Antiviral Drug Resistance in Hepatitis B: An Asia Pacific Perspective

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North Melbourne, Victoria 3051,
AUSTRALIA

# HBV Treatment in 2013

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Manufacturer</th>
<th>Date Approved for Hepatitis B</th>
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<tr>
<td>Interferon alfa-2b</td>
<td>INTRON® A</td>
<td>Schering Corporation</td>
<td>1991</td>
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<tr>
<td>Peginterferon alfa-2a</td>
<td>PEGASYS®</td>
<td>Hoffman La-Roche</td>
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<td>Lamivudine</td>
<td>EPIVIR-HBV®</td>
<td>GlaxoSmiKline</td>
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<td>Adefovir dipivoxil</td>
<td>HEPSERA™</td>
<td>Gilead Sciences</td>
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</tr>
<tr>
<td>Entecavir</td>
<td>BARACLUDE™</td>
<td>Bristol-Myers Squibb</td>
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<tr>
<td>Telbivudine</td>
<td>TYZEKA™</td>
<td>Idenix/Novartis</td>
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<tr>
<td>Tenofovir</td>
<td>VIREAD™</td>
<td>Gilead Sciences</td>
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</table>
Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update

Yun-Fan Liaw, Jia-Horng Kao, Teerha Piratvisuth, Henry Lik Yuen Chan, Rong-Nan Chien, Chun-Jen Liu, Ed Gane, Stephen Locarnini, Seng-Gee Lim,
APASL Guidelines Recommend Entecavir and Tenofovir as First-Line Agents

Entecavir and tenofovir are potent HBV inhibitors and they have a high barrier to resistance. Thus they can be confidently used as first-line monotherapies.

ETV or TDF is preferred NUC 1A

Drug-Resistant Mutations can Lead to Disease Progression and Death

*Disease progression, defined by the first occurrence of any of the following: an increase of at least 2 points in the Child–Pugh score, spontaneous bacterial peritonitis with proven sepsis, renal insufficiency, bleeding gastric or oesophageal varices, the development of hepatocellular carcinoma or death related to liver disease.1 Patients received lamivudine.

8/10 patients assigned to LVD who died after reaching a clinical endpoint showed evidence of YMDD mutations²

Potential Consequences of Antiviral Drug Resistance in Chronic HBV

<table>
<thead>
<tr>
<th>Category</th>
<th>Consequences</th>
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<tbody>
<tr>
<td><strong>Virologic</strong></td>
<td>Virologic breakthrough and rebound</td>
</tr>
<tr>
<td></td>
<td>Reduced HBeAg seroconversion rates</td>
</tr>
<tr>
<td></td>
<td>HBeAg seroconversion relapse</td>
</tr>
<tr>
<td><strong>Biochemical</strong></td>
<td>Biochemical breakthrough</td>
</tr>
<tr>
<td><strong>Histologic</strong></td>
<td>Histologic progression of disease</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td>Hepatic flare and decompensation</td>
</tr>
<tr>
<td></td>
<td>Increased recurrence post liver transplantation (viral load is strongest</td>
</tr>
<tr>
<td></td>
<td>predictor of HBV recurrence post liver transplant)*</td>
</tr>
<tr>
<td></td>
<td><strong>Increased tumourigenicity</strong></td>
</tr>
<tr>
<td><strong>Public health</strong></td>
<td>Alteration in HBsAg antigenicity</td>
</tr>
<tr>
<td></td>
<td>Transmission of drug resistant HBV</td>
</tr>
<tr>
<td></td>
<td>Development of multi-drug resistant HBV population</td>
</tr>
</tbody>
</table>

Conclusion

- Severely restrict/limit/regulate the use of LOW genetic barrier drugs to THIRD LINE indications only

**THESE CAN BE DANGEROUS DRUGS**

Rates of Development of Resistance (HBeAg+)

Data not from head-to-head studies. Design and inclusion criteria may differ.
Indications of Emergence of Drug-Resistant Virus

