BHIVA ‘Best of CROI’ Feedback Meetings

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BHIVA ‘Best of CROI’ Feedback Meetings 2017
Tuberculosis
XDR-TB - background

- MDR-TB = resistance to Rifampicin + isoniazid
- XDR-TB = MDR + resistance to quinolone + injectable

- Previous experience (Kwazulu Natal 2005-7) 1 year mortality
  - MDR (n= 382) 71%
  - XDR (n= 272) 83%

Gandhi et al, AM J Respir Crit Care Med 2010; 181: 80-6
Nix-TB Trial

Participants are required to have documented XDR-TB, or MDR TB treatment intolerance or failure (TI or Fr)

Pretomanid 200 mg
Bedaquiline 200 mg tiw after 2 week load
Linezolid 1200 mg qd*

Follow up for relapse-free cure over 24 months

6 months of treatment
Additional 3 months if sputum culture positive at 4 months

*Amended from 600 mg bid strategy
 Outcome

31 patients have reached 6 months since completion of treatment
Two relapses/reinfection
- XDR TB on LPA- Genome sequencing will determine whether relapse or new infection
- DS-TB on LPA - appears at this stage to be a reinfection.
Four patients have died (all in the first 8 weeks)
- 3 had multi-organ TB on autopsy
- 1 had a GI bleed due to erosive esophagitis.

SO

- Current results of this greatly simplified and shortened all-oral regimen for drug resistant TB are encouraging in terms of both efficacy and safety
- Mortality is less than 6%
- There has been only one XDR TB relapse
- No participant has had to have extended treatment

Francesca et al., Abstract 80LB
Drug resistant TB: transmission networks indicate person-to-person spread

Transmission of MDR/XDR TB

Transmission of extensively drug-resistant (XDR) TB (TRAX) cohort (KZN S Africa) Almost 70% XDR TB due to transmission not treatment failure
Drug resistance not associated with a clinically relevant fitness cost

Whole genome sequencing (WGS) and spatial analysis of XDR transmission Kristin N. Nelson

70% genotypically linked cases not close contacts or hospital admissions; does geographic proximity (living/obtaining healthcare nearby) explain transmission?
Only 17% lived or diagnosed at health facility within 20km of case-pair

Shah et al. , Abstract 77
RCT of prednisolone to prevent paradoxical TB IRIS

Meintjes et al., Abstract 81LB
Endpoints

- **Primary endpoint = Paradoxical TB-IRIS**
  - International Network for the Study of HIV-associated IRIS (INSHI) case definition
  - Adjudicated by an independent expert committee
  - By intention to treat

- **Secondary endpoints included**
  - Time to TB-IRIS
  - Mortality
  - Hospitalisation
  - Interruption of ART or TB treatment for adverse events

- **Safety endpoints included**
  - Severe infections and malignancies
  - ACTG graded adverse events
  - CD4 count & HIV viral load at week 12

1. Meintjes, Lancet Infect Dis 2008;8:516

Meintjes et al., Abstract 81LB
Primary endpoint: Paradoxical TB-IRIS

In patients at high risk of paradoxical TB-IRIS and improving on TB treatment, prednisolone during the first 4 weeks of ART

- Reduced the incidence of TB-IRIS by 30%
- Reduced requirement for corticosteroids to treat TB-IRIS by 53%
- Was well-tolerated with no excess risk of infection or malignancy

Open-label corticosteroids for TB-IRIS treatment

Relative risk = 0.70 (95% CI = 0.51 - 0.96)

Denominator = all participants in each arm

Relative risk = 0.47 (95% CI = 0.27 - 0.83)
Temprano/ANRS 12136: Long-term follow-up study (A Abadje)

Anani D. et al, Abstract O78
Temprano: Long-term follow-up study

Anani D. et al., Abstract O78
A Multi-centre diagnostic accuracy study of the Expert Ultra for TB diagnosis

Global TB in 2015
- ~10.4 million new cases
- ~580,000 rifampin-resistant cases

>40% of TB patients and 80% of MDR-TB patients not diagnosed in 2015

Xpert® MTB/RIF Assay
- Rapid, sensitive near-patient Dx of TB and MDR in hours
- Recommended for use for pulmonary and extrapulmonary TB in adults and children
- Being used in 120 countries

Limitations of current Xpert MTB/RIF assay
- Imperfect sensitivity for paucibacillary disease (HIV, early disease, children etc.)
- Imperfect sensitivity for RIF-resistance detection in case of heteroresistance
- Imperfect specificity for RIF-resistance detection due to silent mutation detection
- Cross-reactivity with some NTMs

