

## ART for HIV/HBV co infection

### Recommendations

1. HBsAg testing is recommended for all individuals before initiate ART. (Conditional recommendation, moderate quality of evidence)
2. In HIV/HBV co-infected individuals who require treatment for HBV infection, ART should be initiated irrespective of CD4 cell count or WHO clinical stage. (Strong recommendation, low quality of evidence)
3. In HIV/HBV co-infected individuals eligible for treatment, 1<sup>st</sup>-line ART regimen should include TDF and 3TC or FTC. (Strong recommendation, moderate quality of evidence)
4. In HIV/HBV co-infected individuals who are failing therapy, second and subsequent ART regimens should include TDF+3TC or FTC, both should be continued in the 2<sup>nd</sup>-line regimen for anti-HBV activity and to reduce the risk of hepatic flares, irrespective of the selected 2<sup>nd</sup>-line ART regimen. (Conditional recommendation, moderate quality of evidence)
5. In patients who are already being treated with 3TC without TDF and are subsequently found to be HBsAg positive, treatment should be changed to include two drugs that target HBV (TDF+3TC or FTC). (Conditional recommendation, moderate quality of evidence)

### Domains and considerations

#### Quality of evidence

The systematic review on this topic did not find RCTs which addressed critical HIV outcomes, and the GRADE profile reported only outcomes related to HBV (HBV viral load and HBV drug resistance).

On the question of **when to start ART in HIV/HBV co-infection**, there are no trials comparing early versus late initiation of ART. However, observational data support that those with HIV/HBV co-infection have an increased risk of fibrosis and cirrhosis (Marra 2007). Some studies found 3- to 6-fold risk of developing chronic HBV (Bodsworth,1991, Hadler 1991, Gatanaga 2000) and a 17-fold increase risk of death (Thio 2002) in HIV/HBV co-infected patients when compared with HIV-negative individuals. Three observational studies also showed a reduction in liver related disease (LRD) in HIV/HBV co-infected individuals with earlier and HBV active combination ART (Thio 2002, Hoffman 2009, Jain 2009).

On the question of **what ART to start in HIV/HBV co-infection**, data supporting the use of at least 2 agents with activity against HBV in an ART regimen come from one RCT (Matthews 2008) with better HBV viral load response and less development of HBV drug resistance. However, severe limitations (small sample size and short duration of follow up) were reported in the GRADE profile of this study.

On the question of **adding TDF** to those with HIV/HBV co-infection already taking 3TC, 3 observational studies found no significant differences in HBV response between the 3TC-naïve and 3TC-experienced patients. (Alvarez 2009, Matthews 2009, Schmutz 2006)

On the question of **retaining TDF+(3TC or FTC)** in 2<sup>nd</sup> line or subsequent ART regimens, 1 study reported better HBV VL response and no TDF mutations (Benhamou 2006).

**No uncertainty**

While HBV has minimal effect on the progression of HIV, those with HIV/HBV co-infection have an increased risk of fibrosis and cirrhosis (Marra 2007). Some studies found **three to six** fold risk of developing chronic HBV (Bodsworth, 1991;Hadler, 1991,Gatanaga, 2000) and a 17 fold increase risk of death (Thio, 2002) in HIV/HBV co-infected patients when compared with HIV negative individuals. Three observational studies also showed a reduction in liver related disease (LRD) in HIV/HBV co-infected individuals with earlier and HBV active combination ART. (Thio 2002, Hoffman 2009, Jain 2009). TDF, 3TC and FTC treat both infections.

On the question of **when to start ART in HIV/HBV co-infection**, there are no trials comparing early versus late initiation of ART. Observational data support the reduction in the development of chronic hepatitis in HIV/HBV co-infected individuals with earlier and HBV-active combination ART (Thio 2002, Hoffman 2009, Jain 2009).

On the question of **what ART to start in HIV/HBV co-infection**, data supporting the use of at least 2 agents with activity against HBV in an ART regimen come from observational studies and one RCT (Matthews 2008) with non-critical outcomes of HBV viral load response and development of HBV drug resistance. Limitations (small sample size and short duration of follow-up) were reported in the GRADE profile.

On the question of **adding TDF** to those with HIV/HBV co-infection already taking 3TC, observational studies found no significant differences in HBV response between the 3TC-naïve and 3TC-experienced patients (Alvarez 2009, Matthews 2009, Schmutz 2006).

On the question of **retaining TDF+(3TC or FTC)** in 2<sup>nd</sup>-line or subsequent ART regimens, one study reports better HIV response (Benhamou 2006).

**Some uncertainty about the quality of evidence****Risks/Benefits****Benefits**

- Reduced morbidity and mortality associated with chronic HBV
- Reduction of HBV transmission
- Reduction of HBV resistance
- Reduced incidence of hepatic flares

**Risks**

- TDF not approved in < 18 years old and limited data on its use in pregnancy
- HBV monotherapy results in HBV resistance (90% of HIV/HBV co-infected individuals treated with 3TC as the only anti-HBV drug are resistant to 3TC after 4 years of treatment)
- Increase in ART-related hepatotoxicity in HIV/HBV co-infection (3- to 5-fold)

**Benefits outweigh risks****Values and acceptability**

- It is not acceptable to PLHIV to treat HIV and not to optimally treat HBV
- HIV/HBV co-infection is common (from 5% to more than 20%) and treatment should be directed to both infections
- Improved management of HIV-HBV is likely to be acceptable to physicians and to PLHIV

**Uncertainty No**

<p><b>Cost</b></p> <ul style="list-style-type: none"> <li>• Increased costs from TDF use in first-line</li> <li>• There will be increased costs for laboratory tests for HBV screening and evaluation of disease activity</li> </ul> <p><b>Uncertainty No</b></p>
<p><b>Feasibility</b></p> <ul style="list-style-type: none"> <li>• Management is complicated by limited availability of HBV testing and other markers of disease activity (HBV DNA, HbeAg) in RLS</li> <li>• More laboratory needs for adequate HBV screening, evaluation of disease activity</li> <li>• These components can be implemented in areas where HIV programmes are already in place.</li> <li>• HbsAg is available as a ELISA test and can use the same platform of HIV testing</li> <li>• HBV DNA can use the same lab platform of HIV viral load</li> <li>• Liver biopsy, commonly used in developed settings for evaluation of liver fibrosis, is mostly unavailable in RLS and a major challenge in diagnosis and management</li> <li>• Common drugs used to treat HIV and HBV, and some common epidemiological aspects of management of both diseases, suggest an integrated, programmatic approach as the best strategy</li> </ul>
<p><b>Gaps, research needs, comments</b></p> <ul style="list-style-type: none"> <li>• Access to HBV lab tests for this population in RLS is an important challenge.</li> <li>• Establishment of adequate treatment algorithms using non-invasive tests is needed, particularly for evaluation of liver fibrosis</li> </ul>
<p><b>Final comment</b></p> <p>Strong recommendation</p> <p>In developing these recommendations, the panel placed high value on promoting HBV diagnosis and more effective treatment of HIV/HBV co-infection in RLS</p>