Antivirals in HBV: Safety in Pregnancy & Lactation

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Challenges in pregnancy

- Unique challenge
- Effect on pregnancy outcomes
- Effect of pregnancy on viral replication
- Maternal to child transmission
- Antivirals are used:
  - If patient is already on antivirals having CLD
  - If DNA load is high to minimize chances of transmission
  - To prevent flares during post-partam period

Effect of pregnancy on virus

- Fetus has to tolerate the persistence of paternal alloantigen.
- An alloantigen-independent, systemic expansion of the maternal CD25+ T cell pool during pregnancy and this population contains dominant regulatory T cell activity
  - Suppressing autoimmune responses,
  - Maternal regulatory T cells suppressed an aggressive allogeneic response directed against the fetus
  - Their absence led to a failure of gestation due to immunological rejection of the fetus

Increase risk of viral replication due to transient immuno-suppressed state

Aluvihare VR et al. Nature immunology 2004

Effect of virus on pregnancy

- Chronic Hepatitis B has been shown to have a weak association with obstetric complications
  - Gestational diabetes
  - Antepartum haemorrhage
  - Preterm labour

Serum ALT & Hepatitis B DNA Flares in Pregnant and Postpartum Women with CHB

- The effects of pregnancy on CHB remain not well understood.
- Multicenter retrospective study United States during 1997–2015
  - 113 pregnancies in 101 CHB women who presented during pregnancy

Flares in HBV DNA and ALT can occur during late pregnancy and early postpartum in CHB women, and can be severe. Women with CHB should therefore be closely monitored during pregnancy and early postpartum

- Flares in ALT (99–2522 U/l) observed in
  - 6% (7/112) of women during pregnancy
  - 10% (5/51) of women within the first 3 months of delivery

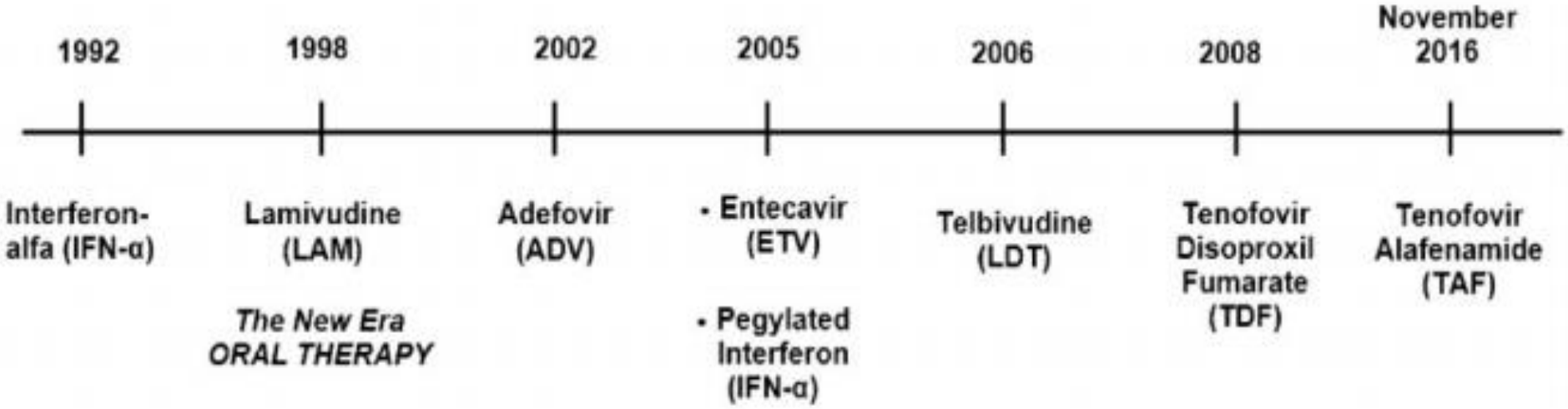
Chang C Y et al. American Journal of Gastroenterology 2016

Predictors for flares in HBV DNA or ALT during pregnancy or postpartum in high and low baseline HBV DNA women

	Univariate		Multivariate	
	OR (95%)	*P* value	aOR (95%)	*P* value
Age	1.06 (0.94–1.19)	0.36	1.09 (0.94–1.25)	0.24
HBeAg+	0.63 (0.18–2.20)	0.47	0.87 (0.09–8.21)	0.90
Baseline HBV DNA	0.91 (0.73–1.14)	0.42	0.92 (0.60–1.42)	0.72
Baseline ALT	1.01 (1.00–1.02)	0.13	1.01 (1.00–1.02)	0.19
Gravida	0.94 (0.65–1.36)	0.75		
Parity	0.77 (0.39–1.49)	0.43	0.58 (0.24–1.44)	0.24

Chang C Y et al. American Journal of Gastroenterology 2016

Antivirals for HBV



Drug	Category	Placental passage (new born: mother drug ratio)	Animal studies	Breast milk excretion
Lamivudine	C	Yes, 1.0	No tumors or anomalies	Yes
Entecavir	C	Unknown	Lung, pancreatic tumors in mice, skeletal malformations in rabbits	Yes (animal studies)
Interferon	C	Minimal due to large size	Abortifacient effect in monkeys	No(due to large size)
Tenofovir	B	Yes, 0.95-0.99	Osteomalacia when given at high doses	Yes
Adefovir	C	Unknown	Fetal malformations at high doses	Unknown
Telbivudine	B	Yes, rat studies	No significant adverse effects	Yes (animal studies)

