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Chronic HBV: Which Pregnant Women Should Be Treated?

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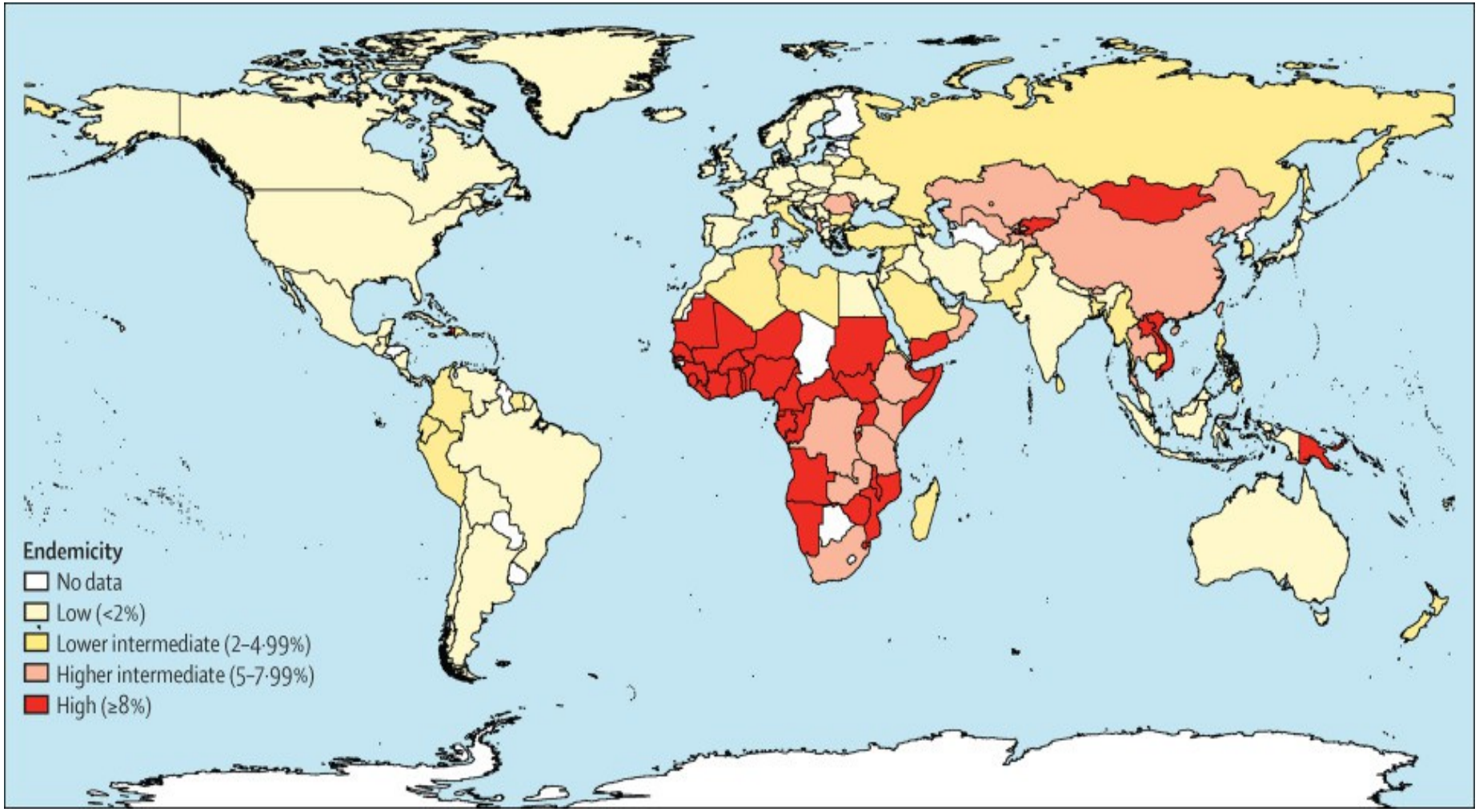
Disclosure

Received lecture fee and consultation fee from:
BMS, MSD, Novartis and Roche pharmaceutical companies in the last 2 years.

Outline

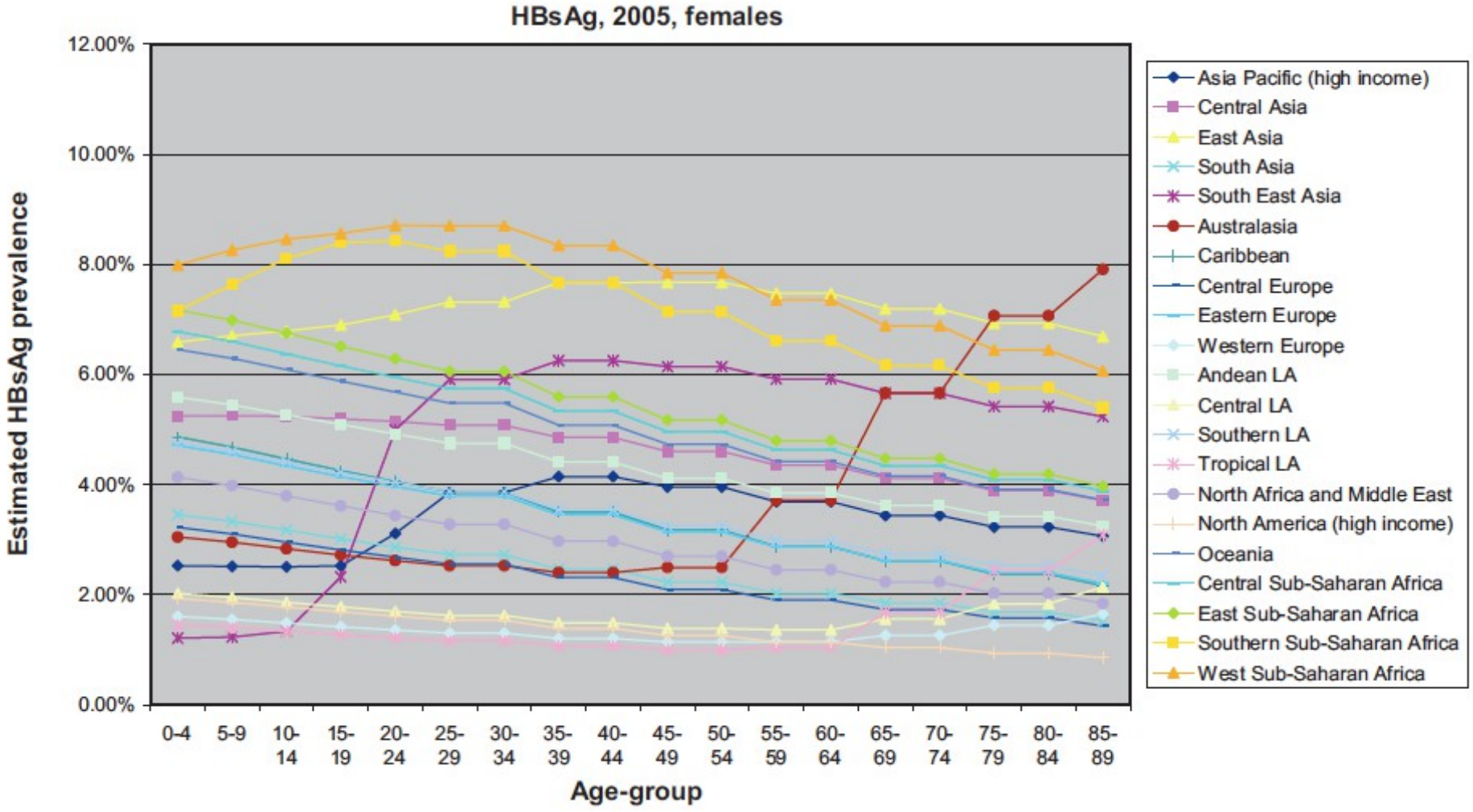
- HBV and pregnancy
- Antiviral therapy to treat active liver disease
- Antiviral therapy to prevent HBV MTCT
- Maternal and fetus safety issues

Global HBsAg Endemicity (1990–2013)



