HIV and HBV

what’s coming next

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Disclosures

• Joop Arends
  – Advisory boards*
    • ViiV, MSD, Janssen, Abbvie, Gilead, BMS
  – (research) grants*
    • BMS, Abbvie, ViiV, MSD

• Andrew Ustianowski
  – Advisory boards & speaker fees
    • ViiV, MSD, Janssen, Abbvie, Gilead, BMS
  – (research) grants
    • Gilead

*money paid to research account UMC Utrecht
Interactive presentation

HIV → Andrew

Joop

HBV
What do these 3 viruses have in common?
Advancement in viral drug therapeutics

- HIV drugs (N=41)
- HCV drugs (N=18)
- HSV drugs (N=10)
- Influenza drugs (N=8)

Historical milestones:
- Discovery of HBV (1963) and dexamethasone (1963)
- Discovery of HPV (1965)
- Discovery of HIV (1983)
- Discovery of HCV (1989)
• Mechanistic insights into viral life cycles and drug therapy targets have also accelerated treatment development in other viral disease like viral hepatitis B and C.
Discovery of in vitro replicon systems

- HIV 1984
- HCV 2003
- HBV 2013

Discovery of drug targets

- HIV 1964 - AZT
- HCV 2003 – NS3 protease
- HBV 2008 - NRTI
Advancements in antiviral treatment

HIV and HCV

% response

number of drugs

Estimated 95-100%

Estimated 65-70%

2nd Stage: 1998-2001
3rd Stage: 2001- present
4th Stage: 2012-2015
5th Stage: 2015-2018

Inhibit. +

PEG-IFN +

Proth. inhib. +/

NS5a inhib. +/

NS5b inhib.
## Similarities in development between 3 viruses

<table>
<thead>
<tr>
<th>Topics</th>
<th>HIV in 2000</th>
<th>HCV in 2014</th>
<th>HBV in 2020</th>
</tr>
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<tbody>
<tr>
<td>Newly identified, effective drugs</td>
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<td>High cost of drugs and tests</td>
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<td>Complex drug regimens, side effects</td>
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<td>✔</td>
<td>✔</td>
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<tr>
<td>Limited data on epidemiologic situation</td>
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<tr>
<td>Lack of advocacy for global access</td>
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<tr>
<td>Lack of political and financial global commitment</td>
<td>✔</td>
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</table>
Major advancements made over time

<table>
<thead>
<tr>
<th></th>
<th>Progress over time</th>
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<tbody>
<tr>
<td>Cost of drugs</td>
<td>&gt;$10,000 -&gt; &lt;$100</td>
</tr>
<tr>
<td></td>
<td>/patient/year</td>
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<tr>
<td>Global funding</td>
<td>Low -&gt; Major global</td>
</tr>
<tr>
<td></td>
<td>initiatives</td>
</tr>
<tr>
<td>Numbers on treatment</td>
<td>~50,000 -&gt; 10</td>
</tr>
<tr>
<td>in low-income countries</td>
<td>million</td>
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</table>
Rapid development of drug resistance with mono-therapy

Is triple therapy the future of HBV?


Where are we going with HBV treatments?

• Firstly we need to briefly run over the life-cycle…. 
What about viral entry into liver cell and then nucleus?

- Viral envelope binds to cell membrane
  - Receptor = sodium taurocholate co-transporting polypeptide
    - (a bile salt transporter)
- Then it is uncoated and viral DNA enters into cell nucleus…
  …and viral genome is converted to cccDNA
    - “covalently closed circular DNA”
    - HBV ‘mini-chromosome’
Transcription and translation….

Other viral proteins including sAg

• Products then encapsulated within virus core particle
  – RNA pregenome, nucleocapsid & polymerase proteins
And then it is released...

- Virus contains a new negative strand DNA which partially synthesises a positive strand
- Coated by envelope proteins ➔ Complete virion ready for release
  - But some is also recycled back into the nucleus and replenishes ccc-DNA
Not all the proteins end up in the virus particle….  

• Why??  
  – Immunomodulatory  
  – Tolerogenic….  
  – Inflammatory….  

Surface proteins  
ER and Golgi  
Noninfectious filamentous and spherical subviral particles  
eAg secretion
OK.. What drugs do we have at present??

- Nucleos(t)ide analogues
  - Tenofovir disoproxil
  - Adefovir
  - Entecavir
  - Lamivudine
  - Emtricitabine
  - Telbivudine

- Newer Nucs
  - Tenofovir alafenamide
  - Besifovir
Interferon alpha

• Naturally occurring immunomodulator
  – Multiple activities… not entirely clear which are most important

• Specifically
  – Induces an antiviral state in cells
    • Induces degradation
  – Inhibits cellular prolifereation
  – Immunomodulates in many ways…
But we know this usually doesn’t result in a proper ‘cure’

- There is still active research into combining interferon and nucleos(t)ides…

- But what are the newer possibilities being actively explored?
Where else could be targeted??

