Current Treatment Options for Hepatitis B

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Comparison of global and Western Pacific mortality by major communicable diseases, 2013

Hepatitis-related deaths in the Western Pacific Region, 2013

Prevalence of HBsAg in 1992 and 2006

Estimated number of persons with CHB in China

- CHB ≈ 90M
- CHB with Rx indication ≈ 20M-30M
- Cirrhosis ≈ 1M
- HCC ≈ 0.3M

Based on data Courtesy of Dr FQ Cui
Therapeutic strategies for chronic hepatitis B

Short-term "curative" treatment

IFN

On treatment response

Follow-up (mo/ys)

HBV DNA < 2000 IU/ml
ALT < UNL
(anti-HBe)

HBsAg Loss

Long-term "suppressive" treatment

NUC

HBV DNA undetectable by PCR (<10-15 IU)

HBsAg loss

Years
替代终点1：病毒学指标

关键临床研究及Real-world临床实践研究均证实了Nas具有高的抗HBV效能
CHB抗病毒治疗1年达到的病毒学终点（短期RCTs）
各种核苷（酸）类似物长期治疗耐药发生率比较

*Collation of currently available data – not from head-to-head studies

- **1st generation**
  - LAM: 70%
  - ADV: 49%
  - LDT: 38%

- **2nd generation**
  - LAM: 67%
  - ADV: 11%
  - LDT: 29%

- **3rd generation**
  - LAM: 0%
  - ADV: 0%
  - LDT: 4%

adapted from EASL HBV Guidelines, J Hepatol 2012
Virologic response during prolonged ETV for ≥96 wks in partial responders at wk 48

Cumulative probabilities of achieving VR (%)

Duration of ETV treatment (weeks)

Point of PVR

Efficacy of TDF ± Lam Rescue Therapy in Lam-R CHB With Failure of Lam+ ADV Combination

Log-rank $P < 0.001$

HBV DNA $< 5.00 \log_{10} \text{IU/mL}$

HBV DNA $\geq 5.00 \log_{10} \text{IU/mL}$

Treatment Duration (mo)

Cumulative Rate of Virologic Response (%)
The Demographics of TDF and ETV treated Chinese patients with CHB

<table>
<thead>
<tr>
<th></th>
<th>TDF group (n = 33)</th>
<th>ETV group (n = 65)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35 (26-61)</td>
<td>39 (20-67)</td>
<td>t = 1.849</td>
</tr>
<tr>
<td>Sex (male, %)</td>
<td>69.7 (23/33)</td>
<td>81.5 (53/65)</td>
<td>χ² = 1.763</td>
</tr>
<tr>
<td>BMI</td>
<td>22.63 ± 2.73</td>
<td>22.85 ± 2.86</td>
<td>t = 0.355</td>
</tr>
<tr>
<td>Follow-up time (months)</td>
<td>13.4 (6.2-28.0)</td>
<td>16 (6.0-27.0)</td>
<td>t = 0.656</td>
</tr>
<tr>
<td>The proportion of Alcohol history (%)</td>
<td>18.2 (6/33)</td>
<td>24.6 (16/65)</td>
<td>χ² = 0.520</td>
</tr>
<tr>
<td>The proportion of Smoking history (%)</td>
<td>42.4 (14/33)</td>
<td>35.4 (23/65)</td>
<td>χ² = 0.462</td>
</tr>
<tr>
<td>Family history of Hepatitis B (%)</td>
<td>33.3 (11/33)</td>
<td>30.8 (20/65)</td>
<td>χ² = 0.067</td>
</tr>
<tr>
<td>ALT baseline (U/L)</td>
<td>194.1 ± 128.5</td>
<td>157.6 ± 216.8</td>
<td>t = 1.043</td>
</tr>
<tr>
<td>HBV DNA baseline (Log10 IU/ml)</td>
<td>6.50 ± 0.69</td>
<td>6.15 ± 1.36</td>
<td>t = 1.701</td>
</tr>
<tr>
<td>Rate of Hepatitis B E antigen positive (%)</td>
<td>60.6 (20/33)</td>
<td>55.4 (36/65)</td>
<td>χ² = 0.244</td>
</tr>
</tbody>
</table>

P>0.05 for all variables

HBV DNA undetectable rates in TDF and ETV group

TDF ± ETV: Virologic response at weeks 48 and 96

Tenofovir disoproxil fumarate monotherapy for nucleos(t)ide analogue-naïve and nucleos(t)ide analogue-experienced chronic hepatitis B patients