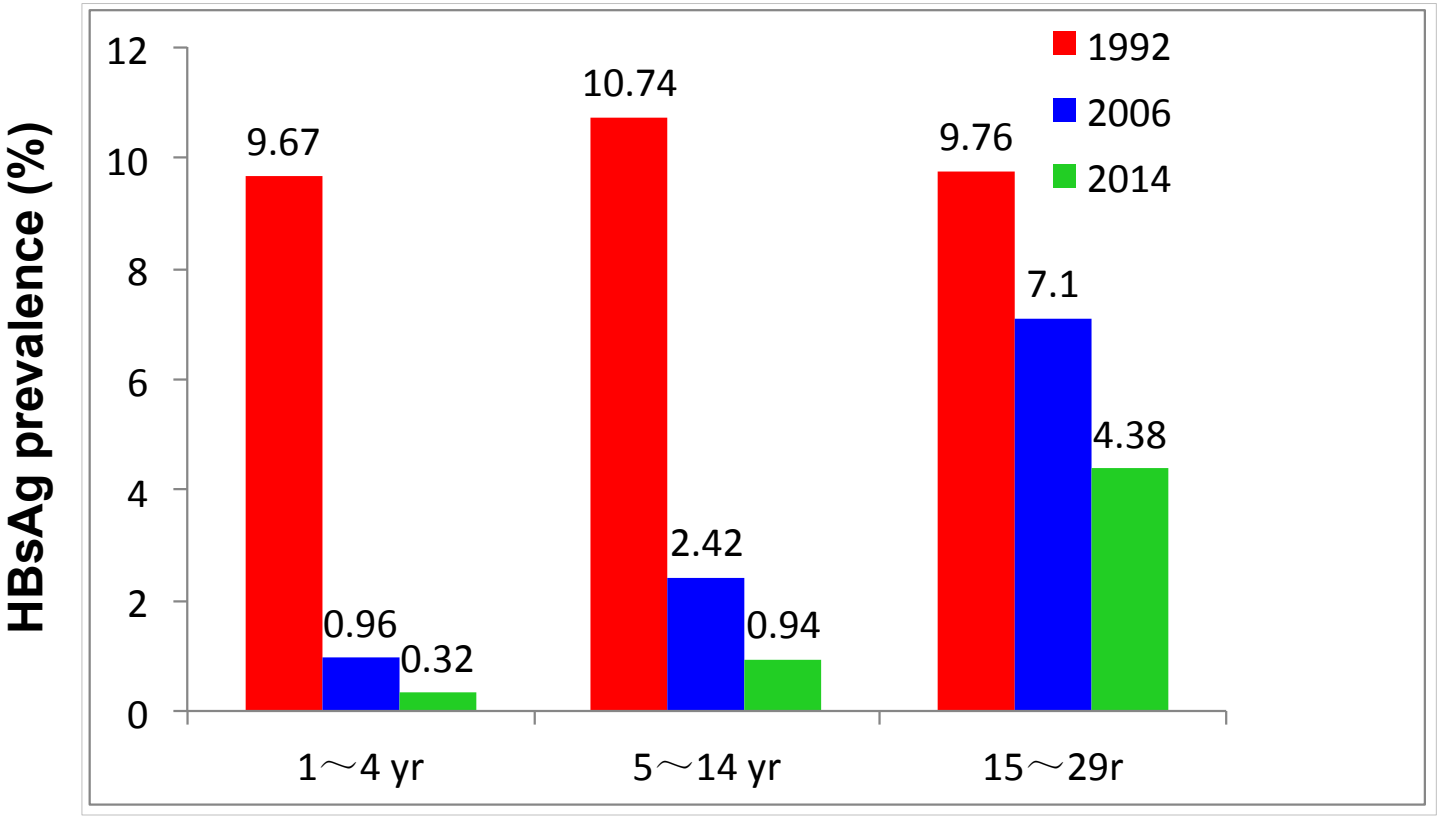
Schweitzer A, et al. LANCET 2015

HBsAg Prevalence in Weman of Different Regions



Ott JJ, et al. Vaccine.2012

Declining HBsAg Prevalence in China



From the 2014 National Seroepidemiology Survey

Prevalence of HBsAg in Child-bearing Women in China

Variable	No. of the observations	HBs Ag		
		Positive cases	Prevalence (%)	95% Confidence Interval (CI)
Age groups:				
15~	1398	81	4.76	3.32~6.19
20~	1538	118	10.23	4.66~15.81
25~	2558	170	5.33	4.14~6.53
30~	3677	242	8.32	5.53~11.12
35~	3984	263	5.28	4.16~6.40
40~	3546	246	6.66	4.35~8.98
40~49	2417	162	6.14	4.24~8.04
Region:				
Eastern	6167	516	5.98	5.30~6.66
Central	6412	368	6.13	5.03~7.23
Western	6539	398	7.70	5.28~10.11

Zheng H, et al. Chin J Vacc Immun. 2010

Women of childbearing age have higher levels of HBV DNA and are more likely to be HBeAg+

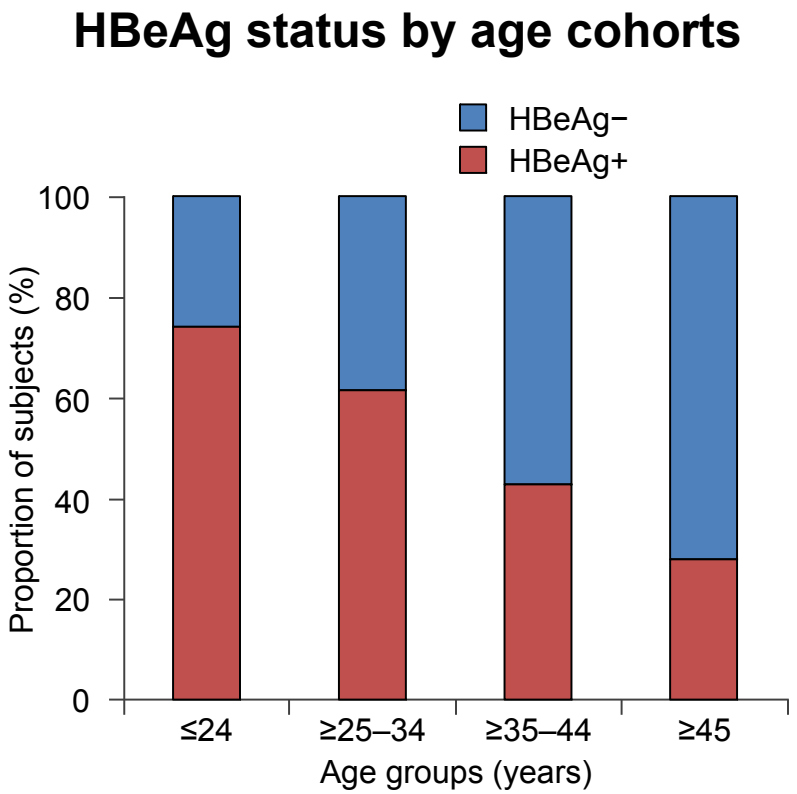
- Retrospective analyses(N=355)
- 41.7% Asian; 44.4% HBeAg+

Younger women (≤44 vs ≥45 yrs) more li kely to have HBV DNA >108 copies/ mL:

- 46.0% vs 25.5% (P<0.0001)

In Asian women

- Higher HBeAg+
- higher % of HBV genotypes B an d C in this population



Tran TT, et al. PLoS ONE 2015;10:e0121632.

HBsAg carriers had increased rates of ante-partum hemorrhage, gestational diabetes and threatened preterm labor

	HBsAg +ve ($n=253$)	HBsAg −ve ($n=253$)	P value
Pregnancy weight gain (kg)	11.31 ± 5.88	10.45 ± 4.87	0.089
Hb before delivery (g/dL)	11.52 ± 1.07	11.66 ± 1.08	0.174
Pre-eclampsia	11 (4.4%)	7 (2.8%)	0.337
Gestational diabetes	48 (19.0%)	28 (11.1%)	0.012
IUGR	3 (1.2%)	6 (2.4%)	0.504
Thrombocytopenia	5 (2.0%)	3 (1.2%)	0.724
Genital tract infection	34 (13.4%)	25 (9.9%)	0.213
PROM	35 (13.8%)	42 (16.6%)	0.386
PPROM	4 (1.6%)	7 (2.8%)	0.544
Antepartum haemorrhage	29 (11.5%)	14 (5.5%)	0.025
Placenta praevia	8 (3.2%)	2 (0.8%)	0.106
Placental abruption	7 (2.8%)	1 (0.4%)	0.068
APH of unknown origin	15 (5.9%)	11 (4.4%)	0.547
Threatened preterm labour	30 (11.9%)	16 (6.3%)	0.030
Preterm birth			
<37 weeks	31 (12.3%)	19 (7.5%)	0.074
<34 weeks	12 (4.7%)	3 (1.2%)	0.033
<32 weeks	6 (2.4%)	1 (0.4%)	0.122
Maternal morbidity	88 (34.8%)	48 (19.0%)	<0.001

Tse KY, et al. J Hepatol. 2005

Women with HBV infection had higher rates of maternal & obstetric complications

Characteristics	Total population	HBV+ ($n = 1458$) %*	HBV − ($n = 1\,668\,911$) %*	*P*-value†
Premature rupture of membrane	18 338	1.78	1.10	**0.01**
Placental abruption	15 517	1.17	0.93	0.3
Placenta previa	9037	0.41	0.54	0.5
Gestational diabetes	73 912	7.20	4.42	< **0.0001**
Diabetes mellitus	11 906	1.99	0.71	< **0.0001**
Labour induction	488 107	28.94	29.22	0.8
Chronic hypertension	20 881	1.03	1.25	0.4
Pre-eclampsia	70 963	4.46	4.25	0.7
Eclampsia	1629	0.14	0.10	0.6
Gestational hypertension	57 749	2.74	3.46	0.1
Endocrine disorder	24 132	1.10	1.45	0.3
Cirrhosis	162	0.07	0.01	**0.02**
Previous cesarean delivery	236 975	15.50	14.19	0.2
Mode of delivery				< **0.0001**
Vaginal delivery	1 154 533	64.27	69.12	
Cesarean delivery	515 836	35.73	30.88	
Anaemia	99 152	10.43	5.93	< **0.0001**
Any pregnancy complications‡	723 065	48.35	43.28	< **0.0001**

