Optimal management of CHB patients with treatment failure

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Treatment failure

- **Primary non-response**
  - Viral load decrease $< 1 \log_{10} \text{IU/mL}$ at M3
  - Mainly with ADV

- **Partial virological response**
  - Persistence of detectable viremia
    - At W24 for drugs with low barrier to resistance (LdT, LAM)
    - At W48 for high barrier to resistance drugs (ETV, TDF)

- **Virological breakthrough**
  - Rebound of viral load by $> 1 \log_{10} \text{IU/mL}$

- **The case of multidrug resistance**
Wild type
Polymorphic mutations
Primary resistance mutations
Secondary resistance mutations

Virologic response
Primary nonresponse
Partial response
Viral rebound

HBV DNA (log_{10} IU/mL)
ULN
ALT (IU/mL)
Nadir

Time

Percent of mutant in the viral quasi-species

Virologic response
Partial response
Virologic breakthrough
Virologic breakthrough
Overt resistance

Wild type
Polymorphic mutations
Primary resistance mutations
Secondary resistance mutations

*rtA181T/V and/or rtN236T cause reduced sensitivity
*rtA194T association with rtL180M+rtM204V (to be confirmed)

* Role of complex mutants: rtA181T+rtN236T ?
Multiple factors are associated with the barrier of resistance

- Antiviral potency
- Number of mutations needed to overcome drug suppression
- Level of exposure to drug
- Chemical structure

- Adherence
- Immune status
- Prior antiviral exposure
- Metabolism
- Body mass

- Replication fitness and space
- Persistence of archived mutations as cccDNA
- Pre-existing mutations

Adherence to nucleos(t)ide analogues for chronic hepatitis B in clinical practice and correlation with virological breakthroughs

Prevention of resistance
Impact of first line therapy

- Choose an antiviral drug with
  1. A potent antiviral activity
  2. A high barrier to resistance
Rates of resistance with lamivudine (LVD), adefovir (ADV), telbivudine (LdT), entecavir (ETV) and tenofovir (TDF) among NA-naïve patients

*Patients confirmed to be viraemic at Week 72 or beyond could add emtricitabine to TDF at the discretion of the investigator. Clinical data on the safety and efficacy of emtricitabine and TDF in CHB are pending

Gish, Jia, Locarnini, Zoulim, Lancet Infect Dis 2012
Entecavir treatment for chronic hepatitis B: Adaptation is not needed for the majority of naïve patients with a partial virological response

Kaplan-Meier curve for the probability of achieving a VR for NA-naïve patients with a PVR according to HBV DNA at week 48. Three patients were switched to TDF plus emtricitabine, and one patient received TDF add-on therapy. P value was determined using log-rank testing.

Mangement of antiviral drug resistance

• Impact of second line therapy
  – Early treatment adaptation to prevent accumulation of mutations
  – Choice always based on cross-resistance data
  – Add-on strategy versus switch?
    • Good results with TDF switch
    • Some cases of suboptimal responses
    • Combination to increase the barrier to resistance
### Cross-resistance data for the main mutants and the commercially available drugs

<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>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-type</td>
<td></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<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>
</tr>
<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>
</tr>
<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>
</tr>
<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>
</tr>
<tr>
<td>Multi-Drug Resistance</td>
<td>A181T+N236T+M250V</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
</tbody>
</table>

Zoulim & Locarnini Gastroenterology 2009; Liver Int 2013
Tenofovir efficacy in LAM Experienced vs. Naïve

Study 102 actively enrolled both LAM experienced and LAM-naïve patients

Study 103 enrolled eight LAM experienced patients despite LAM-naïve inclusion criteria

Combined data includes both HBeAg +/- patients

Manns M, et al., EASL 2008; Oral # 1587.
Virologic response to Entecavir according to Lamivudine exposure

LVD-naïve (N=118)
LVD-experienced without development of LVD-resistance (N=20)
LVD-experienced with a prior history of LVD-resistance (N=14)
LVD-experienced with LVD-resistant mutations at baseline (N=9)

