

# **The Management of Hepatitis B During and After Pregnancy**

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# Potential Conflicts of Interest

- Consultant to Dynavax Technologies

# Today's Mission

- **Chronic hepatitis B**  
Natural history and treatment
- **Mother to child transmission**  
Global health perspective, mechanisms involved
- **Antiviral therapy to further prevent MTCT**  
Selection, safety, efficacy, management implications
- **Breast feeding and anti-HBV therapy**  
Safety, practice management

# Hepatitis B

- 2 billion people in the world have been exposed
- 250 million people have chronic infection
  - ~2 million people in the USA
- Leading cause of primary liver cancer in the world
- Accounts for 600,000 deaths each year (half cancer, half liver failure-related)

# Nomenclature for Today

## HBsAg

Viral envelope protein; signifies ongoing infection

## HBV DNA

Viral genome which is quantifiable in serum

## HBeAg

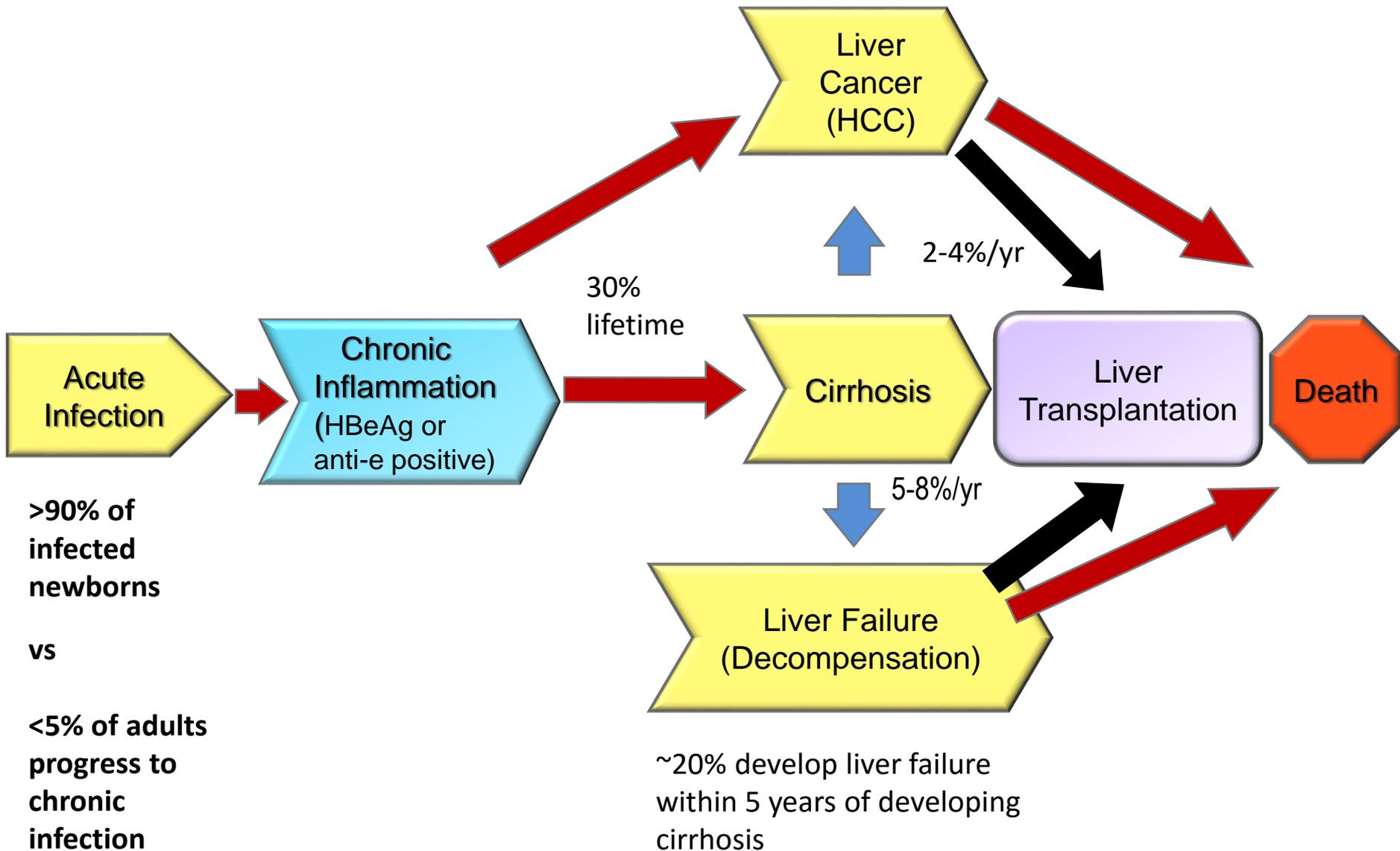
Viral protein associated with high viral replication  
(up to  $10^{5-11}$  copies; *copies divided by 5 = IU*)