Connell LE, et al. Liver Int. 2011

Cirrhosis carries worse outcomes of pregnancy

Outcome	Cirrhosis ($n = 339$)	No cirrhosis ($n = 6625$)	*P*-value	Unadjusted OR (95% CI)
Obstetric outcomes (%)				
Antepartum admission*	33.6	10.8	< 0.0001	4.21 (3.32–5.34)
Caesarean delivery†	41.8	28.3	< 0.0001	1.82 (1.39–2.39)
Assisted delivery†	42.2	56.8	< 0.0001	0.56 (0.42–0.73)
Normal delivery†	16.0	14.9	0.63	1.09 (0.76–1.57)
Multiple gestations†	2.2	2.6	1.0	0.85 (0.35–2.09)
Premature rupture of membranes†	6.2	5.0	0.44	1.26 (0.72–2.18)
Placenta previa†	0	1.0	0.28	–
Placental abruption†	7.1	1.7	< 0.0001	4.41 (2.55–7.60)
Fetal complications (%)				
Death*,‡	5.9	2.1	< 0.0001	2.88 (1.78–4.67)
Preterm†	38.7	10.3	< 0.0001	5.51 (4.16–7.30)
Intrauterine growth restriction†	5.3	2.1	0.003	2.70 (1.47–4.96)
Fetal distress†	6.2	4.7	0.34	1.34 (0.77–2.32)
Congenital anomaly†	0.4	0.5	1.0	0.82 (0.11–6.03)
Any fetal complication†	48.9	17.2	< 0.0001	4.62 (3.52–6.05)
Maternal complications (%)				
Death*	1.8	0	< 0.0001	–
Antepartum uterovaginal haemorrhage*	6.8	1.5	< 0.0001	4.95 (3.10–7.91)
Postpartum uterovaginal haemorrhage†	13.3	3.0	< 0.0001	5.00 (3.31–7.55)
Blood transfusion*	9.7	0.8	< 0.0001	13.63 (8.68–21.40)
Peripartum infection*	2.1	1.4	0.34	1.51 (0.70–3.29)
Hypertension during pregnancy*	14.5	9.4	0.003	1.63 (1.19–2.23)
Preeclampsia	6.8	3.9	0.02	1.78 (1.15–2.78)
Eclampsia	0.03	0	1.0	–
Gestational diabetes*	6.5	6.0	0.64	1.10 (0.70–1.71)
Venous thromboembolism*	0	0.2	1.0	–
Any maternal complication*,§	50.7	24.2	< 0.0001	3.22 (2.59–4.02)

Shaheen AA, et al. Liver Int. 2010

Pregnancy leads to HBV flare up

Study(Author, year)	Number of HBV pregnant women	Postpartum HBV flare rates
ter Borg MJ et al. 2008	38	45%
Tan HH et al. 2008	35	>40%
Nguyen V et al. 2014	71	>40%
Giles M et al. 2015	108	25%
Change CY et al. 2015	74	~31%

Ter Borg MJ et al. J Viral Hepat. 2008

Tan HH et al. Hepatol Int. 2008

Nguyen V et al. Aliment Pharmacol Ther. 2014

Giles M et al. Gut. 2015

Change CY, et al. Hepatology (supl), 2015

Outline

- HBV and pregnancy
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Treatment for the woman's benefit:

With active/advanced liver disease

- To halt progression during pregnancy

Already on therapy

- To avoid flare associated with cessation of therap y

With high viral load

- To Interrupt HBV MTCT
- To prevent post-partum HBV flares

Safety of currently approved drugs for HBV therapy

	LAM	ADV	ETV	TDF	LdT	PEG-IFN
FDA pregnancy category	C	C	C	B	B	C
Crosses the placenta	Yes	Unknown	Unknown	Yes	Yes(rats and rabbits)	Minimal due to large molecules
Excretion in breast milk	Yes	Unknown	Yes in animal studies	Yes in animal studies	Yes in animal studies	Minimal due to large molecular

Visvanathan K, et al. Gut. 2015

Seminar JOURNAL OF CLINICAL AND EXPERIMENTAL HEPATOLOGY

Chronic Hepatitis B Virus Infection and Pregnancy

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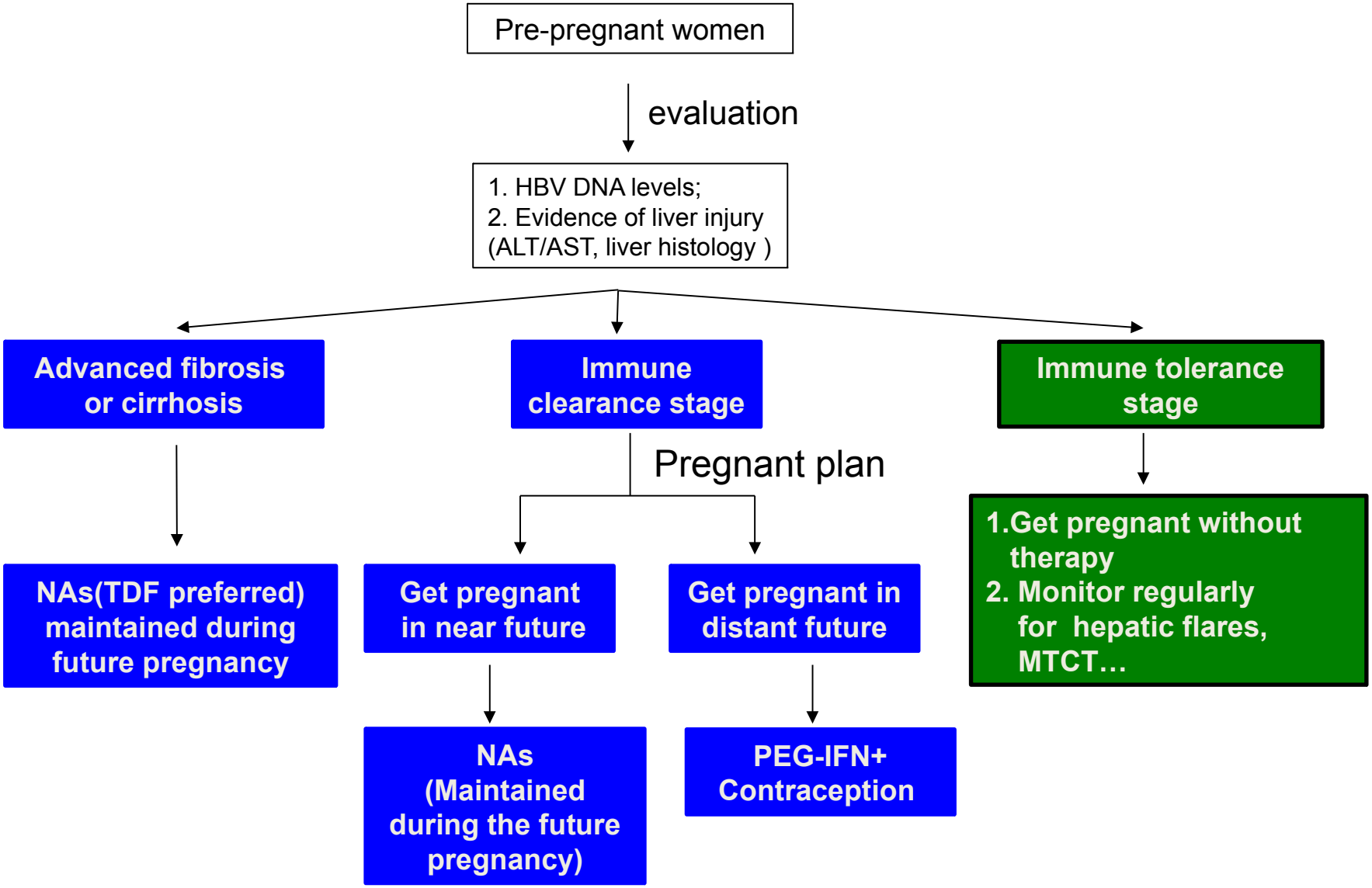
Planning of pregnancy and management of chronic hepatitis B virus during pregnancy includes recognition of maternal virological status, assessment of liver disease severity and minimization of risk for mother to infant transmission of infection. Decisions regarding the use of antivirals during pregnancy need to be individualized. Monitoring for infection and immunization in newborns is also important. For mothers on antiviral therapy, breastfeeding is not recommended. (J Clin Exp Hepatol 2012;2:366–381)