P = 0.007

Reijnders, JGP et al. J Hepatol 2010
Virologic response to Entecavir according to Adefovir exposure

- ADV-naïve (N=119)
- ADV-experienced without development of ADV-resistance (N=30)
- ADV-experienced with ADV-resistant mutations at baseline (N=12)

$P = \text{NS}$

Reijnders, JGP et al.. J Hepatol. 2010
TDF vs. FTC/TDF for Treatment-Experienced Patients: Response by Baseline Resistance at Week 168

Weeks on Study

Berg et al, Gastroenterology 2010; Ms submitted
Patients heavily exposed to NUCs with low barrier to resistance – Risk of MDR selection

- Risk of multidrug resistance by sequential accumulation of resistance mutations

- Risk of partial response, even with the newest NUCs -> long-term impact ?
Sequential therapy with NUCs and the risk of MDR

Accumulation of multiple mutations on the same viral genome

Complete change of the viral quasi-species

Impact of rtA181 and rtN236 mutations on antiviral drug efficacy and cross-resistance

*In vitro* susceptibility to nucleos(t)ide analogs of the rtA181T, rtA181V, rtA181T+N236T, rtA181V+N236T, and rtN236T+N238T mutants isolated from patients with virological failure

<table>
<thead>
<tr>
<th>Mutant</th>
<th>Patient</th>
<th>LAM FR</th>
<th>ADV FR</th>
<th>TDF FR</th>
<th>ETV FR</th>
</tr>
</thead>
<tbody>
<tr>
<td>rtA181T</td>
<td>#2</td>
<td>5.7 ± 2.6</td>
<td>4.5 ± 0.8</td>
<td>2 ± 0.6</td>
<td>nd</td>
</tr>
<tr>
<td></td>
<td>#9</td>
<td>8.7 ± 4.2</td>
<td>3.2 ± 1.6</td>
<td>2.8 ± 1.6</td>
<td>1 ± 0.08</td>
</tr>
<tr>
<td></td>
<td>#7</td>
<td>10.8 ± 2.9</td>
<td>2.1 ± 1</td>
<td>2.9 ± 1.5</td>
<td>1 ± 0.5</td>
</tr>
<tr>
<td>rtA181V</td>
<td>#9</td>
<td>7.7 ± 3.6</td>
<td>7.8 ± 3.5</td>
<td>2.4 ± 1.4</td>
<td>1 ± 0.05</td>
</tr>
<tr>
<td></td>
<td>#4</td>
<td>7.1 ± 3.8</td>
<td>3 ± 0.6</td>
<td>1.2 ± 0.4</td>
<td>1.5 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>#5</td>
<td>1.5 ± 0.3</td>
<td>2.4 ± 0.2</td>
<td>3.2 ± 0.4</td>
<td>1.2 ± 0.4</td>
</tr>
<tr>
<td>rtA181T+N236T</td>
<td>#9</td>
<td>35 ± 5</td>
<td>&gt;10</td>
<td>6.8 ± 2.9</td>
<td>1 ± 0.1</td>
</tr>
<tr>
<td>rtA181V+N236T</td>
<td>#3</td>
<td>43 ± 10</td>
<td>4.5 ± 2.7</td>
<td>1.2 ± 0.2</td>
<td>1 ± 0.05</td>
</tr>
<tr>
<td>rtN236T+N238T</td>
<td>#4</td>
<td>1.5 ± 0.7</td>
<td>2.6 ± 0.6</td>
<td>1.4 ± 0.6</td>
<td>1.1 ± 0.6</td>
</tr>
</tbody>
</table>
Evolution of viral genome during Tenofovir therapy in patients who previously failed ADV

**Patient 1051 data:**
BL viral load = 8.75log
Treatment: TDF
Adherence: 95.2%

Impact of persisting low viremia levels on treatment outcome?
Impact of persisting resistant mutants?