## Anti-HBe

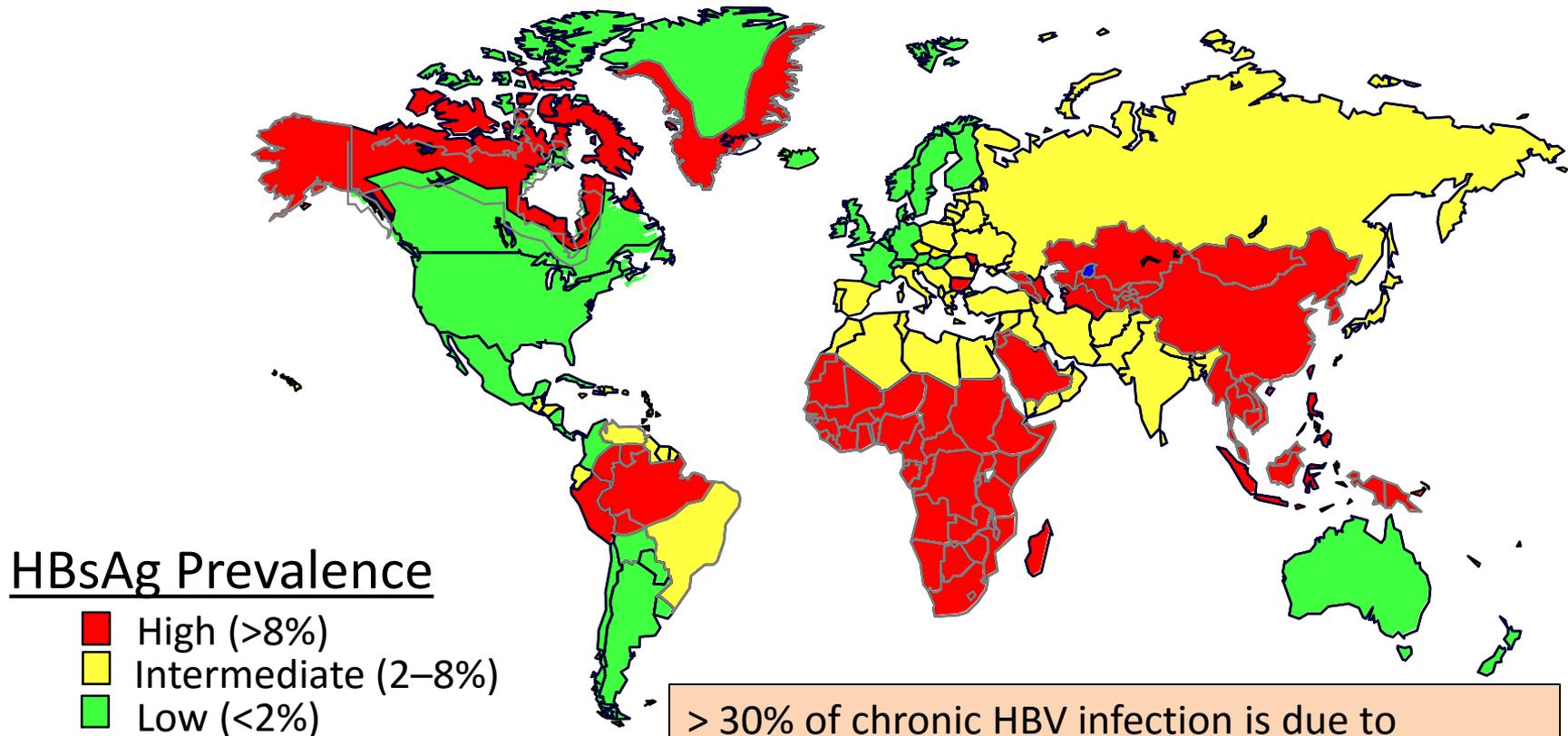
Appears after loss of HBeAg

Associated with non detectable or lower level of HBV DNA  
( $10^{4-8}$  copies) than HBeAg positive status

# Hepatitis B Disease Progression



# World Wide Prevalence of Chronic HBV Infection



> 30% of chronic HBV infection is due to exposure at birth  
60% of CHB in USA occurs in individuals born in intermediate or high risk regions

# Maternal Transmission

- Transplacental (intrauterine)
  - No more than 5-10% of cases
    - Placental invasion by HBV or trafficking of infected PBMCs; HBV infection of spermatozoa or oocyte; amniocentesis-related
- Natal transmission (*perinatal*, intrapartum)
  - Accounts for majority of cases in world [risk increases with premature rupture of membranes]
- Post natal (breast feeding)
  - Reported to be rare

# Efficacy of Immunoprophylaxis

- Maternal status HBeAg positive:
  - 90% of newborns infected
  - 90% of infected become chronically infected
- Maternal status HBeAg negative:
  - 5-15% of newborns infected
- Vaccine alone 85-90% efficacy; vaccine + HBIG: >90%

# Immunoprophylaxis Failure By Predelivery HBV DNA in 869 Infant-Mother Pairs

Predelivery HBV DNA (copies/mL)	Failure (%)
$<10^6$ *	0
$10^{6-6.99}$	3.2
$10^{7-7.99}$	6.7
$\geq 10^8$	7.6

\* 1 million copies equivalent to 200,000 IU

# Is Universal Prevention of MTCT Really Possible?

- Many developing countries have not implemented effective programs
- 95% of new USA cases of chronic HBV infection are “imported” [Mitchell et al PLoS ONE 2011; 6:E277717]
  - Major disparities in access to health care
  - Estimated 65% of cases unaware
- 1,000 neonates infected annually in USA [IOM Report, 2010]
- Failure to deliver birth dose or complete series occurs even in developed nations