Chronic HBV infection in women-

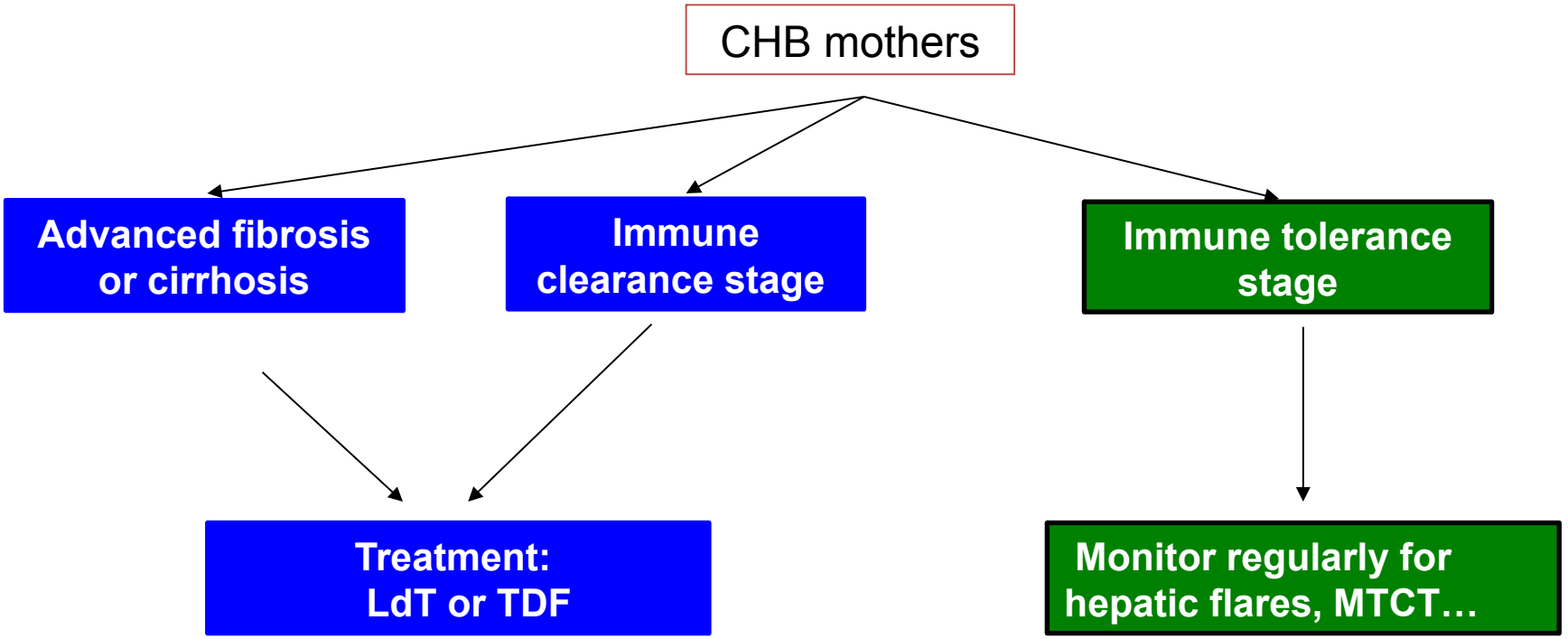
- who desire pregnancy
- who become pregnant while taking antivirals
- who are first detected during pregnancy.

Algorithm for pre-pregnant women with CHB infection



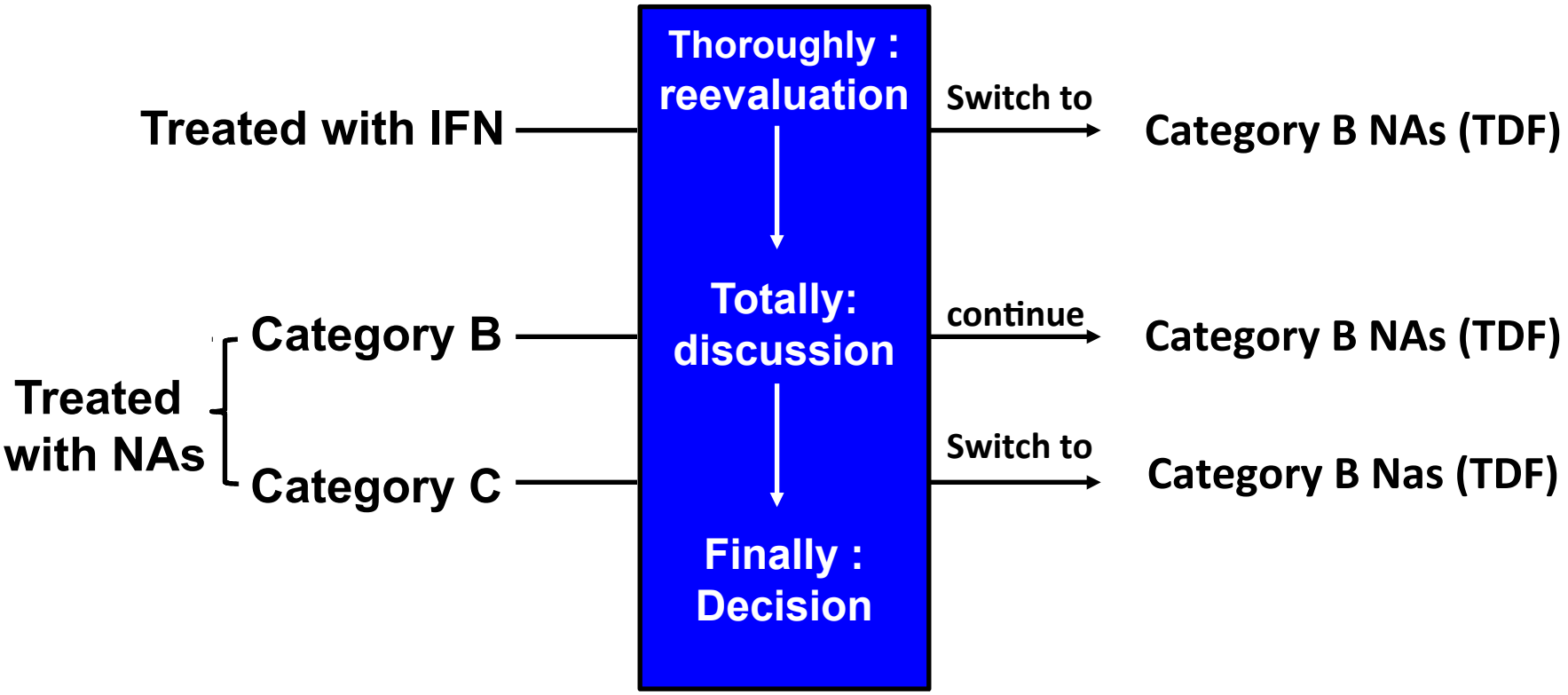
Sarin SK, et al. Hepatol Int. 2015
Lampertico P et al. J Hepatol. 2015
Patton H, et al. Nat Rev Gastroenterol Hepatol. 2014

Algorithm for women with newly diagnosed CHB durin g pregnancy



Sarin SK, et al. Hepatol Int. 2015
Lampertico P et al. J Hepatol. 2015
Patton H, et al. Nat Rev Gastroenterol Hepatol. 2014

Algorithm for pregnant women already on treatment



EASL.J Hepatol. 2012
Jia J, et al. Liver Int. 2015
Patton H, et al. Nat Rev Gastroenterol Hepatol. 2014

Outline

- HBV and pregnancy
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- Maternal and fetus safety issues

Mother to Child Transmission of HBV infection

- In low endemic area(NA &EU): Adulthood, low rate of chronicity
- In high endemic area(AP): Perinatal & early childhood, high rate o f chronicity
  - For infants born to mothers with HBsAg & HBeAg+, 85%~90 % of them would become chronic HBV infection.
  - For infants born to mothers with HBsAg+ only, 30%~40% of t hem would become chronic HBV infection