Safety of Antiviral Agents in Pregnancy

- Therapeutic options: Oral nucleos(t)ide analogues and Peg-INF
- Most safety data are from HIV pts. where combination antiviral regimens are used
- Risk of teratogenicity: Limited human data available
- Available animal and human data have found no evidence of teratogenicity for TDF and telbivudine
- There are less safety data for TAF, Entecavir or Adefovir in pregnancy

Chen HL et al. Hepatology 2015; 62:375, Brown RS Jr et al. Hepatology 2016; 63:319.
Visvanathan K et al. Gut 2016; 65:340, Xu WM et al. J Viral Hepat 2009; 16:94.

Interferon

- Definitive duration
- Can be used only in planned pregnancies which can be delayed
- Teratogenic effects are well known

A systematic review of the fetal safety of interferon alpha, Reproductive toxicology, 2011

Efficacy and safety of telbivudine in highly viremic HBeAg+ pregnancy for the prevention of perinatal transmission

- N=229, telbivudine 600 mg/day from week 20 to 32 of gestation
  - HBeAg+HBV DNA levels>1.0×10(7) copies/ml mothers received (n=135)
  - untreated controls (n=94)
- All infants in both arms received HBIg and recombinant HBV vaccine
- Perinatal transmission rate- HBV DNA results of infants at week 28
  - 33% treated vs 0% controls had undetectable viremia (DNA<500 copies/ml) at delivery
  - Incidence of perinatal transmission (0% vs. 8%; p=0.002)
- No serious adverse events were noted in the telbivudine-treated mothers or their infants.

Han GR et al J Hepatol 2011 Dec;55(6):1215-21

Safety of Antiviral Agents in Pregnancy (contd….)

- **Birth defects-**
- **TDF:**
  - 2.3 % (85 of 3715) of infants born to mothers who took TDF during the first trimester
  - 2.2 % (36 of 1614) of infants born to mothers who took TDF during the 2nd & 3rd trimester
- **Lamivudine:**
  - 3% (154 of 5069) of infants born to mothers who took lamivudine during the 1st trimester
  - 2.9 % (211 of 7369) of infants born to mothers who took lamivudine during the 2nd & 3rd trimesters

Pan CQ Presented at the AASLD Liver Meeting 2015. San Francisco, 2015.
Hoyert DL et al. Pediatrics 2006; 117:168.

Safety of Antiviral Agents in Pregnancy (contd….)

- Registry data on HBV-monoinfected patients, Through July 2018,
  - 837 HBV-monoinfected pregnancies
  - Eleven birth defect among 785 live births.
  - no pattern among types of birth defects

NC: Registry Coordinating Center; 2017.

- There are important limitations to these observations.
  - Registry depends upon voluntary reporting
  - Information is not verified
  - Long-term follow-up is limited
  - There are no efforts to confirm the diagnosis of birth defects.
  - there are no data on miscarriages or subsequent developmental delays
  - Much of the clinical data have been on Lamivudine and TDF because these drugs are also used for treatment of HIV infection.

Safety of Antiviral Agents in Pregnancy (contd….)

- **Other potential adverse events**:
  - Mitochondrial damage
  - Lactic acidosis
  - Acute fatty liver
  - Possibly bone abnormalities

- **Symptomatic lactic acidosis:**
  - Reported in infants born to HIV-infected mothers who exposed to nucleoside reverse transcriptase inhibitor (NRTI) **drug** class in utero
  - not reported in infants exposed to HBV antiviral agents in utero
  - Monitoring for lactic acidosis in the infant is not necessary if the mother received HBV antiviral agents only

Safety of Antiviral Agents in Pregnancy (contd….)

- **Bone abnormalities:**
  - TDF is associated with decreased bone mineral density
  - the effect of maternal TDF on fetal growth and development- no adverse impact seen

Gill US et al. Gut 2011; 60:A230., Gibb DM et al. PLoS Med 2012; 9:e1001217.
Wang L et al. Clin Infect Dis 2013; 57:1773, Salvadori N et al. Clin Infect Dis 2019; 69:144

  - RCT in pregnant HBV monoinfection received TDF or placebo from 28 weeks gestational age to 2 months postpartum, there was no effect on maternal or infant bone density 1 year after delivery in the 140 mothers and 137 infants who were evaluated

Salvadori N et al. Clin Infect Dis 2019; 69:144

  - infants born to HIV-infected mothers who were exposed to TDF had a 12 % lower bone mineral content in the 1st month of life compared with those who had no Tenofovir exposure

Siberry GK et al. Clin Infect Dis 2015; 61:996

- TAF: may have less bone toxicity compared with TDF, but **not** used at this time during pregnancy due to lack of sufficient safety data

Lower Newborn Bone Mineral Content Associated with Maternal Use of Tenofovir Disoproxil Fumarate during Pregnancy

