When to stop and restart antiviral therapy

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- Although nucleos(t)ide analogues are potent inhibitors of HBV DNA replication, they do not result in cure, because nucleos(t)ide analogue therapy does not eliminate the replicative template cccDNA in the nucleus or integrated viral genomes. Therefore, although finite nucleos(t)ide analogue therapy has considerable advantages, both for people with hepatitis B and policymakers, especially in low- and middle-income countries, long-term maintenance of suppressive therapy is generally required.
- A finite duration of treatment may be possible for some HBeAgpositive people who achieve anti-HBe seroconversion and a sustained undetectable HBV DNA viral load and for HBeAg-negative anti-HBe-positive people with low HBsAg concentrations and for whom evidence (using newer biomarkers) indicates low cccDNA transcriptional activity *(1)*.
- However, in resource-limited settings where access to HBV DNA monitoring is limited, it remains unclear under what conditions nucleos(t)ide analogue therapy may be safely stopped *(2–8)*.
- New data also show that HBsAg can be persistently transcribed for people with low levels of HBV replication, from integrated viral genomes, accounting for detectable HBsAg in serum even for HBeAg-negative people with low HBV DNA levels *(9,10)*.

Summary of the evidence

- The outcomes were HBeAg seroconversion, HBsAg loss, undetectable HBV DNA levels, liver-related morbidity (fibrosis, cirrhosis, end-stage liver disease and HCC), progression of liver disease, reversion of fibrosis stage and mortality, severe adverse effects and antiviral resistance.

- In general, viral responses were not durable, and relapse rates after treatment ended (with different definitions) at one year ranged from 40% to 95% if the duration of consolidated treatment was less than one year .

- Only 3% of HBeAg-negative viral responders treated with ETV for about one year had a sustained response (HBV DNA level <300 copies/mL) six months after therapy ended *(22)*. In a further prospective study, the one-year relapse rates (rise in HBV DNA and ALT levels) were 53% and 29%, respectively *(17)*.
- Most relapses occurred more than six months after treatment ended.
- Overall, the data show that most people experience biochemical or viral relapse after therapy ends, and increases in serum aminotransferases and HBV DNA concentrations occur earlier after stopping TDF versus ETV .

- Although the risk of decompensation is **low**, the consequences of discontinuation can be hazardous, and ensuring the safety of **ending therapy requires careful criteria .**

- Moreover, repetitive silent flares in serum aminotransferases are a manifestation of **hepatic injury** and could lead to **progressive hepatic fibrosis.**

- Independent factors associated with an **increased probability of relapse** after therapy ends included the presence of cirrhosis, older age, shorter nucleos(t)ide analogue therapy duration and higher pretreatment HBV DNA levels .

- Although their clinical relevance requires further evaluation in various populations, recent data suggest that HBV RNA and HBcrAg identify active cccDNA transcription and have the potential to identify people at higher risk of relapse after stopping nucleoside analogues.

Balance of benefits and harm

- The **advantages of stopping** nucleos(t)ide analogue therapy are a finite duration of treatment, reduced costs and minimizing renal and bone toxicity.
- The disadvantages are the risk of reactivating previously suppressed disease after discontinuing therapy, resulting in an unpredictable worsening of disease even for people without cirrhosis and possible development of acute-on-chronic liver failure *(32)* or, more commonly, repeated hepatic injury and fibrosis.

- Stringent criteria should be met before stopping treatment. People who discontinue therapy also require **careful immediate and long-term follow-up for early detection of relapse .**

- Overall, the evidence shows that treatment even with potent nucleos(t)ide analogues (ETV or TDF) infrequently leads to HBeAg seroconversion and loss of HBsAg for HBeAg-positive people and (even more rarely) HBsAg loss or anti-HBs seroconversion for HBeAg-negative people .

- In addition, relapse occurs for many after ending treatment, **even with the potent nucleos(t)ide analogues and following HBeAg seroconversion**.