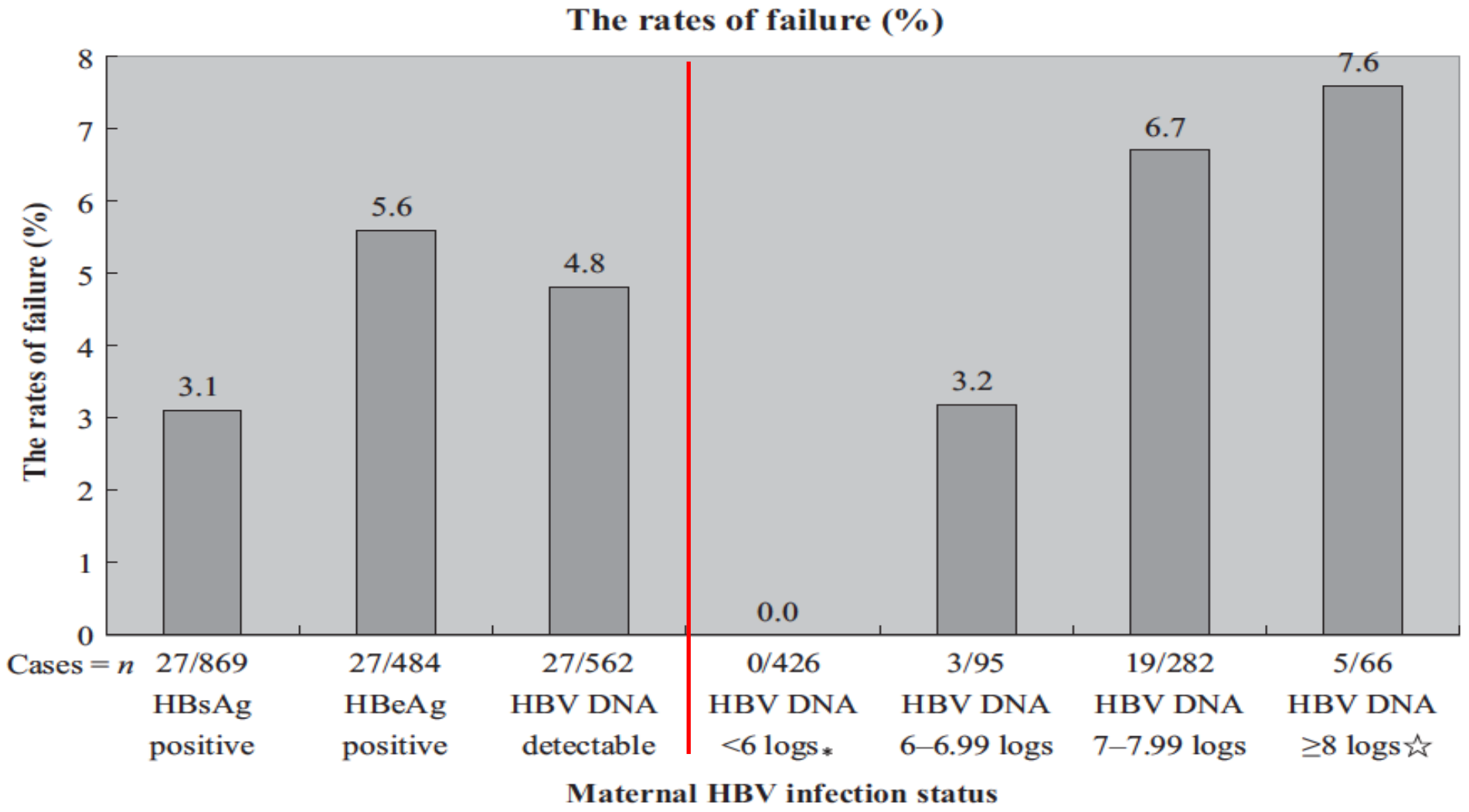
However, even with passive-active immunoprophylaxis,

5%~15% newborns still get chronic HBV infection

NEJM 2012

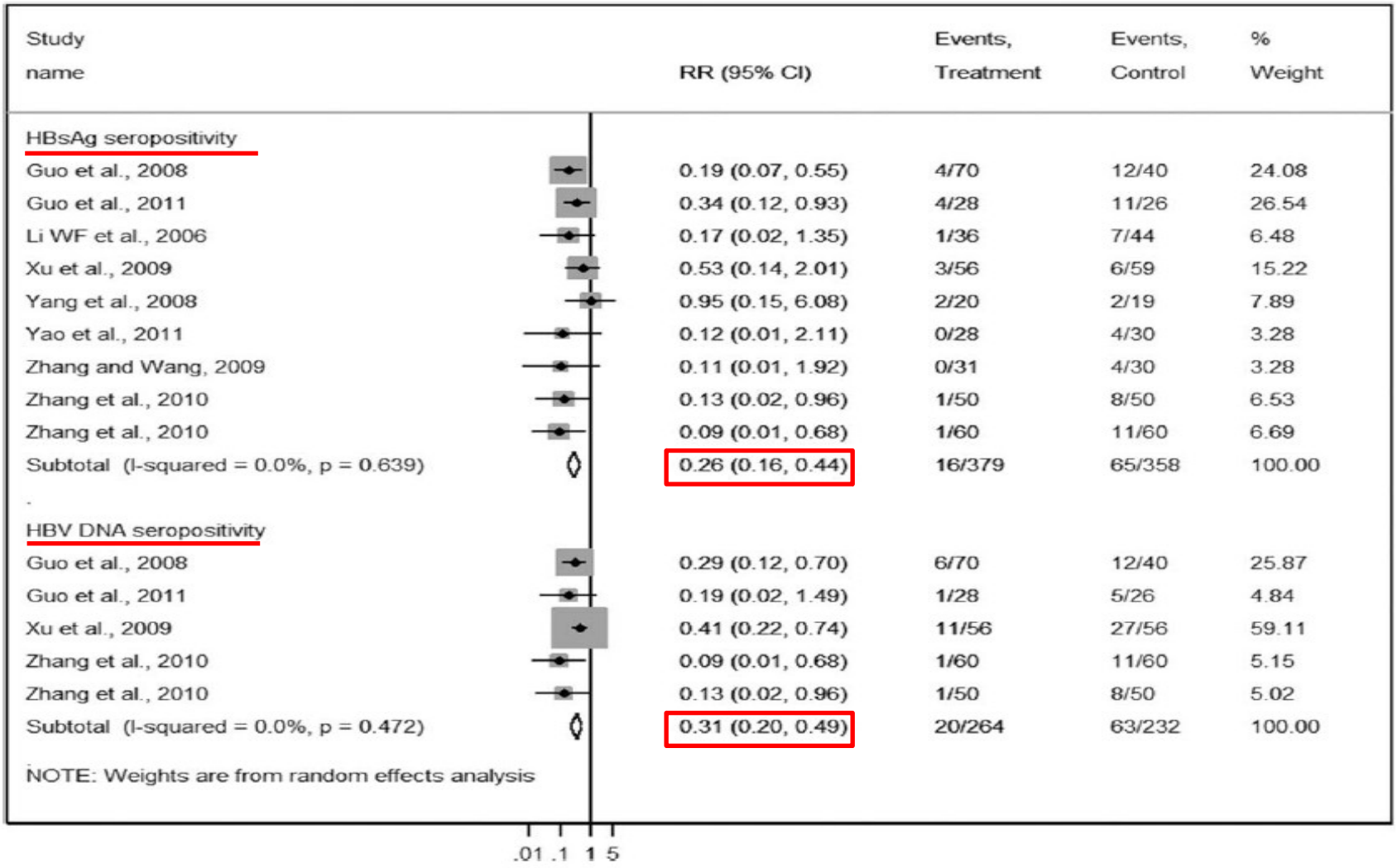
Immunization Practices Advisory Committee (ACIP), CDC. MMWR, 1991, 40: 1-25.

MTCT risk and HBV DNA levels



Zou H, et al. J Viral Hepat. 2012

Meta-Analysis: infant outcomes for RCTs comparing any antiviral therapy versus control at 6-12 months follow-up



Study name	RR (95% CI)	Events, Treatment	Events, Control	% Weight
HBsAg seropositivity				
Guo et al., 2008	0.19 (0.07, 0.55)	4/70	12/40	24.08
Guo et al., 2011	0.34 (0.12, 0.93)	4/28	11/26	26.54
Li WF et al., 2006	0.17 (0.02, 1.35)	1/36	7/44	6.48
Xu et al., 2009	0.53 (0.14, 2.01)	3/56	6/59	15.22
Yang et al., 2008	0.95 (0.15, 6.08)	2/20	2/19	7.89
Yao et al., 2011	0.12 (0.01, 2.11)	0/28	4/30	3.28
Zhang and Wang, 2009	0.11 (0.01, 1.92)	0/31	4/30	3.28
Zhang et al., 2010	0.13 (0.02, 0.96)	1/50	8/50	6.53
Zhang et al., 2010	0.09 (0.01, 0.68)	1/60	11/60	6.69
Subtotal (I-squared = 0.0%, p = 0.639)	0.26 (0.16, 0.44)	16/379	65/358	100.00
HBV DNA seropositivity				
Guo et al., 2008	0.29 (0.12, 0.70)	6/70	12/40	25.87
Guo et al., 2011	0.19 (0.02, 1.49)	1/28	5/26	4.84
Xu et al., 2009	0.41 (0.22, 0.74)	11/56	27/56	59.11
Zhang et al., 2010	0.09 (0.01, 0.68)	1/60	11/60	5.15
Zhang et al., 2010	0.13 (0.02, 0.96)	1/50	8/50	5.02
Subtotal (I-squared = 0.0%, p = 0.472)	0.31 (0.20, 0.49)	20/264	63/232	100.00

