General Medicine/ID Update

Chairs:
Nadia Naous & Dr Clare van Halsema

This educational event is supported by an unrestricted medical education grants from
What’s new in ID and general medicine for HIV physicians?

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Disclosures

- JU has received honoraria for preparing educational materials and served on advisory boards for Gilead Sciences and ViiV Healthcare
What am I going to talk about?

• What’s new in TB?

• What’s new in cryptococcal meningitis?

• What’s new in general medicine?
1.5 million people died of TB in 2020

FIG. 4.14
Top causes of death worldwide in 2016\textsuperscript{a,b}
Deaths from TB among HIV-positive people are shown in grey.

Ischaemic heart disease
Stroke
Chronic obstructive pulmonary disease
Lower respiratory infections
Alzheimer disease and other dementias
Trachea, bronchus, lung cancers
Diabetes mellitus
Road injury
Diarrhoeal diseases
Tuberculosis

Biggest killer of people with HIV

FIG. 4.15
Estimated number of deaths worldwide from TB and HIV/AIDS in 2019\textsuperscript{a,b}
Deaths from TB among HIV-positive people are shown in grey.

The pandemic has made the syndemic worse

**FIG. 6**
Global trends in the estimated number of deaths caused by TB and HIV, 2000–2020.a,b

Shaded areas represent uncertainty intervals.

**FIG. 4.5**
Estimated HIV prevalence in new and relapse TB cases, 2019
Drug resistant TB is a real problem

FIG. 4.30
Percentage of new TB cases with MDR/RR-TB°

Current Rx (WHO 2020)

Fluroquinolones essential MDR drugs

‘Uncomplicated’ MDR
• 9-12 months total
• Only if no fluoroquinolone resistance AND <1 month exposure to 2nd line, not extensive disease
• Moxifloxacin/levofloxacin, clofazimine, ethambutol and pyrazinamide - throughout + 6 months bedaquiline (replace injectable) + high dose isoniazid and ethionamide during the first 4-6 months.

At least 4 drugs for ‘intensive phase’
At least 3 drugs for ‘continuation phase’
Total duration 18-20 months

Table 3.1. Grouping of medicines recommended for use in longer MDR-TB regimens

<table>
<thead>
<tr>
<th>Groups and steps</th>
<th>Medicine</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A:</td>
<td>Levofoxacin or moxifloxacin</td>
<td>Lfx, Mfx</td>
</tr>
<tr>
<td>Include all three medicines</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bedaquiline</td>
<td>Bdq</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>Lzd</td>
</tr>
<tr>
<td></td>
<td>Clofazimine</td>
<td>Cfz</td>
</tr>
<tr>
<td></td>
<td>Cycloserine or terizidone</td>
<td>Cs, Trd</td>
</tr>
<tr>
<td></td>
<td>Ethambutol</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Delamanid</td>
<td>Dlm</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>Z</td>
</tr>
<tr>
<td></td>
<td>Imipenem–cilastatin or meropenem</td>
<td>Jpm–Cln, Mpm</td>
</tr>
<tr>
<td></td>
<td>Amikacin (or streptomycin)</td>
<td>Am (S)</td>
</tr>
<tr>
<td></td>
<td>Ethionamide or prothionamide</td>
<td>Eto, Pto</td>
</tr>
<tr>
<td></td>
<td>P-aminosalicylic acid</td>
<td>PAS</td>
</tr>
</tbody>
</table>
XDR – 6 months Rx!!! (but with substantial toxicity)

34% took linezolid for 6 months
15% completed 1200mg/day
TB-PRACTECAL: A pragmatic Clinical Trial for a more Effective, Concise and Less toxic MDR-TB regimens

Belarus (RR 38%)
Uzbekistan (RR 12%)
South Africa (RR 3.4 %)

Phase II/III RCT in patients with rifampicin resistant pulmonary TB (inc pre-XDR)

What was tested?

