Journal Club

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Publishing for last 15 years

Official journal of the International AIDS Society

18 issues a year
One step closer to ultra-long-acting PrEP

- Could offer simpler regimens
- Potentially improve adherence & effectiveness
- What if side effects emerge?
- Current formulations can’t be removed once injected.
- Implanted dolutegravir via subcut injection
- Solution then solidifies into small biodegradable implant that can be removed
- Sustained levels up to 9 months in 2 models & 5 months in
GlycA, a novel inflammatory marker, is associated with subclinical coronary disease
Martin Tibuakuu et al. John Hopkins USA

• PLWH:
  ➢ living longer
  ➢ higher rates of CVD events
  ➢ increased prevalence atherosclerosis comp to –ve people

• Atherosclerosis is an inflammatory process

• CVD risk stratification tools inadequate

• Chronically elevated systemic inflammation may explain increased CVD risk in PLWH
More background...

- GlycA novel composite biomarker of systemic inflammation
- Measured by nuclear magnetic resonance
- High levels GlycA associated with:
  - CVD events
  - DM
  - Cardiovascular and all cause mortality

- Examined associations between GlycA & subclinical coronary plaque among HIV-infected and HIV-uninfected men participating in Multicenter AIDS Cohort Study (MACS)
Methods

• Cross sectional analysis
• 935 men
• Plasma measurements of GlycA
• Non-contrast cardiac computed tomography
• &/or coronary CT angiography
• MVA Poisson and linear regression
Results and conclusions

- HIV infection associated with higher GlycA levels
- GlycA sig associated with subclinical coronary atherosclerosis in both PLWH and PNLWH
- Could use GlycA in CVD risk stratification in PLWH ie. Add it to the Framingham risk scale
- More study needed
Vaccination with Fendrix of prior non-responding patients with HIV has a high success rate

- Reported seroconversion rate of 34-88%
- 20 international units
- Different adjuvant - AS04 a Toll-like receptor 4 antagonist
- Licensed in Europe
- Not for PLWH
- Study of revaccination in PNLWH performed sig better than Engerix
- One small study (22) in PLWH seroconversion rate of 81.8%
- Aimed to describe outcome of revaccination with Fendrix in PLWHA
- Dutch HIV centres
Results and conclusions

• Retrospective study
• 100 patients
• 81% seroconversion rate (95% CI: 72–88%)
• High success rate
Randomized clinical trial on efficacy of fixed-dose efavirenz/tenofovir/emtricitabine on alternate days versus continuous treatment. Bellagamba et al Italy

- tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) and efavirenz (EFV) have long half lives (Atripla)
- May be suitable for reduced frequency dosing
- Potential for improved adherence and reduced toxicity and costs.
- Aim to investigate the non-inferiority of TDF/FTC/EFV fixed-dose combination on alternate-days versus standard regimen in virologically suppressed patients.
Design

- RC open-label non-inferiority trial
- HIV 1 Rx for at least 6 months with Atripla
- UDVL (<40RNA copies/ml)
- EFV plasma concentrations >1000 mg/ml
- Randomised SOC or switch to Atripla on alternate days
- Primary end point was proportion with UDVL at 48/52
Results and conclusions

• 197, 98 in SOC & 99 in alternate group
• No sig difference in baseline characteristics
• Sig decrease from baseline in EFV concentration in alternate arm
• TDF/FTC/EFV on ATAD non-inferior to SOC regimen through 48 weeks
Optimizing HIV prevention and care for transgender adults. Lake J and Clark J. USA

• Great overview which highlights key issues within epidemiology, prevention & management of Transgender women and explores future areas for HIV related research.
What do we know about the epidemiology?

- Estimate global prevalence in transgender women of 19.1% (95%CI: 17.4-20.7) & OR 48.8 (95%CI:21.2-76.3).
- Lab-confirmed HIV prevalence in US ranged from 2% in San Diego to 40% in NY
- Global estimates ranging from 4% in Spain to 34% in Argentina
- Lack of standardised systems for consistent monitoring and surveillance.
Fig. 1. Biological and behavioral contributors to risk of HIV infection in transgender adults.
Sampling methodology

• Most studies to date used convenience samples from community, clinic, sex on premises venues.
• Needs more work using rigorously applied representative sampling methods
Epidemiological category

• Researchers must work out how to define ‘transgender’

• 2 step method:
  • Current gender identity
  • Natal sex

• However, this doesn’t incorporate sexual identity and minimises sexual orientation as a simple matter of partner gender
PrEP

• Data in trans women limited
• None in trans men
• iPREX STUDY, 339 TRANS WOMEN (14% OF TOTAL)
  • 11 HIV seroconversions in trans women in IA
  • 10 in CA (hazard ratio 1.1, 95% CI: 0.5–2.7)
  • None in trans women with detectable serum drug levels
• ? Poor adherence to drug OR potential interactions ARV and exogenous hormones
Feminizing hormonal therapies