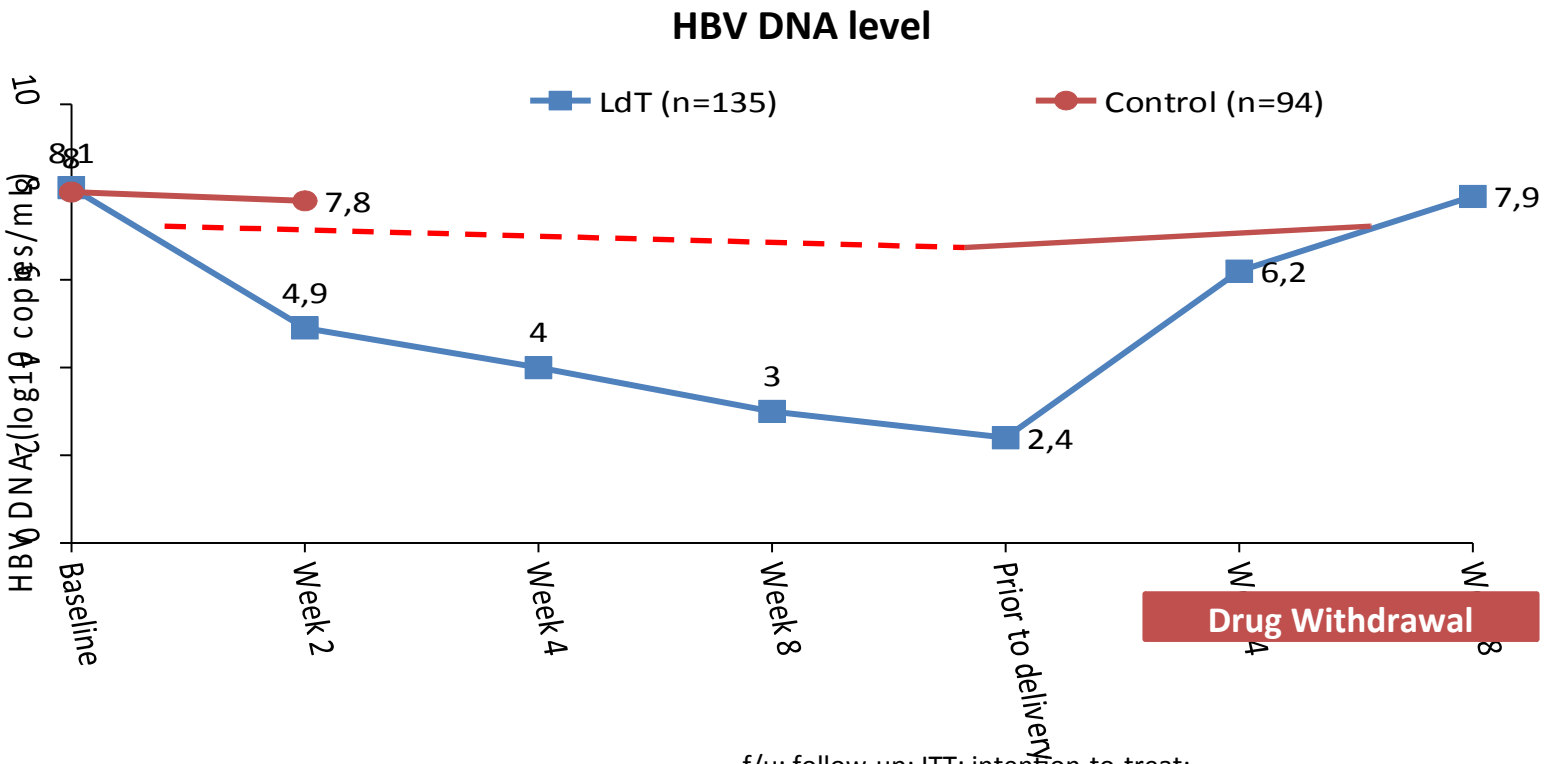
NOTE: Weights are from random effects analysis

.01 .1 1 5

Brown RS Jr, et al. Hepatology. 2015

Case-control study on the 3rd trimester use of LdT on MTCT

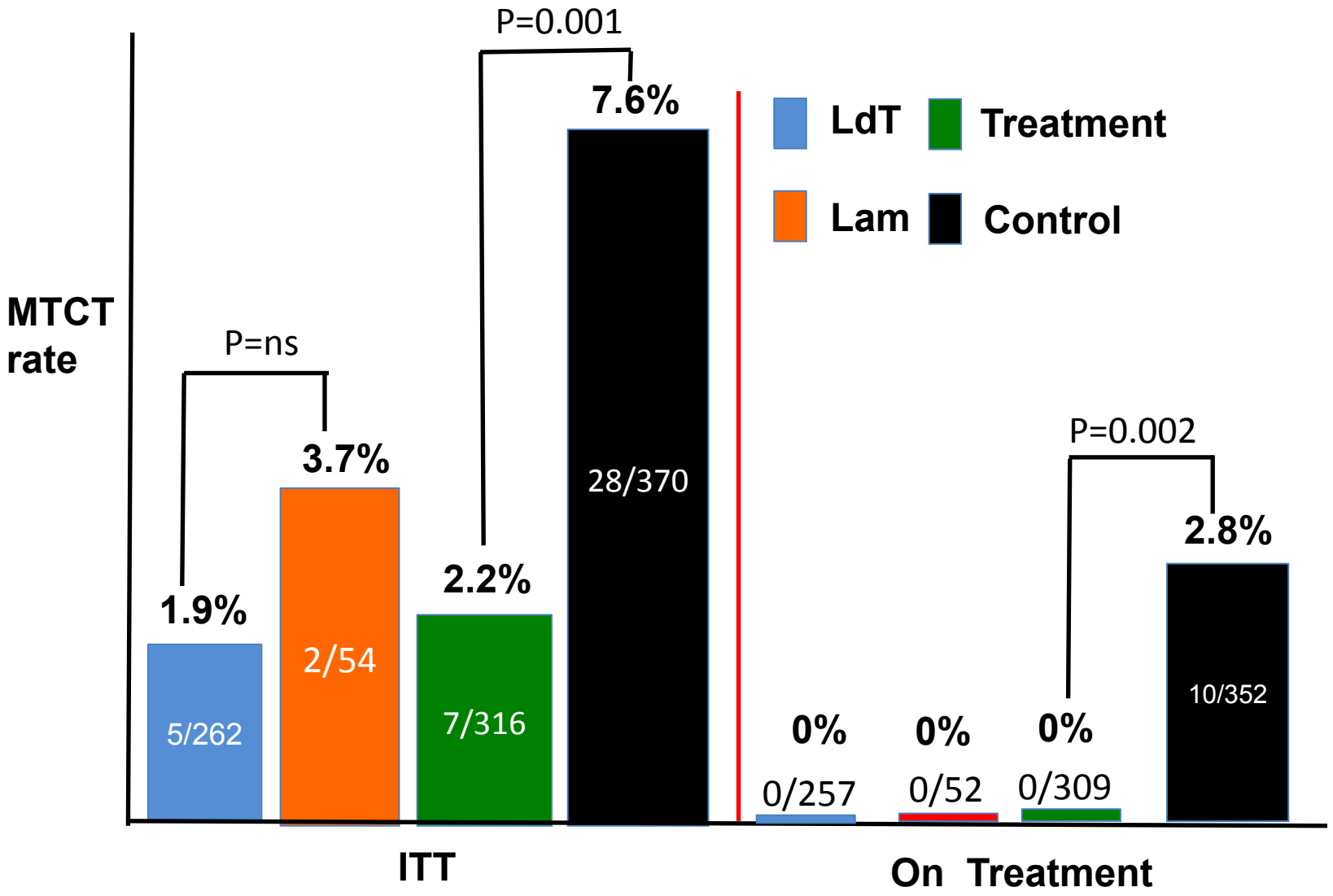
229 pregnant Asian women with HBeAg+ CHB and HBV DNA >7 log10 copies/mL
Infants positive for HBsAg and HBV DNA: 132(0%) in LdT vs 7 of 88(8%) in controls. (p = 0.001)



f/u: follow-up; ITT: intention-to-treat;
LdT: telbivudine; NA: nucleos(t)ide analogue

Han GR, et al. J Hepatol 2011;55:1215–21.

HBV MTCT rates among infants born tomothers who received Lam/LdT or no treatment

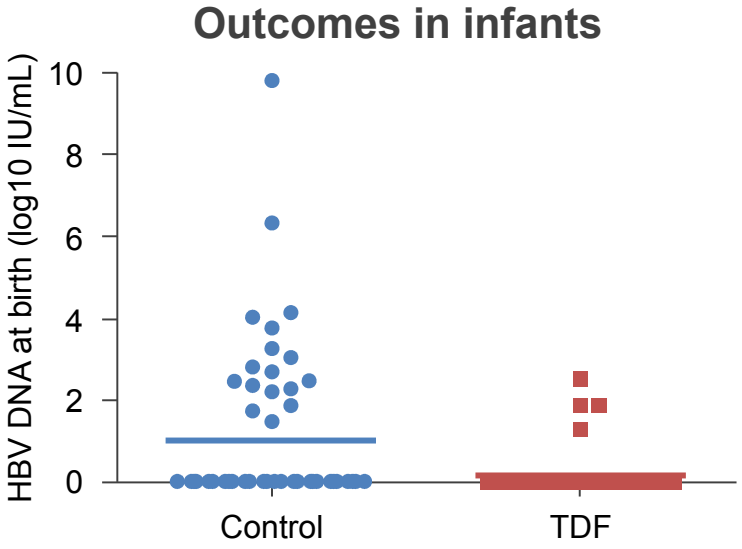


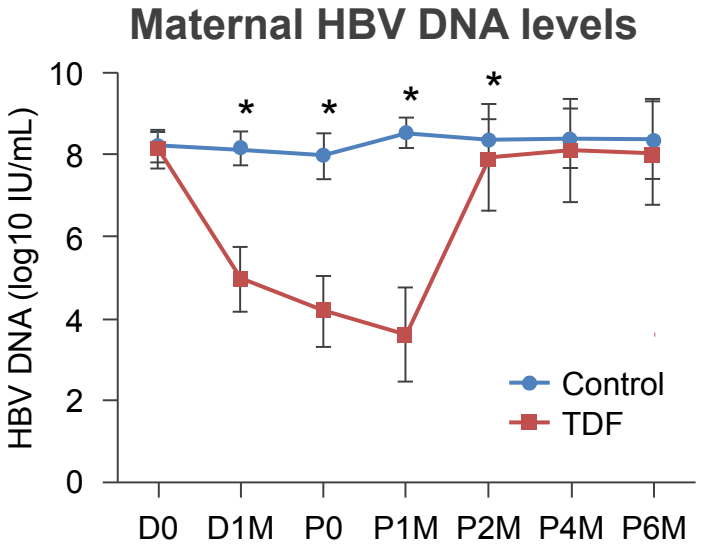
Zhang H, et al. Hepatology 2014;60:468-76

