Professor Karine Lacombe  
Hospital Saint-Antoine, Paris, France

<table>
<thead>
<tr>
<th>Speaker Name</th>
<th>Statement</th>
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<tbody>
<tr>
<td>Prof Karine Lacombe</td>
<td>None</td>
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</tbody>
</table>

**COMPETING INTEREST OF FINANCIAL VALUE > £1,000:**

| Date     | November 2013 |
HBV in HIV patients: is it still an issue?

Dr Karine Lacombe, M.D, PhD
Saint-Antoine Hospital, Paris
Inserm UMR-S707
Université Pierre et Marie Curie, Paris VI
HBV in HIV patients: the continuum of care

- Prevention
- Natural/cART history
- Hepatitis Delta
- Treatment
- Diagnosis
Prevention

Treatment

Hepatitis Delta

Natural/cART history

Diagnosis

Efficacy of immunization?

Isolated HBcAb?

Treatment as prevention?
HBV immunization in HIV

- Unsufficient HBV vaccine coverage and vaccine response:\textsuperscript{1}:
  - 32% of eligible patients were vaccinated
  - in those with one injection, immunization course completed in 57%
  - achievement of protective Ab titer in 37%

\textsuperscript{1}Tedaldi EM, Clin Infect Dis 2004
Increasing HBV immunization

- 2 options:
  - increasing the dosing (40µg instead of 20µg)
  - increasing the number of injections (4 instead of 3)

Confirmed by a meta-analysis of 5 trials (883 patients): OR = 1,82 (1,47 – 2,61) of higher HBsAb titer in 4-doses v. 3-doses schedule


Launay O. et al, JAMA 2011
Treatment as prevention in HBV

- Dutch HIV cohort of 2942 patients\(^1\)
- 871 « HBV susceptible »
- 35 HBV-infected during follow-up
- Treating non protected patients with TDF prevented transmission
- Same results in the study by Gatanaga\(^2\)

\(\Rightarrow\) Should TDF be used within « treatment for prevention » paradigm?

\(^1\)Heuft M, et al. CROI 2013. \(^2\)Gatanaga, Clin Infect Dis 2013
Management of isolated HBcAb

SHOULD WE TREAT?

• Frequency of occult HBV differing regarding geographical origin: <1% in Europe\(^1\), ≈5% in Africa\(^2\)
• Most patient on TDF in Europe: controled « occult HBV »?
• High risk of reactivation at treatment interruption\(^3\)

SHOULD WE IMMUNIZE?

• In 40 patients vaccinated with 1 to 6 vaccine doses\(^4\):
  – anamnestic response: 32%
  – Vaccine response: 74%
  – Durability of response: 74% of patients with median titer = 61UI at 1 year
• In 37 patients vaccinated with 1 to 3 vaccines doses\(^5\)
  – anamnestic response: 22%
  – Vaccine response: 60%
  – Durability of response: 52% of patients at 2 years

➔ anti-HBV treatment is indicated, immunization is not recommended

HBV infection and mortality risk (1)

- multicenter cohort + meta-analysis of 12,382 patients, either HIV+ or HIV/HBV
- 36% excess risk of dying (all cause) if HBs pos. compared to HBs neg.

Higher mortality risk in HIV-HBV compared to HIV patients between 1992 and 2007

Nikopoulous G, Clin Infect Dis 2009
HBV infection and mortality risk (2)

- MACS cohort: (337HBs+ - 343 HCV+) of whom 452 HIV+ ➞ 6728 person-years of F/U, 293 deaths

- RR=2,2 [1,1 – 4,5] of dying of liver-related cause when HBs pos. V. HCV pos.
- No difference between HCV and HBV regarding all cause deaths
Impact of cART on liver-related deaths

Table 3. The adjusted IRR of cause-specific death by year longer on cART.

