BHIVA Workshop: When to Start

Dr Chloe Orkin
Dr Laura Waters
Aims

• To use cases to:
  - Review new BHIVA guidance
  - Explore current data around when to start

• To discuss:
  - Medical decisions, pros and cons
Luigi
Case 1: Luigi

- 27 year old Caucasian MSM
- New HIV diagnosis at annual GU check-up
- Well
- PMH, DH nil of note; NKDA
- SH:
  - Retail manager
  - 10-15 cigarettes/day, 20-30 units EtOH/week
  - Cocaine ‘now & then’
## Luigi: Results

<table>
<thead>
<tr>
<th>Test</th>
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<tbody>
<tr>
<td>CD4</td>
<td>278 (18%) cells/mm³</td>
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<td>Natural immunity (sAb 125)</td>
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<td>Normal range</td>
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Keypad Question
...recommend that patients with chronic infection start ART if the CD4 count is < 350 cells/ml (1A)
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<tr>
<td>STAHRS</td>
<td>INCIDENT</td>
</tr>
</tbody>
</table>
What next?

- Review in 3 months
- Start antiretroviral therapy
- Recruit to trial
Trial Design

• Definition of PHI
  – laboratory evidence of infection within 6 months of a previous negative test, <3 bands WB, RITA incident, antibody negative PCR+

• Randomisation to one of three arms:
  – 48-week short course ART (ART-48)
  – 12-week short course ART (ART-12)
  – No therapy (Standard of Care SOC)

• Primary end point
  – time to CD4 <350 cells/mm³ or long-term ART initiation

• Sample size
  – 360 providing 90% power to detect relative reduction in risk of time to CD4 <350 cells/mm³ of 50% and 25% in ART-48 and ART-12 compared to SOC respectively over an average follow-up of 4 years
Enrolment & Exclusions

SCREENED
429

RANDOMISED
371

SOC
124

ART-12
123

ART-48
124

58 EXCLUDED
15 not PHI
19 protocol exclusions
24 other reasons

SOC
124

ART-12
120

ART-48
123

5 EXCLUDED
2 not equivocal
1 HIV-neg>8 months
1 remained HIV-neg
1 randomisation error
Time to primary endpoint

SPARTAC
Treating recent HIV infection

ART48 HR 0.63
(0.45, 0.90), p=0.01

ART12 HR 0.93
(0.67, 1.29), p=0.67

SOC

Probability of not reaching primary endpoint

Time (years)

SOC 123 109 93 82 75 66 59 46 30 18
ART-12 120 110 95 84 79 71 63 49 32 21
ART-48 123 121 117 109 100 88 80 63 41 19
Time to primary endpoint

<table>
<thead>
<tr>
<th>Time to primary endpoint</th>
<th>SOC</th>
<th>ART12</th>
<th>ART48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, weeks (95% CI)</td>
<td>157 (114,213)</td>
<td>184 (140,214)</td>
<td>222 (189,270)</td>
</tr>
<tr>
<td>Difference vs. SOC</td>
<td>-</td>
<td>27 (-25,79)</td>
<td>65 (17,114)</td>
</tr>
<tr>
<td>Difference vs. ART12</td>
<td>-</td>
<td>-</td>
<td>38 (-3,79)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART12 vs. SOC</td>
<td>0.93</td>
<td>0.67 - 1.29</td>
<td>0.67</td>
</tr>
<tr>
<td>ART48 vs. SOC</td>
<td>0.63</td>
<td>0.45 - 0.90</td>
<td>0.01</td>
</tr>
<tr>
<td>ART48 vs. ART12</td>
<td>0.68</td>
<td>0.48 - 0.96</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Keypad Question
Duration of infection and time to Primary Endpoint