1. Increasing viral load (≥ 1.0 log IU/ml)
2. Identification of known genotypic markers of drug resistance within viral polymerase:
   * primary resistance mutations (rtM204I)
   * secondary resistance mutations (rtL180M with rtM204V)
   * compensatory mutations (rtV173L)
3. Increasing serum ALT levels
4. Clinical deterioration

Clinical Practice Guidelines (EASL, AASLD and APASL)

- Recommend serum HBV DNA levels measured at week 12 and 24
- Week 12: compliance
- Week 24: risk of resistance if using low genetic barrier NA
  : predict likelihood of a sustained virological response
- Thereafter every 3 months

Patterns/Profiles of Drug Resistance: rtM204V/I vs rtA181T±rtN236T

- HBV VL Rebound (>1.0 log IU/ml increase from nadir)
- HBV VL Plateau/Creep (< 1.0 log IU/ml increase from nadir)

**Clinical Impact**

- **Diagnosis:**
  increasing HBV DNA in serum (> 1.0 log IU/ml)
- **Management:**
  As per APASL Guidelines

- **Diagnosis:**
  HBV Pol Sequencing for Resistance Changes
- **Management:**
  ETV add on or switch to TDF
Rates of Development of Resistance (LAM-RES)

Data not from head-to-head studies. Design and inclusion criteria may differ.
Steps in the Management of Antiviral Drug-resistance

- Detection of virologic breakthrough
- Counsel on medication adherence
- Confirm virologic breakthrough
- Test for genotypic resistance in patients with confirmed virologic breakthrough, particularly patients who had been exposed to >1 nucleos(t)ide analog
- Rescue therapy may be initiated on first detection of virologic breakthrough if there is evidence of biochemical breakthrough / decompensation

Lok, A. Personal communication
How Would Resistance Mutation Testing Help in Patient Management?

• Differentiate patients with virologic breakthrough due to medication non-adherence from patients with virologic breakthrough due to drug resistance

• Avoid unnecessary changes in treatment in the former and provide guidance on appropriate rescue therapy based on resistance mutation detected in the latter
What to do on First Virological [Viral Load] Breakthrough/Partial Virological Response

- Repeat HBV DNA testing in a timely manner to confirm VL breakthrough
- If confirmed [HBV VL ≥ 1.0 log IU/mL] THEN perform HBV POL SEQUENCING
- Typical results for the HBV POL:
  1. “WILD-TYPE” SEQUENCE if no known resistance mutations found
  2. rtM204V/I±rtL180M detected
  3. rtA181T/V
  4. rtN236T±rtA181T/V detected
  5. rtT184S/A/I/L+rtS202G/C (and/or rtM250I/V) WITH rtL180M+rtM204V
  6. Complex pattern(s) detected
Patterns and Pathways of Antiviral Drug Resistance in Chronic Hepatitis B in the Context of Cross-Resistance.

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Amino Acid Substitutions in the rt Domain</th>
<th>LMV</th>
<th>LdT</th>
<th>ETV</th>
<th>ADV</th>
<th>TFV</th>
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</thead>
<tbody>
<tr>
<td>Wild-type</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
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<tr>
<td>L-Nucleoside (LMV/LdT)</td>
<td>M204I/V</td>
<td>R</td>
<td>R</td>
<td>I</td>
<td>S</td>
<td>S</td>
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<tr>
<td>Acyclic phosphonate (ADV)</td>
<td>N236T</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>I</td>
</tr>
<tr>
<td>Shared (LMV, LdT, ADV)</td>
<td>A181T/V</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>R</td>
<td>I</td>
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<tr>
<td>Double (ADV, TFV)</td>
<td>A181T/V + N236T</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>R</td>
<td>R</td>
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<tr>
<td>D-Cyclopentane (ETV)</td>
<td>L180M+M204V/I ± I169 ± T184 ± S202 ± M250</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
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</table>

Abbreviations: I, intermediate sensitivity; R, resistant; S, sensitive based on cell culture and clinical responses.

