

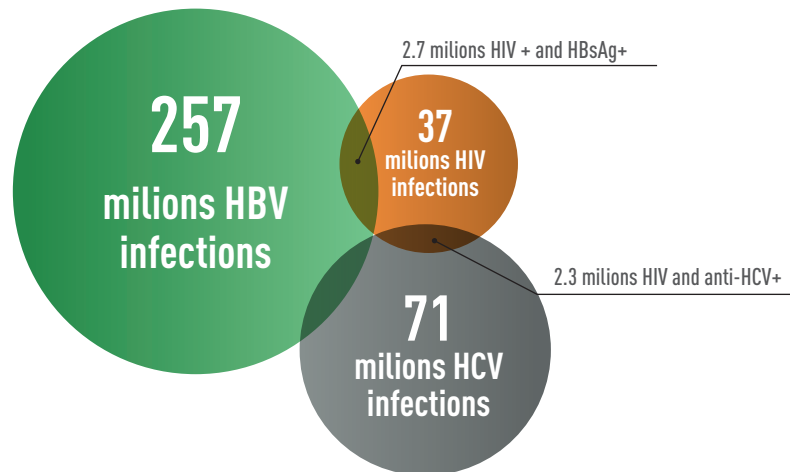
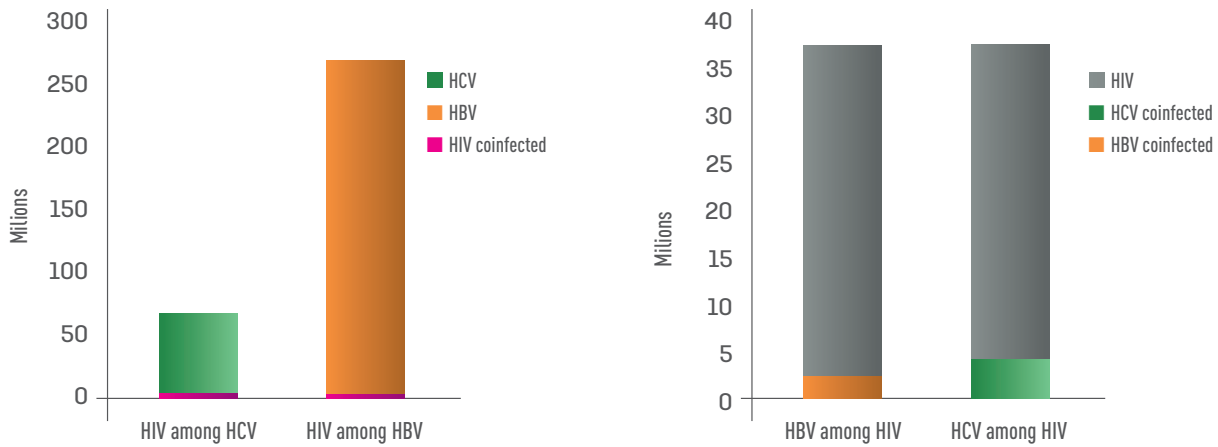
CONSOLIDATED RECOMMENDATIONS FOR

PREVENTION, CARE AND TREATMENT OF VIRAL HEPATITIS B AND C COINFECTION IN PEOPLE LIVING WITH HIV

The human immunodeficiency virus (HIV) and the viral hepatitis B and C viruses are blood borne viruses which share modes of transmission, resulting in overlapping at-risk populations. Rates of Hepatitis C Virus (HCV) and Hepatitis B Virus (HBV) infection in persons with HIV infection are higher than in the general population with HCV

affecting an estimated 2-15% of people living with HIV (PLHIV) worldwide and HBV chronically infecting 5-20% of people living with HIV. It is estimated that HCV affects 2.75 million people living with HIV worldwide, while HBV affects another 2.6 million [1].