# Hepatitis B: Current Treatments in Adults

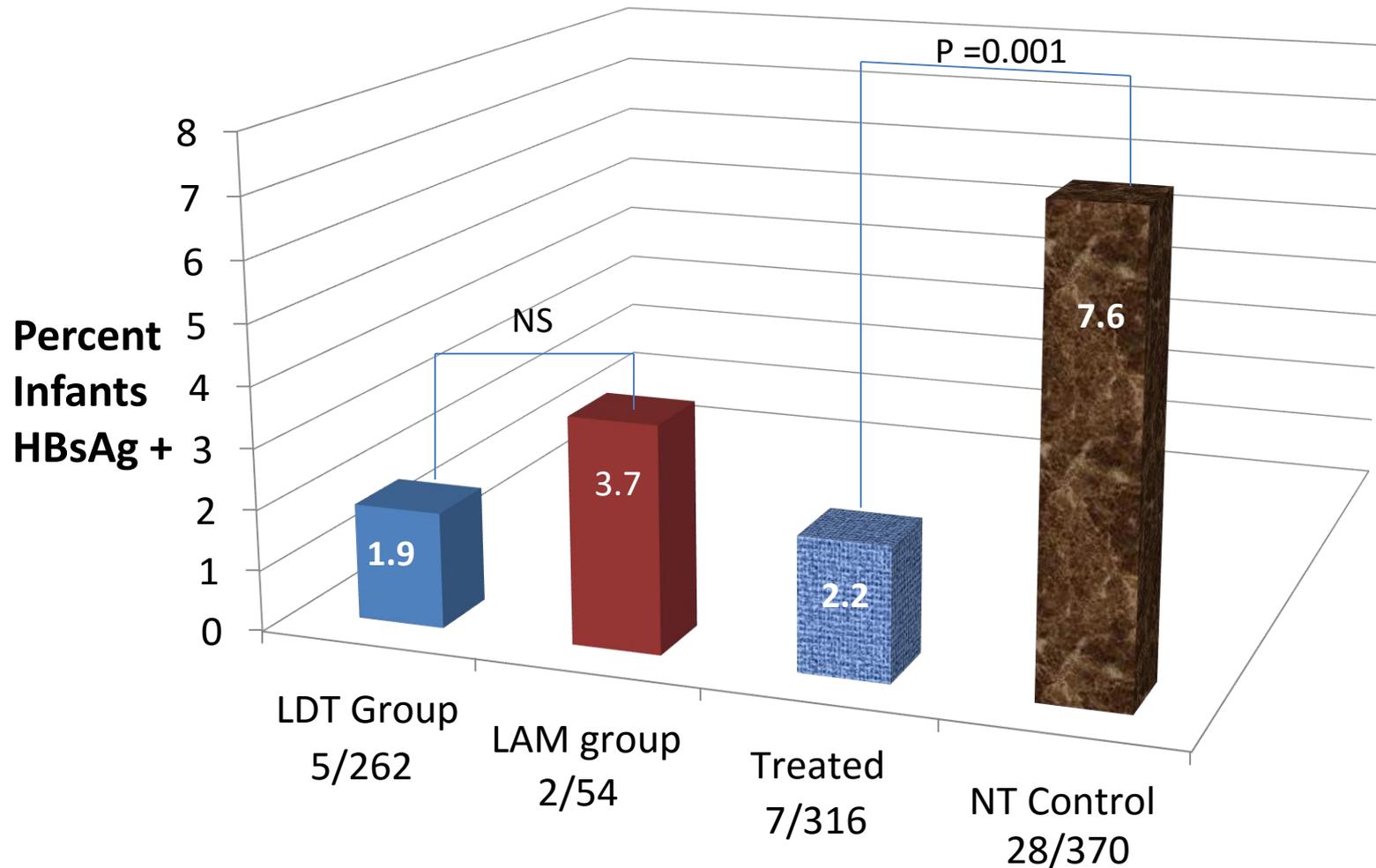
- Interferon alfa
- Lamivudine
- Adefovir
- Entecavir
- Telbivudine
- Tenofovir
  - Tenofovir alafenamide (safer, likely to be approved late 2016)
- Emtricitabine-tenofovir (for HIV coinfecting, off label for HBV mono-infection)

# Oral Anti-HBV Agents and Pregnancy\*

	Year of FDA Approval	COMMENTS
Peg IFN alfa 2a	1992	Contraindicated during pregnancy [Category C with package warning]
Lamivudine (LVD)	1998	High rate of resistance. Category C for pregnancy
Adefovir	2002	Weak antiviral; no longer first line in US
Entecavir	2005	Resistance in < 2% of patients at 8 years. No data during pregnancy. Category C
Telbivudine	2006	Moderate rate of resistance; cross resistance with LVD. <b>Category B</b>
Tenofovir (TDF)	2008	No resistance at 8 yrs. Fanconi syndrome and bone demineralization. <b>Category B</b>

\* None FDA approved during pregnancy

# MTCT Rates in 686 Mother Infant Pairs



# Telbivudine Safety During Pregnancy

(Piravisuth et al, *World J Hepatol* 2016 8:452-60)

