Prevention of mother-to-child transmission of hepatitis B – challenges and solutions –

Philippe Sogni

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Prof. Philippe SOGNI, M.D., Ph.D.

Affiliations

- Paris-Descartes University;
- INSERM U1223 – Pasteur Institute;
- Hepatology Unit, Cochin hospital, Paris; France

Disclosures

- Boards, workshop or meeting invitation: Gilead, Bristol-Myers Squibb, MSD, AbbVie, Janssen, Mayoly-Spindler

Mother-to-Child Transmission (MTCT) of hepatitis B virus

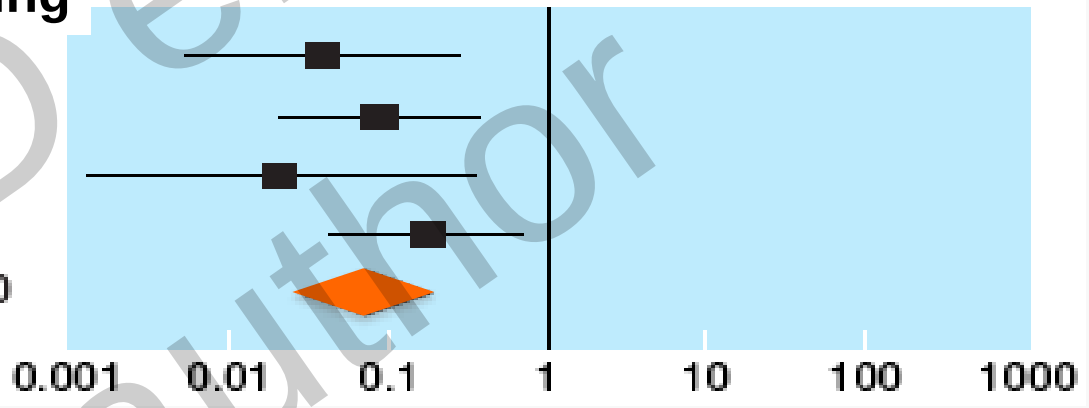
1. MTCT is thought to be responsible for the majority of prevalent cases of HBV worldwide especially in developing countries with high endemicity
2. The risk of MTCT is high and increases with HBeAg+ or HBV-DNA level in pregnant women
3. HBV infection in newborns often leads to chronic infection

Plan

- Serovaccination (HBIg + vaccine)
- Failures of serovaccination and optimization
- Challenging issues in developed countries
- Challenging issues in developing countries

Serovaccination is the more effective method to prevent MTCT

	HBIg + vaccine	Placebo or nothing
Ip 1989 AD*	1/36	12/17
Ip 1989 BD*	2/35	11/17
Liu 1987 CB*	0/27	21/26
Xu 199 CD*	2/28	24/60
Total (95% CI)	5/126	68/120



Serovaccination is more effective than vaccine alone
Serovaccination is more effective than HBIg alone

Lee et al. BMJ 2006

Serovaccination in practice (1)

WHO recommendations (2015)

- Deliver the first dose of vaccine as possible after birth, preferably within 24 hours
- HBIg prophylaxis in conjunction with HBV vaccination may be of additional benefit for newborn infants whose mother are HBsAg-positive, particularly if they are also HBeAg-positive
- Making available HBV vaccine that is not combined with other infant vaccines in all countries is crucial to the strategy of administering the birth dose

Serovaccination in practice (2)

Example: French recommendations (high income country with low endemicity)

Serovaccination of all newborns from HBsAg+ mother beginning in the first 12 hours of life

