ARV treatment
Update 2012

Avondseminarie 18 december 2012
Eric Florence
ITG, Antwerpen
Three big conferences in 2012

- 2012 Seattle
  Washington State Convention Center
  March 5-8, 2012
  19th Conference on Retroviruses and Opportunistic Infections

- AIDS 2012
  XIX International AIDS Conference
  July 22 - 27
  Washington DC, USA
  Turning the Tide Together

Welcome to HIV11.com
Eleventh International Congress on Drug Therapy in HIV Infection
11-15 November 2012 Glasgow, UK

Current situation: some positive things….

Mortality (/100 pts y)

PI Use (/100 pts y)


mortaliteit ITG(/100pts/y)

ITM data
Life expectancy

Temporal changes in life expectancy, 1996-2007

Ref: Hogg R., CROI 2012, Abstract #137
Virological control

Last viral load below detection limit (%)
And some negative!

**New pts seen at ITM (n)**

**Total pts followed at ITM (n)**

ITM data
When to start ARV treatment?

- Int. AIDS Society guidelines: https://www.iasusa.org/guidelines
- European guidelines (EACS): http://www.europeanaidsclinicalsociety.org/

<table>
<thead>
<tr>
<th>Guideline</th>
<th>year</th>
<th>AIDS</th>
<th>CD4&lt;350</th>
<th>CD4 350-400</th>
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<tbody>
<tr>
<td>DHHS</td>
<td>2012</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>IAS-USA</td>
<td>2012</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>EACS</td>
<td>2012</td>
<td>Yes</td>
<td>Yes</td>
<td>some pts</td>
</tr>
<tr>
<td>WHO</td>
<td>2010</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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</table>

Still not reimbursed in Belgium

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When to start ARV treatment?

What are the choices?

Wait for the results of the START study? vs.

Already implement an early start?

(surely a good option to decrease transmission risk
Whether this is good for the patient remains maybe controversial)

Expanded analysis of HPTN052 trial*

Jury still not out!
See webcast pro/contra session from Glasgow congress
http://www.hiv11.com (Monday 12 November)

*B Grinsztejn XIX International AIDS Conference, Washington. THLBB05
What to start with?

- Efavirenz
- Rilpivirine
- Nevirapine
- Atazanavir/ritonavir
- Darunavir/ritonavir
- Lopinavir/ritonavir
- Tenofovir/emtricitabine
- Abacavir/lamivudine
- Not yet possible in Belgium

2 NRTI’s

“Backbone”

“3rd Agent”

NNRTI

Pl/r

(II)

NRTI: nucleoside reverse transcriptase inhibitor, NNRTI: non-nucleoside reverse transcriptase inhibitor; PI/r: Protease inhibitor boosted with ritonavir; II: Integrase Inhibitor
What to start with?

- Al lot of comparative trials, mostly “non-inferior” results.
- ACTG 5202 (JID 2011)
  - Backbone: ABC/3TC vs. TDF/FTC
  - Third agent: ATV/r vs. EFV
- Single Study (ICAAC 2012)
  - DTG + ABC/3TC vs. EFV/TDF/FTC
- ACTG 5257 (ongoing)
  - ATV/r vs DRV/r vs. Ral (backbone of TDF/FTC)
When to change?

<table>
<thead>
<tr>
<th>Guideline</th>
<th>year</th>
<th>Change treatment in case of:</th>
<th>Change to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHHS</td>
<td>2012</td>
<td>Persistent VL &gt;200 copies/ml</td>
<td>2 (preferably 3) fully active drugs</td>
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<tr>
<td>IAS-USA</td>
<td>2012</td>
<td>Sustained VL &gt;50-200 copies/ml</td>
<td>3 active drugs</td>
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<tr>
<td>EACS</td>
<td>2012</td>
<td>Confirmed VL &gt;500-1000 copies/ml</td>
<td>2 (preferably 3) fully active drugs</td>
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</tbody>
</table>

Detectable Viral load under treatment is infrequent
But what is clinically significant?
Recent results against an early switch:
- Charpentier C: no risk of subsequent virological failure with viral loads 20-50 c/ml.
- Wolf E: idem with VL 50-200 c/ml.
- Eron: long-term outcome of experienced pts on raltegravir (VL <50 vs 50-400 vs >400).
- Grennan JT, JID 2012 (VL<500).

Influence of Viral load test (real time PCR)?

Always assess adherence & drug interactions

Ref: all from XIX International AIDS Conference, Washington. Charpentier C WEPDB0102; Eron J TUPE025
What’s new in antiviral therapy?