ART-48 ≤12 wks

ART-48 >12 wks

SOC ≤12 wks

SOC >12 wks

ART48 vs SOC < 12 w HR = 0.48
[0.30, 0.78] p=0.003

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>SOC &gt;12 wks</th>
<th>SOC ≤12 wks</th>
<th>ART-48 &gt;12 wks</th>
<th>ART-48 ≤12 wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>53</td>
<td>70</td>
<td>64</td>
<td>59</td>
</tr>
<tr>
<td>0.5</td>
<td>47</td>
<td>62</td>
<td>63</td>
<td>58</td>
</tr>
<tr>
<td>1</td>
<td>42</td>
<td>51</td>
<td>60</td>
<td>57</td>
</tr>
<tr>
<td>1.5</td>
<td>41</td>
<td>41</td>
<td>55</td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>36</td>
<td>39</td>
<td>39</td>
<td>50</td>
</tr>
<tr>
<td>2.5</td>
<td>32</td>
<td>34</td>
<td>42</td>
<td>46</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>30</td>
<td>38</td>
<td>42</td>
</tr>
<tr>
<td>3.5</td>
<td>24</td>
<td>22</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>16</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>4.5</td>
<td>8</td>
<td>10</td>
<td>11</td>
<td>8</td>
</tr>
</tbody>
</table>
Luigi

• What if he presented with seroconversion meningitis?
Keypad Question
BHIVA Guidelines 2008

- treatment in primary infection (outside a prospective study) should only be routinely considered in those with:
  - Neurological involvement
  - Any AIDS-defining illness
  - A CD4 cell count persistently <200 (i.e. for ≥3M)
BHIVA Guidelines 2012

• We recommend patients presenting with primary HIV infection and meeting any one of the following criteria start ART:
  • Neurological involvement [1D]
  • Any AIDS-defining illness [1A]
  • Confirmed CD4 cell count <350 cells/µL (1C)
BHIVA Guidelines 2012

- We recommend patients presenting with primary HIV infection and meeting any one of the following criteria start ART:
  - Neurological involvement [1D]
  - Any AIDS-defining illness [1A]
  - Confirmed CD4 cell count <350 cells/µL [1C]

This means START & CONTINUE. Although SPARTAC did not continue ART, based on SMART, ART should not be interrupted.
Luigi: 3 months later

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4</td>
<td>500 (38%) cells/mm³</td>
</tr>
<tr>
<td>HIV-RNA</td>
<td>121,000 copies/ml</td>
</tr>
<tr>
<td>HCV antibody</td>
<td>Negative</td>
</tr>
<tr>
<td>ALT</td>
<td>471</td>
</tr>
<tr>
<td>Other bloods/uPCR</td>
<td>Normal range</td>
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# Luigi: Results

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</tr>
<tr>
<td>Other bloods/uPCR</td>
<td>Normal range</td>
</tr>
<tr>
<td>HCV-RNA</td>
<td>5,752,100 IU/l</td>
</tr>
<tr>
<td>Syphilis serology</td>
<td>Negative</td>
</tr>
</tbody>
</table>
Keypad Question
Acute hepatitis C in HIV-infected individuals: recommendations from the European AIDS Treatment Network (NEAT) consensus conference

The European AIDS Treatment Network (NEAT) Acute Hepatitis C Infection Consensus Panel

*AIDS* 2011, 25:399–409
1. HCV-RNA levels should be measured at initial presentation and 4 weeks later (BII)

2. Treatment should be offered to:
   a) Individuals without a $2 \log_{10}$ reduction at week 4 compared with baseline
   b) Persistent serum HCV-RNA 12 weeks after diagnosis of acute HCV
4 weeks later

<table>
<thead>
<tr>
<th>ALT</th>
<th>85</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV-RNA</td>
<td>9987 IU/l</td>
</tr>
<tr>
<td>Syphilis serology</td>
<td>Negative</td>
</tr>
</tbody>
</table>
12 weeks later

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>52</td>
</tr>
<tr>
<td>HCV-RNA</td>
<td>&lt;30 IU/l</td>
</tr>
<tr>
<td>Syphilis serology</td>
<td>Negative</td>
</tr>
</tbody>
</table>
What if.....12 weeks later??