Key technical improvements of Ultra over Xpert
- Multi-copy targets (IS6110 and IS1081) vs rpoB only
- Doubled sample volume in reaction chamber (25ul-50ul)
- Optimized chemistry
- Switched to melt curve analysis from Real time PCR curves

Rothwell, Abstract O76LB
A Multi-centre diagnostic accuracy study of the Expert Ultra for TB diagnosis

Results: Non-inferiority analysis

△ Sensitivity for HIV-infected: +12% (95%CI +4.9, +21)

△ Specificity for Rif: +0.3% (95%CI -0.9, +1.7)

Rothwell, Abstract O76LB
Cryptococcal meningitis
High-dose liposomal Amphotericin B

Conventional AmB complex/toxic to administer in resource-poor settings

**Ambition-CM trial:** 80 patients first episode CM, median CD4 = 34. Botswana/Tanzania

Treated with fluconazole 1200mg daily plus:

1. Single dose L-AmB 10mg/kg
2. L-AmB 10mg/kg d1, 5mg/kg d3
3. L-AmB 10mg/kg d1, 5mg/kg d3 and d7
4. L-AmB 3mg/kg/d 14 days

Early fungicidal activity similar in all arms

Combined arms 1-3 non-inferior to standard therapy (arm 4)

Overall mortality 29% (lower than previous studies)

Jarvis et al., Abstract 82
Cancers
Incident cancers in the U.S. 1996-2012: impact of ART

HIV/AIDS Cancer Match Study

N=448,258 PLWH
N=21,294 incident cancers

Evaluated >50 AIDS defining and non AIDS defining cancers

Risk elevated for some virus-unrelated cancers but not for other common cancers e.g. colorectum, breast, prostate

SIRs decreased significantly for some cancers but not to background levels (figure)

Raül et al, Abstract 600
Effect of smoking cessation on cancer incidence

Adjusted rate ratios for specific cancer

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Smoking unrelated cancer</th>
<th>Smoking related cancer (excl. lung)</th>
<th>Lung cancer</th>
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<tr>
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<td>Current smoker</td>
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<td>Ex at baseline</td>
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<td>Ex: 1 - 2 years</td>
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<td>Ex: &gt;5 years</td>
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</tbody>
</table>

P trend = 0.04
P trend = 0.04
P trend = 0.13

Models were adjusted for age, gender, transmission group, race, BMI, calendar year, cART use, CD4, HIV viral-load, hepatitis B and C status, AIDS defining events (excluding cancers), anaemia, hypertension, diabetes, cardiovascular disease and duration of smoking in D:A:D

Shepherd et al., Abstract 131
HPV related cancers: monitoring and treatment of CIN 2/3 in HIV-infected women

LEEP vs cryotherapy for CIN 2/3

- 400 HIV-infected women (89% on ART, median CD4 380 cells/μl), Kenya
- Randomised: cryotherapy or loop electrosurgical excisional procedure (LEEP)
- Primary outcome: 2-year recurrence cervical disease

- Results: recurrence of HSIL+ per 100 woman-years
  - Cryotherapy 21.1
  - LEEP 14.0

Cryotherapy: 52% more likely to experience recurrence (HR: 1.52, 95% [CI]: 1.07-2.17; P=0.020)

Natural history CIN 2 in HIV+ childbearing age: Women’s Interagency HIV Study (WIHS)

- Rationale: Resection can cause cervical incompetence
- 66/109 (60.6%) confirmed untreated CIN 2
- 21% progressed within 10 years
- No difference progression rates treatment at 2ys (11.1 vs 5.2%) or 5ys (14.8 vs 16.2%)
- cART ~ 80% decrease progression (aHR 0.20; 95% CI 0.05, 0.71)
- Increase 100 CD4+ T-cells ~ 30% decrease progression (aHR 0.68; 95% CI 0.53, 0.85)

Progression CIN2 uncommon; close monitoring an option for those on ART?

Greene, Abstract 22

Colie, Abstract 23
Screening for HSIL

For HIV-infected & uninfected MSM, hrHPV-E6/E7-mRNA & -DNA testing adds value to cytology screening for predicting HSIL over cytology alone. Larger studies are needed.

