above mentioned testing policy was in effect (October 2008 – April 2010).
3. To examine and compare the Hepatitis B prevalence among different age groups, genders and CD4 counts.

Methods:

This was an observational quantitative, cross-sectional, analytical study design.

The study population consisted of all adult HIV patients presenting to the TC Newman ARV center for initiation of treatment after 1 October 2008 and for the duration that the 2008 policy was implemented. All adult patients (aged 18 years and older) were included, thereby avoiding sampling bias and creating a big enough study size to prove significant effect. In cooperation with a statistician, the required study size was estimated at a minimum of 385 patients.

Serum HBsAg is the accepted screening marker of HBV infection, and it is part of the provincial protocol for the Western Cape to diagnose Hepatitis B accurately and is therefore regarded as valid. HBsAg is the marker of active Hepatitis B infection. Chronic HBV is characterised by the presence of HBsAg with or without Hepatitis B envelope antigen (HbeAg). According to the national protocol of 2008, all patients started on ARV's were to be tested for Hepatitis B through testing serum HBsAg as part of baseline screening tests and therefore the results are reproducible and the method is reliable. This protocol has been in place till April 2010 thus enabling a big enough sample size to prove significant effect.

Information regarding all patients started on antiretroviral treatment at the TC Newman ARV center is routinely entered into an electronic database. TC Newman community day centre (CDC) is one of three community day centres in the Drakenstein sub district and is situated in the urban area of Paarl about 40kms from Cape Town. It provides comprehensive primary health care services, including x-ray facilities and rehabilitation, and serves as a referral centre for the surrounding primary health care clinics. It also features the main ARV clinic for this sub district. Since 2004 approximately 2700 patients were started on ART.

Only the required data (gender, age, CD4 counts and HBsAg) for the specific study population was retrieved. The data, without any identifiers as to ensure confidentiality, were then entered into a MS Excel spreadsheet which were analyzed by the statistician using STATISTICA version 8 (StatSoft Inc. (2008)). Summary statistics were used to describe the variables. Distributions of variables were presented with histograms and frequency tables. Medians or means were used as

the measures of central location for ordinal and continuous responses and standard deviations and quartiles as indicators of spread.

The study did look at the association between HIV and Hepatitis B and with analysis at the different variables i.e. age, gender and different CD4 counts and if and how they influence the prevalence of Hepatitis B. These variables were divided into nominal ones (Gender: female or male, Hepatitis B: yes or no) and continuous ones (age, CD4 counts). The relationships between continuous response variables (like CD4 count) and nominal input variables (like gender or HIV) were analyzed using analysis of variance (ANOVA). Relations between nominal variables (like HIV and gender) were investigated with contingency tables and likelihood ratio chi-square tests. A p-value of $p < 0.05$ was set to represent statistical significance in hypothesis testing and 95% confidence intervals are used to describe the estimates of unknown parameters.

As the HBsAg results were not routinely captured on the database, the results had to be retrieved directly from the National Health Laboratory Services' database, using the WWDisa system. For those patients (185) where no results could be found on this system, the patients' folders had to be retrieved manually from the ARV clinic.

A waiver of informed consent and approval by the Health Research Ethics Committee as well as the provincial department of health were obtained before research was started. This research did not incur any extra costs or work for the clinical services, as these tests had already been done as part of the initial protocol and much of the data capturing already formed part of the TC Newman ARV team's everyday tasks.

Results:

Demographics of research sample

A total of 569 entries of patients examined for initiation of HAART at TC Newman were found on the database from the 1st of October 2008 up to the 30th of April 2010, i.e. before the new protocol was fully implemented and HBsAg were no longer routinely done on all patients. This amounted to an average of 30 patients per month started on treatment. Of these 569 entrants only 498 had hepatitis B results available and were thus included in the study population. Of the 71 (12.4%) who had no Hepatitis B result available 64 weren't tested for HBsAg and 7 folders could not be located. When analyzing the 12% of the study population that did not have HBsAg results, it appeared that many of these occurred in the first and last month, i.e. during the phasing in and then phasing out of the initial protocol. In October 2008, 10 of the 20 entrants did not have HBsAg results available and for the month of April 2010, 7 of the 27 entrants did not have HBsAg results available.

The study population of 498 consisted of 299 (60%) females and 199 (40%) males with a mean age of 33y (SD 8.8) among the females and 38y (SD 9.8) among the males (fig.1). With regards to CD4 distribution, the largest number had a CD4 below 200 with 28% between 150-200 (fig.2).