Managing HBV Antiviral Drug Resistance

**Recommendation 14: Patients with drug resistance**

* LAM or LdT resistance: add-on ADV (IA) or switch to TDF (IIA).
  May switch to ETV 1mg/day for LAM resistance (IB).
  ADV resistance: add-on or switch to LAM, Ldt or ETV if the patient was naïve for these drugs or switch to TDF (IIIA).
  ETV resistance: add-on TDF or ADV (IIIA)
  Resistance to LAM or LdT and ADV: switch to ETV+TDF (IIA)
* Switch to IFN based therapy is an option (IIIA)

Switch to or Add on Rescue Therapy?

- Lamivudine-R or Telbivudine-R
  - Adefovir: add-on *(not optimal)*
  - Tenofovir: switch to seems sufficient
  - Entecavir: switch to *(not optimal rescue)*

- Adefovir-R
  - Lamivudine: add-on if no prior LAM-R *(not optimal)*
  - Tenofovir: switch to *(not optimal rescue)*
  - Entecavir: switch to seems sufficient

- Entecavir-R
  - Tenofovir: switch to seems sufficient

- MDR *(rtA181T containing)*
  - Tenofovir plus Entecavir: seems sufficient
Add-On Strategy: ALWAYS?

1. When is That Decision Point?
For high genetic barrier drugs: week 48
Answer is PROBABLY NOT

Entecavir Treatment for Chronic Hepatitis B: Adaptation Is Not Needed for the Majority of Naïve Patients with a Partial Virological Response

Roeland Zoutendijk,1 Jurriën G. P. Reijnders,1 Ashley Brown,2 Fabien Zoulim,3 David Mutimer,4 Katja Deterding,5 Jörg Petersen,6 Wolf Peter Hofmann,7 Maria Buti,8 Teresa Santantonio,9 Florian van Bömmel,10 Pierre Pradat,3 Ye Oo,4 Marc Luetgehetmann,11 Thomas Berg,10 Bettina E. Hansen,1 Heiner Wedemeyer,5 and Harry L. A. Janssen1 for the VIRGIL Surveillance Study Group

Hepatology 2011 Vol.54:443-451
Add-On Strategy: ALWAYS?
For low genetic barrier drugs: week 24
Answer is YES for Add-On Strategy

2. What Has Failed?
• need to know Cross-Resistance Profile
• need to know which of the possible “add-on drugs” will be ADDITIVE or SYNERGISTIC but NOT ANTAGONISTIC with the failing drug
Add-On Strategy: ALWAYS?

3. What Works?

OR

4. What Doesn’t Work?

AND WHEN
ETV is Effective in Patients Pretreated with ADV

ETV achieves similar virological response rates in patients with or without ADV resistance.

Adapted from Reijnders JGP et al. 19th APASL, 2009; Hong Kong. Oral FP036.
Patients with ADV-Resistant Mutations May be at Risk of Sub-Optimal Response to TDF

- Five-year retrospective analysis
  - Probability of achieving complete virological response* with TDF monotherapy in patients with previous ADV failure according to resistance profile and baseline HBV DNA levels
  - n=110, Kaplan–Meier analysis


- ADM resistance (all) (n=21)
  - ADM resistance, HBV DNA <10^7 at BL resistance (n=6)
  - ADM resistance, HBV DNA >10^7 at BL resistance (n=15)
  - ADM experienced, no ADM resistance (n=89)

* HBV DNA <400 copies/mL
Add-On Strategy: ALWAYS?

5. What About Complex (MDR) Pathways?
Multi-Drug Resistance (MDR)

- Sequential addition of resistance mutations to the same viral genome
- **Promoted with sequential monotherapy**, especially by using drugs with similar (structural) characteristics
- **Role of compensatory mutations** virus replication competence (fitness)
- **Need for drug-resistance testing** (Pol sequencing) to determine and monitor therapy:
  - rtA181T ("Shared" Pathway)
  - rtA181T+rtN236T
  - rtA181T+rtI233V+rtN236T+rtM250L
Reduced Viral Load Suppression Observed in TDF-Treated Patients with 181T/V and/or 236T Mutations

- Substitutions selected out de novo or persisted in >10% of ADV-experienced patients when switched to TDF

(A) Presence of rtA181T/V alone.
(B) Presence of rtN236T alone or in combination with rtA181T/V

- Substitutions selected out de novo or persisted in >10% of ADV-experienced patients when switched to TDF