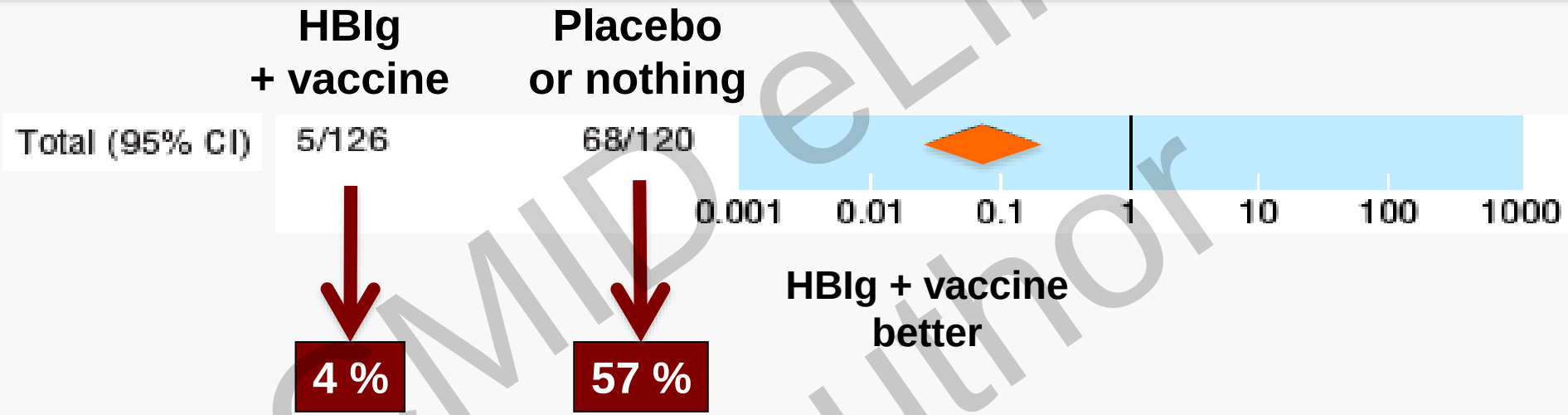
- HBIg 100 IU at D1 (IM in the thigh)
- Vaccination at D1, M1 and M6 with vaccine at 10 µg (IM in the thigh)
- Premature delivery or < 2 kg : HBIg 30 UI/kg and vaccine with 4 doses

Serovaccination in practice (3)

- No EBM for repeated injection of HBIg
- No EBM for higher dosage of HBV vaccine
- No EBM for HBIg in HBeAg – pregnant women
- No EBM to modify mode of delivery for MTCT reasons if serovaccination is used[1]

[1]Visvanathan K et al. Gut 2016
EBM: Evidence-Based Medicine

Serovaccination is not 100% efficient



1. Why?
2. How to optimize MTCT?

Lee et al. BMJ 2006

Failures of serovaccination

- **Why ?**

1. Virus with mutation in HBs domain
2. Screening failure or incomplete serovaccination
3. *In utero* HBV transmission

Failures of serovaccination

- **Why ?**

1. Virus with mutation in HBs domain

2. **Screening failure or incomplete serovaccination**

3. *In utero* HBV transmission

Screening failure of HBsAg in pregnant women in developed countries

References	Countries	Years	Deliveries	Lack of screening
Denis	France	1999	1,356	26.0 %
Beckers	Switzerland	2001	1,513	0.7 %
Stroffolini	Italy	2001	11,858	8.2 %
Papaevangelou	Greece	2003	3,760	8.7 %
Schrag				
Heininger	Switzerland	2005-6	27,131	1.4 %
Braillon	France	2006	22,114	9.9 %
Willis	US	2006	4,762	7.4 %
Frischknecht	Switzerland	2007	723	2.8 %
Giraudon	UK	2007	138,618	3.6 %
Spada	Italy	2008-9	17,260	2.3 %

Lack of screening in clinical practice: 0.7 to 26% !

Incomplete serovaccination in developed countries

References	Countries	Years	N	Lack of serovaccination at birth	Lack of complete serovaccination
Beckers	Switzerland	2001	18	5.6 %	47.0 %
Stroffolini	Italy	2001	182	-	5.0 %
Pa					
Bracebridge	UK	2004	31	-	6.5 %
Heininger	Switzerland	2005-6	143	1.4 %	17.0 %
Willis	US	2006	18	38.9 %	-
Spada	Italy	2008-9	138	0 %	5.1 %