- Singleton infants of women with HIV, who took tenofovir in late pregnancy or no tenofovir during pregnancy were enrolled during late pregnancy or within 72 hours of birth.
- Excluded:
  - Infants born before 36 weeks gestation or
  - with confirmed HIV infection
- Whole-body BMC was measured in the first month of life
- 74 tenofovir-exposed and 69 tenofovir-unexposed infants
- Tenofovir-exposed newborns did not differ from unexposed newborns on
  - mean gestational age (38.2 vs 38.1 weeks)
  - mean length (-0.41 vs-0.18)
  - weight (-0.71 vs-0.48) Z-scores
- The mean BMC of tenofovir-exposed infants was 12% lower than for unexposed infants (56.0 [11.8] vs 63.8 [16.6] g; P =. 002)

Siberry GK et al. Clinical Infectious Diseases 2015

Safety of Antiviral Agents in Pregnancy (contd….)

- **Effects on growth:**
  - Studies mainly in the HIV population have not revealed an effect of TDF on birth weight, although there are conflicting results regarding the effect on head circumference and growth (eg, length)

    Gibb D et al. PLoS Med 2012; 9:e1001217, Wang L et al. Clin Infect Dis 2013; 57:1773.

    Viganò A et al. Antivir Ther 2011; 16:1259, Siberry GK et al. AIDS 2012;26:1151.

  - 646 HIV-infected pregnant receiving TDF
    - no association between duration of in utero Tenofovir exposure and fetal long bone growth by using ultrasound

    Jao J et al. Clin Infect Dis 2016; 62:1604

- **Pregnancy loss:**
  - Interferon has abortifacient effects in rhesus monkeys

    Kenilworth, NJ. Schering Corporation; 1994

  - There are no such reports in humans; data are limited
    - all women receiving interferon therapy must use birth control
    - interferon must be stopped if women become pregnant.

    Trotter JF et al. J Clin Gastroenterol 2001; 32:76.

Safety of Antiviral Agents in Pregnancy (contd….)

- **Other agents:**
  - Entecavir, only 80 infants were reported to be exposed during the first trimester and only two during the 2nd & 3rd trimester, with only two birth defects reported in the 1st trimester group
  - Adefovir, only 82 infants were reported to be exposed in the 1st trimester and only four during the 2nd trimester, with no reports of birth defects
  - TAF, 110 infants were exposed to TAF in the first trimester and 50 in the second trimester, with three birth defects noted in the first trimester
  - Telbivudine: there were a total of 267 exposures to Telbivudine and three reports of birth defects; in addition, Telbivudine had been studied and reported to be safe in several clinical trials

Pan CQ Presented at the AASLD Liver Meeting 2015. San Francisco, 2015.
Hoyert DL et al. Pediatrics 2006; 117:168.
Han GR el al. J Hepatol 2011; 55:1215.
Pan CQ et al. Clin Gastroenterol Hepatol 2012; 10:520.

Maternal antiviral therapy to prevent transmission (contd……)

- Lamivudine, telbivudine
  - reduce mother-to-child transmission
  - appear to be safe during pregnancy
  - associated with high rates of antiviral resistance.
- Therapy can be stopped after delivery
  - Some prefer to continue treatment for 4 to 12 weeks after delivery, in part to reduce the risk of a flare postpartum
- 91 women (101 pregnancies) received antiviral therapy to prevent transmission,
  - extending antiviral therapy beyond delivery did not reduce the frequency of HBV flares
  - median of 48 weeks of follow-up
- Women should be monitored for a flare of their HBV disease by measuring the ALT level every 3 months for 6 months after therapy has been stopped

Chen HL et al. Hepatology 2015; 62:375, Han GR et a. J Hepatol 2011; 55:1215.
Pan CQ et al. Clin Gastroenterol Hepatol 2012; 10:520., **Visvanathan K e al. Gut 2016; 65:340, Nguyen V et al. APT 2014; 39:1225.**

Maternal antiviral therapy to prevent transmission (contd……)

- A meta-analysis of 26 studies, N= 3622 pregnant women,
  - found that antiviral therapy (in addition to passive and active immunization of the newborn) significantly reduced neonatal HBV transmission
  - no increased risk of adverse outcomes (eg, congenital malformations, prematurity, postpartum hemorrhage)
  - limited data on the safety of the antiviral agents in newborns
- RCT of 200 pregnant women from China
  - HBeAg(+) and HBV DNA >$2x10^5$ IU/mL received either TDF (300 mg) or placebo
  - Starting at 30-32 wks gestation and continuing 4 weeks postpartum
- At postpartum week 28, MTCT rate tenofovir-treated vs untreated women (5 vs 18%)
  - Rate of birth defects treated and untreated mothers (2.1 vs 1.1 %)
  - None of the mothers had severe flares or hepatic decompensation.
  - Newborns had significantly lower rates of HBsAg positivity at six months with tenofovir exposed (1.5 vs 10.7 %)

Chen HL et al. Hepatology 2015; 62:375.
Brown RS Jr et al. Hepatology 2016; 63:319.
Pan CQ et al. NEJM 2016; 374:2324.