- Three products approved in 2011
- A few interesting drugs in the pipeline
Drug Approval in 2011

- Rilpivirine (Edurant®)
- Viramune XR (Viramune®)
- Rilpivirine/Emtricitabine/Tenofovir (Eviplera®)
### Pipeline for antiviral drugs in 2012

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Sponsor</th>
<th>Phase</th>
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<tr>
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<td>BMS986001</td>
<td>BMS</td>
<td>II</td>
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<tr>
<td>NRTI</td>
<td>CMX-157</td>
<td>Chimerix</td>
<td>I</td>
</tr>
<tr>
<td>NRTI</td>
<td>GS-7340</td>
<td>Gilead</td>
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</tr>
<tr>
<td>NNRTI</td>
<td>Lersivirine</td>
<td>Pfizer</td>
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</tr>
<tr>
<td>NNRTI</td>
<td>Rilpivirine LA</td>
<td>Janssen</td>
<td>I</td>
</tr>
<tr>
<td>CCR5I/CCR2I</td>
<td>Cenicriviroc</td>
<td>Takeda</td>
<td>II</td>
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<tr>
<td>II</td>
<td>Dolutegravir (DTG)</td>
<td>ViiV</td>
<td>III</td>
</tr>
<tr>
<td>II</td>
<td>Elvitegravir (EVG)</td>
<td>Gilead</td>
<td>Submitted</td>
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<tr>
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<td>II</td>
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<td>GSK-1265744 LA</td>
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<tr>
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<td>BMS663068</td>
<td>BMS</td>
<td>II</td>
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<tr>
<td>PK booster</td>
<td>Cobicistat</td>
<td>Gilead</td>
<td>Submitted</td>
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<tr>
<td>PK booster</td>
<td>SPI-251</td>
<td>Sequoia</td>
<td>Discontinued</td>
</tr>
<tr>
<td>PK booster</td>
<td>CTP-518</td>
<td>GSK</td>
<td>On Hold</td>
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<tr>
<td>FDC</td>
<td>&quot;QUAD&quot;</td>
<td>Gilead</td>
<td>Submitted</td>
</tr>
<tr>
<td>FDC</td>
<td>EVG/cobi/FTC/GS7340</td>
<td>Gilead/Tibotec</td>
<td>II</td>
</tr>
<tr>
<td>FDC</td>
<td>DRV/cobi/FTC/GS7340</td>
<td>Janssen/Gilead</td>
<td>II</td>
</tr>
<tr>
<td>FDC</td>
<td>DTG/ABC/3TC (&quot;Trii&quot;)</td>
<td>ViiV</td>
<td>III</td>
</tr>
</tbody>
</table>

Pipelines in infectious diseases

From “the race against drug resistance” (http://www.cgdev.org)
New treatment strategies

- **Start earlier** ("Test & Treat", START study…)
  - 2 Nucl. analogues + Integrase inhibitor
  - 2 Nucl. analogues + CCR5 inhibitors

- Modify the backbone ("NRTI sparing")
  - Protease inhibitor + Integrase inhibitors - Protease inhibitor + CCR5 inhibitors
  - Protease inhibitor + NNRTI - Simplification (PI/r monotherapy)

- New treatment combinations
New treatment strategies

• **Start earlier** (“Test & Treat”, START study…)

• **Modify the third agent** (PI- or NNRTI free)
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New treatment strategies

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  - Protease inhibitor + NNRTI  
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  - Simplification (PI/r monotherapy)
NRTI sparing therapy: a holy grail?

1. PI + NNRTI
   - EFV + LPV/r → study A5142 (Riddler SA, NEJM 2008)

2. PI + Integrase inhibitor
   - Ral + LPV/r → Progress trial (Reynes J, HIV Clin Trials 2011)
   - Ral + ATV/r → Spartan trial (Kozal MJ, HIV Clin Trials 2012)
   - Ral + DRV/r → Radar study (Bedimo R, 6th IAS, Rome 2011)
   - Ral + DRV/r → ACTG5262 trial (Taiwo B, AIDS 2011)
   - Ral + DRV/r → NEAT001 trial (ongoing)

3. PI + CCR5 inhibitor
   - MVC + ATV/r → Study A4001078 (Mills A XIX AIDS conf TUAB0102)
   - MVC + DRV/r → Midas trial (Taiwo B XIX AIDS conf TUPE099)
   - MVC + DRV/r → Study A4001095 (ongoing)
Is it still a valuable option?

See:

- Mathis S Plos One 2011 (meta-analysis)
- Guiguet M AIDS 2012 (long term observational study)
Generic antiviral drugs

End patent in the coming years for some antiviral drugs.

- Zidovudine 2005
- Lamivudine 2011
- Combivir® 2013
- Nevirapine 2013
- Efavirenz 2013
- Abacavir 2014
- Lopinavir/ritonavir 2015
- Emtricitabine 2016

Will it affect the way we prescribe antiviral drugs in Belgium?

Interesting presentation on how to deal with ARV in time of crisis

Another on the use of generic ARV’s in Europe
New (co-)formulations: STR*

STR: Single Tablet Regimen

Till 2011
• Atripla®

Since 2012
• Eviplera® (Rilpivirine/tenofovir/emtricitabine)

In the future
• Elvitegravir/cobicistat/tenofovir/emtricitabine= « QUAD » (Submitted)
• Dolutegravir/Lamivudine/Abacavir (« Trii ») (phase III)
• Darunavir/cobicistat/GS7340/emtricitabine (phase II)
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Is STR better than QD?*

* Uthman OA, XIX International AIDS Conference, Washington. TUPE096
Long-Acting drugs

• Rilpivirine LA
• SGSK 1265744

Both phase I studies

Take Home Message

• Tritherapy remains the gold standard

But:
  – Products works far better than in 1996.
  – Better safety profile, much better tolerance.
  – Administration is much easier (Once a day, STR).

• Big questions remains
  – What is the optimal timing to start antiretroviral treatment?
  – Is there something better than the classical tritherapy?
  – …
Bedankt voor jullie aandacht

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