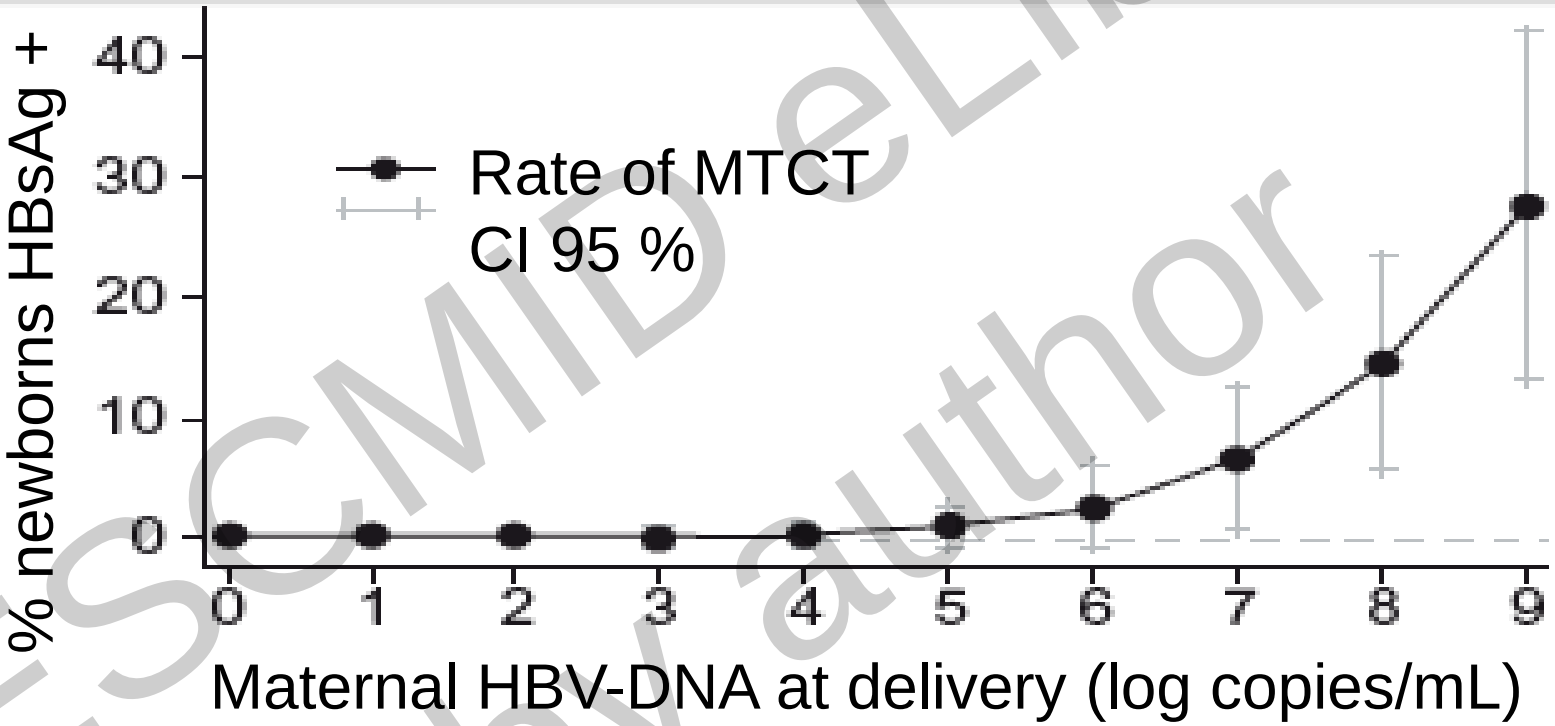
Lack of complete serovaccination in clinical practice: 5 to 47% !

Failures of serovaccination

- **Why ?**

1. Virus with mutation in HBs domain
2. Screening failure or incomplete serovaccination
3. ***In utero* HBV transmission**