Maternal antiviral therapy to prevent transmission (contd……)

- RCT, N=331 from Thailand- maternal TDF in pregnant women with chronic HBV and a median HBV viral load of 10^8 IU/mL
- TDF or placebo was given at week 28 and continued for 2 months postpartum
  - no difference in rates of transmission (0 vs 2%, not significant)
- Although TDF did not demonstrate a clear benefit in this trial, these findings do not alter approach to maternal antiviral therapy since the generalisability is limited

Jourdain G et a. NEJM 2018; 378:911
Hill HA et al. MMWR Morb Mortal Wkly Rep 2017; 66:1171

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Research Article
Viral Hepatitis

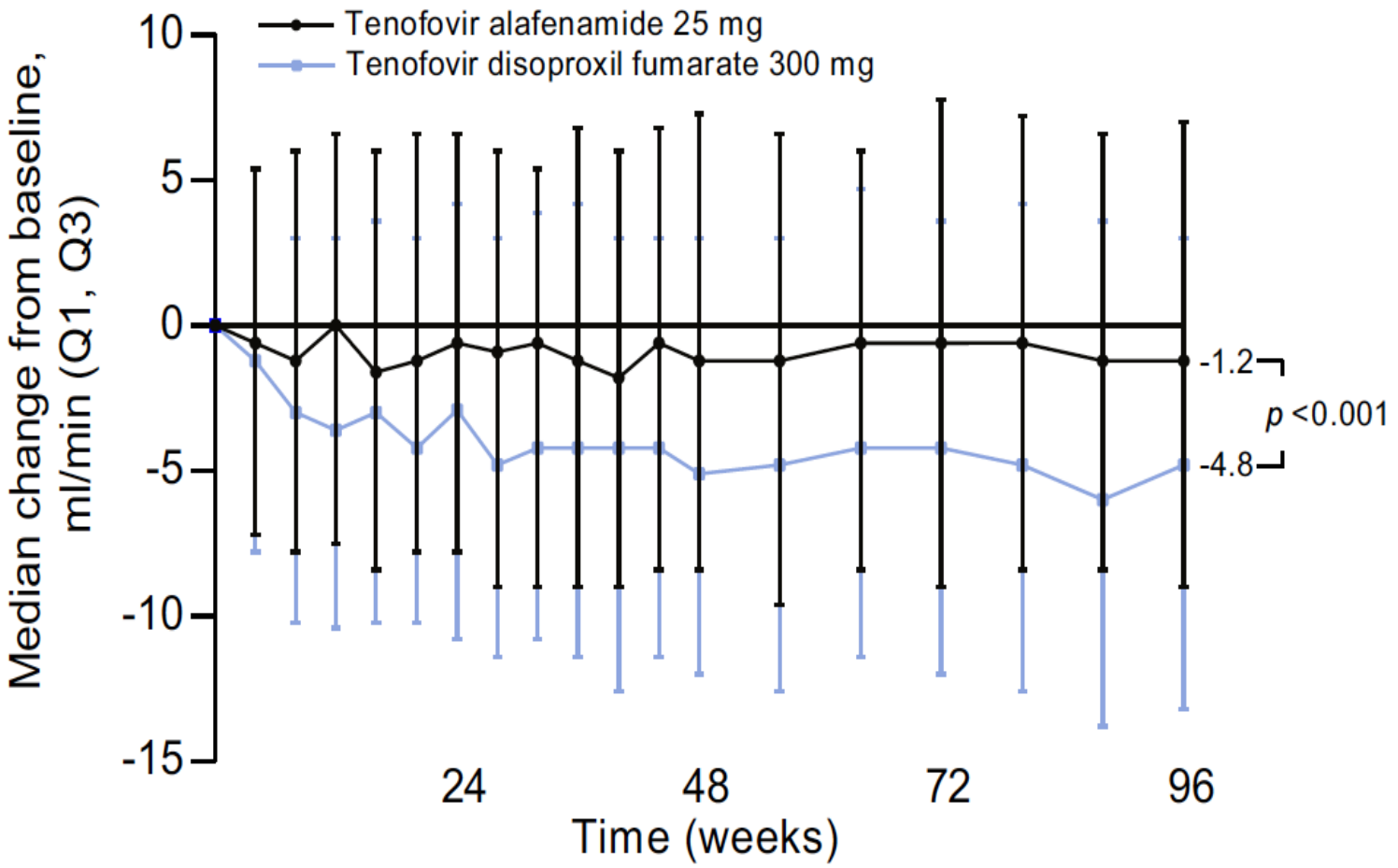
JOURNAL
OF HEPATOLOGY

96 weeks treatment of tenofovir alafenamide *vs.* tenofovir disoproxil fumarate for hepatitis B virus infection