Target the sodium taurocholate co-transporting polypeptide

Antisense & RNAi approaches
- Antisense molecules or ribozymes that are complementary to DNA or RNA templates
- Interfere with transcription and translation
SiRNA: RNA interference therapy

Reduction of HBsAg in treatment-naïve CHB patients after a single dose of 4 mg/kg ARC-520

Hepatocyte Targeting - ALN-HBV
- N-acetyl galactosamine (GalNAc) ligand binds to asialoglycoprotein receptor (ASGPR)

Direct ccc-DNA inhibitors

Multiple potential agents, including
- Disubstituted sulfonamide (DSS) compounds
- DNA cleavage enzymes
  - CRISPR/Cas9
- Epigenetic silencing
- HDAC inhibitors etc.
JNJ-379: Effect on cccDNA in HBV-infected PHHs

Dose-dependent inhibition of cccDNA formation in presence of JNJ-379

Berke et al. AASLD 2016
Capsid Inhibitors

Capsid inhibitors interfere with HBV RNA packaging and capsid assembly.
Capsid assembly modulators

- CAMs induce the formation of two types of capsids *in vitro*
  - Empty capsids with normal geometry and size (class I MOA)
    - Phenylpropenamides (e.g. AT130) and sulfamoylbenzamide derivatives
  - Empty capsids with abnormal geometry and size (class II MOA)
    - Heteroaryldihydropyrimidines (e.g. BAY41-4109)

**Electron microscopy**
Recombinant HBV core dimers + 150mM NaCl +/- 30µM CAM (24h)
sAg secretion inhibitors

Interfere with intracellular processing and release of HBsAg
?toxicity potential
LLOQ = lower limit of quantification (0.05 IU / mL)
TND = HBsAg not detected (0.00 IU / mL)

9/9 HBsAg response > 1 log

6/9 HBsAg response > 1 log

Bazinet et al. AASLD 2016
Elevation in serum anti-HBs correlated with extent of HBsAg reduction

Prot. Imm. = Architect defined threshold for protective immunity (10 mIU / mL)
absent = no significant anti-HBs present (≤ 0.1 mIU / mL)

Bazinet et al. AASLD 2016
And there are others…
NVR 3-778, a **HBV Core Inhibitor**, in HBeAg-Positive Patients

- HBeAg-positive CHB patients
- Serum HBV DNA >20,000 IU/mL
- ALT levels 1-7 times upper limit of normal
- Randomized to NVR 3-778 capsules at 4 doses (vs placebo) x 28 days

Mean viral load change (HBV DNA) from Day 1

NVR 3-778 600 mg bd associated with mean 1.72 $\log_{10}$ IU/mL HBV DNA reduction in 28 days

Yuen M-F *et al*. AASLD 2015, San Francisco. #LB-10
Host-directed agents?

Immune stimulators
- Toll-like receptor agonists
  - TLR 9 (Goldstein and Goldstein, 2009)
- Others...

Checkpoint inhibitors
- PD-, PD-L1, CTL-4 inhibitors etc.

Therapeutic vaccines
- S and Pre-S antigen vaccines
- DNA vaccines (especially of S)
- T cell vaccines
TLR agonists

**Clinical Efficacy**
HBsAg changes during GS 9620 therapy

- HBsAg changes were minimal in all cohorts (no patients with >0.5-log10 declines in HBsAg at week 24)
- No patients had HBsAg loss at week 24

Boni et al. AASLD 2016
But there are major issues…

It is quite likely that a single drug or target will not be sufficient. Therefore some kind of combination….

• But how do we decide what to combine with what?

What do we mean by cure?
What are we aiming for and how do we know we have got there?

What is our endpoint for studies?
There is a full pipeline for HBV drugs in development

Durantel D et al. J Hepatol. 2016 Apr;64(1 Suppl):S117-31
Do we need more and newer drugs for HIV?

- Viral suppression after start of combination antiretroviral therapy (cART) in previously treatment-naïve individuals
- Other countries lower suppression rates
  - Compliance issues?
  - Resistance issues?

Dutch Monitoring Rapport 2016
What do we need more in future HIV drugs?

• More convenience
  – NRTI and PI

• Less side-effect / drug-drug interactions
  – NNRTI

• New drug classes
  – Maturation inhibitors, CD4 attachment/ entry inhibitors
### Newer Investigational ART Agents (partial list)

<table>
<thead>
<tr>
<th>Phase</th>
<th>NRTI</th>
<th>NNRTI</th>
<th>PI</th>
<th>Entry Inh</th>
<th>II</th>
<th>Maturaton Inhibitor</th>
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<tr>
<td>Phase 3</td>
<td></td>
<td>doravirine</td>
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<td>Fostemsavir</td>
<td>cabotegravir</td>
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<td>Phase 2</td>
<td>apricitabine</td>
<td>BILR 355</td>
<td></td>
<td>cenicriviroc</td>
<td>GS-9883</td>
<td>BMS-955176</td>
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<td>dextevucitabine</td>
<td>festinavir</td>
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<td>Phase 1/2</td>
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<td>TMC 310911</td>
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<td>Phase 1</td>
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<td>RDEA 806</td>
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<td>SCH532706</td>
<td>BI 224436</td>
<td>GSK-2838232</td>
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<td>VIR-576</td>
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MK-8591 (EFdA)