- Immunometabolic effects of FHT mixed
- Effects vary by type and route
- Modulate inflammatory & coag pathways
- Increased CVD & thromboembolic risk cisgender and trans women
- Ethinyloestradiol associated with greatest risk
- Oestradiol has milder effects
- Many trans women still taking former drug
Feminizing hormonal therapies

- Low dose ethinyl oestradiol reduced 30% by RTV & cobicistat
- No data on higher dose interactions
- Exogenous & endogenous hormones may influence ART absorption

- Much more in article, worth a read
The pharmacokinetics, pharmacodynamics, and mucosal responses to maraviroc-containing pre-exposure prophylaxis regimens in MSM. McGowan et al, USA & Canada

- TDF/FTC safe and effective as PrEP
- TDF associated with reduction in renal function & bone density loss
- Only active against CCR5 tropic virus
- MCV has good safety profile
- Given low use may be valuable as PrEP
Pharmacokinetics/Pharmacodynamics

• Increasingly used
• Candidate ARV added to tissue samples in vitro then challenged
• Deliver drug in vivo, collect tissue sample & expose to virus ex vivo
RC & blinded trial

- Randomised to receive:
  - MVC alone
  - MCV & FTC
  - MCV & TDF
  - TDF & FTC (control)
Really complicated methods ......

- In the parent study, drugs discontinued at Week 48 and a final visit was conducted at Week 49.

At each study visit:
- interval history, targeted physical examination, safety bloods, adherence assessments, risk-reduction counseling, condom distribution, HIV testing, study drugs dispensed.
- rectal fluid and blood samples were collected and stored for drug concentration measurements.
- Flexible sigmoidoscopy was performed at baseline, 24, 48, and 49 with collection of 20 rectal biopsies acquired at approximately 15cm from the anal verge.
What did they find?

- No virological suppression with MCV alone
Success and failure of initial antiretroviral therapy in adults: an updated systematic review (SR)

Andrew Carr et al. Australia

- Updated a prior systemic review (2008, 2012)
- SRs can:
  - determine if RCT provide a true view of real world efficacy
  - evaluate changes efficacy changes by year
  - Improve study power
  - Allow analysis of factors associated with efficacy & failure & help identify limitations in data collection
Method

• Studies (1994 to July 2017) were drawn from PubMed,
• ClinicalTrials.gov, Cochrane Library, and major conferences;
• Collected design, eligibility, patient & ART data
• Outcomes are expressed as group size-weighted means.
• Mixed-effects meta-regression was used to identify sources of efficacy heterogeneity
What is heterogeneity?

- Aim of systematic reviews is to combine studies to give a more precise estimate of effect.

- Differences between studies not due to chance.
2 types of heterogeneity

**Clinical**
- Differences in:
  - Clients/study settings
  - Study design/quality
  - Interventions
  - Outcomes

Judgements about clinical heterogeneity require no calculations

**Statistical**
- Individual study results differ
  - Benefit vs. harm
  - Size of benefit or harm

Evaluated statistically
Quantifying Heterogeneity

- $I^2$
  - Percentage of variation across studies due to heterogeneity and not chance
    - 25% low
    - 50% moderate
    - 75% high
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Sensitivity analyses

• Phase 3 vs. phase 4
• Africa/Asia vs. America/Europe/Australia
• TDF/TAF/FTC vs. ABC/3TC
• TDF/FTC/EFV vs. TDF/3TC/EFV
• Current US DHHS regimens vs. WHO regimens
• VL ≤100,000 vs. >100,000
Results summary

354 groups, 181 studies, 77999 participants

Principle backbone:
• 44% Tenofavir-emtricitabine (TDF/TAF-FTC)
• 28% Thymidine based
• 10% abacavir-lamivudine

Principle anchors:
• 50% non-nuc analog
• 28% boosted PI
• 12% integrase inhibitor

Heterogeneity of 96.1%
Independent Predictors of greater efficacy

• TDF/TAF-FTC & Insti

• At 48 weeks:
  • Pre-ART resistance genotyping
  • Higher baseline CD4
  • Once daily ART

• At 144 weeks few pills predicted greater efficacy
Conclusions

• Initial ART efficacy continues to improve globally
• However, more than 20% of post-2010 patients failed over 3 years
• Real world efficacy is lower than in phase 3 trials
• Guidelines should list non-insti-based initial ART as non preferred
• Strategies needed to improve access to pre-ART genotyping
• Increase access to once-daily ART regimens
Strengths and Weaknesses

- Systematic review
- Big data
- Good processes for choosing studies
- $I^2$ assessed
- Sensitivity analyses complete
- Love a bubble plot

- Large heterogeneity