Efficacy of maternal TDF to Prevent HBV

118 HBsAg– and HBeAg+ pregnant women with HBV DNA ≥7.5 log10 IU/mL
TDF 300 mg/d (n=562, HBV DNA 8.18±0.47 log10 IU/mL) vs no medication (controls; n=5 56, HBV DNA 8.22±0.39 log10 IU/mL) from 30–32 w GA to 1 month post-partum

- **Primary outcome: infant HBsAg status at 6 months: 1.54% vs 10.71% (P=0.0481)**





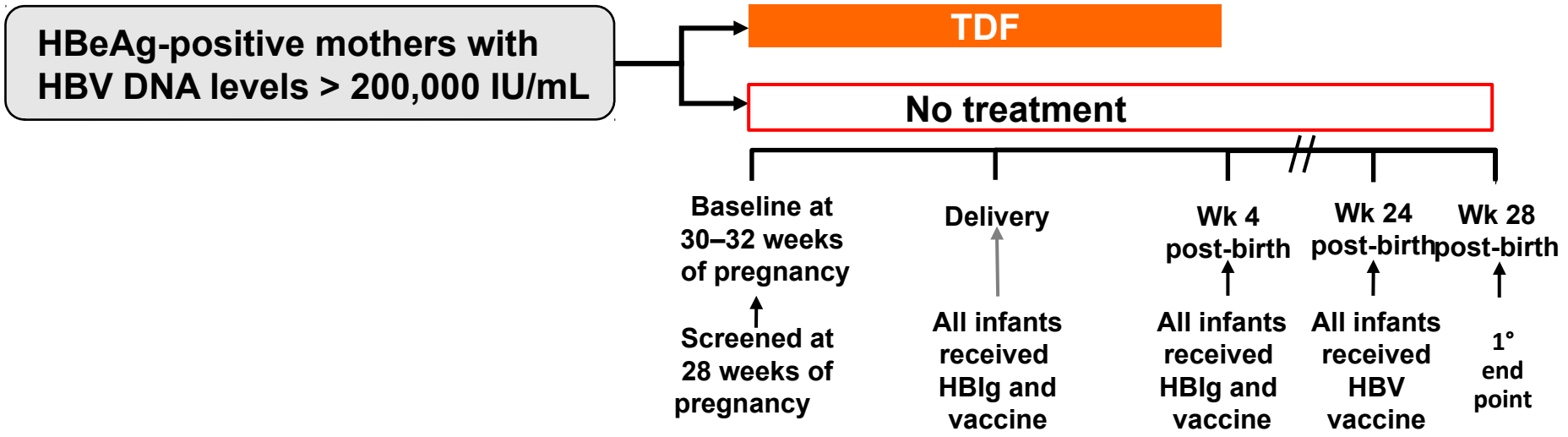
- TDF group vs controls:
  - HBV DNA+ at birth: 6.14% vs 31.48% (P=0.0003)

*P<0.0001 at D1M, P0, and P1M; P<0.01 at P2M

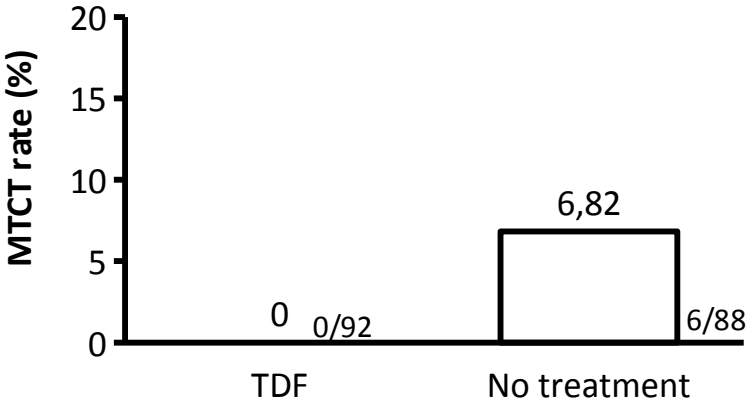
D0: day 0, initiation of TDF (baseline); D1M: 1 month after TDF treatment;
MTCT: mother-to-child transmission; P0: at partum;
PXM: X months post-partum; wGA: weeks gestational age

Chen HL, et al. Hepatology 2015;62:375–86.

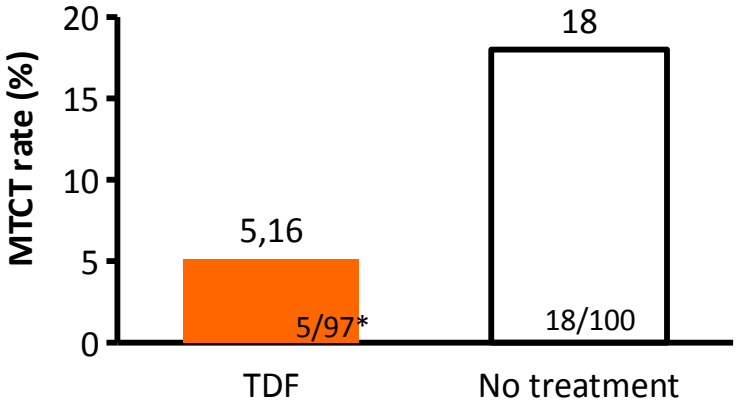
TDF during pregnancy: randomized study in China



MTCT Rate at Postpartum Week 28 (PP)



MTCT Rate at Postpartum Week 28 (ITT)



*1 mother W/D consent prior to delivery, 1 mother lost fetus prior to delivery, 2 mothers LTFU, and 1 newborn death due to trauma

Pan C, et al. AASLD 2015; Oral #209

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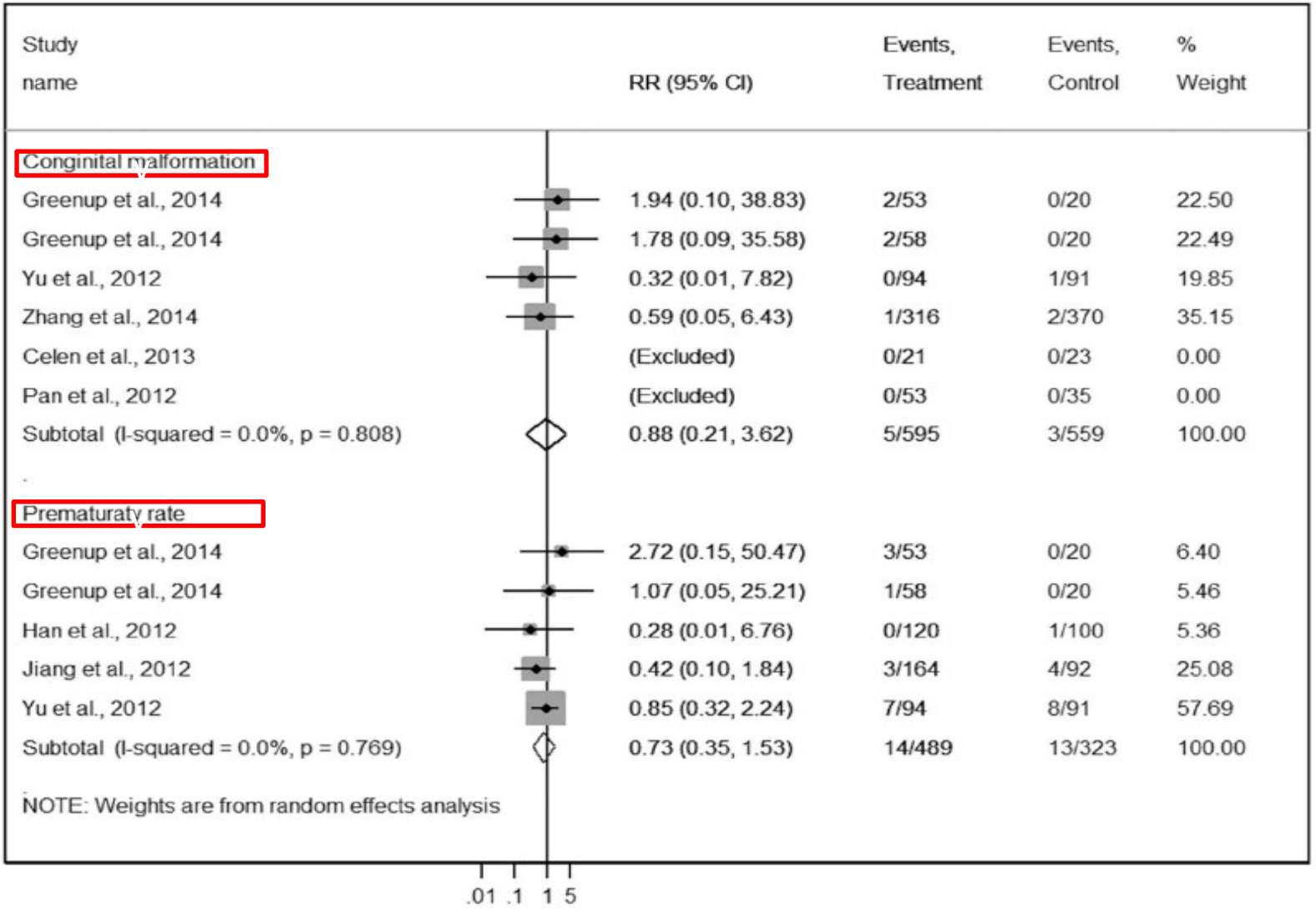
Flare after stopping antiviral agents during pre gnancy: retrospective cohort study