- after ETV. Newer biomarkers such as HBV RNA and HBcrAg can predict the severity of relapse but are not widely available .
- A decline in HBV RNA can predict fibrosis regression among people being treated.

- The Guidelines Development Group in 2015 *(11)* **strongly recommended** that people with cirrhosis never discontinue antiviral therapy.
- Since they have much less hepatic reserve, life-threatening hepatic decompensation may occur after exacerbation based on moderate to low-certainty evidence.

- People with both hepatitis B and HIV initiating therapy should also remain on long-term HBV suppressive therapy.
- Given the limited access to monitoring of HBV DNA levels as well as regular monitoring of HBsAg or HBeAg serology in resourcelimited settings, the Guidelines Development Group had previously considered that longterm antiviral suppressive therapy will be necessary for the majority and recommended a very conservative approach to stopping therapy – **only for a few carefully selected people with evidence of sustained HBsAg loss, without cirrhosis.**

- Everyone who stops treatment **should be closely monitored with serum ALT and preferably HBV DNA.**

- Although the evidence base is limited, ALT and HBV DNA could be measured monthly for the first three months and then every three months during the first year to avoid severe exacerbations because of the high early risk of relapse (defined as a rise in HBV DNA and serum ALT concentrations or seroreversion to HBeAg positivity), and the need to reinstitute treatment for active disease.
- Later reactivation will require occasional testing for HBsAg.

- Newer biomarkers such as HBV RNA and HBcrAg can predict the severity of relapse but are not widely available.
- Retreatment is required for **elevated HBV DNA** concentrations (HBV DNA>2000 IU/mL) and/or **persistently abnormal serum aminotransferases**.
- In a multicentre cohort study of HBeAg-negative people, the cumulative incidence of hepatic decompensation at **60 months after stopping treatment** among the total cohort was 1.8% and 1.1% for the subgroup without cirrhosis .

- Although the risk of decompensation is relatively rare, the outcome can be severe.
- Less clinically obvious flares may also injure the liver.
- People with **cirrhosis** or **HBeAg positive** when starting therapy require **careful assessment** to prevent hepatic decompensation.

- More recent data suggest that HBsAg seroclearance is restricted to people with **low HBsAg concentrations: <100 IU/mL** or preferably less than 10 IU/mL for Asians and <1000 IU/mL or preferably <100 IU/mL for Caucasians .

- Those who do **stop therapy** (in addition to those who continue therapy) after HBeAg seroconversion or suppression of HBV DNA but remain HBsAg positive **require continued long-term follow-up and careful monitoring .**

- Given the more limited access to monitoring in low- and middle-income countries, both people with hepatitis B and caregivers need access to regular serum ALT and HBV DNA monitoring to determine **reactivation and the need to restart treatment.**

- The ability to monitor the resumption of HBV replication for everyone after stopping therapy **requires HBV DNA monitoring**.
- HBV DNA testing is relatively costly and is not available in most low- and middle-income countries. The evidence base for monitoring with liver enzymes alone, which is less expensive, is limited, and this is not recommended currently for disease relapse.
- Long-term TDF or ETV therapy also has cost implications, especially if paid out of pocket.
- Generic TDF is widely available at low cost in many low- and middle-income countries (about US$ 30–50 per person per year) and also as part of national ART programmes. The costs are currently higher for ETV, but it can be manufactured at lower cost since it is both off patent and the daily dose is low.

- The decision to stop any nucleoside analogue therapy must be weighed carefully.

- Biochemical relapse has been variously defined but includes ALT elevation to >2 times the ULN.
- A hepatitis flare has been defined as ALT elevation >5 times the ULN and

- **severe hepatitis flare** has been defined as
- ALT level >1000 U/L **or**
- ALT <1000 U/L plus a total bilirubin ≥3.5 mg/ dL **or** an international normalized ratio ≥1.5.

- Viral relapse has been defined as HBV DNA >2000 IU/mL.