MTCT of HBV despite serovaccination



Wen WH et al. J Hepatol 2013

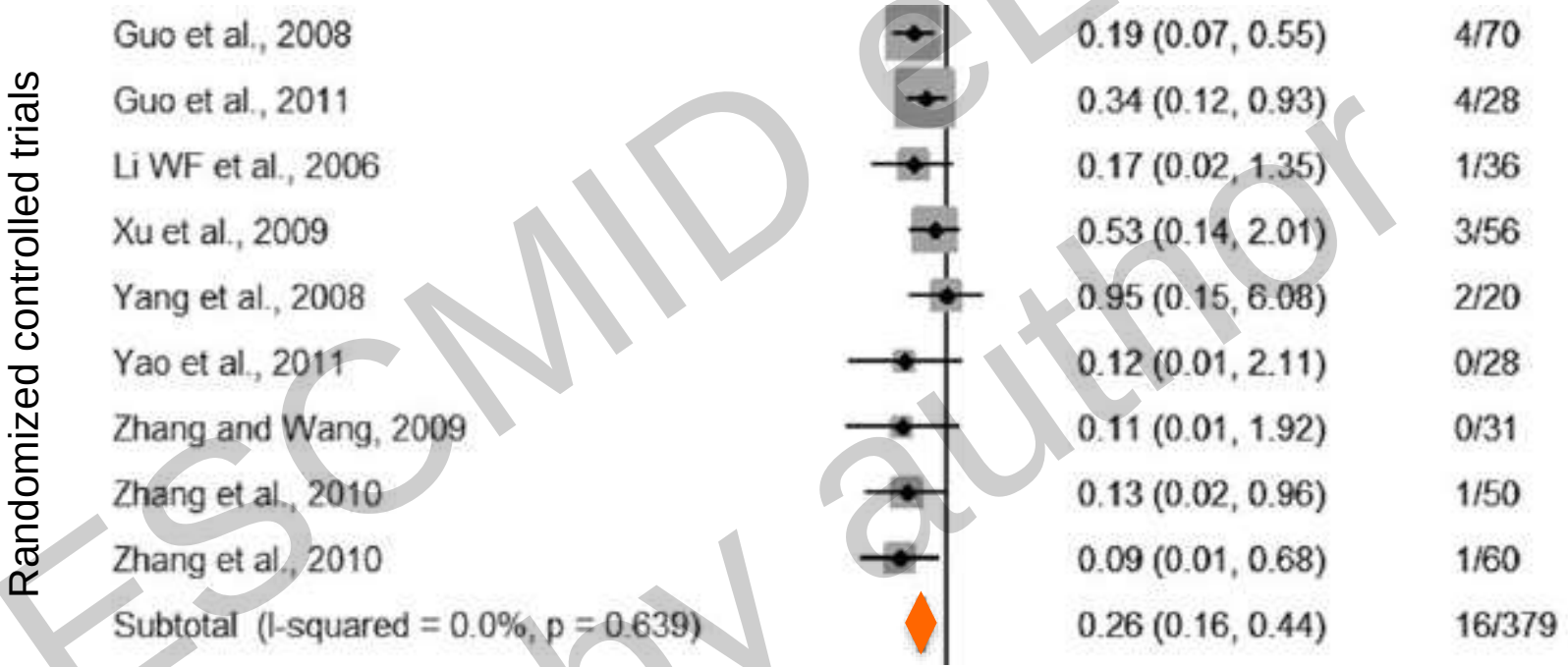
How to prevent *in utero* HBV transmission?

- HBIg during pregnancy ➔ NO
- Programmed caesarian delivery ➔ probably NO

- Antiviral treatment in late pregnancy ➔ YES

Anti-HBV treatment during pregnancy associated with serovaccination

HBsAg + in newborns (6-12 mo)



RR (95% CI)

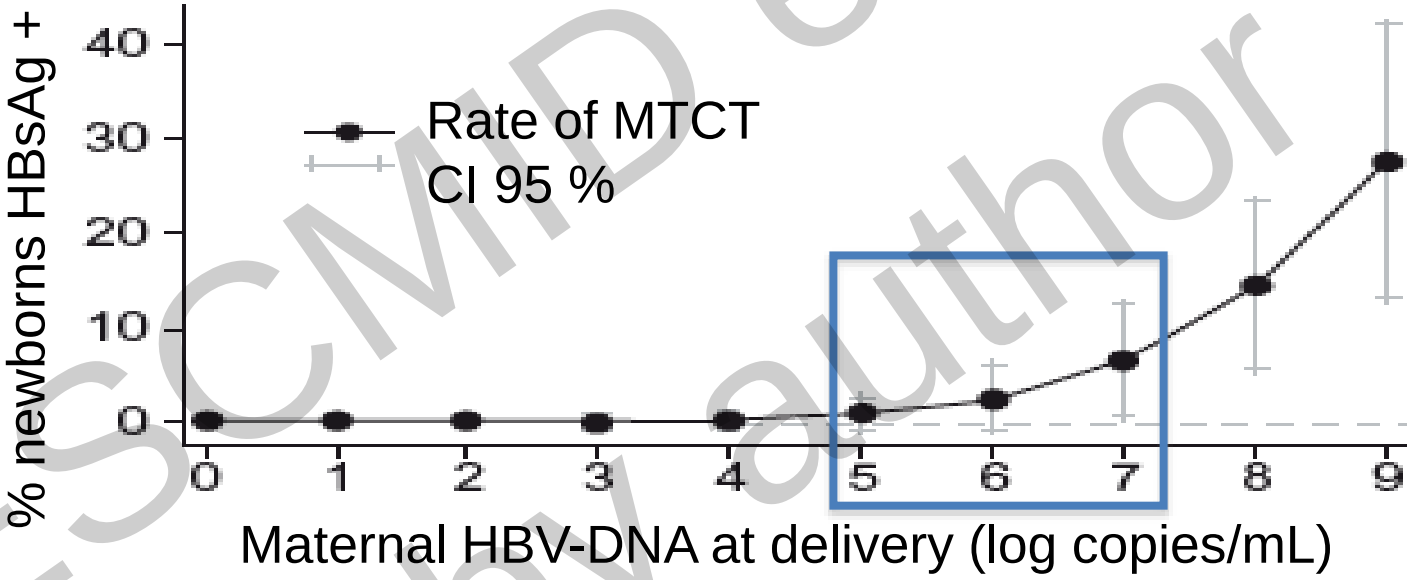
Brown RS et al. Hepatology 2016

Challenging issues in developed countries

- Which cut-off for maternal HBV-DNA for beginning antiviral treatment?
- Which antiviral drug can be used?
- What is the best timing for using antiviral drug?

