CME on Liver Disease in Pregnancy: 27.7.19

Happy World Hepatitis Day

HBsAg Positive Pregnant Woman:
Hepatologists View Point

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A Deemed Liver University

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Conflict of Interest and Disclosures

NONE

ILBS : Residents

9th Rank in all Medical Universities,
2nd Rank in Teaching, Resource, Learning, next to AIIMS Delhi,

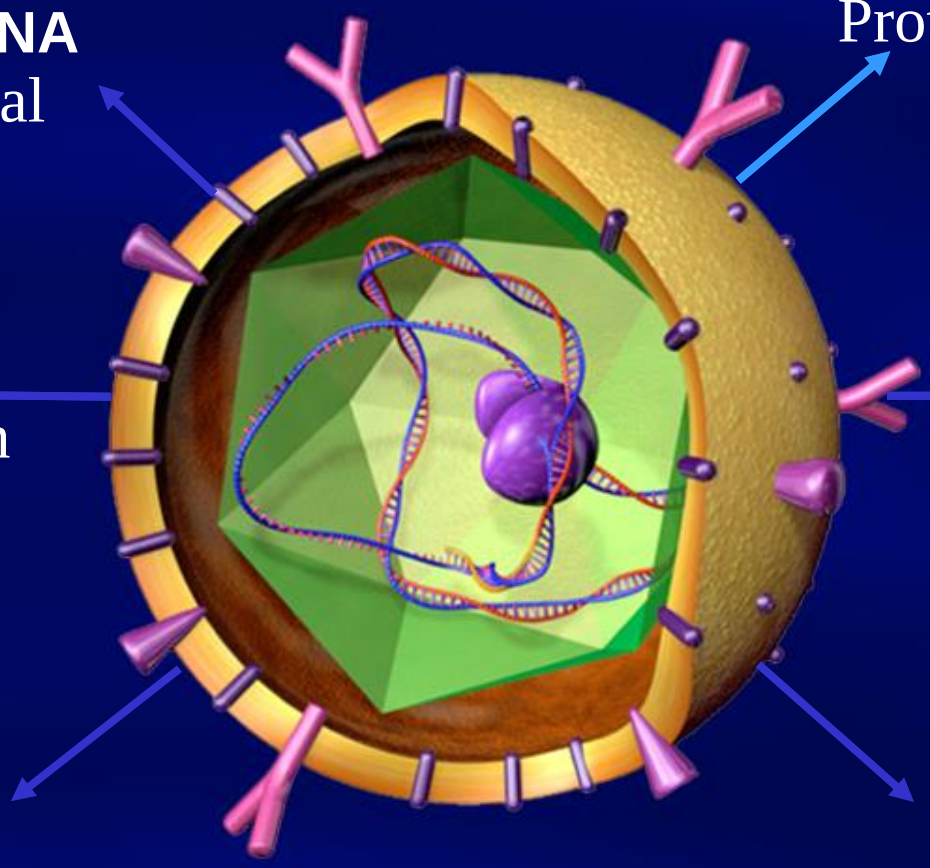
ILBS : Faculty

2018 = 109,000 patients, 30,000 Day care, 9,000 ER

HEPATITIS B VIRUS

Anti HBs
Protection (>10 IU/L)

HBV DNA
Genetic material



HBsAg
Marker of infection

Anti HBe
non-replication

HBeAg
Marker of replication

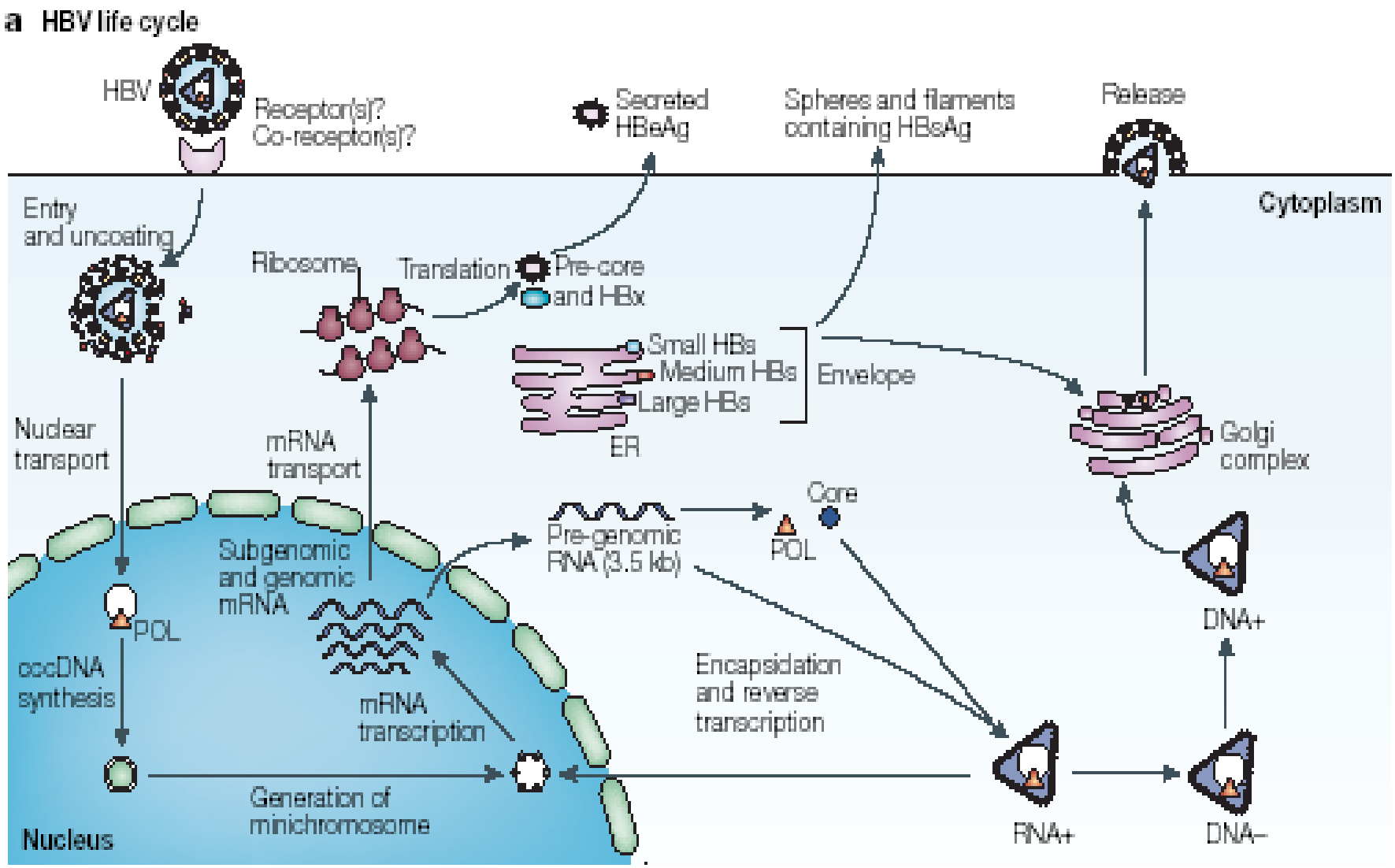
SGPT - Injury

Markers of HBV

▪ Infection	HBsAg, HBVDNA +
▪ Replication	HBeAg, HBV DNA +++ IgM anti HBc
▪ Exposure	Anti HBc IgG, Anti HBe Anti HBs
▪ Protection	Anti HBs