Kosh Agarwal[1,*], Maurizia Brunetto[2], Wai Kay Seto[3], Young-Suk Lim[4], Scott Fung[5], Patrick Marcellin[6], Sang Hoon Ahn[7], Namiki Izumi[8], Wan-Long Chuang[9], Ho Bae[10], Manoj Sharma[11], Harry L.A. Janssen[12,13], Calvin Q. Pan[14], Mustafa Kemal Çelen[15], Norihiro Furusyo[16], Dr. Shalimar[17], Ki Tae Yoon[18], Huy Trinh[19], John F. Flaherty[20], Anuj Gaggar[20], Audrey H. Lau[20], Andrea L. Cathcart[20], Lanjia Lin[20], Neeru Bhardwaj[20], Vithika Suri[20], G. Mani Subramanian[20], Edward J. Gane[21], Maria Buti[22], Henry L.Y. Chan[23,*], and the GS-US-320-0108 Investigators

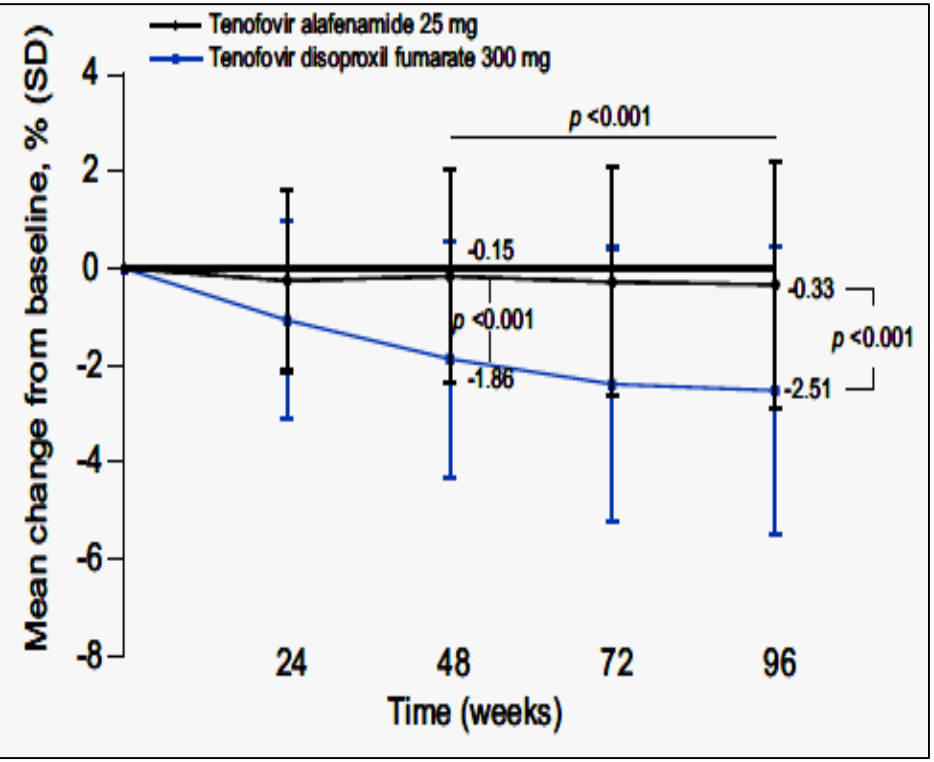
- TAF is a new prodrug of tenofovir developed to treat patients with chronic hepatitis B virus (HBV) infection at a lower dose than TDF)through more efficient delivery of tenofovir to hepatocytes.
- In 48-week results from two ongoing, double-blind, randomized phase III trials, TAF was non-inferior to TDF in efficacy with improved renal and bone safety. We report 96-week outcomes for both trials.
- In two international trials, patients with chronic HBV infection were randomized 2:1 to receive 25 mg TAF or 300 mg TDF in a double-blinded fashion. One study enrolled HBeAg-positive patients and the other HBeAg-negative patients. Efficacy was assessed in each study and safety in the pooled population.
- In patients with HBV infection, TAF remained as effective as TDF, with continued improved renal and bone safety, two years after the initiation of treatment
- In both studies the proportions of patients with alanine aminotransferase above the upper limit of normal at baseline, who had normal alanine aminotransferase at week 96 of treatment, were significantly higher in patients receiving TAF than in those receiving TDF. In the pooled safety population, patients receiving TAF had significantly smaller decreases in bone mineral density than those receiving TDF in the hip (mean % change -0.33% vs. -2.51%; $p < 0.001$) and lumbar spine (mean % change -0.75% vs. -2.57%; $p < 0.001$), as well as a significantly smaller median change in estimated glomerular filtration rate by Cockcroft-Gault method (-1.2 vs. -4.8 mg/dl; $p < 0.001$).