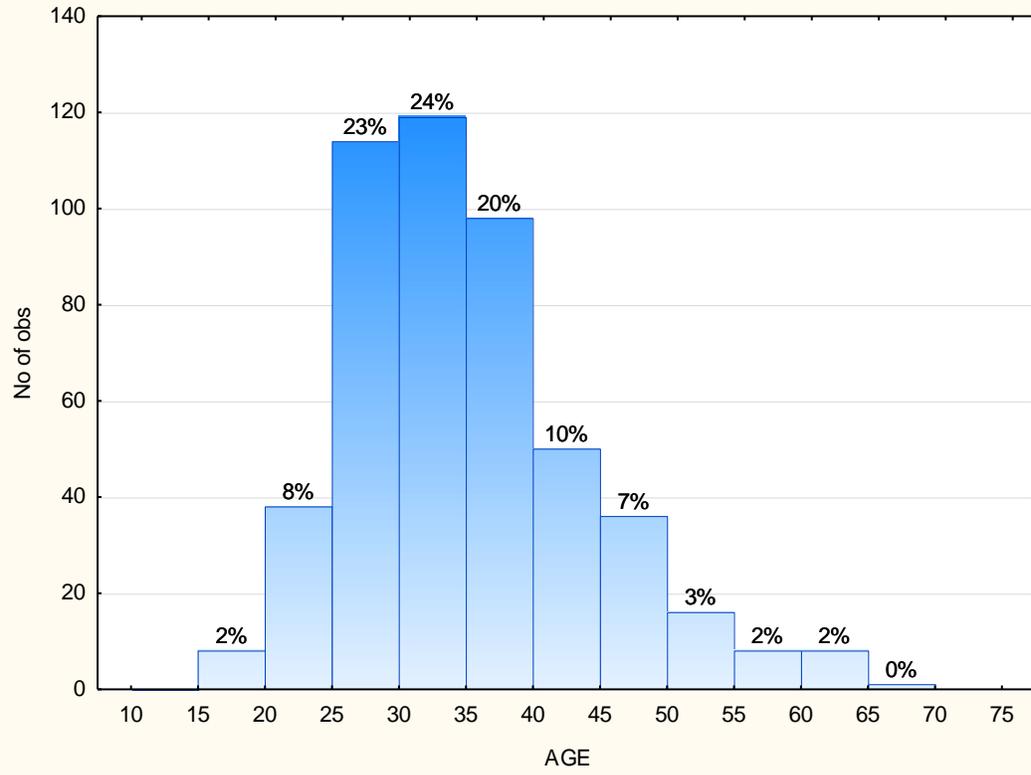


Fig. 1: Age distribution of the study population

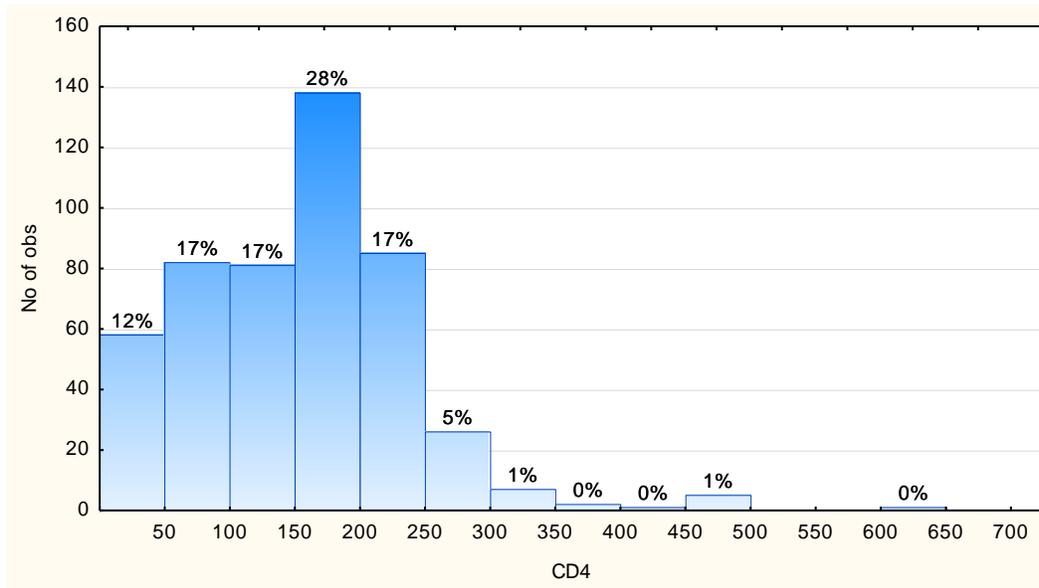


Fig. 2: CD4 distribution of the study population

Hepatitis B surface antigen results and correlations

The overall prevalence for HBsAg positivity was found to be 7.6% (38/498), with a prevalence among males of 9% (18/199) and among females of 6.6% (20/299), however no significant relationship between HBsAg positivity and gender could be shown {Chi-square (df=1)=0.93 p = 0.33}. The highest prevalence of Hepatitis B was found in the age group 50-59y old of 17.2% (5/29), followed by 12% (12/100) in the ages 40-49, 5.9% (13/220) in the ages 30-39, 5.8% (8/137) in the ages of 18-29 and 0% (0/10) in the ages 60-69 (fig.3). There was no significant relationship between HBsAg positivity and age {Chi-square (df=4)=8.47 p = 0.0757}.