- Quantitative HBsAg at the end of treatment predicts HBsAg loss or relapse **after stopping nucleoside analogues**, but the levels predicting relapse are lower for Asian versus Caucasian people.

- Stopping nucleoside analogues before HBsAg loss should only be considered if HBsAg seroclearance is likely based on prediction with current biomarkers, especially HBsAg levels, at the time of stopping.

- • People with hepatitis B should be educated about the importance of long-term monitoring to ensure adherence to monitoring and care.

- The benefits versus the disadvantages of stopping treatment should be also clearly explained.

- The ability to monitor everyone for safety after stopping therapy for resumption of HBV replication requires HBV DNA monitoring and recall policies.

- Postpartum, women who have started nucleoside analogue prophylaxis to prevent vertical transmission should be strongly advised to continue treatment if indicated for their own health and especially if multiple subsequent pregnancies are anticipated.

- This would also avoid the risk of liver flare when treatment ends after each pregnancy and delivery.

- Monitoring for and managing relapse:
- HBV DNA concentrations typically rise rapidly before serum ALT concentrations.
- Treatment should be reinstated if concentrations rise to >4 log10 IU/mL before any rise in serum aminotransferases to circumvent the immune-mediated flare .

- Delayed resumption of therapy may have severe outcomes for these people.

- An array of immunosuppressive agents may induce HBV reactivation. These include cancer chemotherapy, checkpoint inhibitors, immunosuppressive therapy, bone marrow and stem cell treatment, anti-tumour necrosis factor and novel immunobiologics, including tyrosine kinase inhibitors, chimeric antigen receptor T-cell treatment and after treatment for comorbid hepatitis C.

- Since the composite risk can be difficult to determine, **pre-emptive antiviral therapy is recommended .**

Lifelong nucleos(t)ide analogue therapy

- All people with cirrhosisa based on clinical evidence (or APRI or transient elastography score) require lifelong treatment with nucleos(t)ide analogues and should not discontinue antiviral therapy because of the risk of reactivation, which can cause an acute hepatitis flare.
- *(strong recommendation, moderate-certainty evidence)*

- **<u>Antiviral therapy is lifelong. Discontinuing nucleos(t)ide analogue therapy may be considered exceptionally for:</u>**
- • people without clinical evidence of cirrhosis (or based on a non-invasive test score – APRI or transient elastography;

  and
- • who can be followed carefully after discontinuation and long term for reactivation;

  and
- • if there is evidence of HBeAg loss and seroconversion to anti-HBe (for people initially HBeAg-positive) and after completion of at least one additional year of treatment;

  and
- • in association with persistently normal ALT levelsb and persistently undetectable HBV DNA levels (if HBV DNA testing is available).

If HBV DNA testing is not available:

- discontinuing nucleos(t)ide analogue therapy may be considered for people who have evidence of persistent HBsAg loss and after completion of at least one additional year of treatment, regardless of previous HBeAg status.
- *(conditional recommendation, low-certainty evidence)*

Retreatment

- Relapse is common after stopping therapy with nucleos(t)ide analogues.
- Retreatment is recommended if there are consistent signs of reactivation: HBsAg or HBeAg becomes positive, ALT levels increase or HBV DNA becomes detectable again (if HBV DNA testing is available).
- *(strong recommendation, low-certainty evidence)*

- a Clinical features of decompensated cirrhosis: portal hypertension (ascites, variceal haemorrhage and hepatic encephalopathy), coagulopathy or liver insufficiency (jaundice). Other clinical features of advanced liver disease or cirrhosis may include: hepatomegaly, splenomegaly, pruritus, fatigue, arthralgia, palmar erythema and oedema.

- b The ULN for ALT has been defined as <30 U/L for men and boys and <19 U/L for women and girls. Persistently normal or abnormal may be defined as two ALT values below or above the ULN at unspecified intervals during a 6- to 12-month period.
- ALT levels fluctuate with CHB and require longitudinal monitoring to determine the trend.


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