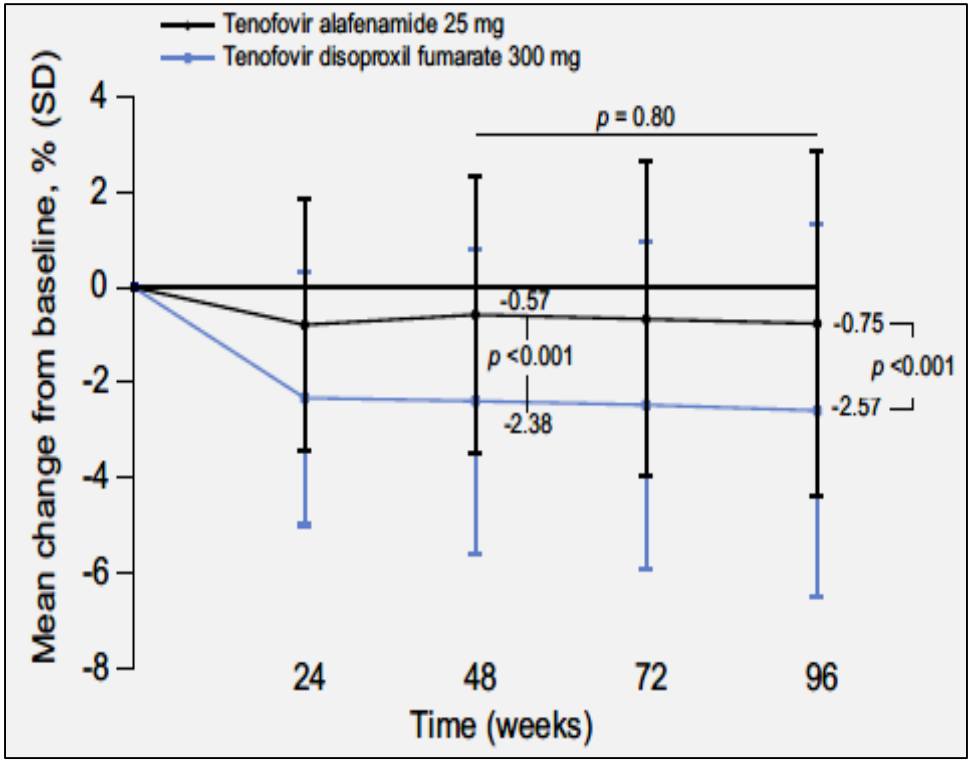
Tenofovir alafenamide



Median change from baseline in eGFR over 96 weeks
TAF 25 mg (n=866) vs. TDF 300 mg (n=432)

Agarwal K, et al. J Hepatol 2018;68:672–81





Median change from baseline in BMD over 96 weeks
TAF 25 mg (n=866) vs. TDF 300 mg (n=432)

- Due to the above adverse effects TAF maybe a better alterative to TDF
- However data on its safety and efficacy in pregnancy is still not available

Agarwal K, et al. J Hepatol 2018;68:672–81

Breastfeeding

- Infants after 1st dose of immunization can be breastfed
- Feeding mothers should exercise care to prevent bleeding from cracked nipples
- Carrier mothers should not participate in donating breast milk
- Discussions of breastfeeding and HBV transmission and newborn immunization are found below
- For women with chronic HBV who continue antiviral treatment after delivery, the safety data on the use of HBV antiviral therapy during breastfeeding is unclear.
- Thus, the benefits of breastfeeding, and the availability of alternatives to breastfeeding, should be discussed with women who require postpartum antiviral therapy. The decision to breastfeed should be based upon patient preference
- Drug labels have typically recommended that nucleos(t)ide analogues be avoided
- However only low levels of tenofovir are detected among women receiving TDF, and these are unlikely to have any biologic effects on the nursing infant.
- As an example, one study found that the median breastmilk dose from mothers receiving TDF represented 0.03 % of the proposed oral infant dose, and simulated neonatal plasma concentrations were extremely low

Hepatitis B Management in the Pregnant Patient: An Update, J. Clin Trans. Hepatology, 2016
Concentrations of tenofovir and emtricitabine in breast milk of HIV-1-infected women in Abidjan,2011
EASL & AASLD guidelines

Maternal antiviral therapy to prevent transmission

- Treatment is started at the beginning of the third trimester
- Check HBV DNA level 4 weeks after starting therapy.
  - almost always have a drop by at least 2 to 3 log in their HBV DNA level
  - If no drop, we assess for potential barriers to adherence
- TDF is preferred
  - as resistance is rare
  - is safe during pregnancy

Chen HL et al. Hepatology 2015; 62:375
Brown RS Jr et al. Hepatology 2016; 63:319
Pan CQ, et al. NEJM 2016; 374:2324

