Clinical Education Session

https://ashm.org.au/training/SSHC-sessions/

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Journal Club

February 2019

Vickie Knight

Publishing for last 15 years

Official journal of the International AIDS Society

18 issues a year

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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 dolutagravir 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.

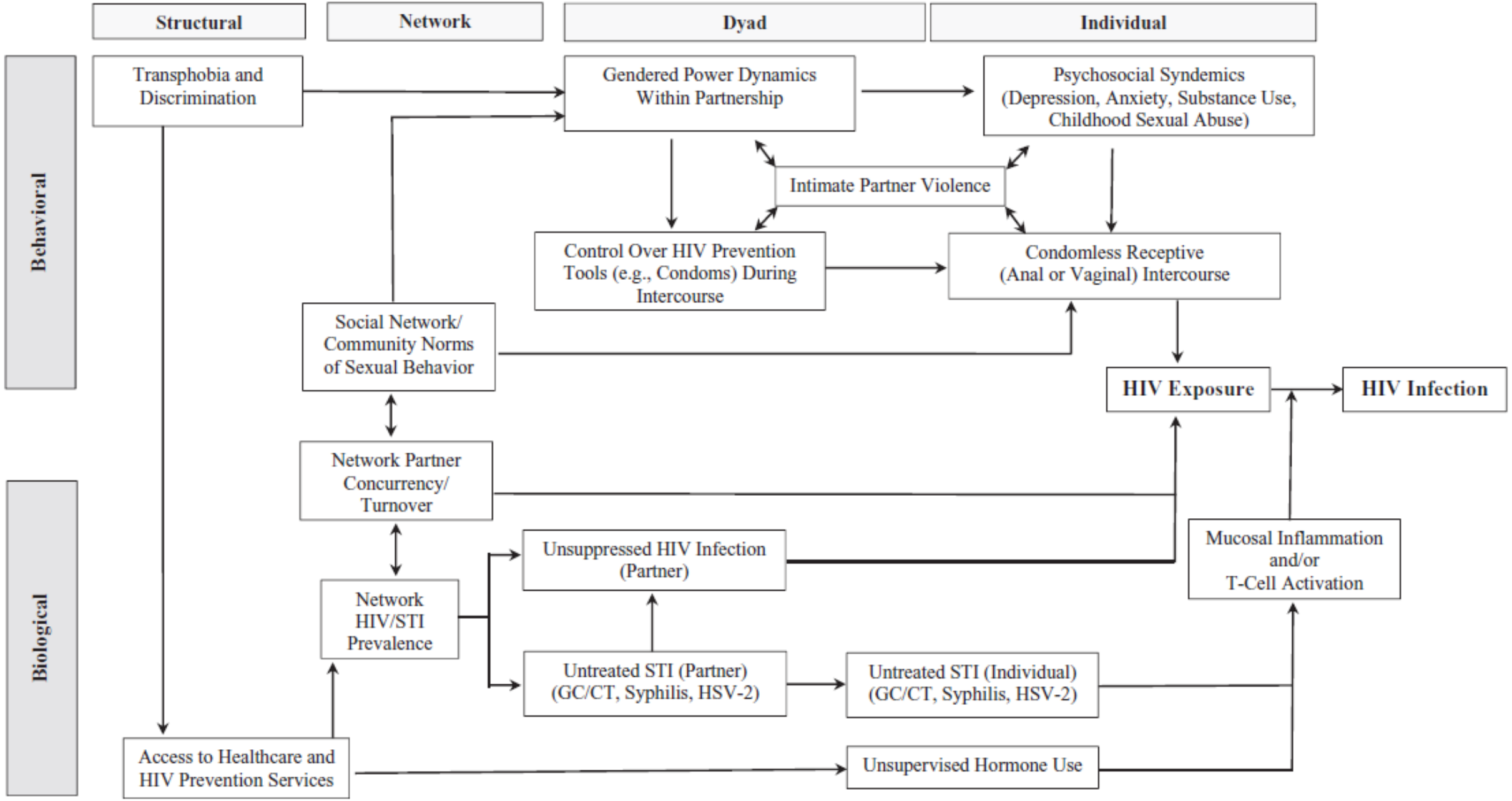

Fig. 1. Biological and behavioral contributors to risk of HIV infection in transgender adults.