In vitro, the double mutant rtA181V+rtN236T showed a 10-fold reduction in TDF activity compared with wild type (EC$_{50}$=0.92 vs 10, respectively)$^2$

## TF109 HBV DNA < LLOD by Resistance Pathways

<table>
<thead>
<tr>
<th>Resistance Pathway</th>
<th>Amino Acid substitutions in the rt domain</th>
<th>Number % (Total n=58)</th>
<th>HBV DNA undetectable (%)</th>
<th>Median time to undetectable (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-type</td>
<td>-</td>
<td>35% (15)</td>
<td>80% (12)</td>
<td>10.5 (range 3-51)</td>
</tr>
<tr>
<td>L-Nucleoside (LAM/LdT)</td>
<td>M204I/V</td>
<td>25% (21)</td>
<td>100% (21)</td>
<td>12 (range 3-45)</td>
</tr>
<tr>
<td>Acyclic phosphonate (ADV)</td>
<td>N236T</td>
<td>8% (5)</td>
<td>60% (3)</td>
<td>6 (range 1-18)</td>
</tr>
<tr>
<td>181 Containing (LAM/LdT/ADV/TFV)</td>
<td>A181T/V +/- N236T</td>
<td>28% (17)</td>
<td>82% (14)</td>
<td>24 (range 3-48)</td>
</tr>
</tbody>
</table>

Patterson, S et al 2011. GUT; 60:247–54
Lim, L., Locarnini, S. and Angus, P. 2012
Entecavir plus tenofovir combination as rescue therapy in pre-treated chronic hepatitis B patients: An international multicenter cohort study

Jorg Petersen¹,*, Vlad Ratziu², Maria Buti³, Harry L.A. Janssen⁴, Ashley Brown⁵, Pietro Lampertico⁶, Jan Schollmeyer⁷, Fabien Zoulim⁸, Heiner Wedemeyer⁹, Martina Sterneck¹⁰, Thomas Berg¹¹, Christoph Sarrazin¹², Marc Lutgehetmann⁷,¹³, Peter Buggisch¹,†

Journal of Hepatology 2012 vol. 56 | 520–526
Table 2. Patients characteristics prior to combination therapy (n = 41) with genotypic data available.

<table>
<thead>
<tr>
<th>No.</th>
<th>Adv. fibrosis cirrhosis</th>
<th>Lines of pre-treatment</th>
<th>Last treatment</th>
<th>HBV DNA [baseline, IU/ml]</th>
<th>Genotypic resistance</th>
<th>Time to DNA &lt; LLoD (months)</th>
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<td>#1</td>
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<td>ADV + LAM</td>
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<td>WT</td>
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<td>ETV</td>
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<td>181V 204V 202S</td>
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Probability of HBV DNA Below LLoD (<80 IU/ml)

Preventing Resistance – Appropriate Patient Management

• The APASL guidelines advocate the use of a potent drug with a high genetic barrier to resistance as first-line therapy
  – HBV DNA monitoring is critical to detect treatment failure
  – HBV DNA levels should be monitored at Week 12 to ascertain virological response and then every 12 to 24 weeks
  – HBV DNA reduction to undetectable levels by real-time PCR (i.e. <10–15 IU/mL) should ideally be achieved to avoid resistance

Preventing Resistance from the Start to Ensure Long-Term Treatment Success

Prevention
- Judicious timing of treatment
- Education regarding adherence

First-line therapy
- High potency drug with a high genetic barrier to resistance, eg, ETV or TDF
- Consider PEG IFN in suitable patients (eg, high ALT, low HBV DNA)

Monitoring
- Regular 3-6 monthly monitoring of viral load with sensitive HBV DNA assay
- Genotypic resistance testing in patients with virological breakthrough

Salvage therapy
- Early initiation of “add on” salvage therapy
- Avoid “switch” sequential monotherapy
- Avoid combination therapy using drugs with similar cross resistance profiles

“Price Paid” by Patients with Sub-Optimal Virological Response

- If use NA of low potency and low genetic barrier by week 24 then greater than 2% of patients (HBeAg-positive and HBeAg-negative) develop resistance (Zeuzem, S et al 2009. J Hepatol;51:11-20)