<p>| | |</p>
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<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>52</td>
</tr>
<tr>
<td>HCV-RNA</td>
<td>2,700,298 IU/l</td>
</tr>
<tr>
<td>CD4</td>
<td>540 (29%)</td>
</tr>
</tbody>
</table>
Keypad Question
“We recommend patients with HIV and hepatitis C virus co-infection and CD4 count between 350-500 cells/µL start ART:

i) immediately if HCV treatment is deferred,

ii) after initiation of HCV treatment if this is starting immediately. (1C)”
EACS v6: When to start

<table>
<thead>
<tr>
<th></th>
<th>CURRENT CD4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>350-500</td>
</tr>
<tr>
<td>HCV for which anti-HCV treatment is</td>
<td>R</td>
</tr>
<tr>
<td>being considered or given</td>
<td></td>
</tr>
<tr>
<td>HCV for which anti-HCV treatment</td>
<td>R</td>
</tr>
<tr>
<td>not feasible</td>
<td></td>
</tr>
</tbody>
</table>

R = Recommend
C = Consider
D = Defer
Luigi: 3 months later

- Well
- New RMP who is HIV-negative
- Wants to discuss transmission..........and wants to start ART
- What do you say?
Keypad Question
“We recommend that treatment with ART lowers the risk of transmission be discussed with all patients, and an assessment of the current risk of transmission to others be made at the time of this discussion. (GPP)

“We recommend following discussion, if a patient with a CD4 count above 350 cell/μL wishes to start ART to reduce the risk of transmission to partners, this decision is respected and ART is started. (GPP)”
10,838 Individuals Screened

Major reasons for exclusion:
- 3058 HIV+ but CD4 count out of range
- 2565 HIV- but HIV+ partner ineligible
- 308 Seroconcordant couples
- 155 Ineligible due to sexual history

1763 Couples (3526 Individuals) Randomized

Immediate Arm
886 Couples

Delayed Arm
877 Couples

HPTN 052

Cohen M. 6th IAS Rome 2011
HPTN 052

Linked HIV transmission

Cumulative Probability

No. at Risk
Immediate 893 658 298 79 31 24
Delayed 882 655 297 80 26 22

Years since Randomization

0 1 2 3 4 5

Immediate
Delayed

All HIV transmission

Cumulative Probability

No. at Risk
Immediate 893 658 298 79 31 24
Delayed 882 655 297 80 26 22

Years since Randomization

0 1 2 3 4 5

Immediate
Delayed
What about anal sex?

• HPTN052
  • Included only 37 MSM couples but
  • Heterosexuals have anal sex too:
    • US 16-20% recent [1,2] 35% lifetime [3]
      • 16% 15-21 year olds last 3 months[2]
    • 10% of women and 14% men in South African survey of >4500 individuals [4]

• Case report of MSM transmission in setting of undetectable VL [5]

Luigi: 1 month later

• Luigi and his partner have both attended for gonorrhoea treatment
• Decision made to commence ART
Agnes
Agnes

- 58 year old Caribbean woman
- Diagnosed by GP March 2011
- Hypertensive, impaired glucose tolerance
- DH:
  - Amlodipine 10mg daily
- SH
  - Divorced, not sexually active currently
  - Non-smoker, minimal EtOH
Agnes: Results

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<tr>
<td>CD4</td>
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<tr>
<td>HIV-RNA</td>
<td>7,420 copies/ml</td>
</tr>
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<td>Negative</td>
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<tr>
<td>HBV serology</td>
<td>Vaccinated (sAb 125)</td>
</tr>
<tr>
<td>Creatinine/eGFR</td>
<td>132/55</td>
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</table>
## Agnes: Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total-chol</td>
<td>6.9</td>
</tr>
<tr>
<td>HDL-chol</td>
<td>1.2</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>4</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>150/98</td>
</tr>
<tr>
<td>JBS-2 CV risk</td>
<td>23%</td>
</tr>
</tbody>
</table>
Keypad Question
“..treatment may be started or considered before the CD4 count is below 350 cells/mL........ established CVD or a very high risk of cardiovascular events (e.g. Framingham risk of CVD >20% over 10 years).”
“..treatment may be considered before the CD4 count is below 350 cells/mL…….

established CVD, or a very high risk of cardiovascular events (e.g. Framingham risk of CVD >20% over 10 years).”