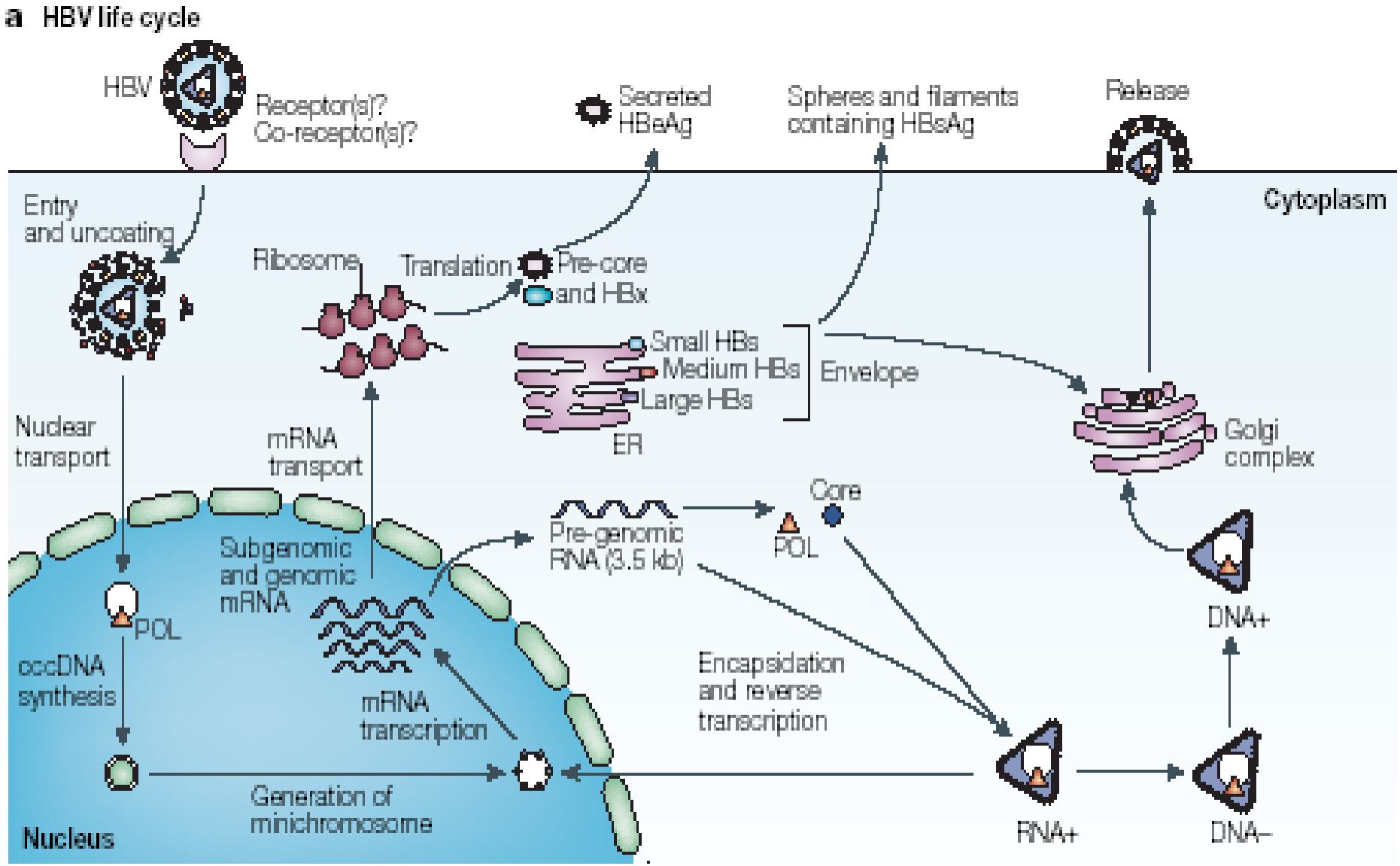
Liver Cell

Nature Reviews Immunol, 2005



Liver Cell

Nature Reviews Immunol, 2005



Once Chronic HBV infection : Always

Scenarios:
HBsAg Positive Pregnant Women

1. **Newly diagnosed HBV during pregnancy**

2. Known HBV+, become pregnant, on antiviral

3. Women Plans a family in future

24 Yr. Primipara,
First time detected HBsAg +ve

Characteristic	Value
HBeAg status	Positive
ALT	56 IU/ml
HBV DNA	4.5×10^6 IU/mL
US	No cirrhosis
Comorbidities	None

Issues

- Impact of HBV on Pregnancy
- Risk of MCT, Abortion !
- Antivirals !
  - Cut-off maternal HBV DNA?
  - Which trimester?
  - Which drug?
  - When to stop?
- Risk to fetus ?