- 4’-ethynyl-2-fluoro-2’-deoxyadenosine (EFdA)
- Non-obligate chain terminator
- Inhibits RT by preventing translocation (NRTTI)
- Potent antiviral activity (PBMC EC50 = 0.2 nM) with broad coverage (HIV-1, HIV-2, MDR strains)

![Graph showing viral load drop from baseline over time](image)

- A single 10 mg oral dose in HIV-infected patients results in 1.6 log decrease in viral load at day 7-10
- Intracellular MK-8591-TP t_{1/2} = 103 hr
- No evidence of resistance out to Day 10
Cabotegravir (CAB, GSK 1265744)

- Integrase inhibitor similar to DTG; similar resistance
- Potent in HIV+ individuals (5, 10, 30, 60 mg oral)
- Nanotechnology formulation; SC + IM injections
- T ½ 21-50 days!
- Supports monthly or quarterly dosing

Safety: ISR (all mild) and nodules with SC dosing

**Pharmacokinetics**

*Figure 4. Mean Plasma S/GSK1265744 Concentration-Time Profiles Following Single Dose LAP Formulation Administration*

LATTE-2: CAB + RPV IM Maintenance

Phase 2b multicenter, parallel group, open-label study
Study population: Rx-naïve individuals (N=309)
LATTE-2: Virologic Suppression

Induction period

Maintenance period

<table>
<thead>
<tr>
<th>Study visit</th>
<th>Oral CAB induction (ME population)</th>
<th>Q8W (n=115)</th>
<th>Q4W (n=115)</th>
<th>Oral CAB (n=56)</th>
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<td>W32</td>
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Snapshot success: D1

- Q4W: 99%
- Q8W: 95%
- Oral CAB: 98%
LATTE-2 Week 32 Primary Endpoint: HIV-1 RNA <50 c/mL by Snapshot (ITT-ME)

Virologic outcomes

- 95*
- 94*
- 91

- 100%
- 80%
- 60%
- 40%
- 20%
- 0%

HIV-1 RNA <50 c/mL, %

Virologic success

- Q8W (n=115)
- Q4W (n=115)
- Oral CAB (n=56)

Virologic non-response

- 4
- <1
- 4
- <1

No virologic data

- 5
- 5

Treatment differences (95% CI)

Oral

IM

Q8W

- 4.8
- 3.7

Q4W

- 5.8
- 2.8

Both Q8W and Q4W comparable to oral CAB at Week 32
LATTE-2: Injection Site Reactions

<table>
<thead>
<tr>
<th>Number of injections</th>
<th>Q8W IM (n=115)</th>
<th>Q4W IM (n=115)</th>
<th>IM subtotal (N=230)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of ISRs</td>
<td>1623</td>
<td>2663</td>
<td>4286</td>
</tr>
<tr>
<td>(events/injection)</td>
<td>1054 (0.65%)</td>
<td>1228 (0.46%)</td>
<td>2282 (0.53%)</td>
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</tbody>
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**Grades**

- **Grade 1**: 839 (80%), 1021 (83%), 1860 (82%)
- **Grade 2**: 202 (19%), 197 (16%), 399 (17%)
- **Grade 3**: 12 (1%), 10 (<1%), 22 (<1%)
- **Grade 4**: 0, 0, 0

**Duration, days**

- ≤7 days: 943 (89%), 1121 (91%), 2064 (90%)
- Median: 3.0, 3.0, 3.0

- Most common ISR events overall were pain (67%), swelling (7%), and nodules (6%)
- Number of subjects reporting ISRs decreased over time, from 86% (Day 1) to 33% (Week 32)\(^{a}\)
- 2/230 subjects (1%) withdrew as a result of injection reactions (Q8W)
Ibalizumab – HIV entry inhibitor

- Monoclonal antibody (im or iv) binding to CD4 receptor
- Dosing every 1-4 weeks
  - Phase 1/2-studies in 2004-2009
- FDA orphan drug breakthrough designation

Documented resistance to at least 1 AVR from 3 classes
Is compliance a possible drawbacks to these developments?

- Rheumatoid arthritis patients for longer treated at monthly intervals
- 775 RA patients registered in the Danish biologics database (DANBIO)
- Treatment as monotherapy
Are adverse events a possible drawbacks to these developments?

- Newly developed monoclonal antibodies reverse anticoagulant effects of DOACs
- Search for antidote against long-acting anti-HIV drugs in case of adverse events
It isn’t always new drugs that will lead to longer acting agents…
Implants

Full-scale TAF-TFPD prototype device
4 cm long x 2-2.5mm diameter
Osmotic Pump

- This osmotic flow is directly proportional to the gradient of concentration of osmolytes in the osmotic chamber
- The inward H$_2$O flow creates an increased pressure in the osmotic chamber, which exerts a force on the piston
Nano-channel Implants
Conclusions

• There are significant overlaps between HIV, HCV & HIV in many ways
  – But also significant differences

• We are just commencing a new era in HBV
  – Better understanding
  – New agents
    • But we have a long way to go…

• There are new agents for HIV
  – Especially those that will allow intermittent dosing
  – And there are technologies that might help too
Thank you for your attention