Which cut-off for maternal HBV-DNA?

MTCT of HBV despite serovaccination



Wen WH et al. J Hepatol 2013

Which cut-off for maternal HBV-DNA?

- Comparison Lamivudine versus Placebo or no treatment
- Maternal HBV-DNA at delivery under Lamivudine treatment

- Risk of MTCT (Lamivudine and serovaccination):
- If HBV-DNA < 6 log copies/mL (5 studies) : RR 0.33 [0.21-0.53]
- If HBV-DNA > 6 log copies/mL (2 studies) : RR 1.26 [0.70-2.27]

Significant benefit on MTCT if maternal HBV-DNA is < 6 log copies/mL at delivery under antiviral treatment

Han L et al. World J Gastroenterol 2011

Which cut-off for maternal HBV-DNA?

- No benefit if maternal HBV-DNA < 5 log IU/mL

➔ serovaccination alone is sufficient

- Clear benefit if maternal HBV-DNA > 7 log IU/mL

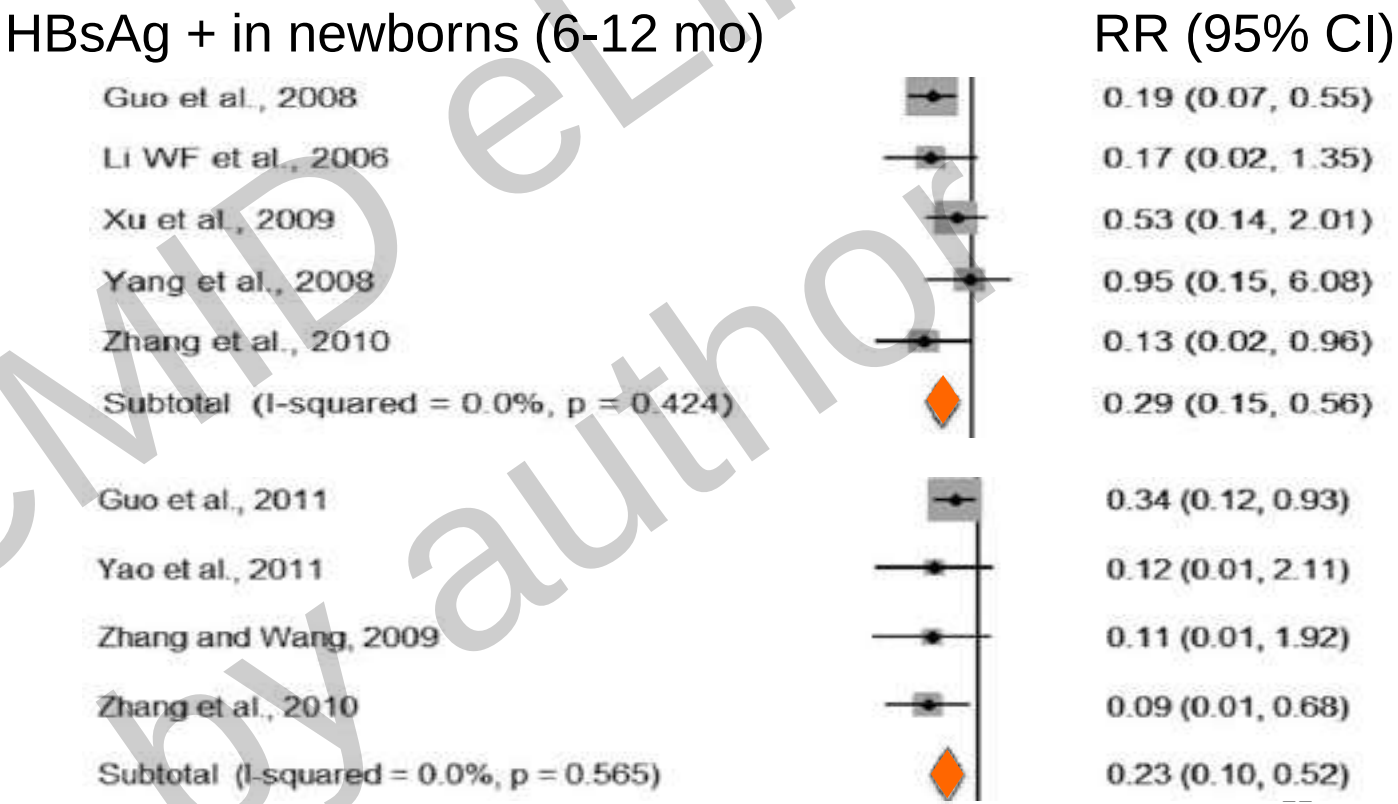
➔ association of antiviral drug for pregnant women + serovaccination for newborns

- No clear response between 5 and 7 log IU/mL

Which antiviral drug can be used?