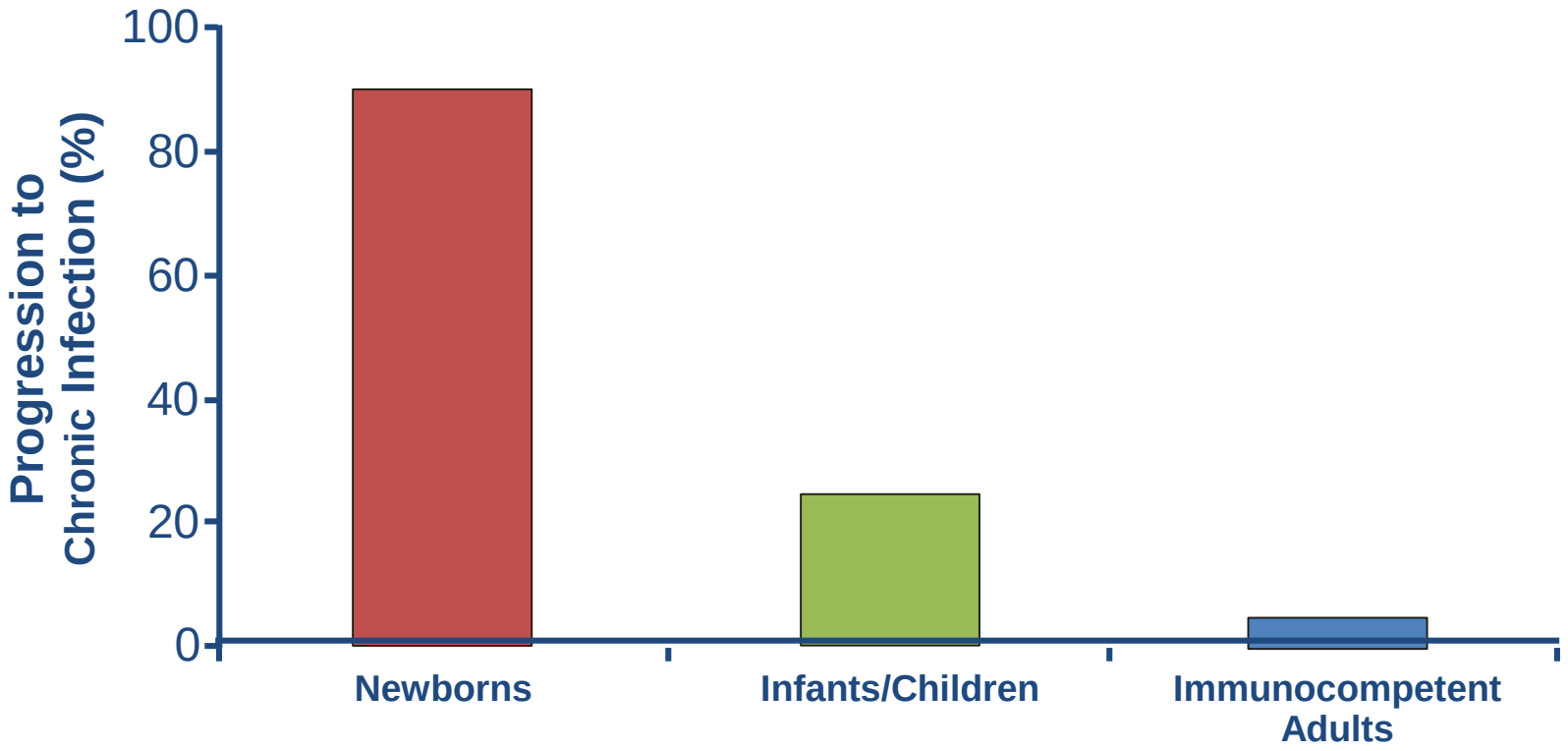
Impact of HBV on Pregnancy

Possible associations between chronic HBV

- Gestational DM *(Lao et al Hepatology 2007)*
- Prematurity *(Tse at al J Hep 2005)*
- Lower birth weight
- Antepartum hemorrhage *(Tse at al J Hep 2005)*

Risk of MCT
Why Is It So Important?

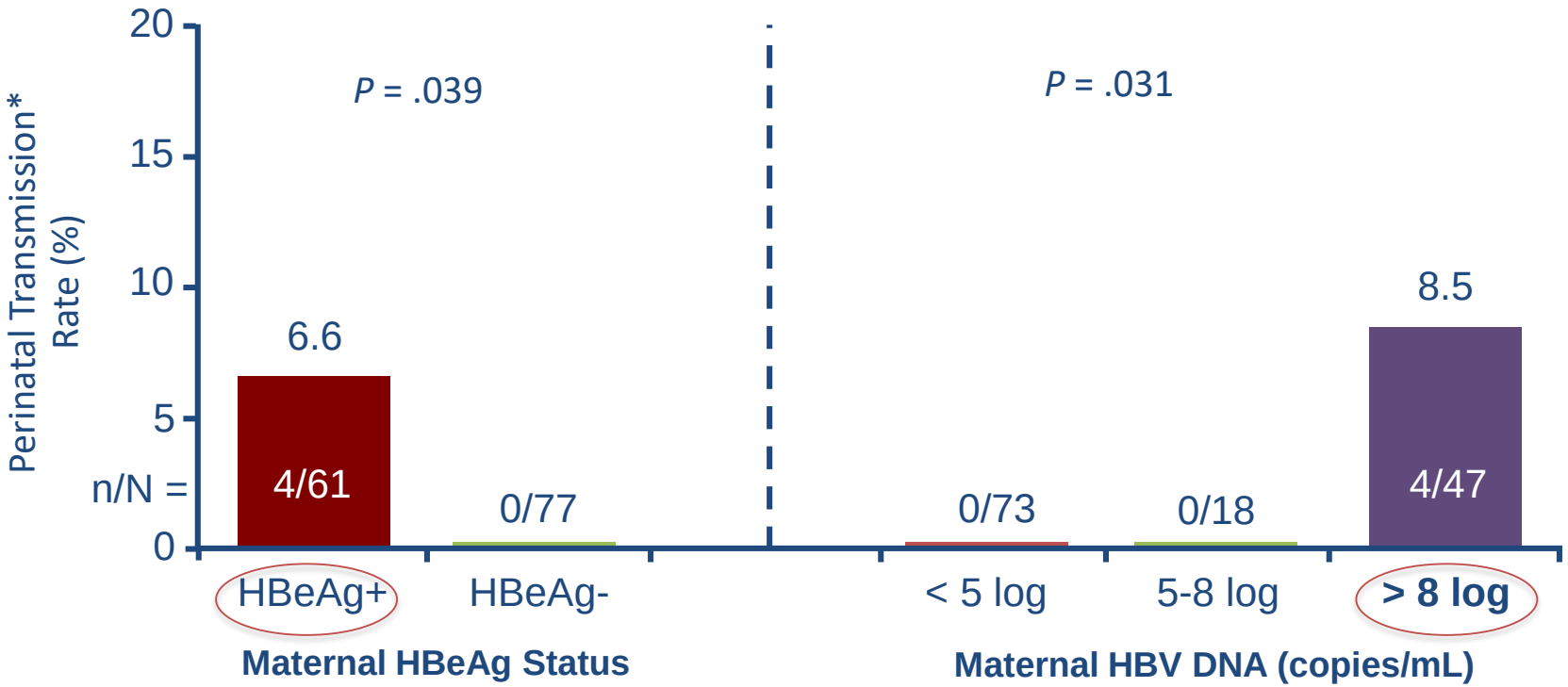
- Chronicity is inversely related to age at HBV infection



Lok AS, et al. Hepatology. 2009;50:661-662.

MCT related to Maternal HBV DNA Level

- Infants received HBIG + HBV vaccine within 12 hrs of birth and additional doses at 2, 4, and 6 mos



*Perinatal transmission = HBsAg positive at Mo 9.

Wiseman E, et al. Med J Aust. 2009;190:489-492.

Which nucleos(t)ide analogue?

- Safety to fetus, including exposure during first trimester
  - Tenofovir, Lamivudine,, telbivudine
- Risk of drug resistance
  - Lamivudine > telbivudine > tenofovir
- Preferred drug: tenofovir
  - Established safety; potent; low risk of drug resistance
- Benefit vs risk discussed with patient and spouse
  - Inform if become pregnant

Prevent MCT by Decreasing HBV DNA
Treat Mother with Antiviral : Which Drug!

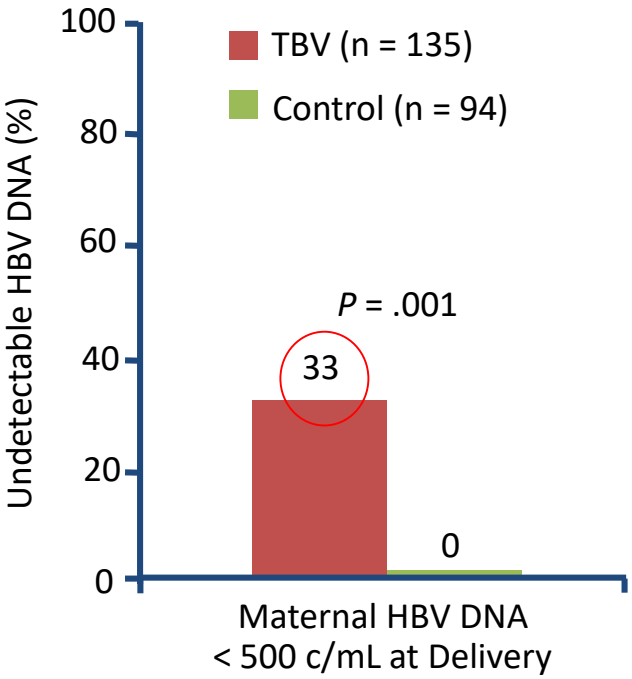
- FDA classification:
  - Pregnancy class B: Tenofovir DF, telbivudine
  - Pregnancy class C: Entecavir