Lavocat et al, AASLD 2010 & Ms submitted
Virologic response to TDF according to ADV resistance mutations at baseline
The Australian Experience

Patterson S J et al. Gut 2011;60:247-254
Tenofovir + Emtricitabine in patients with treatment failure – treatment intensification

HBV DNA kinetics after TDF+FTC initiation in 59 patients with treatment intensification

Viral load initiation

- ≤ 4 logs
- > 4 logs

Si-Ahmed et al, Antiviral Research 2011
Rescue therapy with ETV + TDF in CHB patients with advanced liver disease and complex viral resistance patterns or showing partial antiviral responses to preceding therapies (Virgil network)

Management algorithm

Antiviral treatment

Viral load assessment

Treatment failure

Viral genome sequence analysis

Wild type virus

Check compliance

Primary non response

Switch to more potent drug

HBV drug resistant mutant

Second line therapy based on cross-resistance data (Add-on or switch…)

Check compliance

Zoulim and Perrillo, J Hepatol, 2008; EASL CPG J Hepatol 2012
<table>
<thead>
<tr>
<th>Type of failure</th>
<th>Treatment adaptation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine resistance</td>
<td>1) add TFV (add ADV if TFV not available)</td>
</tr>
<tr>
<td></td>
<td>2) a switch to TFV is also advised by some guidelines</td>
</tr>
<tr>
<td>Adefovir resistance</td>
<td>1) switch to TFV (if available) and a 2\textsuperscript{nd} drug</td>
</tr>
<tr>
<td></td>
<td>2) if no history of LMV, switching to ETV is also effective.</td>
</tr>
<tr>
<td></td>
<td>3) If rtN236T substitution, consider adding LMV, ETV, or LdT to the TFV or switch to TFV plus FTC</td>
</tr>
<tr>
<td></td>
<td>4) If rtA181V/T substitution, alone or in combination with rtN236T, switch to TFV plus ETV</td>
</tr>
<tr>
<td>Telbivudine resistance</td>
<td>1) add TFV</td>
</tr>
<tr>
<td></td>
<td>2) a switch to TFV has been considered in some guidelines</td>
</tr>
<tr>
<td></td>
<td>3) a switch to ADV is not recommended</td>
</tr>
<tr>
<td>Entecavir resistance</td>
<td>add TFV</td>
</tr>
<tr>
<td>Tenofovir resistance</td>
<td>1) not been confirmed so far</td>
</tr>
<tr>
<td></td>
<td>2) genotyping and phenotyping required</td>
</tr>
<tr>
<td></td>
<td>3) may add ETV</td>
</tr>
</tbody>
</table>
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## Suggested treatment adaptation in patients with treatment failure

<table>
<thead>
<tr>
<th>Type of failure</th>
<th>Treatment adaptation</th>
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</table>
| Lamivudine resistance   | 1) add TFV (add ADV if TFV not available)  
2) a switch to TFV is also advised by some guidelines  
3) a switch to ADV is not recommended due to a high rate of resistance and its low potency |
| Adefovir resistance     | 1) switch to TFV if available and add a second drug without cross resistance.  
2) if no history of LMV, switching to ETV is also effective.  
3) If rtN236T substitution, consider adding LMV, ETV, or LdT to the TFV or switch to TFV plus FTC; if no history of LMV prior, consider switching to ETV  
4) If rtA181V/T substitution, alone or in combination with rtN236T, switch to TFV plus ETV; as before, if no history LMV, consider switching to ETV; |
| Telbivudine resistance  | 1) add TFV  
2) a switch to TFV has also been considered in some guidelines  
3) a switch to ADV is not recommended |
| Entecavir resistance    | add TFV                                                                                                                                               |
| Tenofovir resistance    | 1) not been confirmed so far  
2) genotyping and phenotyping required  
3) may add ETV |
Fig. 2 Kaplan-Meier analysis giving the probability of HBV-DNA negativity according to HBV-DNA level at baseline (A), HBeAg status at baseline (B), previous treatment history (C), gender (D), fibrosis at baseline (E), and age (F).

