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tenofovir and chronic hepatitis B

NEW INDICATION

Adolescents: an antiviral drug with inadequately documented adverse effects on the kidneys and bone

● **Reduces viral load, but more data needed about adverse effects on kidneys and bone.**

POSSIBLY HELPFUL

Most children carrying hepatitis B virus (HBV) since birth are symptom free, and they grow and develop normally without treatment. However, some children develop chronic active hepatitis B (1), which can lead to cirrhosis and hepatocellular carcinoma in adulthood.

As specific paediatric studies are lacking, treatment of children and adolescents is usually based on results obtained in adults (1-3). In the short term, complications can be prevented by suppressing viral replication.

For patients who need antiviral treatment, *interferon alfa* therapy for several months is a first-line option despite its frequent and often poorly tolerated adverse effects. One alternative is regular oral therapy with *lamivudine* or another nucleoside or nucleotide inhibitor (1-3).

In adults, *tenofovir* (Viread°, Gilead Sciences), a nucleotide inhibitor, is active on viral load and rarely leads to viral resistance, but it can cause kidney failure and bone disorders (4).

Tenofovir is the first antiviral drug to be approved for HBV-infected adolescents over 12 years old. How effective is it in these patients, and what are its adverse effects?

Confirmed antiviral activity. Clinical evaluation of *tenofovir* is based on a double-blind, randomised, placebo-controlled trial in 106 adolescents, most of whom were aged between 15 and 18 years (5-7). They had been infected an average of 10 years previously and had high viral loads. HbeAg was detectable in 91% of patients. 76% of patients had previously been treated with *interferon alfa*, 59% with *lamivudine*, and 42% with both drugs.

Liver histology was not carried out. Results obtained after 72 weeks of treatment confirmed the antiviral activity of *tenofovir,* with viral load below 400 copies per ml in 89% of adolescents in the *tenofovir* group versus none in the placebo group ($p < 0.001$) (5,6).

At baseline, 73% of the adolescents had elevated transaminase activity. In this subgroup, transaminase activity normalised in 74% of cases in the *tenofovir* group versus 31% in the placebo group ($p < 0.001$). Changes in HBeAg and anti-HBe did not differ between the groups.

Bone and kidney problems: close monitoring needed. In addition to the common adverse effects of nucleoside and nucleotide inhibitors, *tenofovir* can cause kidney failure, proximal tubulopathy (including Fanconi syndrome), hypophosphataemia, decrease in bone density, and weight loss (8). It is unclear whether or not renal adverse effects are reversible (5). *Tenofovir* was associated with a loss of bone density in the adolescent trial, although the possible long-term clinical repercussions are unclear (5,6). No renal disorders occurred during this trial.

A 10-year review of *tenofovir* use in the United States identified 79 reports of adverse reactions in children, most of whom were treated for HIV infection; 6 of these children had bone disorders (decrease in bone mineral density and rickets) and 19 experienced renal dysfunction, mainly tubular dysfunction, renal failure, and Fanconi syndrome (9).

In practice. *Tenofovir* is effective in suppressing hepatitis B virus replication. However, more data are needed on its harm-benefit balance, especially in adolescents, particularly because of its adverse effects on the kidneys and growing bone. Whenever possible, it is best to defer treatment until after the pubertal growth spurt.

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tenofovir Tablets

VIREAD°

- **245 mg** of *tenofovir disoproxil* (fumarate) per tablet

antiviral drug, nucleotide inhibitor

■ **New indication:** *"(…) chronic hepatitis B in adolescents 12 to < 18 years of age with (…) active viral replication, persistently elevated serum ALT levels and histological evidence of active inflammation and / or fibrosis".*

[EU marketing authorisation, centralised procedure]

Selected references from Prescrire's literature search.

In response to our request for information, Gilead Sciences provided us with no documentation on its product.

1- Broderick A and Jonas MM "Overview of hepatitis B virus infection in children" (updated February 2013) UpToDate, Waltham 2013; version 21.2: 27 pages.

2- Prescrire Rédaction "Hépatite virale B chronique: traitement" Idées-Forces Prescrire mises à jour November 2012: 5 pages.

3- "Hepatitis" In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 24 May 2013: 13 pages.

4- Prescrire Editorial Staff "Tenofovir. In chronic hepatitis B: beware bone toxicity" *Prescrire Int* 2009; **18** (101): 116.

5- EMA - CHMP "Assessment report-Viread. EMEA/H/C/419/II/119" 20 September 2012: 56 pages.

6- US FDA - CDER "Clinical review. NDA 021356/S-042 and 022577/S-002. Viread" 24 July 2012: 65 pages.

7- Murray KF et al. "Randomized, placebo- controlled trial of tenofovir disoproxil fumarate in adolescents with chronic hepatitis B" *Hepatology* 2012; **56** (6): 2018-2026.

8- Prescrire Rédaction "11-1. Patients infectés par le HIV" *Rev Prescrire* 2012; 32 (350 suppl. interactions médicamenteuses).

9- US FDA-CDER "Pediatric Postmarketing Adverse Event Review-Viread" 15 March 2012: 21 pages.

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