Figur2 1. Prevalence of hepatitis B and C among HIV infected individuals and vice versa [1]



The presence of HIV infection increases the risk of viral hepatitis acquisition and the development of chronic infection. This is a result of impaired initial immune response to acute hepatitis B or C reducing the likelihood of spontaneous clearance of hepatitis infection in adulthood. Liver disease progression is faster in HIV hepatitis coinfection (though treatment for either will reduce progression) leading to a more rapid progression to cirrhosis and hepatocellular carcinoma (HCC), higher liver-related mortality, and decreased response to treatment compared to persons without HIV infection. In addition, HCV and HBV infection may also interfere with HIV treatment due to increased risk of ART-related hepatotoxicity, drug interaction and cross resistance with HIV and viral hepatitis drugs [2, 3].

Nevertheless, both HIV as well as HBV and HCV infection are readily treatable. With new direct-acting antivirals (DAAs), HCV cure rates in HIV/HCV coinfection are equal to that of HCV

mono-infection. Several HIV antiretrovirals can be also used to treat HBV infection, so standard HIV treatment regimens will also be active against HBV in HIV/HBV coinfection.

Regarding the national structures developed in the Region of the Americas to support the response to the viral hepatitis epidemics, 84% of reporting Member States (21/25) have created a specific department or coordination within the Ministry of Health to lead the response to viral hepatitis. Sixteen of them have the viral hepatitis program incorporated with the HIV/AIDS program, demonstrating that the responses to the two epidemics in the Region are closely connected and may benefit from joint planning and implementation. [4]

This document summarizes WHO's current recommendations for prevention, care and treatment of chronic viral hepatitis B and C among people at risk or living with HIV.

Recommendations for Hepatitis B and HIV

Prevention: Vaccination

- All HIV-positive individuals should be vaccinated for HBV as early as possible with the HBV vaccine. Post-vaccination testing of people living with HIV is recommended 1-2 months after administration of the last dose of the vaccine series [2].
- The hepatitis B vaccine is safe, effective and HIV-infected people should follow the same schedule for people without HIV infection (3 doses at 0, 1 and 6 months). At the moment, there is no strong evidence to support changes in the current recommendations related to booster doses, interval between doses and vaccine titers for people with HIV [5, 6].
- Catch-up hepatitis B immunization strategies should be instituted for people from vulnerable populations in settings where infant immunization has not reached full coverage. Vulnerable populations include persons who inject drugs (PWID), men who have sex with men (MSM), sexual partners of PLHIV, prisoners and healthcare workers (HCW) [6, 7].
- It is suggested to offer PWID the rapid hepatitis B vaccination regimen with 3 doses at 1, 7 and 21 days. [8] (*Conditional recommendation, very low-quality evidence*).
 - PWID may be less likely to complete a six-month schedule, and may benefit from a higher-dose, rapid schedule with 3 doses at 1, 7 and 21 days.
 - Completion of three doses is more important than following a specific schedule, and both rapid and standard regimens should be available.

Prevention of Mother to Child Transmission of HBV

- All infants, including HIV exposed ones, should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours, followed by two or three subsequent doses [6, 2].
- The use of Hepatitis B immunoglobulin (HBIG) in conjunction with HBV vaccination may be of additional benefit for newborn infants whose mothers are HBsAg-positive, particularly if they are also HBeAg positive [6].
- No recommendation is made on the routine use of antiviral therapy to prevent mother-to-child HBV transmission. In HBV-monoinfected pregnant women, the indications for treatment are the same as for other adults, and tenofovir is recommended. (*A small but growing body of data suggests that maternal treatment with nucleotides analogues in the third trimester of pregnancy in addition to vaccine and HBIG for the infant may also reduce HBV transmission to the infant*). [2]
- Antiretroviral therapy (ART) should be initiated in all pregnant and breastfeeding women living with HIV regardless of clinical stage and at any CD4 cell count and continued lifelong. In HIV/HBV-coinfected pregnant women, a tenofovir-containing regimen is also highly effective against HBV infection [9, 2]. (*Strong recommendation, low to moderate quality of evidence*)