Si-Nafa Si-Ahmed, Pierre Pradat, Roeland Zoutendijk, Maria Buti, Vincent Mallet, Claire Cruiziat, Katja Det...

Efficacy and tolerance of a combination of tenofovir disoproxil fumarate plus emtricitabine in patients with chronic hepatitis B: A European multicenter study
Antiviral Research Volume 92, Issue 1 2011 90 - 95

http://dx.doi.org/10.1016/j.antiviral.2011.07.003
New targets

Immune system
Adherence to nucleos(t)ide analogues for chronic hepatitis B in clinical practice and correlation with virological breakthroughs
Evolution of viral genome during Tenofovir therapy in patients who previously failed ADV

Patient #1051

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Impact of persisting low viremia levels on treatment outcome?
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Lavocat & Zoulim, AASLD 2010.
ETV + TDF combination in patients with treatment failure

Rescue therapy with ETV + TDF in CHB patients with advanced liver disease and complex viral resistance patterns or showing partial antiviral responses to preceeding therapies (Virgil network)

$\Delta 3 \log_{10} \text{c/mL reduction}$

$P=0$

Entecavir treatment for chronic hepatitis B: Adaptation is not needed for the majority of naïve patients with a partial virological response

Zoutendijk et al Hepatology

Figure 3. Adjusted HR of achieving a VR for both NA-naïve and NA-experienced patients. Based on the Cox model adjusted for HBeAg status, mean baseline HBV DNA, LAM experience, history of LAM resistance, LAM resistance at baseline, ADV experience, and history of ADV resistance.
1. entry
2. trafficking
3. cccDNA formation
4. transcription viral RNA
5. translation
6. nucleocapsid formation pgRNA packaging
7. DNA synthesis
8a. morphogenesis and secretion
8b. trafficking
9. integration into the host DNA

Adaptive immune responses
CD8 + cells
CD4 + cells
B cells

Innate responses
NK cells
PRRs
Type I IFN induction
polymerase
pgRNA
HBsAg
HBeAg

Zoulim, Antiviral Research, 2012
HBV resistance: new challenges

- Poorer response in second or third line therapy
  - Persisting low viremia levels
- Risk of selection of MDR mutants
- Potential risk of transmission of mutants
- Early detection of mutants (UDP sequencing)
- Identification of new targets for true combination therapy, prevention of resistance, and finite duration therapy
Treatment failure

Primary non response
Partial response

Secondary treatment failure
Antiviral drug resistance

Host factors
Drug metabolism
Patient’s compliance

Drug factors
Antiviral potency

Drug factors
Barrier to resistance

Viral factors
Resistant mutants

Fig. 2  Probability of HBV DNA below LLoD (80 < IU/ml). A Kaplan-Meier analysis was used to analyze the probability of reaching HBV DNA undetectability. For the entire cohort, the median time to HBV-DNA undetectability was 6...

Jorg Petersen, Vlad Ratziu, Maria Buti, Harry L.A. Janssen, Ashley Brown, Pietro Lampertico, Jan Schollmeye...

Entecavir plus tenofovir combination as rescue therapy in pre-treated chronic hepatitis B patients: An international multicenter cohort study

Journal of Hepatology Volume 56, Issue 3 2012 520 - 526

http://dx.doi.org/10.1016/j.jhep.2011.09.018
The target of nucleos(t)ide analogues

The main differences between HIV, HBV and HCV

**HIV**
- Host cell
  - Host DNA
  - Proviral DNA
  - Nucleus

Lifelong suppression of viral replication

**HBV**
- Host cell
  - Host DNA
  - cccDNA
  - Integrated DNA
  - Nucleus

Long-term suppression of viral replication

**HCV**
- Host cell
  - Host DNA
  - HCV RNA
  - Nucleus

Definitive viral clearance and SVR