Sang Kyung Jung¹, Kyung-Ah Kim¹, So Young Ha¹, Hyun Kyo Lee¹, Young Doo Kim¹, Bu Hyun Lee¹, Woo Hyun Paik¹, Jong Wook Kim¹, Won Ki Bae¹, Nam-Hoon Kim¹, June Sung Lee¹, and Yoon Jung Jwa²

¹Department of Internal Medicine, Ilsan Paik Hospital, Inje University College of Medicine, Goyang; ²Health promotion center Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Korea
Cumulative probability of CVR to TDF according to previous responses

Tenofovir disoproxil fumarate has a substantial efficacy against multidrug-resistant strains of hepatitis B virus

Bulent Baran¹, Ozlem Mutluay Soyer², Asli Cifcibasi Ormeci², Suut Gokturk², Sami Evirgen², Filiz Akyuz², Cetin Karaca², Kadir Demir², Fatih Besisik², Derya Onel³, Mine Gulluoglu⁴, Selim Badur³ and Sabahattin Kaymakoglu²

1 Department of Gastroenterology, Koç University Hospital, Zeytinburnu, Istanbul, Turkey
2 Department of Gastroenterohepatology, Istanbul Faculty of Medicine, Istanbul University, Capa, Istanbul, Turkey
3 Department of Microbiology, Istanbul Faculty of Medicine, Istanbul University, Capa, Istanbul, Turkey
4 Department of Pathology, Istanbul Faculty of Medicine, Istanbul University, Capa, Istanbul, Turkey
Complete virological response (CVR) to TDF in NA-naive vs. ADF-R vs. ADF-S groups

TDF-Based Rescue Therapy in CHB With Suboptimal Responses to ADV with Lam-R

TDF-Based Rescue Therapy in CHB With Suboptimal Responses to ADV with Lam-R

P = 0.069

% of patients with HBV DNA < 20 IU/mL

Time (Weeks)

TDF ± ETVT in ADV-R CHB with multiple drug failure: results of a randomised trial

替代终点2：组织学指标

长期NA治疗改善肝脏组织学
CHB患者抗病毒治疗1年所达到的组织学终点（短期RCTs）

Dienstag JL. Hepatology 2009;49:s112-s121
ETV长期治疗CHB获得组织学改善（中位时间：5.6年,n=57）

Chang TT, et al. HEPATOLOGY 2010;52:886-93
TDF治疗5年的组织学结果
第5年，348/641(54%) 名患者进行组织学检查

Knodell 炎症评分

Ishak纤维化评分

临床终点1：疾病进展

抗病毒治疗改善CHB肝硬化患者的临床结局
香港研究
ETV长期治疗—显著降低肝硬化患者全因死亡及肝脏相关死亡风险

- 香港研究，ETV治疗组共1446例CHB患者，平均随访36个月；对照组424例未治疗患者，平均随访114个月
- 肝硬化患者中，与对照组相比，ETV治疗显著肝脏相关死亡（P<0.001）及全因死亡风险（P<0.001）

抗病毒治疗可改善肝硬化患者的临床结局

- 对6项研究（3644例患者）进行meta分析，其中有4项研究中报告了代偿期肝硬化患者的数据。
- 研究显示接受核苷(酸)类药物治疗的肝硬化患者，长期并发症*发生率（8.5%，65/745）明显低于未接受治疗的患者（26.9%，125/465）（RR:0.28, 95%CI: 0.13-0.58）

<table>
<thead>
<tr>
<th>研究</th>
<th>治疗 (n/N)</th>
<th>未治疗/安慰剂 (n/N)</th>
<th>相对危险度 95% CI</th>
<th>比重 (%)</th>
<th>相对危险度 95% CI</th>
<th>年</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liaw, et al.</td>
<td>26/260</td>
<td>29/139</td>
<td>33.96</td>
<td>0.48</td>
<td>[0.29, 0.78]</td>
<td>2004</td>
</tr>
<tr>
<td>Matsumoto et al.</td>
<td>0/65</td>
<td>23/67</td>
<td>5.92</td>
<td>0.02</td>
<td>[0.00, 0.35]</td>
<td>2005</td>
</tr>
<tr>
<td>Eun et al.</td>
<td>5/111</td>
<td>36/111</td>
<td>24.99</td>
<td>0.14</td>
<td>[0.06, 0.34]</td>
<td>2007</td>
</tr>
<tr>
<td>Jong Ryul Eun. Et al</td>
<td>32/309</td>
<td>37/148</td>
<td>35.12</td>
<td>0.41</td>
<td>[0.27, 0.64]</td>
<td>2010</td>
</tr>
<tr>
<td>Subtotal(95%CI)</td>
<td>745</td>
<td>465</td>
<td>100.00</td>
<td>0.28</td>
<td>[0.13, 0.58]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 63 (Treatment), 125 (no treatment /placebo)
Test for heterogeneity: Chi²=11.83, df=3 (P=0.008), I²=74.6%
Test for overall effect: Z=3.42 (P=0.06)