<p>Screening</p>	<ul style="list-style-type: none"> · HBsAg serological testing (rapid test or laboratory based) should be offered to populations most affected by HBV infection, including HIV-infected persons and others who have a history of exposures or vulnerabilities for HBV infection (e.g. healthcare workers, PWID, people in prisons and other closed settings, MSM and sex workers, partners, family members and children of HBV infected persons) [11]. <i>(Strong recommendation, low quality of evidence)</i> · All persons with HIV infection should be screened for HBV at the time of enrolment into HIV care or at initiation of ART, and those who are not infected with HBV, should be vaccinated [10]. · Directly following a positive HBsAg serological test, the use of quantitative or qualitative nucleic acid testing (NAT) for detection of HBV DNA is recommended as the preferred strategy and to guide the treatment decision [2, 11]. <i>(Strong recommendation, moderate/low quality of evidence)</i>. · Individuals eligible for PrEP use should be tested for HBsAg and vaccinated if non-immune. People with positive HBsAg should be referred and evaluated for hepatitis B treatment [10].
<p>Staging</p>	<ul style="list-style-type: none"> · Liver biopsy is considered the gold standard method to stage liver disease, however it is expensive, invasive, associated with complications and requires expert histological diagnosis. Alternatively several non-invasive tests (NIT) are available to assess the stage of liver fibrosis based on image methods or blood tests. The NITs can reduce the need for liver biopsy, simplifying and increasing the access to liver disease assessment, particularly in resource-limited settings. · The APRI¹ index is recommended as the preferred non-invasive test to assess for the presence of cirrhosis (APRI >2). Transient elastography² or Fibrotest³ may be preferred in settings where they are available and cost is not a major constraint [2]. <i>(Conditional recommendation, low quality of evidence)</i>. · Although the data on HIV/HBV coinfection are limited, the performance of NITs in such persons is unlikely to be significantly different from that in HBV-monoinfected persons. The decrease in the platelet count that may occur due to HIV infection and/or ART may cause falsely high APRI scores. The FIB-4⁴ test could also be affected by thrombocytopenia but this scoring system was first evaluated in patients with HIV and was found to perform well [2, 12, 13].
<p>Treatment: When to start</p>	<ul style="list-style-type: none"> · All HIV-infected individuals should initiate ART regardless of CD4 count [9]. <i>(Strong recommendation, moderate-quality evidence)</i> · In places where that strategy is not fully implemented and prioritization is required, ART should be initiated in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count ≤350 cell/mm³ [9]. <i>(Strong recommendation, moderate-quality evidence)</i> · Individuals coinfecting with HIV and HBV should be prioritized to initiate ART at any CD4 cell count in the presence of severe chronic liver disease [9, 2]. <i>(Strong recommendation, low-quality evidence)</i>

¹ APRI = [(AST (IU/L)/AST Upper limit of normal (IU/L)) × 100] / platelet count (10⁹/L). The aspartate aminotransferase/platelet ratio index (APRI) is a score that uses simple and widely available blood markers.

² The transient elastography is a technique based on ultrasound technology and assesses the degree of fibrosis and cirrhosis by measuring the liver stiffness. The high cost of the equipment and the need of trained operators make this method less readily available.

³ Fibrotest is a patented test that measure direct markers of fibrosis including haptoglobin, bilirubin, A1 apolipoprotein, 2-macroglobulin, and should be performed at specialized laboratories.

⁴ FIB-4 = age (yr) × AST (IU/L)/platelet count (10⁹/L) × [ALT (IU/L)]^{1/2}.

Note: AST: aspartate aminotransferase, ALT: alanine aminotransferase.

**Treatment:
What to start**

- HIV/HBV-coinfected persons should receive ART preferably with a tenofovir (TDF) and lamivudine (3TC) (or emtricitabine (FTC))-based regimen, that is active against both viruses [2, 10]. (*Strong recommendation, moderate-quality evidence*)
- Tenofovir + lamivudine (or emtricitabine) + efavirenz as a fixed-dose combination is recommended as the preferred option to initiate ART [10]. (*Strong recommendation, moderate-quality evidence*)
- If ARVs need to be changed because of HIV drug resistance or drug toxicity, then tenofovir/lamivudine or tenofovir/emtricitabine should be continued together with the new ARV drugs to maintain anti-HBV activity and to reduce the risk of virological and clinical relapses [10, 2].
- If tenofovir is absolutely contraindicated, entecavir may be an option, together with an active ART regimen (and not alone). However this may be an option only in persons who have never been exposed to lamivudine, since the use of lamivudine is related to the emergence of HBV resistance to entecavir [2].