- 1793 pregnancy outcomes (pooled data from clin. trials, used in combination with immunoprophylaxis)
- Prevalence of life birth defects (3.6/1000) no different with non antiviral maternal controls (3.0/1000)\*
- Prevalence of spontaneous abortion (4.2/1000) no different from overall prevalence 16/1000\*
- MTCT rate significantly lower (0.70% vs 11.9% non treated controls,  $p < 0.0001$ )

\* Compared to data from APR: [www.APRegistry.com](http://www.APRegistry.com), through Jan, 2015)

# Tenofovir Safety From Exposure Throughout Pregnancy

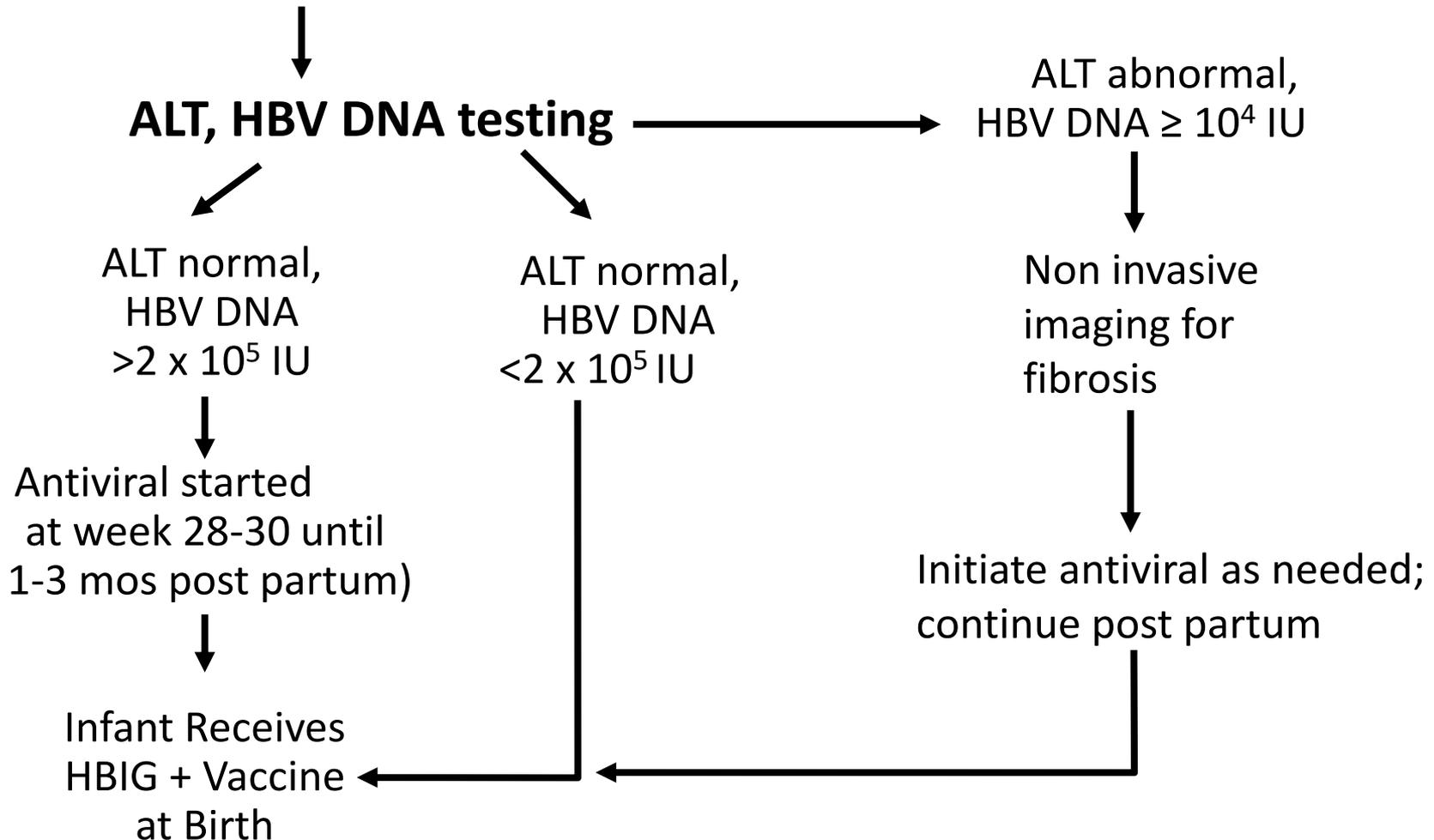
- Long term safety data incomplete
- USPHACS cohort (426 children) reports no impairment of fetal growth but possible delayed growth at 1 year [Siberry et al, *AIDS* 2012, 26:2119-20]
- Five studies with exposure throughout pregnancy show normal growth at birth and 12 months of age [Wang et al *HIV/AIDS* 2013; 1773-80 ]