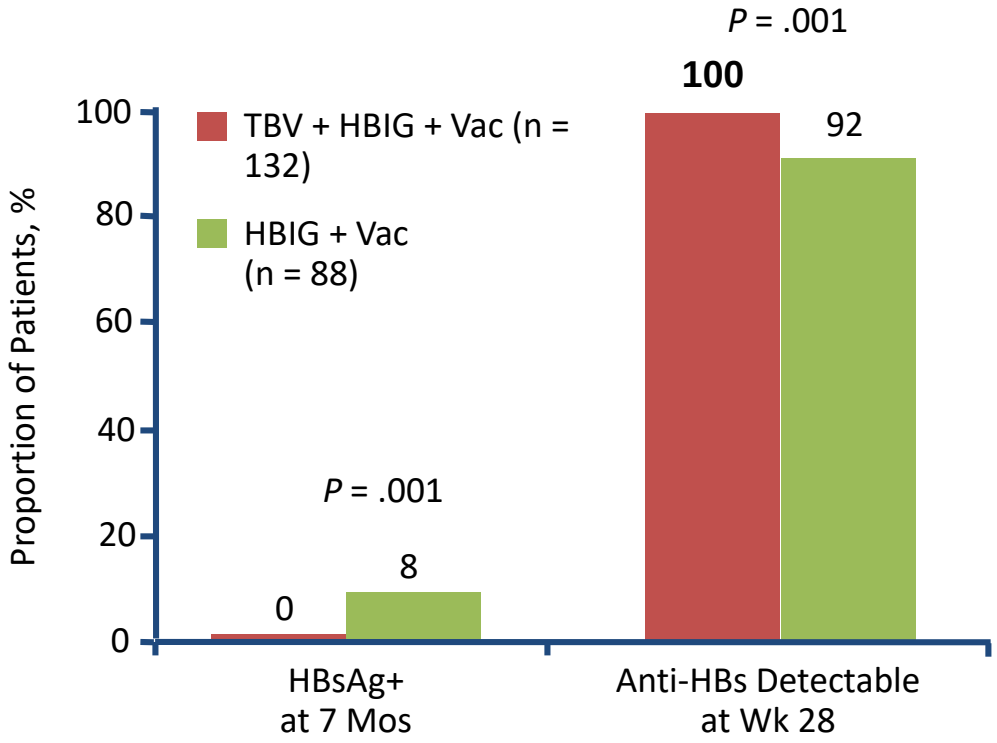
- Human data:
  - Antiretroviral pregnancy registry: safe Lam, Tenofovir, *including exposure in first trimester*[1]
  - Clinical studies: lamivudine, telbivudine, tenofovir mainly exposure in 3rd trimester[2-5]

1. *Antiretroviral Pregnancy Registry. December 2012. 2. Xu WM, et al. J Viral Hepat. 2009;16:94-103. 3. Shi Z, et al. Obstet Gynecol. 2010;116:147-159. 4. Han GR, et al. J Hepatology. 2011;55:1215-1221. 5. Pan CQ, et al. Clin Gastroenterol Hepatol. 2012;10:520-526*
2. *NEJM 2017*

Tenofovir: Starting Wk 20-32

- HBeAg-positive, HBV DNA > 10^7 copies/mL received TBV 600 mg/day beginning in **Wk 20-32**
  - Not randomized; controls chose not to receive treatment



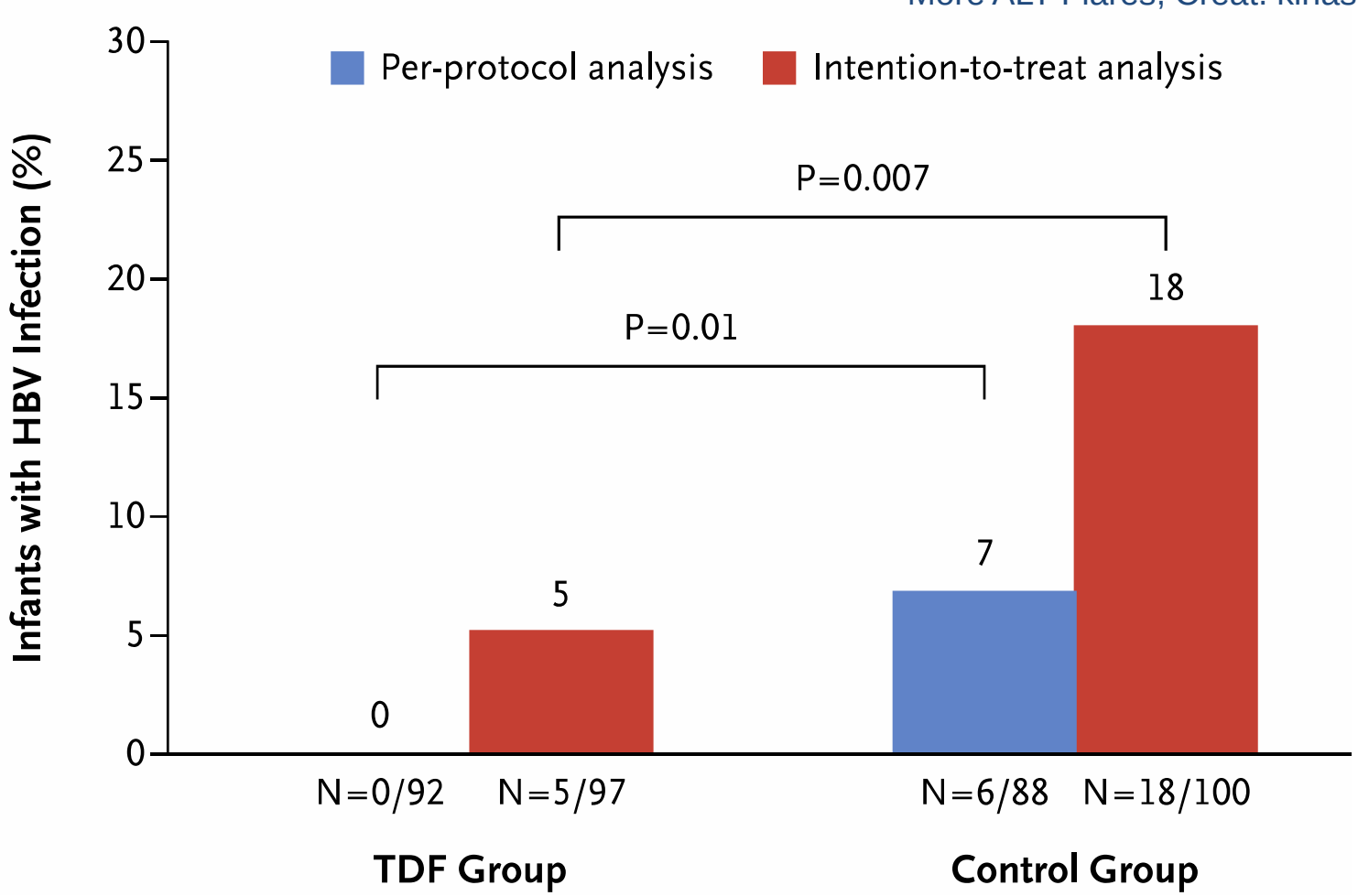


Han GR, et al. J Hepatol. 2011;55:1215-1221.