**Monitoring
and
secondary
prevention**

- Individuals receiving HBV treatment should be monitored at least annually for [2]:
 - ALT and AST levels, HBsAg, HBeAg and HBV-DNA levels (where available)
 - Non-invasive tests (APRI or elastography) to assess for presence of cirrhosis. (*Strong recommendation, moderate quality of evidence*)
- A more frequent monitoring (at least every 3 months in the first year) is recommended for persons co-infected with HBV and HIV [2]. (*Conditional recommendation, very low quality of evidence*)
- Routine surveillance for hepatocellular carcinoma (HCC) with abdominal ultrasound and alpha-fetoprotein testing every six months is recommended for:
 - Persons with cirrhosis, regardless of age or other risk factors. (*Strong recommendation, low quality of evidence*)
 - Persons with a family history of HCC. (*Strong recommendation, low quality of evidence*)
 - Persons aged over 40 years (lower age may apply according to regional incidence of HCC), without clinical evidence of cirrhosis (or based on APRI score ≤ 2), and with HBV DNA level >2000 IU/mL (where HBV DNA testing is available) [2]. (*Conditional recommendation, low quality of evidence*)
- Measurement of baseline renal function and assessment of baseline risk for renal dysfunction should be considered in all persons prior to initiation of antiviral therapy. Renal function should be monitored annually in persons on long-term tenofovir or entecavir therapy, and growth monitored carefully in children [2]. (*Conditional recommendation, very low quality of evidence*)

Recommendations for Hepatitis C and HIV

Prevention

- HCV is rarely transmitted through heterosexual sex, however, sexually transmitted HCV infection have been reported among HIV-positive men who have sex with men. Correct and consistent condom use is important to prevent HCV transmission [7].
- All people who inject drugs should have access to sterile injecting equipment through needle and syringe programmes. And those who are dependent on opioids should be offered and have access to opioid substitution therapy [7]. (*Strong recommendation, low quality of evidence*)
 - It is suggested that needle and syringe programmes also provide low dead-space syringes for distribution to PWID [8]. (*Conditional recommendation, very low-quality evidence*)
 - It is also suggested to offer peer interventions to PWID to reduce the incidence of viral hepatitis. Peer-driven interventions or peer education can reduce risk behaviors, enhance engagement and improve the acceptability of services, including adherence to prevention and treatment [8]. (*Conditional recommendation, very low- to low-quality evidence*)

Screening

- Serological testing for HCV antibody (anti-HCV), in either rapid test (RDT) or laboratory-based immunoassay format, should be offered to populations most affected by HCV infection, including HIV-infected persons and others who have a history of exposures or high-risk behaviors for HCV infection (e.g. PWID, people in prisons and other closed settings, MSM and sex workers, children of mothers with chronic HCV infection especially if HIV-coinfected) [7, 11, 13]. (*Strong recommendation, low quality of evidence*)
- All persons with HIV infection should be screened for HCV at the time of enrolment into HIV care, and those who are not infected with HCV but practice behaviors that place them at risk for HCV infection, such as injection drug use, should be retested annually [10, 13, 12].
- In addition, MSM eligible for PrEP use should be tested for anti-HCV, referred for assessment and treatment for hepatitis C infection if positive, or retested annually while on PrEP if negative [14].
- Directly following a reactive HCV antibody serological test result, the use of quantitative or qualitative nucleic acid test (NAT) for detection of HCV RNA is recommended as the preferred strategy to diagnose viraemic infection [11]. (*Strong recommendation, moderate/low quality of evidence*)
- There are limited data on the diagnostic accuracy of RDTs to detect antibodies to HCV in persons who are HIV co-infected. Theoretically, the sensitivity of serological assays that detect antibodies may be reduced in immunocompromised patients; however it occurs more often among persons with advanced immunosuppression due to HIV and during early HCV infection. Equally, there are also reports of a large proportion of false-positive HCV serological tests among HIV-infected persons [11].