“There are insufficient data to inform whether CVD risk should affect the decision to start ART”
Balance in favour of treating early for CVD Risk

- Reduced risk of AMI due to HIV
- AMI risk due to ART
  - No evidence ART ↓AMI
  - Cost

Start Early

Defer
HIV Confers AMI Risk Comparable to Traditional CVD Risk Factors

Carotid IMT is Increased in HIV Elite Controllers

Hsue AIDS 2009
CD4+ cell count and CHD risk in HIV-infected patients

- Cohort study of 20,775 patients HIV+ matched to 215,158 patients HIV- Kaiser Permanente members for age, sex and center (1996–2008)

- Overall, increased risk of CHD: 1.2 (P < 0.001), MI: 1.4 (P < 0.001) in HIV+ vs HIV-

- Increased risk of CHD in HIV+ patients with lowest recorded CD4+ < 200 cells/mm³

*Adjusted for age, race, sex, tobacco use, alcohol/drug abuse, obesity, diabetes, and use of lipid-lowering and antihypertensive therapy. The following factors were time varying in the analysis: ART, CD4+ count, age, diabetes, lipid-lowering therapy, antihypertensive therapy, remaining factors were fixed variables.

Klein D, et al. 18th CROI; 2011 Feb 27-Mar 2; Boston, MA, USA: Poster 810.
Balance against treating early for CVD Risk

- Reduced risk of AMI due to HIV
- AMI risk due to ART
  - No evidence ART ↓AMI
- Cost

Start Early

Defer
Figure 1. Risk of Myocardial Infarction According to Exposure to Combination Antiretroviral Therapy.

Figure 2. Risk of Myocardial Infarction According to Exposure to Protease Inhibitors and Nonnucleoside Reverse-Transcriptase Inhibitors.
### SMART

#### FATAL OR NON-FATAL CVD EVENTS

<table>
<thead>
<tr>
<th>DC ARM (n=2720)</th>
<th>VS ARM (n=2752)</th>
<th>HR (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>Rate (per 100 PY)</td>
<td>No.</td>
<td>Rate (per 100 PY)</td>
</tr>
<tr>
<td>48</td>
<td>1.3</td>
<td>31</td>
<td>0.8</td>
</tr>
</tbody>
</table>

El-Sadr et al. NEJM 2006.
SUN Study

- SUN cohort: n=389
- Suppressed viral load (at all visits): n=235
- Detectable viral load (at ≥ 1 visit): n=153
- Detectable viral load: On ART (at baseline): n=80, Off ART (at baseline): n=73

2 year change in cIMT (mm)

P<0.001 for SUN cohort
P=0.86 for Detectable viral load

Baker et al. JID 2011.
Decision

- No clinical end-point data to support earlier ART in CVD (hence change in guidelines)
Keypad Question
Poorer immunological response in older patients supports earlier ARV therapy

- Studies involving >55,500 ART-naïve patients started on ART therapy show that older age is an independent predictor of lower CD4 count increases\(^1\)\(^-\)\(^4\)
  - Significantly poorer immunological response is regardless of baseline HIV RNA levels (p<0.0001)\(^4\)

- Older patients have poorer clinical outcomes, with significantly faster progression to AIDS (p<0.001) and shorter survival (P<0.001)\(^2\),\(^5\)

2. COHERE study group. AIDS 2008;22(12):1463-1473.
“Therapy is recommended regardless of CD4 cell count in the following settings ........ old than 60 years”
“The absolute risk of disease progression is significantly higher for a given CD4 count in older people (see Table 2.1), so consideration should be given to starting at higher CD4 counts in older persons.”
Agnes

• Attends 3 months later
• Markers similar
• Has a new HIV-negative partner....
Thank you!