Tenofovir in MTCT

Pan et al NEJM 2016

Wk 30-32, HBV DNA >2.10 (5)
DNA < 4.7 log,
More ALT Flares, Creat. kinase



Incidence of Birth Defects With in Utero Exposure to HBV Nucleos(t)ide Analogues

- Antiretroviral Pregnancy Registry, 1/1989 - 7/2012[6]

Drug	First Trimester		Second or Third Trimester	
	Exposed, n	Birth Defects, % (95% CI)	Exposed, n	Birth Defects, % (95% CI)
Lamivudine	4185	3.2 (2.7-3.8)	6843	2.8 (2.4-3.2)
Tenofovir	1612	2.4 (1.7-3.3)	838	2.3 (1.4-3.5)

- Metropolitan Atlanta Congenital Defects Program, a population-based birth defects surveillance program administered by CDC[6,7]
  - **Overall birth defects: 2.72% (95% CI: 2.68-2.76)**
- **We give tenfovir in first trimester as well, safe**

6. Antiretroviral Pregnancy Registry. December 2012.
7. Correa A, et al. Birth Defects Res A Clin Mol Teratol. 2007;79:65-186.

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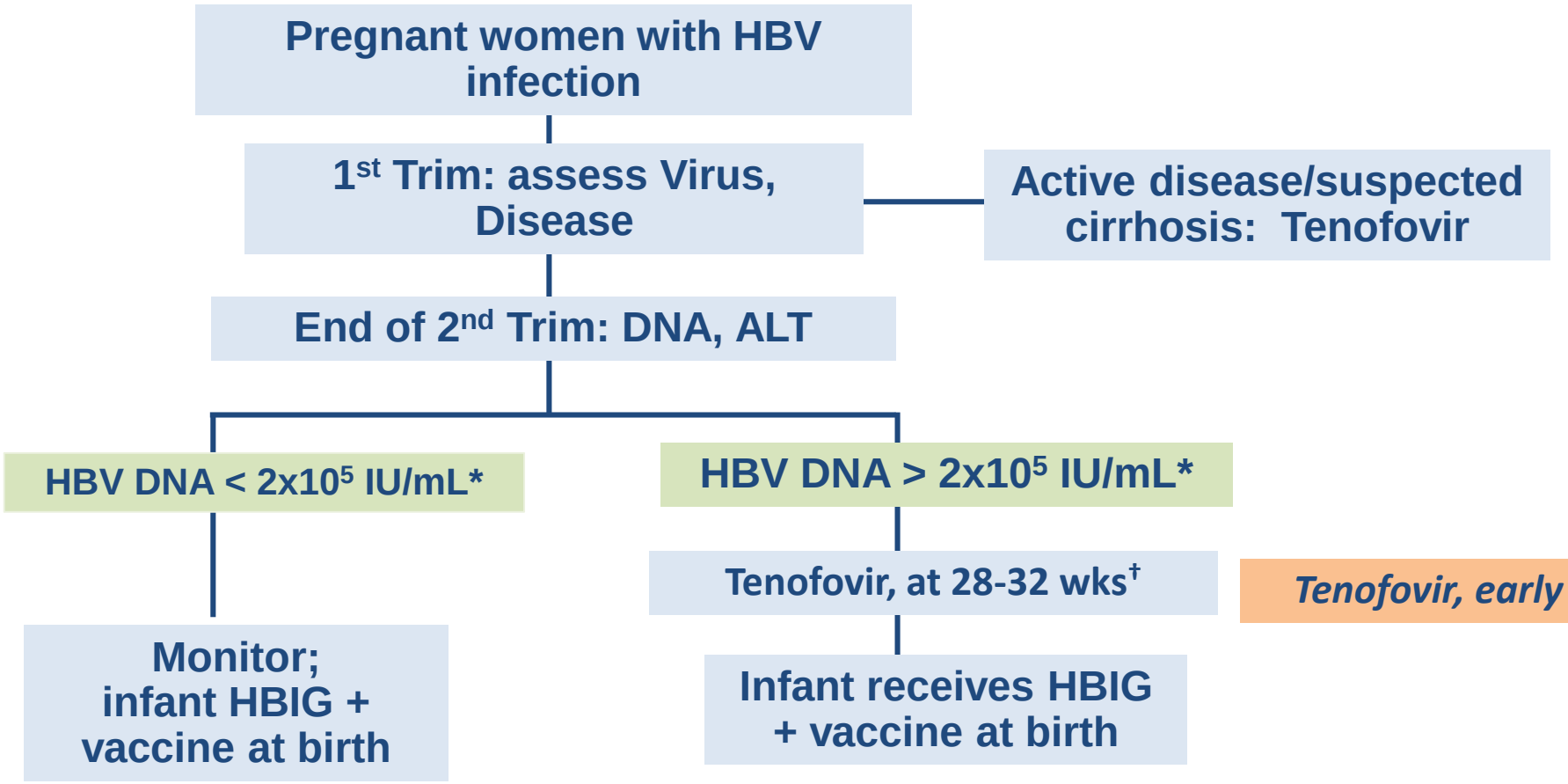
Summary 1: Algorithm for HBsAg Positive Pregnant Woman



The cut-off level of maternal HBV DNA level for initiation of therapy is unclear, and HBV DNA from 6-8 $\log_{10}$ IU/mL can be considered for therapy based on physician and patient preference.

†Tenofovir is preferred if treatment is expected to be > 12 weeks or if treatment is expected to continue while breastfeeding.

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Guidelines: Management of HBV in Pregnancy

- HBV DNA > 200,000 IU/mL or HBsAg > 4 $\log_{10}$ IU/mL TDF from Wk 24-28 up to 12 wks after delivery[2]
- Already on TDF to continue; or switch to TDF[2]
- Breastfeeding is not contraindicated[1,2]