Current recommendations

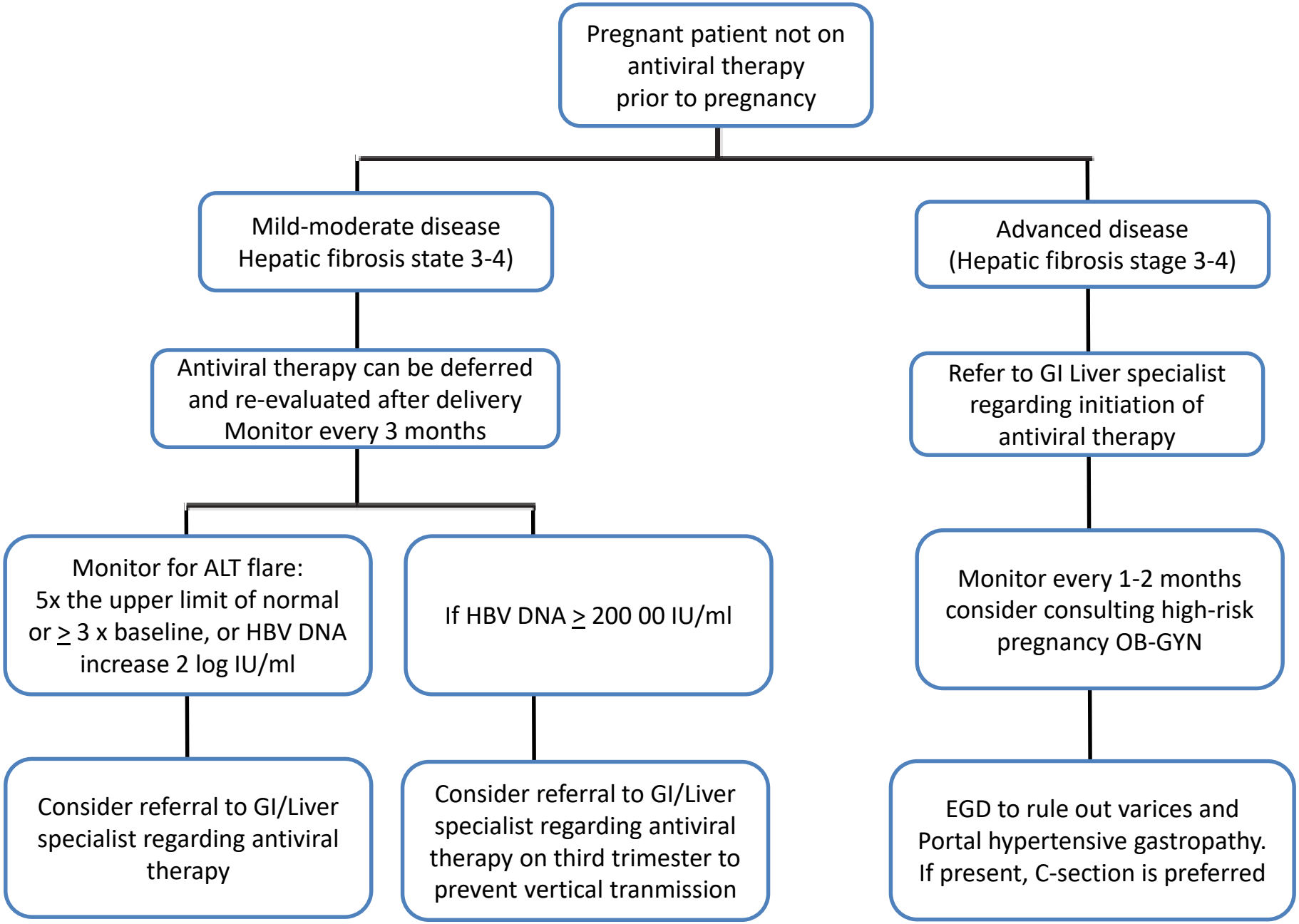
Recommendations		
Screening for HBsAg in the first trimester is strongly recommended	I	1
In women of childbearing age without advanced fibrosis planning a pregnancy in the near future, it may be prudent to delay therapy until the child is born	II-2	2
In pregnant women with chronic hepatitis B and advanced fibrosis or cirrhosis, therapy with TDF is recommended	II-2	1
In pregnant women already on NA therapy, TDF should be continued while ETV or other NA should be switched to TDF	II-2	1
In all pregnant women with HBV DNA >200,000 IU/ml or HBsAg >4 $\log_{10}$ IU/ml, antiviral prophylaxis with TDF should start at Week 24–28 of gestation and continue for up to 12 weeks after delivery	I	1
Breast feeding is not contraindicated in HBsAg-positive untreated women or those on TDF-based treatment or prophylaxis	III	2