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>IRR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause</td>
<td>0.95</td>
<td>0.92–0.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AIDS</td>
<td>0.86</td>
<td>0.81–0.91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-AIDS</td>
<td>0.97</td>
<td>0.95–1.00</td>
<td>0.061</td>
</tr>
<tr>
<td>NARI-death</td>
<td>0.97</td>
<td>0.90–1.05</td>
<td>0.417</td>
</tr>
<tr>
<td>LR-death</td>
<td>0.94</td>
<td>0.89–1.00</td>
<td>0.052</td>
</tr>
<tr>
<td>NADM-death</td>
<td>1.07</td>
<td>1.00–1.14</td>
<td>0.056</td>
</tr>
<tr>
<td>CVD-death</td>
<td>0.99</td>
<td>0.93–1.06</td>
<td>0.885</td>
</tr>
<tr>
<td>Violent death</td>
<td>0.90</td>
<td>0.81–0.99</td>
<td>0.027</td>
</tr>
<tr>
<td>Other death</td>
<td>1.01</td>
<td>0.94–1.09</td>
<td>0.725</td>
</tr>
<tr>
<td>Unknown death</td>
<td>0.94</td>
<td>0.86–1.01</td>
<td>0.096</td>
</tr>
</tbody>
</table>

CI, confidence interval; CVD, cardiovascular disease; IRR, incidence rate ratio; LR, liver-related; NADM, non-AIDS-defining malignancies; NARI, non-AIDS-related infection. Models’ adjustment as in Table 2.

• Eurosida cohort: 12069 patients included in analysis

Kowalska, et al. AIDS 2012
Clinical outcomes in the era of cART

- 92 patients, 82% treated with FTC/TDF median f/u=39 months

- \( I(\text{death}) \): 2,2 / 100 p.y
- \( I(\text{liver dec.}) \): 2,9 / 100 p.y
  ➔ Close to what is observed in HIV general population

- Liver fibrosis stability in 75% of patients

*Fig. 1. Survival and liver decompensation in the HIV-hepatitis B virus coinfect ed study population.*

Martin-Carbonero, et al. AIDS 2011
Survival rate in transplanted patients: data from France

- 13 patients (1HDV+, 2 HCV+, 4 HCV-HDV+)
- Indication for OLT: decompensated cirrhosis (10) and HCC (3)
- Treatment after OLT: combination of TDF / 3TC + HBIg
- Overall survival rate at 32 months: 100%
  - No mitochondrial toxicity
  - Controled HBV-DNA, HDV-RNA, HIV-RNA
  - Successful treatment with PR in 1/3 HCV-RNA+

Tatteo, et al. AIDS 2009
Survival rate in transplanted patients: data from the USA

- 22 patients (2 HCV+) matched with 20 HBV mono-infected patients
- Indication for OLT: decompensated cirrhosis (19), HCC (2), fulminant (1)
- Overall survival: 85% in HIV-HBV, 100% in HBV (p=0.09)
  - 3 deaths due to causes unrelated to HBV
  - Persistent low replicating HBV-DNA in 6/7 patients with available HBV-DNA after OLT

Prevention

Natural/cART history

Diagnosis/evaluation

Hepatitis Delta

Treatment

Rapid tests?

Fibrosis?
Increasing screening in HIV patients

Can rapid tests increase screening efficacy?

Performance of 3 HBsAg rapid tests on capillary blood in the community:

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>AUC, [95% CI]</th>
<th>Se</th>
<th>Sp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vikia® HBsAg</td>
<td>3956</td>
<td>0.98 [0.96 - 1.00]</td>
<td>96.5</td>
<td>99.9</td>
</tr>
<tr>
<td>Quick Profile™ HBsAg</td>
<td>3950</td>
<td>0.95 [0.92 - 0.98]</td>
<td>90.5</td>
<td>99.7</td>
</tr>
<tr>
<td>Determine™ HBsAg</td>
<td>2478</td>
<td>0.97 [0.93 - 1.00]</td>
<td>93.6</td>
<td>100</td>
</tr>
</tbody>
</table>

👀 In African rural settings\(^2\), performance of Determine test: Se=96% / Sp=100%

👀 Are rapid tests reliable in the HIV settings?
- YES\(^3\) \(\kappa\) correlation coefficient = 1 / Se=100% and Sp=100% in study done in Liverpool on 300 sera from HIV+ patients from Malawi (CD4 = 175)

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Non invasive Fibrosis Evaluation: still challenging

134 patients, 11 scores tested

<table>
<thead>
<tr>
<th>scores</th>
<th>AUC</th>
<th>Cut-offs</th>
<th>(HCV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrometer*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ F2</td>
<td>0.74</td>
<td>0.46</td>
<td>0.5</td>
</tr>
<tr>
<td>≤ F3</td>
<td>0.83</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>F4</td>
<td>0.89</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>Fibrotest*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ F2</td>
<td>0.77</td>
<td>0.43</td>
<td>0.49</td>
</tr>
<tr>
<td>≤ F3</td>
<td>0.80</td>
<td>0.59</td>
<td>0.59</td>
</tr>
<tr>
<td>F4</td>
<td>0.87</td>
<td>0.74</td>
<td>0.75</td>
</tr>
</tbody>
</table>