1. Terrault NA, et al. Hepatology. 2016;63:261-283. 2. EASL. J Hepatol. 2017;67:370-398.

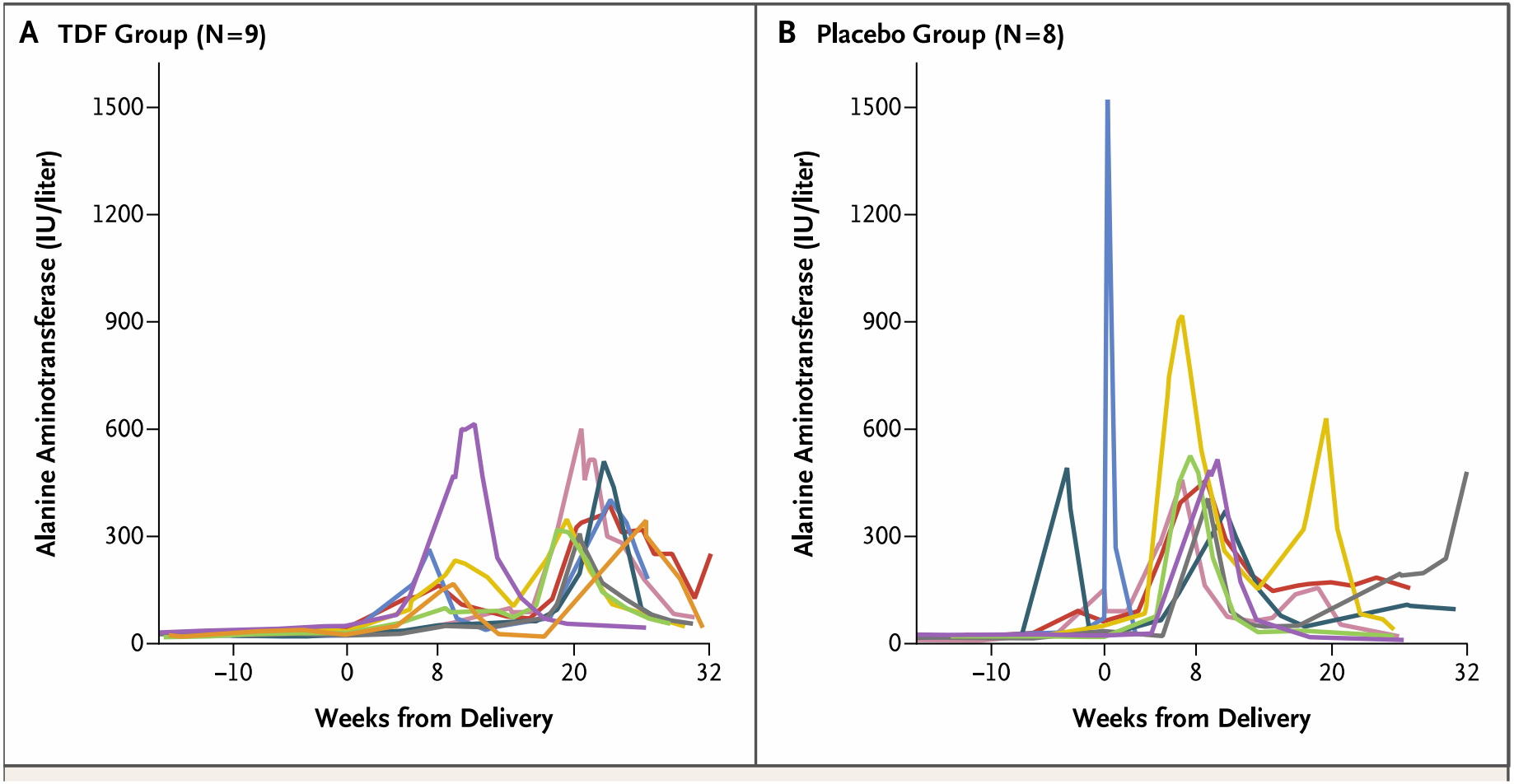
Scenarios: Chronic HBV in Women of Reproductive Age

1. Newly diagnosed HBV during pregnancy
2. **Known HBV+, becomes pregnant, on antiviral**
3. Women Plans a family in future

Known HBsAg+, on antiviral, becomes pregnant: Summary 2

- On Tenofovir, lamivudine, continue
- On entecavir, TAF, Switch to Tenofovir
- Continue for 12 wks after delivery
- When stopping or switching, monitor for hepatic flares
- We generally continue, woman may plan subsequent pregnancy

Post-partum ALT Flare

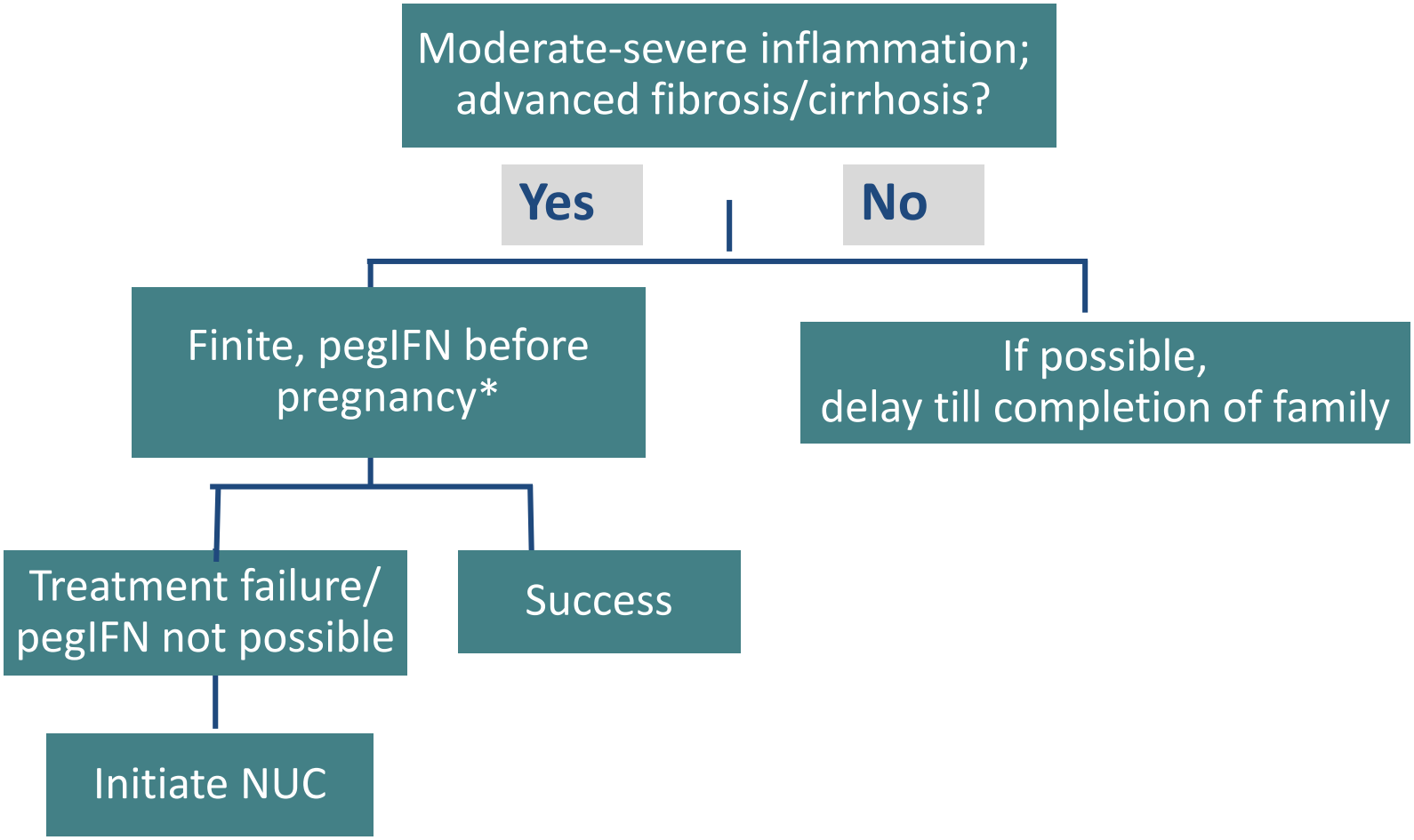


Jourdain et al NEJM 2018

Scenarios: Chronic HBV in Women of Reproductive Age

1. Newly diagnosed HBV during pregnancy
2. Known HBV+, becomes pregnant, on antiviral
3. **HBsAg Positive Women Plans a family in future**

HBsAg+ve Young F, Planning Family



*Effective contraception indicated.

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TO THE EDITOR: The ethics of conducting a placebo-controlled trial is a concern when it is apparent that nucleoside and nucleotide analogues can reduce the risk of HBV transmission. Guidelines from the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver also suggest the use of nucleoside or nucleotide analogues in pregnant mothers with a high viral load.[1,2] TDF that is initiated at 32 weeks of gestation raises the question of the adequacy of viral-load reduction at delivery, because perinatal transmission is affected by the HBV DNA level at delivery. Although the safety of these drugs in early pregnancy is a concern, some data support the use of TDF as not unsafe in early pregnancy, as suggested by the Antiretroviral Pregnancy Registry data.[3] The avoidance of breast-feeding in early infancy may be detrimental, especially in low-income environments, in which HBV endemicity is highest. Guidelines from the World Health Organization (WHO) recommend breast-feeding during treatment with TDF-containing antiretroviral regimens for human immunodeficiency virus (HIV) infection.[4] The safety with long-term use of TDF is still unknown, although reduced bone density has been reported.[5] Only well-defined studies can provide guidance regarding the appropriate use of nucleoside and nucleotide analogues during pregnancy, provide guidance regarding when to initiate and stop these drugs, and address the long-term safety concerns.