Experimental arms (24 weeks):

1. Bedaquiline + Pretomanid + linezolid + moxifloxacin
2. Bedaquiline + Pretomanid + linezolid + clofazimine
3. Bedaquiline + Pretomanid + linezolid

Control arm:
Locally accepted standard of care which is consistent with WHO recommendations for the treatment of M/XDR-TB

• includes shorter course MDR & bedquiline etc

Trial stopped early by DSMB

- n=122 (control) vs n=120 in experimental arm (BPaLM)

- Enrolment discontinued because:
  - Clear difference in proportion of unfavourable outcomes
    - >3 sigma difference
    - Favours experimental arm (0 vs 5 deaths)
  - NO PROSPECT further recruitment will change this

A new treatment regimen for MDR?

- Data checking, cleaning etc for WHO

- BPaLM and other regimens will be assessed by WHO for next guidelines
**ZeNIX – phase 3, partially blinded RCT**

**Primary Outcome**
Incidence of bacteriologic failure, relapse or clinical failure – 6/12

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**Extensively Drug-Resistant, Pre-Extensively Drug-Resistant + Treatment-Intolerant or Non-responsive Multidrug-Resistant TB Participants**

**B-Pa-L**
- $L=1200 \text{ mg/d} \times 6 \text{ mos}$
- 6 MONTHS OF TREATMENT*
- 18 MONTHS OF FOLLOW-UP

**B-Pa-L**
- $L=1200 \text{ mg/d} \times 2 \text{ mos}$
- 6 MONTHS OF TREATMENT*
- 18 MONTHS OF FOLLOW-UP

**B-Pa-L**
- $L=600 \text{ mg/d} \times 6 \text{ mos}$
- 6 MONTHS OF TREATMENT*
- 18 MONTHS OF FOLLOW-UP

**B-Pa-L**
- $L=600 \text{ mg/d} \times 2 \text{ mos}$
- 6 MONTHS OF TREATMENT*
- 18 MONTHS OF FOLLOW-UP

*Additional 3 months if sputum culture positive between week 16 and week 26 treatment visits

- Pa: pretomanid dose = 200 mg daily
- B: bedaquiline dose = 200 mg x 8 weeks, then 100 mg x 18 weeks

† Pre-2021 WHO Definitions of XDR-TB and Pre-XDR-TB

Conradie et al. IAS 2021 abstract 2405 https://theprogramme.ias2021.org/Abstract/Abstract/2405
Who was recruited and what happened?

<table>
<thead>
<tr>
<th>Category</th>
<th>Total (N=181)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, years)</td>
<td>37.1</td>
<td></td>
</tr>
<tr>
<td>Sex (male)</td>
<td>122 (67.4%)</td>
<td></td>
</tr>
<tr>
<td>Race: White</td>
<td>115 (63.5%)</td>
<td></td>
</tr>
<tr>
<td>Race: Black</td>
<td>66 (36.5%)</td>
<td></td>
</tr>
<tr>
<td>HIV Positive</td>
<td>36 (19.9%)</td>
<td></td>
</tr>
<tr>
<td>Current TB type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDR-TB (NR)</td>
<td>12 (6.6%)</td>
<td></td>
</tr>
<tr>
<td>MDR-TB (Rx intolerant)</td>
<td>9 (5.0%)</td>
<td></td>
</tr>
<tr>
<td>Pre-XDR</td>
<td>85 (47.0%)</td>
<td></td>
</tr>
<tr>
<td>XDR</td>
<td>75 (41.4%)</td>
<td></td>
</tr>
</tbody>
</table>

Favorable Response (%)

- B + Pa + L 1200 mg for 26/52: 93%
- B + Pa + L 600 mg for 26/52: 89%
- B + Pa + L 1200 mg for 9/52: 91%
- B + Pa + L 600 mg for 9/52: 84%

Conradie et al. IAS 2021 abstract 2405 https://theprogramme.ias2021.org/Abstract/Abstract/2405
Time to culture conversion was rapid
Incidence of adverse events

Dose modification: 51% 28% 13% 13%

- Linezolid 1200mg 26/52
- Linezolid 1200mg 9/52
- Linezolid 600mg 26/52
- Linezolid 600mg 9/52

- Peripheral neuropathy
- Optic neuropathy
- Worsening anaemia

Conradie et al. IAS 2021 abstract 2405 https://theprogramme.ias2021.org/Abstract/Abstract/2405
An improved regimen for XDR

• Reduced doses and shorter durations of linezolid:
  – efficacious
  – fewer adverse events and treatment modifications
  – reduce costs

• Further analyses ongoing
Cryptococcal meningitis kills ~180,000 per year

• Second biggest cause of death in PWH

• Conventional treatment with amphotericin B (AmB) is associated with significant toxicity

• WHO SoC induction for HIV-associated cryptococcal meningitis:
  – AmB + 5-FC (7 days) then fluconazole (1200mg 7 days)

• Liposomal amphotericin (AmBisome) is less toxic, has a long half-life and gets into the CNS well

Lancet Infect Dis. 2017 August ; 17(8): 873–881
Can Rx be improved?