Lamivudine
Randomized controlled trials

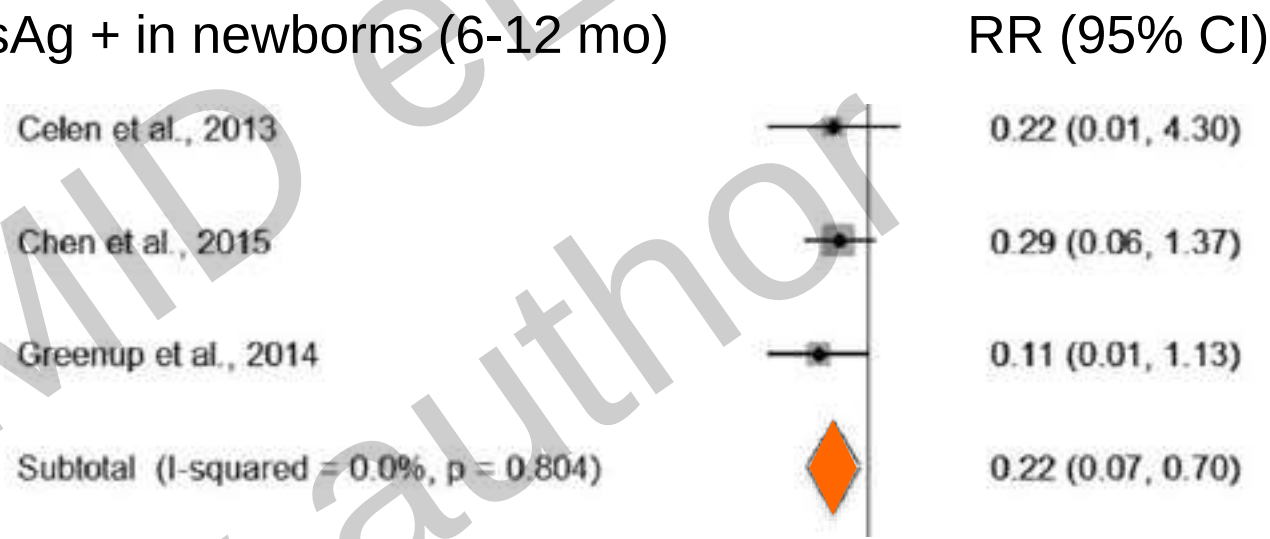
Telbivudine
Randomized controlled trials



Brown RS et al.
Hepatology 2016

Which antiviral drug can be used?

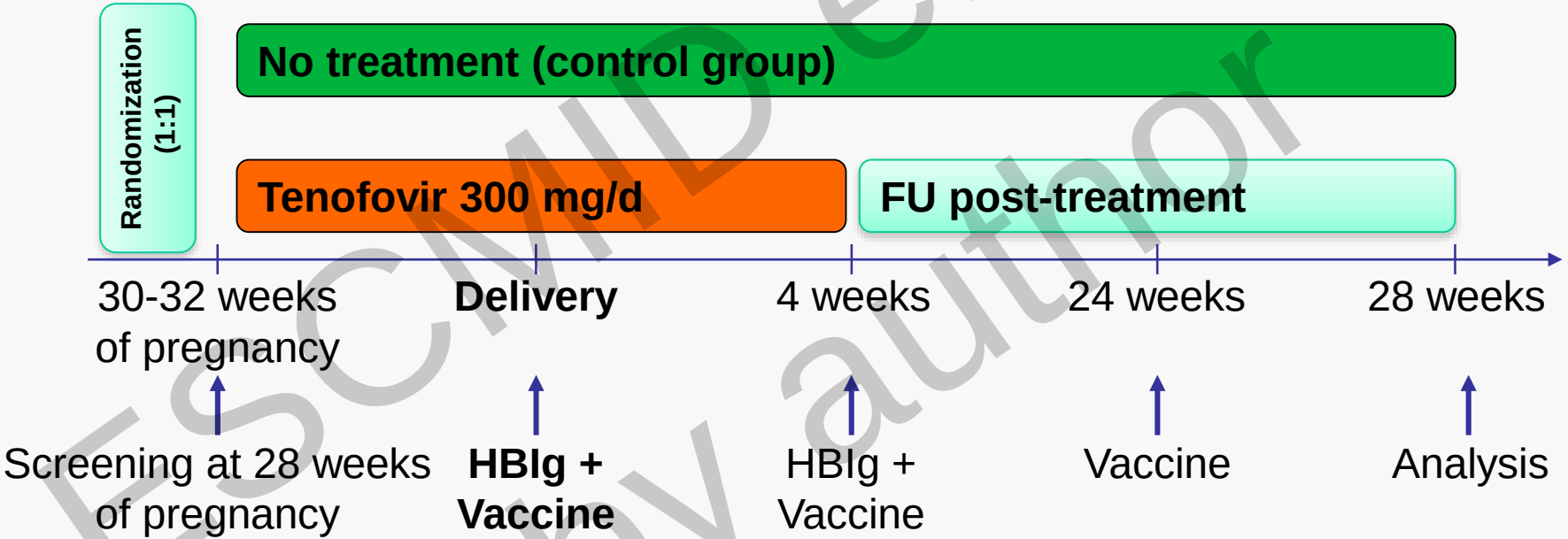
Tenofovir
Non-randomized controlled trials