57 patients, elastmetry

1 Bottero J. J Hepatol, 2009. 2 Miailhes P. J Viral Hepat 2010
Treatment algorithms

Assessment of Treatment Indications for HBV in Persons with HBV/HIV Co-infection

- HBsAg+
  - Cirrhosis
    - Yes: HBV DNA ≥ 2000 IU/mL
    - No: HBV DNA < 2000 IU/mL
      - ALT Elevated: Treatment indicated
      - ALT Normal: No treatment indicated

- HBV DNA ≥ 2000 IU/mL
  - CD4 > 500 cells/μL AND No indication for ART
  - CD4 < 500 cells/μL or Symptomatic HIV or Cirrhosis

- No HBV Rx indicated
  - 3TC experienced
  - 3TC naive

- ART including TDF with FTC

Note: In persons with significant liver fibrosis (F2-F4), anti-HBV treatment might be considered even when serum HBV-DNA is below 2000 IU/mL and liver enzymes are not elevated.
Treatment efficacy with TDF

• 102 patients (61% HBeAg+) with a median 5 years of follow-up

• 120 patients (63% HBeAg +) with a minimum of 1 year of TDF and a median 6 years (3 – 8) of follow-up

Figure 1. Kaplan-Meier curve for the cumulative probabilities of achieving virologic response, defined as HBV-DNA levels less than 20 IU/mL, for HBeAg-positive (n = 67) and HBeAg-negative (n = 15) HIV/HBV with patients with detectable HBV DNA at baseline (n = 82).
Role of Peg-IFN in TDF-treated patients

EMVIPEG: pilot study evaluating the addition of Peg-IFN to TDF in HIV-HBV patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>W0 N=51</th>
<th>W12 N=50</th>
<th>W24 N=50</th>
<th>W48 N=50</th>
<th>W72 N=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ALT &lt; ULN¹: [n(%)]</td>
<td>39 (76)</td>
<td>26 (52)</td>
<td>26 (52)</td>
<td>34 (68)</td>
<td>43 (86)</td>
</tr>
<tr>
<td>HBV DNA &gt;100 copies/ml: [n(%)]</td>
<td>20 (39)</td>
<td>19 (38)</td>
<td>10 (20)</td>
<td>5 (10)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>HBeAg loss: [n (%)]²</td>
<td>2 (4)</td>
<td>2 (4)</td>
<td>8 (16)</td>
<td>10 (20)</td>
<td>10 (20)</td>
</tr>
<tr>
<td>Anti-HBe seroconversion: [n (%)]³</td>
<td>0</td>
<td>3 (6)</td>
<td>5 (10)</td>
<td>4 (8)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>HBV sustained response: [n(%)]</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>4 (8)</td>
</tr>
<tr>
<td>HBsAg loss [n(%)]</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td>2 (4)</td>
</tr>
<tr>
<td>% CD4: [median(range)]</td>
<td>29 (11-45.3)</td>
<td>32 (11-46)</td>
<td>34 (10-51)</td>
<td>31.5 (12-49.6)</td>
<td>31.8 (14-47.2)</td>
</tr>
<tr>
<td>CD4 cell count: [median (range)]</td>
<td>506 (175-1316)</td>
<td>369 (139-955)</td>
<td>368 (102-879)</td>
<td>372 (149-834)</td>
<td>516 (176-1292)</td>
</tr>
<tr>
<td>HIV RNA &lt;50 copies/ml: [n (%)]</td>
<td>49 (96)</td>
<td>45 (90)</td>
<td>49 (98)</td>
<td>45 (90)</td>
<td>44 (88)</td>
</tr>
</tbody>
</table>

⚠️ No benefit of adding Peg-IFN regarding antiHBe seroconversion or HBs loss rate

¹ Miailhes P, et al. CROI 2013
Persistent HBV replication

- **MAGNITUDE:** 5 to 10% of patients on TDF after > 3 years
  
- **PATTERNS:** blips, persistent viremia, rebound

- **CAUSES:**
  - suboptimal adherence: YES
  - suboptimal treatment: NO (maybe in pre-treated patients)
  - resistant strains: NO
  - failing immunological control?