# Liver Society Guidelines for Antiviral Therapy During Pregnancy

Organization	When to treat	Which Agent to Use
AASLD (American)	Maternal HBV DNA level >200,000 IU (1 million copies)	Lamivudine, telbivudine, or tenofovir with preference for tenofovir Breastfeeding not contraindicated
APASL (Asian)	HBV DNA level >6 log IU (5 million copies)	Tenofovir or telbivudine Breastfeeding discouraged with antiviral
EASL (European)	HBV DNA level > 6 log IU	Lamivudine, telbivudine, or tenofovir Breast feeding may not be considered a contraindication

# A Hepatologist's View of Hepatitis B Management During Pregnancy

**HBsAg Positive**



# Hepatitis Flares After Completion of Pregnancy

- Described in HBeAg positive and HBeAg negative HBsAg positive women:
  - Recovery of cellular immunity post partum in HBV DNA positive untreated mothers ([setting 1](#), uncommon)
  - *Rapid resurgence* of HBV replication after treatment withdrawal with *immune rebound* ([setting 2](#), more common, ~ 10-20 %)
- Requires follow up of mothers for at least 3 months (ALT surveillance with reflex HBV DNA testing)

# Important Elements of Care

- Additional blood testing for HBV DNA needed to identify HBsAg-positive women with high viral level replication
- Maternal education about prevention should always be done and may prove vital in cultural acceptance of drug therapy
- Mothers treated in the last trimester have need for follow up after treatment withdrawal

# Consultation Assistance

- Care of the pregnant HBsAg positive mother often facilitated by consultation with hepatologist or other health care provider skillful in the management of hepatitis B

# Breast Feeding and Antiviral Therapy

- Breast feeding is acceptable for untreated HBsAg carriers but not when undergoing antiviral therapy
  - Small quantities of antiviral found in breast milk (2-4% of maternal plasma level)
  - Far more drug exposure to baby across the placenta
  - Parent drug >>active metabolite
  - Some risk that sudden withdrawal of antiviral therapy in highly replicative mothers can promote hepatitis flares
- Safety shown in newborns of HIV positive mothers treated with lamivudine or tenofovir *throughout* pregnancy ([www.APRegistry.com](http://www.APRegistry.com) )

# Licensed Antivirals in the Pediatric Population

- Interferon alpha-2b (1 yr or older)
- Lamivudine (2 yrs or older)
- Entecavir (2 yrs or older)
- Adefovir\* and tenofovir\*\* (12 yrs or older)
- Telbivudine (16 yrs or older)

\* Shown to be no more effective than placebo in 2-11 yr olds

\*\* Associated with rare renal dysfunction in adults and dec. bone mineral density in HIV infected children

# Summary/Perspective

- MTCT occurs in 3-8% of properly immunized newborns
- Most of these cases can be prevented if highly viremic mothers are treated with antiviral Rx during the 3rd trimester
  - Conservative (high viremia is > 200,000 IU = 1 million copies)
  - More practical (high viremia is > 1 million IU = 5 million copies)
- Oral antivirals are safe for the mother and child during pregnancy
- Hepatologists abruptly terminate treatment at birth if mother is breast feeding. There are reasons to question this as a routine or standard of care measure.