Brown RS et al. Hepatology 2016

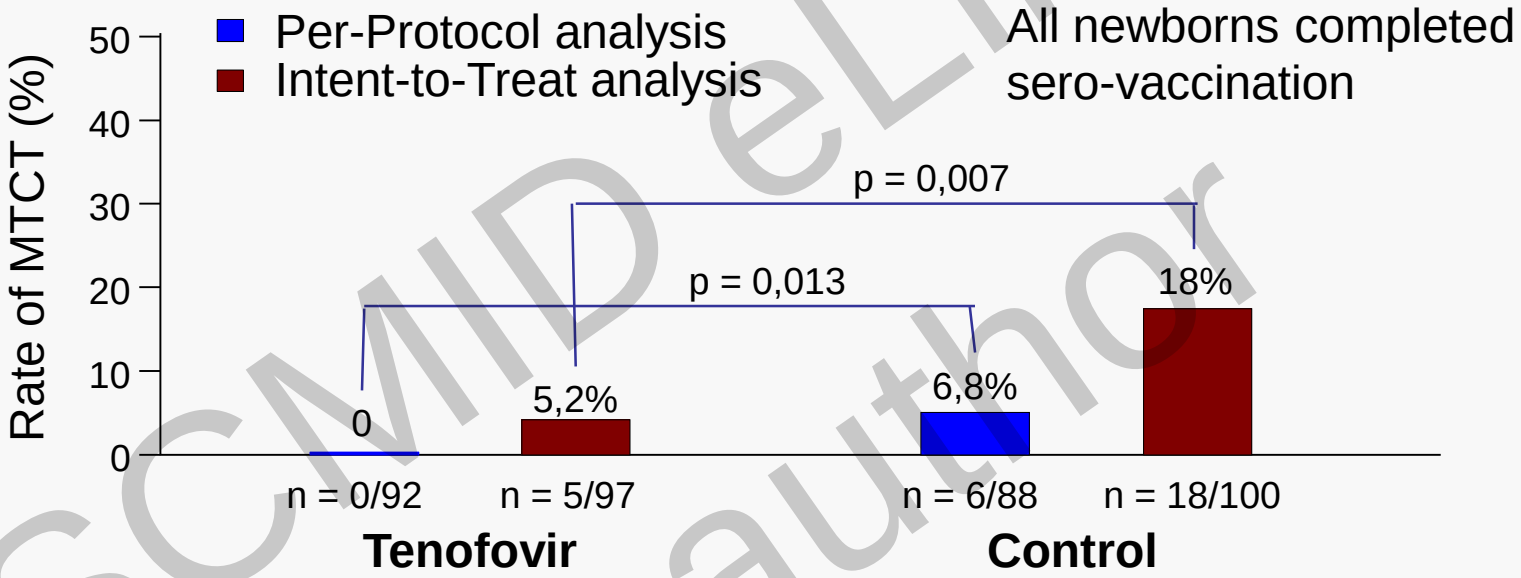
1st randomized study with tenofovir (1)

200 pregnant women HBsAg+, HBeAg+ and HBV-DNA > 200,000 IU/mL



Pan CQ et al. AASLD 2015

1st randomized study with tenofovir (2)



- ↘ rate of MTCT of HBV in Tenofovir group (ITT and PP analysis)
- ↗ ALT and CPK in Tenofovir group
- No difference in secondary effects in newborns

Pan CQ et al. AASLD 2015

Which antiviral drug can be used?