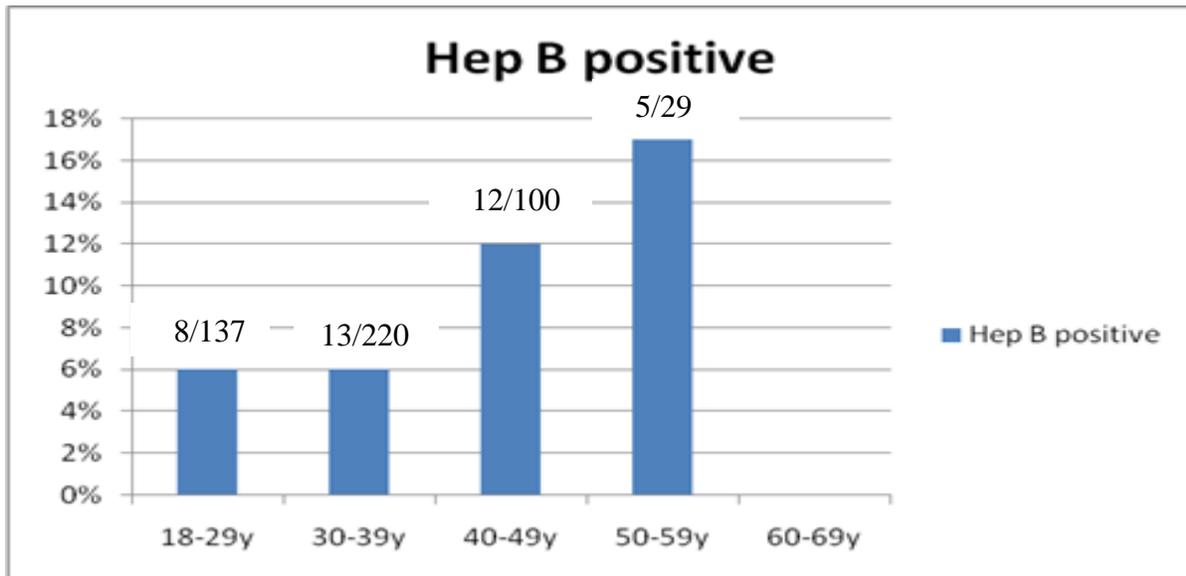


Fig.3: Hepatitis B positivity rate with regards to different age groups

With regards to CD4 the highest prevalence of 12%(7/58) was found in the CD4 group 0-50, followed by 8.3% (25/301) in those with a CD4 of 51-200 as well as those (1/12) who had no CD4 registered and 3.9% (5/127) in those with a CD4 above 200 (fig.4). There was no significant relationship between HBsAg positivity and CD4 count {Chi-square (df=2)=4.53 p = 0.1025}.

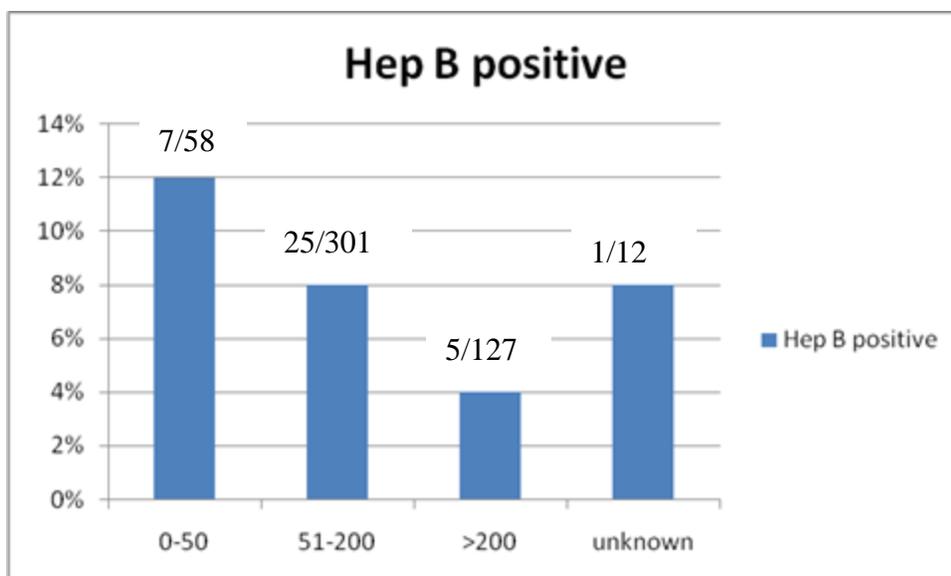


Fig.4: Hepatitis B positivity rate with regards to different CD4 groups

Discussion:

When interpreting the characteristics of the study population, the fact that the biggest portion had a CD4 below 200 can be attributed to the fact that according to the 2008 protocol a CD4 of 200 was the cut off point to start ARV's.

The prevalence of Hepatitis B antigen positivity in HIV positive patients of 8% lies within the estimates from earlier studies of an HBsAg prevalence of 0.3-15% in sub-Saharan Africa and it correlates with recent studies done in South Africa. A study done in an urban HIV clinic demonstrated a prevalence of chronic HBV-HIV co-infection of 4.8% (HBsAg positive), while a study done in a rural South African ARV clinic in the Eastern Cape demonstrated a prevalence of 7.1% with male sex being strongly associated with HBsAg positivity.^{21,22} The higher prevalence among men also fit in with studies done in South Africa as well as other countries like China.^{18,23,24,25}

The rate of 7.6% of active chronic infections found in this study might reflect a higher rate of chronification in the HIV-positive population as suggested in the literature, and the rate in the

HIV-negative population might thus be lower. When concluding the findings of this study, the increased risk with Hepatitis B and HIV co-infection for liver cirrhosis and end-stage liver disease as well as death in especially patients with a low CD4 count and the 3-fold increased risk of anti-retroviral related hepatotoxicity in patients with underlying chronic HBV infection is thus a realistic concern for us in South Africa, especially as this study found the highest prevalence of HBsAg positivity in those with a CD4 below and equal to 50 / μ L.

Another concern would be that if we have a prevalence of 8% this means that 8% of our patients who are started on ART have an active chronic Hepatitis B infection and thus if we manage them on a Hepatitis B suppressing regimen with either Emtracitabine, Lamivudine or Tenofovir they run an increased risk of developing fulminant hepatitis once the need arises for them to be switched to another regimen not containing these Hepatitis B active drugs, whether the reason be adverse drug reactions or HIV treatment failure. A further concern is that if patients are no longer routinely tested for HBV when presenting for ART then those who are unexposed to HBV (test HBsAg negative) will not have the benefit of being vaccinated against Hepatitis B once immune reconstitution has taken place (CD4>200) as was advised in the ART guidelines published by the South African HIV clinician's society in 2008.

A strength of this study is the fairly complete cohort, with only 12% of the study population not having HBsAg results available. A limitation might be the selection of the study population, all patients had been found to require ARV treatment (because of CD4 value or clinical staging), thus representing a sample of advanced cases of HIV infection.

Conclusions

The overall prevalence of Hepatitis B antigen positivity found in this study was 7.6%.

11.2% of the study population had no HBsAg done while 1.2% of the folders could not be found.

There was a trend towards a higher prevalence among men, the age group 50-59 as well as those with a CD4 below 50 / μ L, however these findings were not statistically significant.

Recommendation.

In line with the above findings, one would recommend that all patients who are diagnosed as HIV positive be tested routinely for Hepatitis B in order to either vaccinate those that are HBsAg negative or to decide on appropriate treatment for those who are HBsAg positive. This would include an added focus on the clinical management of Hepatitis B infections in the Infectious Diseases (ID)/ Anti-retroviral treatment (ARV) clinics in our primary care facilities. Clinicians in these facilities need to be skilled (by means of training and mentorship) to appropriately manage chronic Hepatitis B infections besides the other conditions commonly encountered such as tuberculosis, gastroenteritis, sexually transmitted diseases and HIV.

The findings of this study also support the recommendation in the recent (April 2011) guideline on the Management of HIV-Hepatitis B co-infection by the Southern African HIV Clinicians Society, which advises to test all HIV positive clients at the onset of the diagnosis and vaccinating those that are Hepatitis B negative.²⁶ According to the WHO, all infants should receive hepatitis B vaccine as well as all children and adolescents younger than 18y (not vaccinated before) as well as people in high risk groups. The complete vaccination series induces protective antibody levels in more than 95% infants, children and young adolescents with levels just below 90% after 40y and 65-75% at age 60. In many countries where 8 to 15% of children used to become chronically infected with HBV, vaccination has reduced the rate of chronic infections to less than 1 %.¹

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