- **IMPACT:** no Hbe or HBs loss in patients w/ persistent replication, no clinical event

- **MANAGEMENT:**
  - confilting results regarding addition of ETV
  - check adherence
  - stay on same therapy if regular decrease > 1 year
  - add ETV only long-term stagnation of HBV-DNA
  - reconsider after 6 months

Long term tolerance of TDF

240 patients with a 3-year-time follow-up, normal eGFR at baseline\(^1\): no difference with other NUC
Available data on renal and bone impairment over time in HIV-infected patients on long-term use of TDF (> 6 years)
TDF-associated tubular nephropathy very rarely described in HBV-infected patients\(^2,3\)

**MANAGEMENT:**

- Check the imputability of TDF in alteration of renal Cl. (send to kidney specialist and biopsy)
- Decrease TDF dosage(1cp/2-3 days)
- No place for ADV
- Add probenecide?
- Switch for ETV if no previous exposure to 3TC?

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## Emergence of treatment and immune escape mutants

<table>
<thead>
<tr>
<th>Groups of mutations</th>
<th>% of patients with incident mutations</th>
<th>TDF±LAM/FTC</th>
<th>numerous switches</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkyl phosphonate-associated pol-gene</td>
<td>(n=49)</td>
<td>6.1%</td>
<td>(n=15)</td>
</tr>
<tr>
<td>Immune-associated S-gene</td>
<td>(n=73)</td>
<td>1.4%</td>
<td>(n=18)</td>
</tr>
<tr>
<td>L-nucleoside-associated pol-gene/antiviral-associated S-gene</td>
<td>(n=64)</td>
<td>9.4%</td>
<td>(n=15)</td>
</tr>
</tbody>
</table>

> Emergence of antiviral-associated S mutations conferring resistance to current NUCs and potential vaccine escape strains

Lacombe K, Hepatology 2013
Prevalence of HDV markers in HIV

Manesis EK. EASL Monothematic Conference Delta Hepatitis. Sept 2010. Istanbul

Soriano V. et al. AIDS 2011

\[ P(\text{HDV/HIV-HBV}) = x2 \cdot P(\text{HDV/HBV}) \]
Increased fibrosis in HDV-infected patients

Risk of liver fibrosis ≥ F3

Predictors of clinical outcomes in HDV-infected patients, EUROSIDA

- **Clinical outcomes**
  - Progression to death: 2.23 (1.17-4.28)
  - Progression to liver related events: 4.44 (1.46-13.55)
  - Progression to AIDS: 1.60 (0.56-4.56)
  - Progression to AIDS or death: 2.17 (1.22-3.87)

Lacombe K, et al. AIDS 2007
Soriano V, et al. AIDS 2011
Persistent HDV-DNA replication in all 17 patients (including those treated with Peg-IFN + TDF after Peg-IFN interruption)

Sequential treatment with Peg-IFN (normalisation of transaminases, stabilization of liver fibrosis?)

Future:
Can we think of cure?
### HBs loss with current treatment

<table>
<thead>
<tr>
<th>Studies</th>
<th>Duration of F/U</th>
<th>Hbe loss</th>
<th>HBs loss</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment experienced</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Vriis Sluijt, 2010 (n=102)</td>
<td>5 years</td>
<td>46%</td>
<td>12%</td>
</tr>
<tr>
<td>Maylin, 2013 (n=143, Hbe+=67%)</td>
<td>3 years</td>
<td>43%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Treatment naive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matthews, 2013 (n=47, Hbe+=57%)</td>
<td>2 years</td>
<td>48%</td>
<td>13%</td>
</tr>
</tbody>
</table>

→ HBs loss is low with NUCs, HBs seroconversion is even lower...

Maylin S. AIDS 2012
New therapeutic strategies

Drugs targeting virus or host\textsuperscript{1}

New targets for « functional cure »\textsuperscript{2}

\textsuperscript{1}Zoulim F, Expert Opin Emerg Drugs 2013. \textsuperscript{2}Zoulim F. Antivir Res 2012
ACKNOWLEDGMENTS

Pierre-Marie Girard, Jürgen Rockstroh, Sanjay Bhagani, Fabien Zoulim, Serge Eholié, Maud Lemoine, Anders Boyd, Julie Bottero, Hayette Rougier, Patrick Mialhies, clinical teams of Biliver – French HIV-HBV Cohort, the patients