ID no.	Age (years)	Antiviral drug	At initiation of LAM			Duration of antiviral before pregnancy (month)	At stopping antiviral				Maximum during pregnancy			Maximum within 6 months after delivery		
			HBV DNA (log copies/mL)	HBeAg	ALT (U/L)		GA (weeks)	HBV DNA (log copies/mL)	HBe Ag	ALT (U/L)	GA (weeks)	HBV DNA (log copies/mL)	ALT (U/L)	PP (weeks)	HBV DNA (log copies/mL)	ALT (U/L)
1	24	LAM	8.0	+	565	16.4	5	3.3	+	13	12	8.0	875	24	5.0	22
2	35	LAM	8.0	+	977	4.1	5	3.4	–	29	14	8.1	657	8	3.4	73
3	28	LAM	8.0	+	151	11.7	7	5.5	+	14	19	8.0	200	10	5.5	110
4	27	LAM+ADF	6.3	+	122	70	5	6.9	+	13	31	8.8	205	16	8.2	161
5	35	LAM+ADF	8.0	+	279	48.9	7	5.9	+	20	40	6.5	264	20	3.3	14
6	32	ETV	5.9	+	398	26.9	6	1.5	+	20	35	8.8	248	5	5.6	67
7	30	LAM	7.8	+	180	14.2	7	1.7	–	23	24	1.7	10	20	1.5	15
8	27	LAM	7.5	+	54	11.6	7	8.0	+	92	17	8.0	76	22	6.0	120
9	32	ADF	8.0	+	118	46.2	4	4.0	–	11	30	6.0	20	15	3.5	17
10	31	ETV	8.0	+	305	131.3	7	1.5	–	12	18	5.3	26	12	3.4	26
11	28	LAM	8.0	+	105	3.1	8	1.5	+	33	27	6.2	86	7	8.0	107
12	33	LAM	8.0	+	88	6.8	5	5.9	+	20	25	8.0	56	5	8.0	851

LAM: lamivudine; ADF: adefovir; ETV: entecavir; GA: gestational age; HBV: hepatitis B virus; ALT: alanine aminotransferase, PP: postpartum.

Kim HT, et al. J Clin Virol. 2013

Infants outcomes after antiviral therapy: meta-analysis of 7 non-RCTs



Brown RS Jr, et al. Hepatology. 2015

APR data show Lower risk of major birth defects or non-live births with LAM or TDF

Antiretroviral Pregnancy Registry (APR) is the largest safety database in pregnancy for antivirals for HIV and CHB: 16,428 cases analysed1,2

Overall birth defect prevalence/100 live births: 2.9%, 95% CI 2.6–3.1%, which is comparable with:1

- **CDC case control population-based data: 2.72/100 live births (2.7%, 95% CI 2.7–2.8%, P=0.87)2**
- **Two prospective antiretroviral-exposed newborn cohorts (2.8%, 95% CI 2.5–3.2%, P=0.90 and 1.5%, 95% CI 1.1–2.0%, P< 0.001)2**

Birth defects prevalence between first and second/third trimesters exposure was similar (2.9% vs 2.8%)1

1. Antiretroviral Pregnancy Registry. Interim Report, Jan 1989–Jan 2015. Available at: www.APRegistry.com (accessed December 2015);
2. Brown RS, et al. J Hepatol 2012;57:953–9.

CI: confidence interval;
HIV: human immunodeficiency virus

Adjusted Whole Body Mineral Content in TDF-exp ose Newborn of Mothers with HIV

Characteristic	Mean Difference (g) in Whole Body Bone Mineral Content (With Head)			
	Unadjusted		Adjusted[a]	
	Mean Difference (95% CI)	*P* Value	Mean Difference (95% CI)	*P* Value
Primary exposure				
Tenofovir vs no tenofovir exposure	−7.8 (−12.6, −3.1)	.001	−5.3 (−9.5, −1.2)	.013
Maternal characteristics				
Age, per year	0.08 (−.3, .5)	.69	0.04 (−.24, .33)	.77
Did not smoke in pregnancy	2.5 (−3.8, 8.7)	.43	1.1 (−3.4, 5.7)	.62
CD4 count ≥500 cells/mm^3 in 3rd trimester	1.7 (−4.4, 7.8)	.58	. . .	
Viral load ≥400 copies/mL in 3rd trimester	0.4 (−9.1, 9.8)	.94	. . .	
Infant characteristics				
Female sex	−2.6 (−7.5, 2.3)	.30	−0.20 (−3.4, 3.8)	.91
Gestational age at birth, per week	3.8 (1.8, 5.9)	.0003	2.1 (.50, 3.7)	.013
Age at dual-energy X-ray absorptiometry, days	0.5 (.2, .9)	.004	0.53 (.23, .82)	.0006
Non-black vs black, non Hispanic	8.7 (3.8, 13.6)	.0006	3.2 (−1.2, 7.6)	.16
Body length (cm)	3.0 (2.3, 3.8)	<.0001	2.4 (1.7, 3.2)	<.0001

Abbreviation: CI, confidence interval.

[a] Model also adjusted for clinical site in addition to age, smoking, CD4 count, viral load, sex, gestational age, age at dual-energy X-ray absorptiometry, race, and body length.

Siberry GK, et al. Clin Infect Dis. 2015

HBV, NAs and Breastfeeding

CDC and WHO: it is safe for an HBV-infected woman to breastfeed

EASL guidelines: Safety of NA therapy during lactation is uncertain

AASLD guidelines: Breastfeeding is not contraindicated. These antivirals are minimally excreted in breast milk an are unlikely to cause significant toxicity.

APASL guidelines: Breast-feeding is discouraged during maternal NAs treatment.

1. EASL. J Hepatol 2012
2. AASLD Hepatology 2015
3. APASL Liver Int 2015
4. Hepatits B Foundation. Hepatitis B guidelines for pregnant women. Available at: www.hepb.org/pdf/pregnancy.pdf (accessed December 2015)

Guidelines Recommendations on Antivirals during pregnancy

EASL	2012	"If antiviral therapy is needed, **TDF** is recommended. as it is the only third generation NA with FDA category B approval for pregnancy and a large registry showing no increase of birth defects"
AASLD AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES	2015	"**TDF** is considered a preferred choice, owing to its antiviral potency, the available safety data of use during pregnancy, and concerns for resistance with the other antiviral agents"
Asian Pacific Association for the Study of the Liver APASL	2015	"In pregnant females with chronic HBV infection who need antiviral therapy, **TDF** is the drug of choice for mothers indicated for antiviral treatment during the first through third trimester of pregnancy.."
" World Health Organization	2015	"**TDF** is preferred antiviral, because it has a better resistance profile and more extensive safety data in pregnant HBV+ women.

Current guidelines for Prevention of HBV MTCT

EASL	2012	LAM, LdT TDF	last trimester of pregnancy	HBV DNA >106–7 IU/mL
AASLD AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES	2015	LAM, LdT TDF	28-32 weeks of gestation	HBV DNA >2×105 IU/mL.
APASL	2015	TDF, LdT	28-32 weeks of gestation	HBV DNA >106–7 IU/mL
World Health Organization	2015	No	No	No

CHB: Which Pregnant Women should be treated Take Home Message

Women of childbearing age with CHB are more likely to have high HBV viral load and be HBeAg+

Pregnant women with active liver could be safely initiated or switc hed to safer NA therapy (preferably TDF)

MTCT risk is greatest in those with HBV DNA >6~8 log

Third-trimester NA treatment (preferably TDF) could further reduc e the risk of HBV MTCT

Maternal, obstetric and foetal safety is acceptable

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