- These rates, can increase exponentially
- Thus, need more laboratory monitoring and a “road-map” approach to manage patients including genotypic resistance testing
- Emergence of resistance means biochemical exacerbation and histological progression
- Resistance is also associated with an increased HCC risk (Papatheodoridis, GV et al 2010. J Hepatol;53:348-356)
Summary

- Resistance emerges when replication occurs in the presence of the drug selection pressure.
- The best cost-effective strategy is to prevent or avoid the emergence of antiviral drug-resistance.
  - (No Replication = No Resistance [NR=NR])

Current emerging patterns of antiviral drug resistance to HBV Pol are complex:

- But five major pathways can be defined (L-NA rtM204V/I; ADV rtN236T; shared rtA181T/V; double rtA181T/V+rtN236T [ADV/TFV-resistant]; ETV [naïve])
- Primary resistance mutations across NA groups: A181T/V
- Requirement for HBV Pol sequencing to determine profile of antiviral drug resistance
- Emergence of Multi Drug Resistance (MDR) clear cause for concern
Summary

**KEEP IT SIMPLE**

- The APASL CPGs recommend the use of high genetic barrier drugs (Entecavir or Tenofovir) as First Line Agents
- Reduces laboratory-based monitoring (DNA/Pol Sequencing)
- Reduces/eliminates the burden of managing NA-resistant Patients in the clinic
- By treating appropriately……
  
  **NO Replication = No Resistance**

  **NR = NR**
Indonesia to override patents for live-saving medicines

JAKARTA, 25 March 2013 (PlusNews)
The Indonesian government hopes to implement one of the largest ever examples of “compulsory licensing”, which will enable the generic manufacture of drugs still under patent.

In this latest move, a September 2012 presidential decree announced the government would procure generic equivalents of the international patents for seven HIV/AIDS and hepatitis B medicines, citing the “urgent need” to control these diseases.

DECREE OF THE PRESIDENT REPUBLIC OF INDONESIA

NUMBER 76 OF 2012

REGARDING

EXPLOITATION OF PATENT BY THE GOVERNMENT ON

ANTIVIRALS AND ANTIRETROVIRALS MEDICINES

BY THE GRACE OF GOD MAHASA ESA

THE PRESIDENT OF THE REPUBLIC OF INDONESIA,

Considering: a. that in line with the urgent need in the effort to control Human Immunodeficiency Virus-Acquired Immuno Deficiency Syndrome (HIV / AIDS) and Hepatitis B in Indonesia, it is necessary to continue and expand the access policies to provide access to Antiviral and Antiretroviral medicines that are still protected by patent;
PRESIDENTIAL DECREE OF REPUBLIC OF INDONESIA

NUMBER 76 OF 2012

REGARDING

EXPLOITATION OF PATENTS BY THE GOVERNMENT ON ANTIVIRAL AND ANTIRETROVIRALS MEDICINES

ACTIVE SUBSTANCE NAME, NAME OF PATENT HOLDER, PATENT NUMBER, AND DURATION OF PATENTS FOR ANTIVIRAL AND ANTIRETROVIRAL MEDICINES

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<th>NO.</th>
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<td>Efavirenz</td>
<td>Merck &amp; Co., INC</td>
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PRESIDENT OF THE REPUBLIC OF INDONESIA,

DR. H. SUSILO BAMBANG YUDHOYONO
Gilead to Buy Pharmasset for $11 Billion

Published: Monday, 21 Nov 2011 | 7:56 AM ET
By: Reuters

Gilead Sciences struck a deal to buy Pharmasset for about $11 billion in a huge bet on hepatitis C treatments to diversify its portfolio.

Gilead [GILD.O 53.73 ▼ -0.54 (-0.99%) ▶], the world's largest maker of HIV drugs, will pay $137 per share for each Pharmasset share, a whopping 89 percent premium to Pharmasset's Friday closing price.

Pharmasset [VRUS.O Unavailable () ▶] has been one of the hottest biotech companies, based on the promise of its experimental hepatitis C medicines.

Pharmasset shares jumped 85.4 percent in pre-market trade.