Phase III, multi-centre, non-inferiority RCT

**Primary outcome:**
- All-cause mortality at 10 weeks (NI margin 10%)

**Secondary outcomes**
- All-cause mortality at 2, 4, and 16 weeks (non-inferiority),
- All-cause mortality at 10 weeks (superiority),
- Fungicidal activity, safety, relapse and IRIS, PK/PD, cost

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**Adults ≥18 with HIV & first episode of HIV-associated cryptococcal meningitis (n = 844)**

**Liposomal AmB** 10 mg/kg single dose +
5-FC 100 mg/kg OD for 14 days +
FLU 1200 mg OD for 14 days
(n = 421)

**AmB** 1 mg/kg for 7 days +
5-FC 100 mg/kg OD for 7 days followed by
FLU 1200 mg OD for 7 days
(n = 423)

**FLU** 800 mg OD for 8 wk;
ART initiated 4-6 wk after start of antifungal therapy

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Lawrence et al. IAS 2021 abstract 2370 [https://theprogramme.ias2021.org/Abstract/Abstract/2370](https://theprogramme.ias2021.org/Abstract/Abstract/2370). Adapted with permission
Who did they enrol?

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AmBisome (N=407)</th>
<th>Control (N=407)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex – % male</td>
<td>60%</td>
<td>60%</td>
</tr>
<tr>
<td>Median age – years (IQR)</td>
<td>37 (32-44)</td>
<td>37 (32-43)</td>
</tr>
<tr>
<td>Prior ART use</td>
<td>63%</td>
<td>65%</td>
</tr>
<tr>
<td>Median weight – kg (IQR)</td>
<td>53 (47-60)</td>
<td>53 (48-60)</td>
</tr>
<tr>
<td>Glasgow Coma Scale score &lt;15</td>
<td>28%</td>
<td>29%</td>
</tr>
<tr>
<td>Median CSF fungal count – CFU/ml (IQR)</td>
<td>48,500 (300-420,000)</td>
<td>42,000 (585-365,000)</td>
</tr>
<tr>
<td>CSF opening pressure &gt;25cm</td>
<td>41%</td>
<td>40%</td>
</tr>
<tr>
<td>Median CSF white-cell count – cells/mm³ (IQR)</td>
<td>6 (4-75)</td>
<td>5 (3-52)</td>
</tr>
<tr>
<td>Median CD4+ count – cells/mm³ (IQR)</td>
<td>26 (9-56)</td>
<td>28 (11-59)</td>
</tr>
</tbody>
</table>

All cause mortality at 10 weeks

Ambisome: 24.8% vs Control: 28.7%

Log Rank p-value = 0.24

All cause mortality risk difference (90% CI)

Prespecified Noninferiority Margin

<table>
<thead>
<tr>
<th></th>
<th>ITT (n=814)</th>
<th>PP (n=784)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for site, age, sex, baseline GCS, CSF fungal count, ART, Hb, CSF opening pressure.

Lawrence et al. IAS 2021 abstract 2370 [https://theprogramme.ias2021.org/Abstract/Abstract/2370](https://theprogramme.ias2021.org/Abstract/Abstract/2370). Adapted with permission
No difference in early fungicidal activity