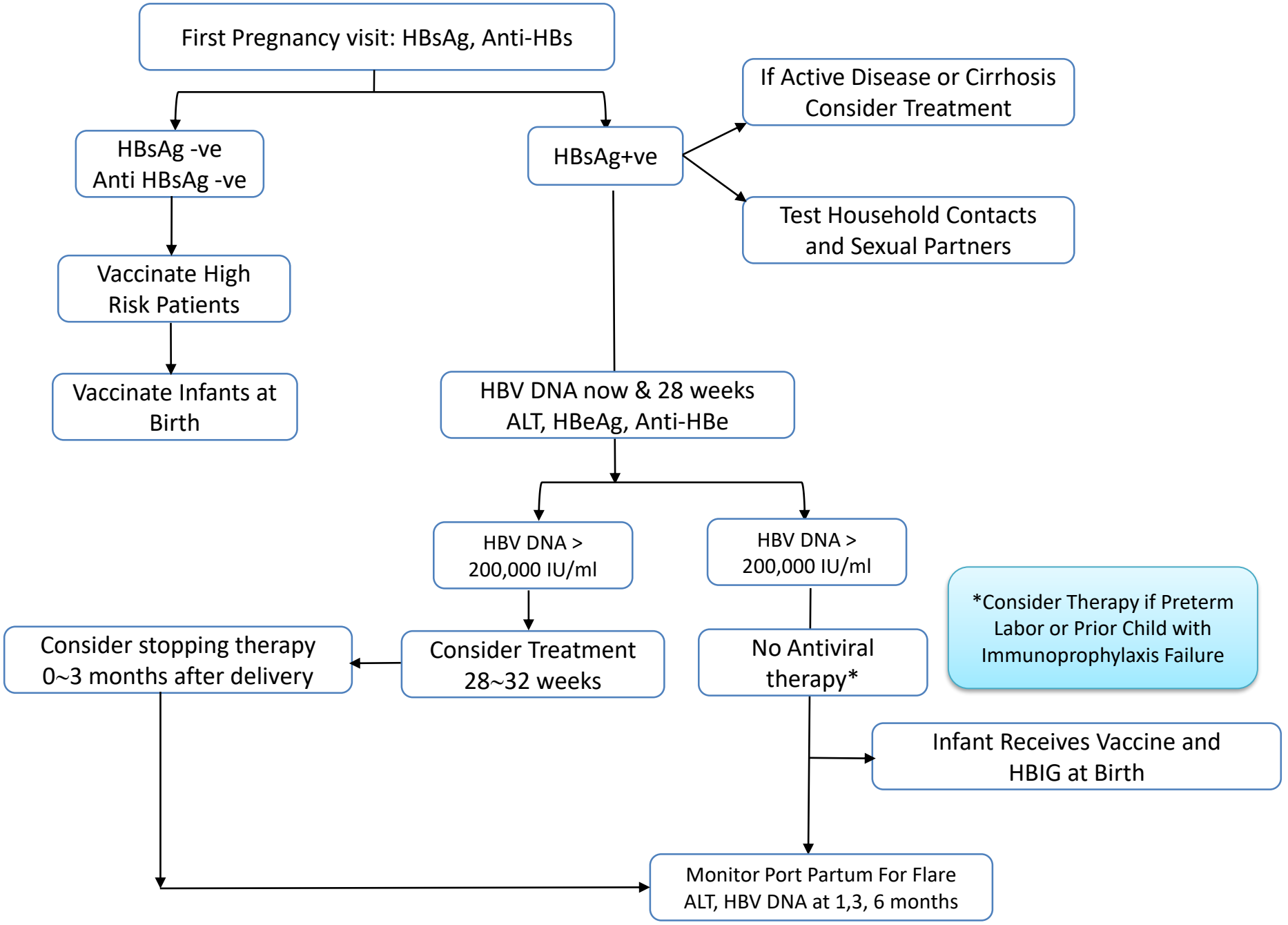
EASL recommendations

Summary

- INF should be avoided because of concerns of pregnancy loss
- Prior to the approval of TAF, entecavir and TDF were front-line therapy for CHB
- Entecavir, is contraindicated in pregnancy use due to its significant carcinogenic potential in animal studies
- There are sufficient safety reports on the safety of TDF use during pregnancy
- TDF is increasingly recommended due to its lowest risk of viral resistance
- There is no increased incidence of congenital anomalies associated with TDF
- TDF, has been associated with loss of bone mineral density
- The clinical consequences of these results are unknown and further research is necessary to determine the long-term growth and bone health of these infants
- Given the improved safety of TAF on bone mineral density and renal function, it appears to be an attractive alternative treatment option for pregnant women
- Currently, there is no clinical recommendation on TAF use in pregnancy, though a clinical trial is ongoing to evaluate its efficacy and safety in this special HBV population
- No evidence of TAF-related impaired fertility or harm to the fetus in animal studies
- Ongoing and further studies on TAF will, hopefully, establish its safety profiles in both pregnant women and the newborns

Thank You


Pregnant patient not on antiviral therapy prior to pregnancy
Mild-moderate disease Hepatic fibrosis state 3-4)
Advanced disease (Hepatic fibrosis stage 3-4)
Antiviral therapy can be deferred and re-evaluated after delivery Monitor every 3 months
Refer to GI Liver specialist regarding initiation of antiviral therapy
Monitor for ALT flare: 5x the upper limit of normal or ≥ 3 x baseline, or HBV DNA increase 2 log IU/ml
If HBV DNA ≥ 200 00 IU/ml
Monitor every 1-2 months consider consulting high-risk pregnancy OB-GYN
Consider referral to GI/Liver specialist regarding antiviral therapy
Consider referral to GI/Liver specialist regarding antiviral therapy on third trimester to prevent vertical tranmission
EGD to rule out varices and Portal hypertensive gastropathy. If present, C-section is preferred


First Pregnancy visit: HBsAg, Anti-HBs
HBsAg -ve
Anti HBsAg -ve
Vaccinate High Risk Patients
Vaccinate Infants at Birth
HBsAg+ve
If Active Disease or Cirrhosis Consider Treatment
Test Household Contacts and Sexual Partners
HBV DNA now & 28 weeks
ALT, HBeAg, Anti-HBe
HBV DNA > 200,000 IU/ml
HBV DNA > 200,000 IU/ml
Consider Treatment 28~32 weeks
Consider stopping therapy 0~3 months after delivery
No Antiviral therapy*
*Consider Therapy if Preterm Labor or Prior Child with Immunoprophylaxis Failure
Infant Receives Vaccine and HBIG at Birth
Monitor Port Partum For Flare
ALT, HBV DNA at 1,3, 6 months