Staging

- The APRI index is recommended as the preferred non-invasive test to assess for the presence of cirrhosis (APRI >2). Transient elastography or Fibrotest may be preferred in settings where they are available and cost is not a major constraint [13]. (*Conditional recommendation, low quality of evidence*)
- The diagnostic accuracy of APRI does not significantly differ between HCV-monoinfected and HIV/HCV-coinfected patients [12].
- The decrease in the platelet count that may occur due to HIV infection and/or ART may cause falsely high APRI scores. The FIB-4 test could also be affected by thrombocytopenia but this scoring system was first evaluated in patients with HIV and was found to perform well [2, 13]

**Treatment:
When to
start**

- All adults and children with chronic HCV infection should be evaluated for antiviral treatment of HCV infection, preferably with direct-acting antiviral regimens [13]. (Strong recommendation, moderate quality of evidence)
- In places where access to treatment for HCV infection is limited, some populations should be prioritized [12]:
 - Advanced fibrosis or cirrhosis;
 - Post-liver transplantation;
 - Extrahepatic manifestations;
 - Risk of accelerated fibrosis, including **HIV or HBV co-infection**;
 - Populations at high risk of transmitting HCV infection aiming the reduction in incidence.
- HCV treatment using older regimens (pegylated interferon and ribavirin) generally yielded low rates of success among HCV/HIV coinfecting patients, when compared to HCV mono-infected patients. Fortunately the outcomes for the newer, all-oral direct-acting antiviral HCV regimens (DAAs) produce similar rates of sustained virological response regardless of HIV status, and can reach cure rates higher than 90%. Therefore, HIV/HCV-coinfecting patients are no longer considered difficult-to-treat population [12].
- Both ART and treatment for HCV infection may slow the progression of HCV related liver disease; therefore, treating both infections is a priority for persons with HIV/HCV coinfection [13].
- In general, clinical stabilization of HIV disease with ART is advisable prior to starting treatment for HCV, especially in persons with advanced immunosuppression (CD4 count <200 cells/mm³) [13].
- In some circumstances would make sense to treat HCV infection first and then initiate therapy for HIV: persons with moderate-to-severe fibrosis at risk of rapid liver disease progression and no advanced immunosuppression caused by HIV infection [12].

**Treatment:
What to start**

- Persons with HIV and HCV co-infection require special consideration regarding the selection of an antiretroviral regimen. Potential harmful effects of antiretroviral (ARV) drugs include their hepatotoxic effects that may be worsened in the presence of concomitant HCV infection [13].
- Assessment of potential drug-drug interactions is critical in HIV-infected persons who are about to start HCV treatment. Careful consideration of such interactions is important to avoid toxicity and to ensure efficacy of the regimens used to treat both HIV and HCV in order to avoid the development of ARV resistance and to increase the likelihood of sustainable virologic response (SVR) [12]:
 - Simeprevir and the combination of ombitasvir + paritaprevir + ritonavir plus dasabuvir should not be co-administered with any PI or NNRTI;
 - Daclatasvir is associated with significant drug interactions with many NNRTIs and PIs, and its concomitant use requires caution, dose adjustments or consideration of alternative DAAs;
 - Ledipasvir and sofosbuvir have shown reduced potential for drug interactions with ARV drugs due to their use of different metabolic pathways;
 - Ribavirin and interferon, when administered with AZT, have been associated with an increased risk of anemia and hepatic decompensation;
 - A complete list of drug-drug interactions is available at www.hep-druginteractions.org.

Seguimiento y prevención secundaria

- Raised liver enzymes may be the result of ART-induced drug toxicity and/or opportunistic infections, making interpretation of liver enzyme elevations more problematic than for persons with HCV infection alone. ALT and AST should be monitored at 1 month after ART initiation and then every 3–6 months. A significant elevation of AST/ALT may prompt careful evaluation for other causes of liver impairment (e.g. alcoholic hepatitis, hepatobiliary disease), and may require short-term interruption of the ART regimen or specific drug suspected of causing the elevation [13].
- An alcohol intake assessment is recommended for all persons with HCV infection, followed by the offer of a behavioural alcohol reduction intervention for persons with moderate-to-high alcohol intake [13]. (*Strong recommendation, moderate quality of evidence*)

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