Lawrence et al. IAS 2021 abstract 2370 https://theprogramme.ias2021.org/Abstract/Abstract/2370. Adapted with permission
<table>
<thead>
<tr>
<th>Safety Parameter</th>
<th>AmBisome (n=420)</th>
<th>Control (n=422)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of Grade 3 or 4 adverse events</td>
<td>382</td>
<td>579</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any adverse event – n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>173 (41%)</td>
<td>225 (53%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade 4</td>
<td>91 (22%)</td>
<td>127 (30%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Anaemia – n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>44 (10%)</td>
<td>108 (26%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade 4</td>
<td>12 (3%)</td>
<td>62 (15%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean change in haemoglobin level to day 7 – g/dl</td>
<td>-0.3</td>
<td>-1.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Received a blood transfusion – n (%)</td>
<td>32 (8%)</td>
<td>76 (18%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine increase – n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>17 (4%)</td>
<td>22 (5%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Grade 4</td>
<td>5 (1%)</td>
<td>3 (1%)</td>
<td>0.505</td>
</tr>
<tr>
<td>Mean % change in creatinine level to day 7</td>
<td>20.2%</td>
<td>49.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypokalaemia – n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>6 (2%)</td>
<td>27 (6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0 (0%)</td>
<td>3 (1%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Thrombophlebitis requiring abx – n (%)</td>
<td>8 (2%)</td>
<td>28 (7%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Lawrence et al. IAS 2021 abstract 2370 [https://theprogramme.ias2021.org/Abstract/Abstract/2370](https://theprogramme.ias2021.org/Abstract/Abstract/2370). Adapted with permission
A new standard of care?

• Better efficacy (?) and fewer side effects
  – what does this mean for UK practice?

• Cost effectiveness analyses on going

• BUT mortality still very high - 25%
  – earlier diagnosis and Rx important
  – Better to diagnose and Rx HIV early to prevent AIDS
General medicine
Get your third dose of vaccine when available


https://ig.ft.com/coronavirus-chart/

3rd dose approved
SGLT2 inhibitors – the new statins

End with _gliflozin

- canagliflozin
- dapagliflozin
- empagliflozin

- Originally developed for type 2 diabetes....
They work for heart failure – DAPA-HF

n=4,744
Blinded RCT
NYHA II-IV, LVEF <40%
42% diabetes
The work in CKD – DAPA-CKD

n=4,304
Double blind RCT
eGFR 25-75 & ACR 200-5000
68% type 2 diabetes
And now in HFpEF - EMPEROR-Preserved

Composite of Cardiovascular Death or Hospitalisation for Heart Failure

n=5,988
Double blind RCT
NYHA II-IV, LVEF >40%
49% diabetes

Hospitalisations for Heart Failure
They mix well with ART

<table>
<thead>
<tr>
<th>HIV Drugs</th>
<th>Co-medications</th>
<th>Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>cob</td>
<td>empa</td>
<td></td>
</tr>
<tr>
<td>A-Z</td>
<td>A-Z</td>
<td></td>
</tr>
</tbody>
</table>

- Darunavir + ritonavir (DRV/r)  
- Efavirenz (EFV)               
- Dolutegravir (DTG)            
- Darunavir/cobicistat (DRV/c)  
- Atazanavir/cobicistat (ATV/c) 
- Darunavir/cobicistat (DRV/c)  
- Darunavir/Cobicistat/Emtricitabine/Tenofovir alafenamide (DRV/c/FTC/TAF) 
- Elvitegravir/Cobicistat/Emtricitabine/Tenofovir alafenamide (DRV/c/FTC/TAF) 

Potential Interaction
- Darunavir + ritonavir (DRV/r)  
- Canagliflozin

Look for alternatives
- More Info

No Interaction Expected
- Darunavir + ritonavir (DRV/r)  
- Dapagliflozin

https://www.hiv-druginteractions.org
Intensive blood pressure control reduces CVD events in older adults - STEPS

Primary outcome composite of stroke, ACS, acute decompensated heart failure, PCI, AF, or CVD death

n=8,511
RCT 60-80 year olds
Intensive 110-130mm Hg vs 130-150 mm Hg

But all cause mortality similar
Abstinence makes the heart beat better

n=140
RCT abstinence vs continued drinking

88% reduction in alcohol Rx group vs 19% reduction in control

Conclusions

• Better treatment regimens for drug resistant TB are coming

• Better treatment regimens for cryptococcal meningitis coming to resource limited settings

• SGLT-2 inhibitors are amazing and will be coming to a patient near you soon

• Laying off alcohol is good for your heart
Thanks for listening

• Any questions?