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 effectice 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

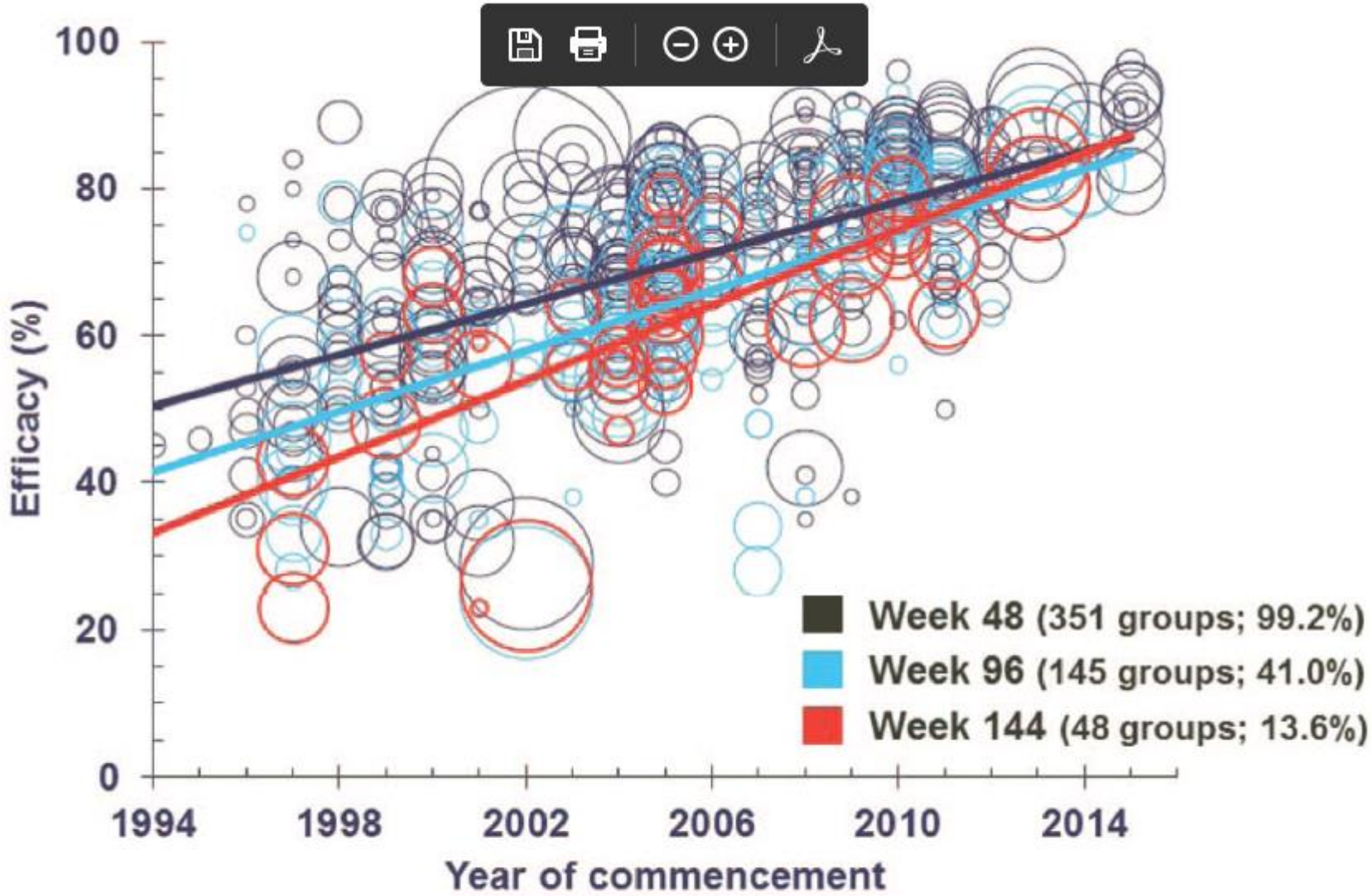
Principle backbone:

- 44% Tenofavir-emtricitabine (TDF/TAF-FTC)
- 28% Thymadine based
- 10% abacavir-lamivudine

Principle anchors:

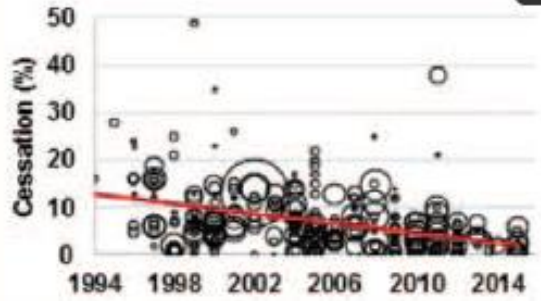
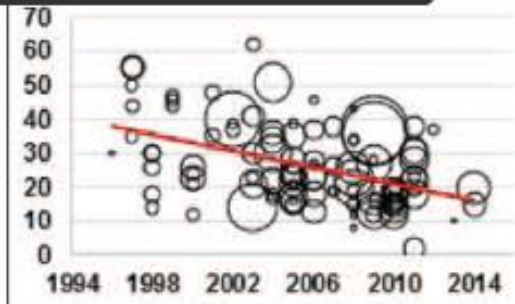
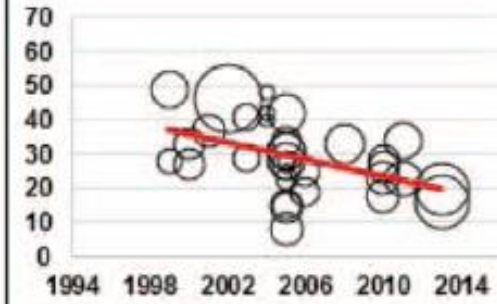
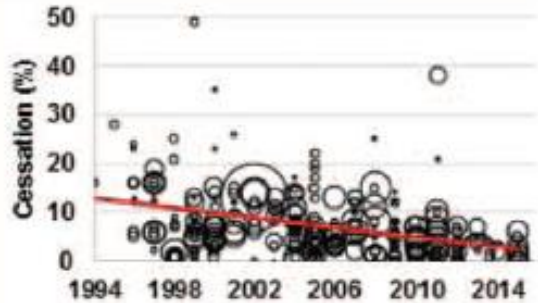
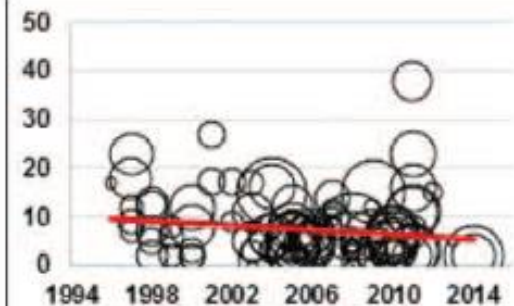
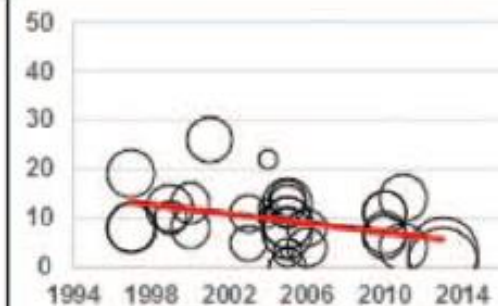
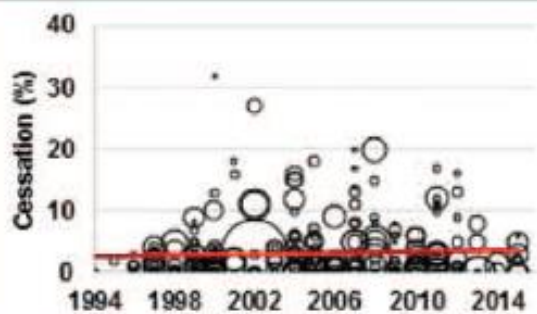
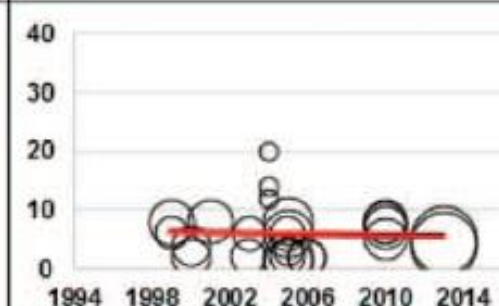
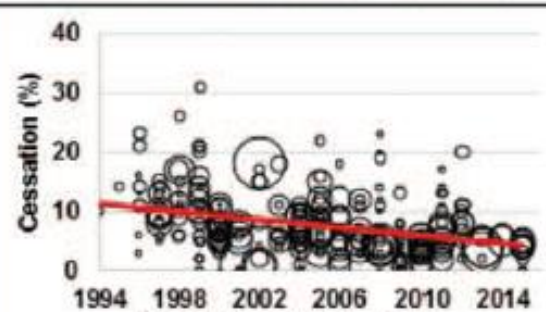
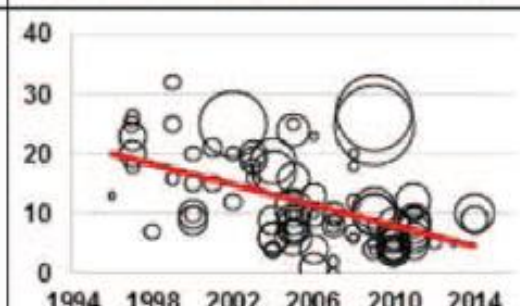
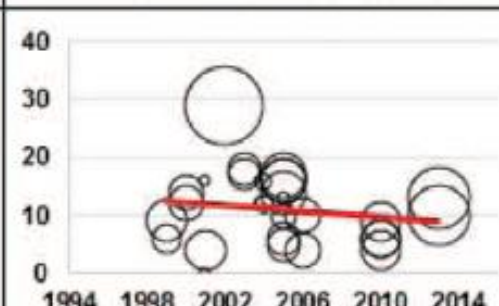
- 50% non-nuc analog
- 28% boosted PI
- 12% integrase inhibitor

Heterogeneity of 96.1%



Wk 48	57.2%	68.8%	76.9%	83.8%	p<0.001
Wk 96	51.6%	60.5%	64.8%	79.9%	p<0.001
Wk 144	45.1%	54.5%	71.6%	77.1%	p<0.001

Mean
71%
63.5%
61.8%

Cessation	Week 48		Week 144
Overall			
Adverse event			
Virological failure			
Subject choice			

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