*长期并发症定义为：CHB引起的死亡、HCC、或失代偿期肝硬化。

Long-Term Effect of Antiviral Therapy on Disease Course After Decompensation in Patients With Hepatitis B Virus–Related Cirrhosis

Jeong Won Jang, Jong Young Choi, Young Seok Kim, Hyun Young Woo, Sung Kyu Choi, Chang Hyeong Lee, Tae Yeob Kim, Joo Hyun Sohn, Won Young Tak, and Kwang-Hyub Han

AVT significantly modifies the natural history of decompensated cirrhosis, improving liver function and increasing survival.

The results underscore the importance of promptly administering potent antiviral drugs to patients under consideration for LT.
Analysis of PSM cohort

(A) Survival in treated and untreated cohorts.

(B) Survival according to treatment response.

*Bonferroni-adjusted P value.

Mean changes in (A) Child-Pugh score and (B) MELD score. *P<0.05.

Long-term safety of NAs in 53,500 pts

All subjects with diagnosis codes of ‘viral hepatitis’
N = 107,800

- 33,090 subjects excluded

CHB patients fulfilled inclusion and exclusion criteria
N = 74,710

- 21,210 subjects excluded in the 3-year landmark analysis

Included in the 3-year landmark analysis
N = 53,500

- 30,972 no CHB diagnosis code and no HBsAg
- 1,264 pre-existing renal events
- 765 co-infected with HCV
- 9 co-infected with HDV
- 41 co-infected with HEV
- 34 co-infected with HIV
- 5 younger than 18 years old at baseline

11,700 follow-up duration < 3 years
8,152 deaths within 3 years
1,358 renal/bone events within 3 years

Weighted cumulative incidence of renal failure

Weighted cumulative incidence of bone fractures

Sequential or combination therapy for HBV

- A strategy of switching or late addition of Peg-IFN to ongoing NA may increase rates of HBeAg seroconversion and HBsAg loss.
- But only the patients who had received NA for a relatively long time, achieved higher virological response, and even partial serological response can benefit from this strategy.
- No guidelines recommend that all patients who had received NA switch to or add on IFN.
**Tenofovir Alafenamide (TAF): Next-Generation Prodrug of Tenofovir**

- **TFV**: Tenofovir
- **TDF**: Tenofovir Disoproxil Fumarate
- **TAF**: Tenofovir Alafenamide

- Improved stability in plasma:
  - Enhanced delivery of TFV-DP to hepatocytes
  - Lower doses with TAF; ↓ systemic exposures of TFV

**Diagram**:

- GUT
  - TFV
  - TDF
  - TAF

- PLASMA
  - TFV
  - TDF/TFV
  - TAF

- LYMPHOID CELLS/HEPATO CYTES
  - TAF
  - TFV
  - TFV-MP
  - TFV-DP

**Equations**:

- CES1 = Carboxylesterase 1

**References**:

Agarwal K et al. AASLD 2013, Abstract 973
Safety of TAF in HIV infection (Phase 2)

- Less decline in $\text{CL}_{\text{Cr}}$ with TAF
- Less decline in BMD ($\% \Delta$ in hip/spine BMD) with TAF

*In combination with elvitegravir/cobicistat/emtricitabine.
Sax P, et al. JAIDS 2014:May 27 ePub (ahead of print)
Novel therapy in the future

GS-4774 structure

<table>
<thead>
<tr>
<th>M</th>
<th>X</th>
<th>Large S (env)</th>
<th>Core</th>
<th>His$_6$</th>
</tr>
</thead>
</table>

X = 60 amino acids

Large S = 399 amino acids

Core = 182 amino acids

M = MADEAP metabolic stability tag

His$_6$ = 6 histidine-tag

GS-4774 recombinant antigen
关键点

● 尽管维持HBV DNA抑制与HBV清除关系不大，但却可降低肝脏并发症的发生率。初步数据显示，长期的HBV DNA抑制可使部分患者实现肝硬化的逆转。

● 对于肝硬化患者，持久的HBV DNA抑制不能完全避免发生HCC的风险。
# TDF Recommended for HBV Therapy by Major Guidelines

