

Reviewer #1

Specific Comments to Authors:

Manuscript entitled 'Treatment of Hepatitis B Virus Infection in Children and Adolescents' by Stinco M et al. is a nice compilation of the current treatment for HBV chronic infection. It is well-written and worthy of publication. However, I have few minor comments that need to be addressed before publication.

R - We thank the reviewer for this positive comment.

1. Authors should include mode of action (briefly), major strength and limitations of each drug.

R - A brief description about the mode of action has been added in the corresponding paragraph for each drug (tracked changes version); a "Pros and cons of anti-HBV treatment" paragraph has been added before the indication for treatment, regarding major strength and limitations of drugs (see page 10).

2. Peginterferon alfa-2b and Telbivudine are better to be deleted from Table 2, as because of the heading of the table

R - The table has been modified accordingly.

3. There are some typos, that should also be carefully checked and corrected, e.g. in page 9, HIV confection should be HIV coinfection, and in page 14, antibodis should be antibodies.

R - According to the comment, the paper has been entirely revised and the typos mistakes have been corrected.

4. Table number should be included where has been indicated that 'Abbreviations used in Table 1/Table 3

R - The tables have been modified accordingly. Specifically, the following sentence has been added to each table: "Abbreviations used in table 1/ table 3".

Reviewer #2

Specific Comments to Authors:

It is an interesting review about "Treatment of Hepatitis B Virus Infection in Children and Adolescence". My concern is determined in the following points. Drugs in the Pipeline for HBV. The primary goal of current therapeutic research for chronic hepatitis B is to achieve a functional cure after a finite course of therapy. Both direct-acting antivirals, targeting different aspects of the hepatitis B virus (HBV) replication cycle, and immunotherapeutic approaches are being explored as monotherapies and /or in combination with other agents. The key molecular objective is estimation of HBV

covalently closed circular DNA, which is the source of viral transcription associated with chronic infection, but minimally affected by current therapies. Direct-acting antivirals under clinical investigation include entry inhibitors, core protein inhibitors, and RNA silencers. Immunotherapeutic approaches include TLR-7 and TLR-8 agonists, therapeutic vaccines, checkpoint inhibitors, RIG-I agonist, and anti-HBV antibodies. Results of preclinical and early clinical studies are promising; in the next few years, anticipated phase 2 and 3 data will establish which drugs or combinations may contribute to a functional cure. Above mentioned should be referred to.

R - We thank the reviewer for this positive and stimulating comment. The following sentence has been added to the “natural history of HBV infection in children” paragraph: “Another biomarker to monitoring HBV infection is the covalently closed circular DNA (ccc-DNA), a new biomarker related to viral replication and persistence of infection. A “complete cure” of HBV infection requires also the clearance of ccc-DNA, as well as HBsAg loss and undetectable serum HBV DNA (otherwise it is defined “functional cure”); in addition, a “New prospective antiviral treatment strategies” paragraph has been added before the indication for treatment (see page 10 of the tracked changes version).