Elimination of Hepatitis B: Is It a Mission Possible

Tai-Chung Tseng
National Taiwan University Hospital, Taipei, Taiwan

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Outline

• Introduction
• Effective primary prevention
• Management of CH-B patients
  – Treatment response of nucleos(t)ide analogue (NUC)
  – New treatment to clear HBsAg (functional cure)
• Conclusions
Chronic hepatitis B (CHB) is a significant health problem

- An estimated 240 million people worldwide are living with CHB\(^1\)

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CHB = chronic hepatitis B; HBsAg = hepatitis B surface antigen. Map adapted from CDC
1. WHO. Hepatitis B fact sheet. www.who.int/mediacentre/factsheets/fs204/en/. Updated July 2016. Accessed March 17, 2017; 2. Chen et al. Slow decline of hepatitis B burden in general population. J Hep. 2015.
HBV Replication Cycle

- HBV DNA level
- HBsAg level
Natural History of HBV Carriers

Liaw & Chu. Lancet 2009.
How to Control Chronic Viral Infection

• To prevent new viral infection
• To clear the virus in the patients with chronic infection
  – If not, is it possible to minimize the damage?
To Prevent New Viral Infection
HBV Transmission

- Transfusion
- Individuals with multiple sexual partners
- Organ and tissue transplantation
- Contaminated needle
- Mother to baby
- Child to child
HBV is Prevented By Currently Available Safe & Effective Vaccine

• Vaccination is the mainstay of hepatitis B prevention.¹
• Since 1984, countrywide immunization for newborns in Taiwan
• The vaccine coverage rate is 97%

¹http://www.who.int/mediacentre/factsheets/fs204/en/.
HBsAg Prevalence In Children <15 Years Of Age In Taiwan

% HBsAg prevalence children <15 years

- 1984: 9.8%
- 1999: 0.7%
- 2004: 0.5%

Adapted from: Ni YH, et al. Gastroenterology 2007;132:1287–1293: Sarin S, et al. Hepatol Int 2016; 10:1–98.
Maternal Viral Load & Mother to Children Transmission (MTCT) rates

Wen et al. J Hepatol 2013;59:24
TDF Reduces MTCT of HBV in Highly Viremic Mothers (Taiwan)

- Prospective, multi-center, non-randomized trial
- 118 HBeAg-positive pregnant women
- All the newborns received HBV vacc + HBIG
- TDF (n=62) from weeks 30-32 of gestation until 1 month post-partum or received no HBV therapy (n=56, control)

| Infant Outcomes, n/N (%)                  | TDF n=62     | Control n=56 | p-value   |
|------------------------------------------|--------------|--------------|-----------|
| HBV DNA positive at birth                | 4/65 (6.15)  | 17/56 (31.48)| 0.0003    |
| HBsAg-positive at Month 6                | 1/65 (1.54%) | 6/56 (10.71) | 0.0481    |

Chen HL et al. Hepatology 2015, 62:375-86
TDF Reduces MTCT of HBV in Highly Viremic Mothers (China)

- A RCT enrolling 200 HBeAg-positive pregnant women
- MTCT rate defined as the proportion of infants with serum HBV DNA >20 IU/mL or HBsAg positivity at 28 weeks of age.
- Similar safety profile between groups
- No difference in birth defect rates

Pan et al. NEJM, 2016; 374:2324-34
TDF May Not Reduce MTCT of HBV in Highly Viremic Mothers (Thailand)

- Prospective, multi-center, randomized trial
- 331 HBeAg-positive pregnant women with CHB
- TDF from 28 weeks of gestation to 2 months post partum vs. Control
- Median time from birth to HBV vacc: 1.2hrs
- Median time from birth to HBIG: 1.3Hrs

| Infant Outcomes, n/N (%) | TDF n=147 | Control n=147 | p-value |
|--------------------------|-----------|---------------|---------|
| HBsAg-positive at Month 6| 0/147 (0%)| 3/147 (2%)    | 0.12    |

Jourdain et al, NEJM 2018 8;378:911-923
Primary Prevention is Effective

- Timely vaccination
- HBIG
- NUC at the 3rd trimester in highly viremic mother
- Development of Anti-HBs is protective
Management of CHB patients
### Treatment response of 8 year TDF

|                                | HBeAg- | HBeAg+ |
|--------------------------------|--------|--------|
| **HBV DNA <29 IU/mL (ITT)*** % | 74     | 58     |
| **HBV DNA <29 IU/mL (Observed), %** | 99.6   | 97     |
| **HBeAg loss / seroconversion†, %** | NA     | 47/ 31 |
| **HBsAg loss*/seroconversion (KM%)‡** | 1.1/0.7| 12.9/10.3|

*Missing = failure; add one OAV not approved for HBV = failure[LTE-TDF]*
† Missing = excluded; add one OAV not approved for HBV = included)
‡ KM% = Kaplan-Meier % (KM-ITT)
NA, not applicable

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*aHBsAg loss in Study 102 (HBeAg-): 3 patients; Study 103 (HBeAg+): 28 patients

Marcellin, AASLD, 2014, Oral #229
Indefinite NUC Tx Improves Outcomes In CHB Patients With Advanced Fibrosis

Adapted from: Liaw Y-F, et al. NEJM 2004;351:1521-31.
FIB-4 $<$1.29 (F2 marker) Defines Low HCC risk in HBV carriers on Indefinite NUC Tx

Tseng et al Am J Gastroenterol. 2017 112:1564-1574
NUC treatment

• NOT effective in clearing HBsAg
• Effective in suppressing viral replication
  – It lowers risks of HCC and disease progression
  – HCC risk could be minimized if initiating NUC earlier
New Treatment to Clear HBsAg?

Taking immunotherapy as example
Potential Immunotherapeutic targets of CHB

Yang N & Bertoletti A, Hepatol Int, 2015
A Clinical Trial of HBV Therapeutic DNA Vaccine

Fontaine H et al. Gut. 2015;64: 139-47
Conclusions

| Primary prevention | Early NUC Tx | New Tx to clear HBsAg | When to eliminate HBV | Control of HCC and cirrhosis |
|--------------------|--------------|-----------------------|-----------------------|------------------------------|
| ✔                  | ✔            |                       | 80 years later        | No                           |
| ✔                  | ✔            |                       | 80 years later        | Lower the risks              |
| ✔                  | ✔            | ✔                     | Within decades        | Minimize the risks           |
Taiwan
Formosa, Beautiful Island

Thank You for Your Attention