<table>
<thead>
<tr>
<th>Year</th>
<th>Guideline</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>AASLD</td>
<td>Treatment may be initiated with any of the seven approved antiviral medications, but PEG-IFN, <strong>TDF</strong> or <strong>ETV</strong> are preferred.</td>
</tr>
<tr>
<td>2010</td>
<td>China</td>
<td><strong>If possible</strong>, drugs with high potency and low resistance <strong>should be chosen</strong> for NUC-naïve patients.</td>
</tr>
<tr>
<td>2012</td>
<td>EASL</td>
<td><strong>ETV or TDF</strong> are the <strong>preferred</strong> NUCs for NUC-naïve CHB patients. LAM, ADV and LdT may only be used…if more potent drugs with a high barrier to resistance are not available or appropriate.</td>
</tr>
<tr>
<td>2012</td>
<td>EASL</td>
<td><strong>ETV and TDF</strong> are potent HBV inhibitors with a high barrier to resistance. Thus, they can be confidently used as <strong>first-line monotherapies</strong>.</td>
</tr>
<tr>
<td>2013</td>
<td>NICE</td>
<td><strong>PEG-IFN /ETV/TDF first</strong></td>
</tr>
</tbody>
</table>
Suboptimal Selection of NAs in China
\( (n=30\ 526/75\ 517) \)

- ADV: 27.0%
- ETV: 37.8%
- LAM: 23.2%
- TBV: 11.2%
- TDF: 0.7%

CR-HepB data as of March 14, 2015
Consolidate prevention: vaccination + PMTCT

Source: WHO China (preliminary results)
Mortality and incidence rates of CLDs/cirrhosis and HCC pre- & post launch of viral hepatitis therapy program in 2003 in Taiwan

WHO's response: Hepatitis area of work

- 2010: World Health Assembly Resolution on Viral Hepatitis
- 2011: Establishment of Global Hepatitis Programme (GHP)
- 2012: Global Framework for Prevention & Control of Viral Hepatitis Infection
- 2013: Reorganization of Global Hepatitis Programme
- 2014: HCV Guideline
- 2015: HBV Guideline

- Hep B immunization
- Blood/injection safety
- Outbreak control
- Water and sanitation
WHO HBV guideline release at APASL 2015
<table>
<thead>
<tr>
<th>TOPIC</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staging/ non-invasive test (NIT)</td>
<td>▪ APRI preferred NIT to assess for the presence of cirrhosis</td>
</tr>
<tr>
<td>Who to treat</td>
<td>▪ Decompensated cirrhosis or cirrhosis (clinical criteria or APRI score &gt;2), regardless of ALT levels, HBeAg, or HBV DNA.</td>
</tr>
<tr>
<td></td>
<td>▪ No cirrhosis but persistently abnormal ALT levels +/- ongoing HBV replication, (HBV DNA &gt;20,000 IU/mL or HBeAg +ve).</td>
</tr>
<tr>
<td>First line treatment</td>
<td>▪ Drugs with a high barrier to resistance (TDF or ETV).</td>
</tr>
<tr>
<td></td>
<td>▪ ETV in children aged 2-11 years.</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>▪ Switch to TDF if evidence of resistance to 3TC, ETV, ADF, TBV.</td>
</tr>
<tr>
<td>Treatment discontinuation</td>
<td>▪ Never discontinue in persons with cirrhosis.</td>
</tr>
<tr>
<td></td>
<td>▪ If no cirrhosis, discontinuation on case-by-case basis (persistent HBeAg and/or HBsAg loss or undetectable HBV DNA)</td>
</tr>
<tr>
<td>Monitoring (treatment response/toxicity)</td>
<td>▪ <strong>On or pre-treatment:</strong> ALT + HBV DNA (HBsAg, HBeAg + APRI pre-treatment) annually. More frequent monitoring with cirrhosis.</td>
</tr>
<tr>
<td></td>
<td>▪ Assessment of baseline renal function prior to treatment initiation.</td>
</tr>
<tr>
<td>Monitoring for HCC</td>
<td>▪ Ultrasound + AFP every 6 months in persons with cirrhosis and/or family history of HCC.</td>
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Chinese WHO HBV guideline release in Beijing