Wiley et al. Abstract 592
Multiple HPV infections and anal pre-cancer in HIV+ men

Cheng et al., Abstract 594
Subjects who have >=5 types of HPV have 20x risk of anal ASCUS+. Multiple anal HPV infections in HIV+ patients warrant aggressive follow-up

Cheng et al., Abstract 594
HPV related cancers: Screening for anal lesions
What might work…And what doesn’t

Swiss HIV Cohort: Mathematical model of screening & ART on anal CA incidence
- Yearly anoscopy to prevent most anal CA
- CD4 dependent anoscopy to prevent most/test
- Expanding ART: modest effect

P16/Ki-67 dual staining cytology for precancerous anal lesions

Rationale: High risk HPV up-regulate p16 expression and increase proliferation (Ki67 expression)

Blaser et al., Abstract 596

Serrano-Villar et al., Abstract 595
Cardiovascular disease
• Previous findings
  • Increased risk of CVD with cumulative exposure to eg. Lopinavir
  • However main PIs now used = Atazanavir and Darunavir
  • Follow-up time has not been long enough to report on associations in D.A.D.

• Aim: Is cumulative exposure to ATV/r and DRV/r associated with increased risk of CVD?
  • CVD = MI, Stroke, Sudden cardiac death, Invasive CVD procedure, e.g. CABG

• Results expressed as per 5 year exposure to PI/r

Ryom et al., Abstract 128 LB
D:A:D - Adjusting (primary model) for confounders

Time updated:
- Use of LPV/r, ABC
- VL, prior AIDS
- Smoking, CVD family history, Hypertension
- HBV, HCV

Fixed at baseline:
Gender, Race, Age, prior CVD, Enrollment cohort, Baseline date, HIV acquisition risk, HBV, HCV, CD4 nadir

Values fixed at baseline*:
CD4, Diabetes, BMI, Dyslipidaemia, CKD

*On causal pathway

Ryom et al., Abstract 128 LB
Crude Incidence Rates of CVD per 1000 PYFU
Stratified by Cumulative Use of ATV/r and DRV/r

Ryom et al., Abstract 128LB

Incidence rate / 1000 PYFU (95% CI)

ATV/r

Cumulative years of exposure

0 0-1 1-2 2-3 3-4 4-5 5-6 >6


DRV/r

PyFU 163785 12886 7631 6369 6144 5757 4898 9278 185246 8845 6591 5285 4100 2940 1768 1975
Association Between CVD & Cumulative ATV/r and DRV/r Use

Primary Model; Baseline Adjustment Only for Variables Potentially on the Causal Pathway between PI/r Use and CVD

Multivariate models were adjusted for gender, age, race, HIV risk of acquisition, enrolment cohort, baseline date, prior CVD, CD4 nadir, CD4, BMI, diabetes, dyslipidemia, eGFR (all fixed at baseline), cumulative exposure to DRV/r, ATV/r, LPV/r and IDV, recent exposure ABC, prior AIDS, viral load, hepatitis B & C, family history of CVD, hypertension, smoking (all time updated)
Association Between CVD & Cumulative ATV/r and DRV/r Use; Additional Time-updated Adjustment for Factors Potentially on the Causal Pathway between PI/r use and CVD CD4, BMI, CKD, Dyslipidaemia, Diabetes

CVD Incidence rate ratio (95%CI)

ATV/r

- Never exposed to
- Univariate/5 yrs exp
- Multivariate PRIMARY/5 yrs exp
- Time-updated adjustment

DRV/r

- Never exposed to
- Univariate/5 yrs exp
- Multivariate PRIMARY/5 yrs exp
- Time-updated adjustment

1.01 [0.88-1.16]

1.53 [1.28-1.84]
Association Between CVD & cumulative ATV/r and DRV/r Use; Additional Adjustment for Bilirubin Levels (Time-updated)

CVD Incidence rate ratio (95% CI)

- ATV/r: 1.05 [0.89-1.23]
- DRV/r: 1.60 [1.31-1.96]
Bilirubin and CVD risk

- Bilirubin associated with $^1$:
  - Reduces oxidative stress
  - Lower Lipids
  - Inhibition of platelet activity

- In ACTG 5257:
  - ATV associated with lower D dimers and hs-CRP $^2$

Marconi et al., Abstract 127

1 Perlstein 2008, Bulmer 2013, Kundar 2015
2 Kelesidis 2015
Bilirubin and CVD risk

- Mainly men 97%
- 48% African American
- Mean age = 48 years

**Objective** – determine whether total bilirubin at baseline associated with:
- Heart Failure
- Acute MI
- Ischaemic Stroke
- CVD (all 3 of above)

- Adjusted for demographics and CVD risk factors + liver fibrosis, substance use, HIV markers

Marconi et al., Abstract 127
BHIVA ‘Best of CROI’ Working Party 2017

Dr Tristan Barber
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