- Lamivudine, Telbivudine and Tenofovir are effective[1]

- No risk of HBV resistance with Tenofovir
- Tenofovir is classified in FDA class B (LdT in B and LAM in C)[2]
- Possibility of breastfeeding with Tenofovir (benefit/risk balance)[2]
  - Dose ingested by newborns corresponds to < 0.03% of therapeutic dose[3]

[1]Brown RS et al. Hepatology 2016
[2]Visvanathan K et al. Gut 2016
[3]Benaboud S et al. Antimicrob Agents Chemother 2011

Which antiviral drug can be used?

- Lot of experience with Tenofovir (and Lamivudine) in HIV-infected pregnant women:

  « In HIV-infected pregnant and breastfeeding women, a once-daily fixed-dose combination of Tenofovir + Lamivudine (or emtricitabine) + efavirenz is recommended as first-line ART »[1]

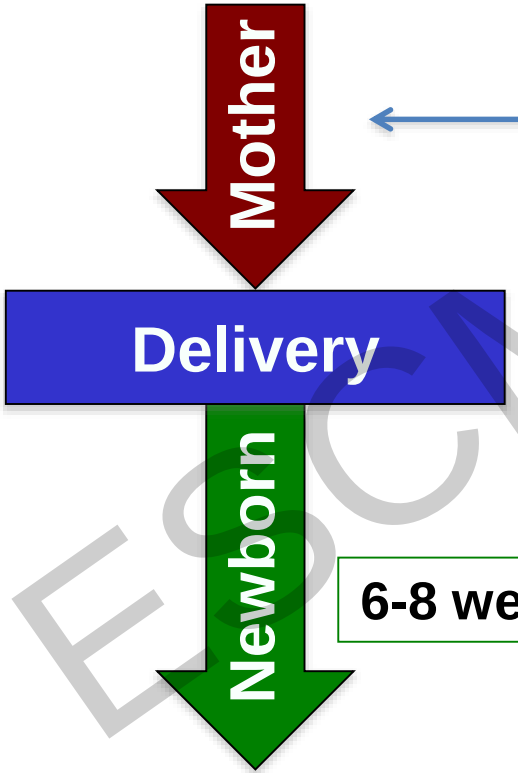
Tenofovir appears as the drug of choice in pregnant women with high HBV-DNA level associated to serovaccination to prevent MTCT

[1]World Health Organization; 2013

What is the best timing for using antiviral drug?

- Starting antiviral drug at 28 weeks gestation
- Stop treatment between 4 and 12 weeks post-partum
- Monitor carefully for ALT flares after this period

Challenging issues in developing countries



HBV screening during (or before) pregnancy

PMTCT HBV close to the delivery
- Presence of health-care workers at delivery
- Availability of vaccine at delivery
- Availability of HBIg at delivery

6-8 weeks of life

Universal infant
HBV vaccination (pentavalent vaccine)
(WHO recommendation)

Challenging issues (1)

HBV screening during (or before) pregnancy in developing countries

Use of (multiplex) Point-of-Care methods ?

Multiplo screening: HIV, Hepatitis B, Hepatitis C, Syphilis

Challenging issues (2)

PMTCT HBV close to the delivery

- **Presence of health-care workers at delivery**
- **Availability of vaccine at delivery**
- **Availability of HBIg at delivery**

- **Lack of HBIg availability**
- **First injection of HBV vaccine administered at 6-8 weeks of life**

➔ **Peri-exposure prophylaxis (PEP) ?**

Administration of LAM or TDF in newborns during the first weeks of life (similar hypothesis than HIV)? And then HBV vaccination beginning at 6-8 weeks of life

Conclusion

- Serovaccination if highly effective to prevent MTCT of HBV
- Screening HBsAg during pregnancy and full serovaccination program have to be regularly evaluated and reinforced by health authorities
- In pregnant women with HBV-DNA > 5 – 7 log IU/mL, antiviral drug between 28 weeks gestation and 4 – 12 weeks post-partum has demonstrated efficacy in association with serovaccination. In this indication, Tenofovir appears as the drug of choice.
- In developing countries Point-of-Care tests could be helpful for screening HBsAg (and HBV-DNA ?) in pregnant women
- New strategies have to be implemented in developing countries to avoid HBIg use and to manage early post-partum period