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Prevention of Peripartum Hepatitis B Transmission.
Jindal A, Singh A, Sarin SK.
N Engl J Med. 2016 Oct 13;375(15):1496-1498. No abstract available.
PMID: 27732823

Mode of delivery: risk of transmission

Mode of delivery	HBs Ag +ve	Chronic HBV
Normal vaginal	8.1	7.3
Forceps/Vaccum	7.7	7.7
Ceserean section	9.7	6.8

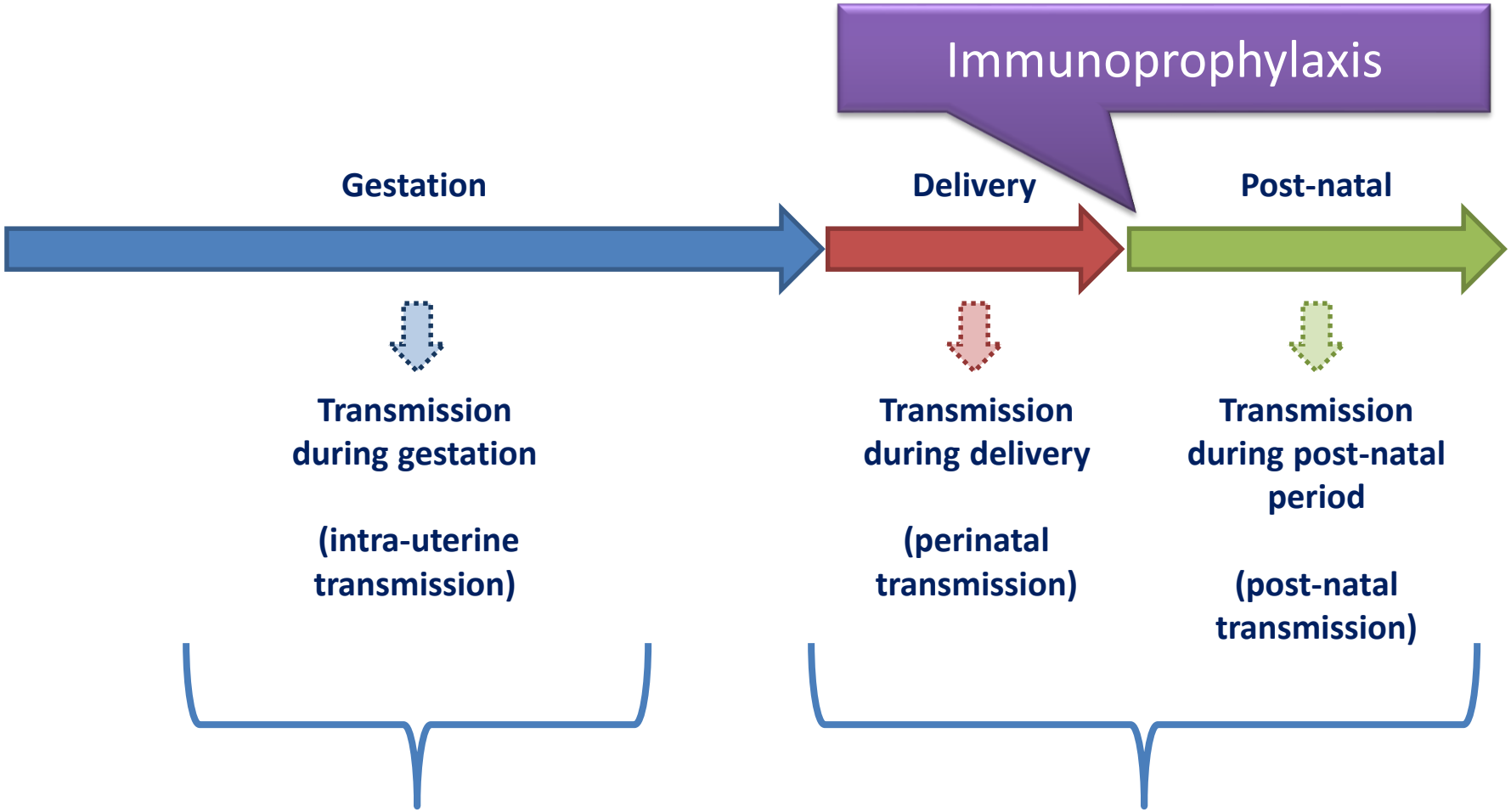
CS Not helpful

Prevention of Perinatal HBV Transmission

- Cornerstone: HBIG + HBV vaccine
  - HBIG + first dose vaccine within 12 hrs of birth, different sites
- Efficacy: ~ 95%
- Reasons for failure
  - Delay in administration of HBIG + vaccine
  - Intrauterine Transmission
  - Mother HBeAg positive and/or high HBV DNA
  - Failure to complete vaccine series

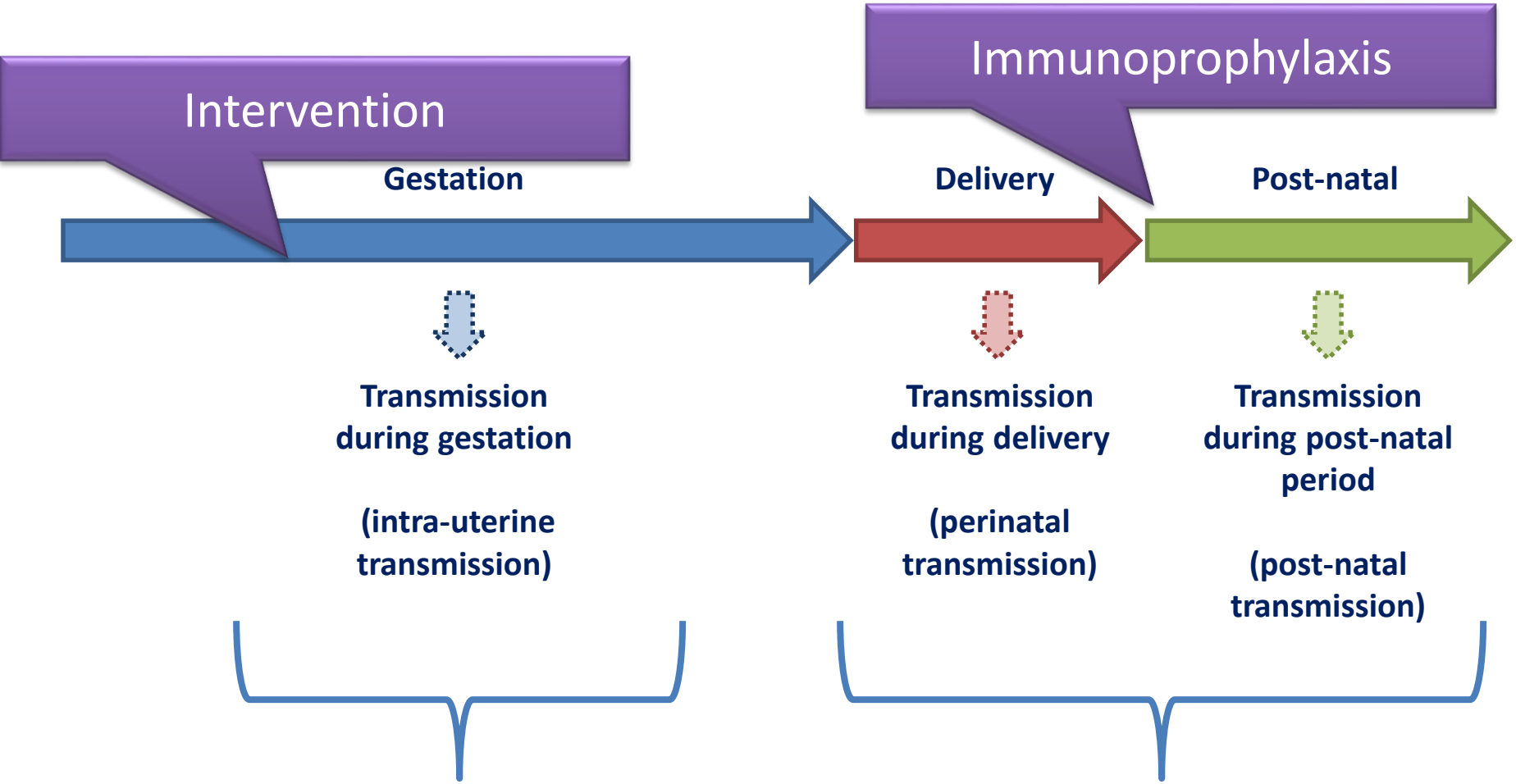
Lok AS, et al. Hepatology. 2009;50:661-662. 13. Mast EE, et al. MMWR Recomm Rep. 2005;54(RR-16):1-31.

Time of HBV Transmission



Guntupalli, Crit Care Med, 2005

Time of HBV Transmission



Sarin et al Gastroenterology 2012

Guntupalli, Crit Care Med, 2005

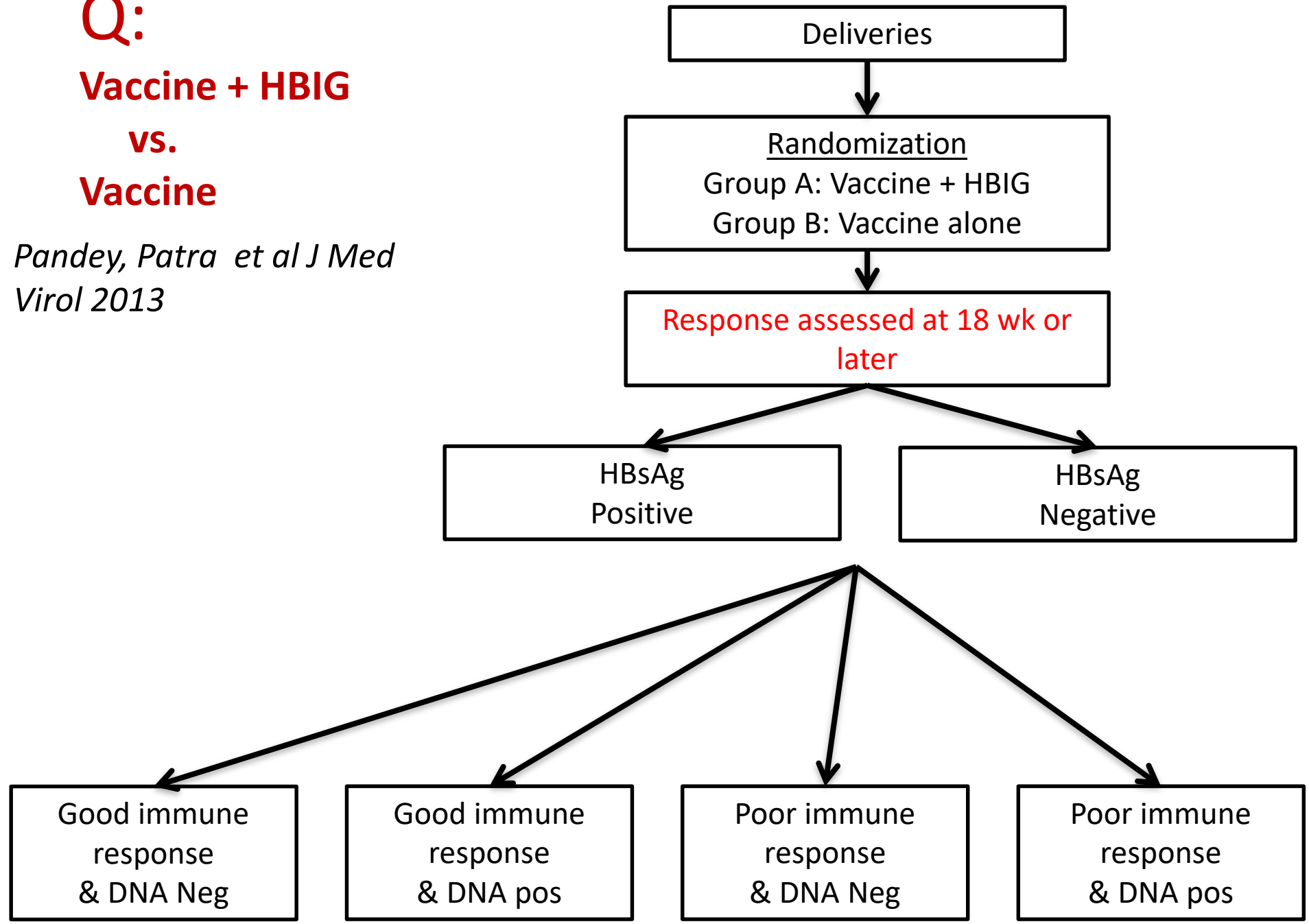
Q:

Vaccine + HBIG

vs.

Vaccine

Pandey, Patra et al J Med Virol 2013



Outcome of Intervention: Wk 18

Outcome	Group A (Vaccine+HBIG) (n=106)		Group B (Vaccine only) (n=116)		P
Overt HBV infection	2	(2%)	7	(6%)	NS
Occult HBV infection	52	(49%)	54	(47%)	NS
No HBV infection but poor immune response	19	(8%)	10	(9%)	NS
Primary endpoint (no infection and good immune response)	43	(41%)	45	(39%)	NS

Pandey, Patra et al J Med Virol 2013

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Anti-HBs Titres at 18 Weeks or beyond

Anti-HBs titres	Group A (n=106)	Group B (n=116)	P Value
Adequate (≥10 IU/mL) (Responders)	80 (75%)	79 (68%)	NS
Inadequate (<10 IU/mL) (Non-responders)	26 (25%)	37 (32%)	

Pandey, Patra et al J Med Virol 2013

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Summary 3

- Babies born to HBV +ve mothers
  - High occult HBV infection despite HBIG + Vaccine
  - Screen at mo. 1, 6, 12, 24 after completing vaccine + HBIG
- Antivirals be tested in 1st trimester to prevent immunoprophylaxis failure

How many of you are Immunized against Hepatitis B !

Vaccination is
NOT
Equivalent to Immunization
(Protection)

Vaccination is NOT Equivalent to Immunization (Protection)

Antibody, Anti-HBs > 10 IU/L,

better >100 IU/L

Non-response in doctors = 7%

GYANECOLOGIST, PEDIATRCIAN, PHYSICIAN

NO EPP ANTI HBS <10 IU/ml