BHIVA ‘Best of CROI’ Feedback Meetings

London | Edinburgh

Wakefield | Cardiff

Birmingham | Haydock

Newcastle

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%

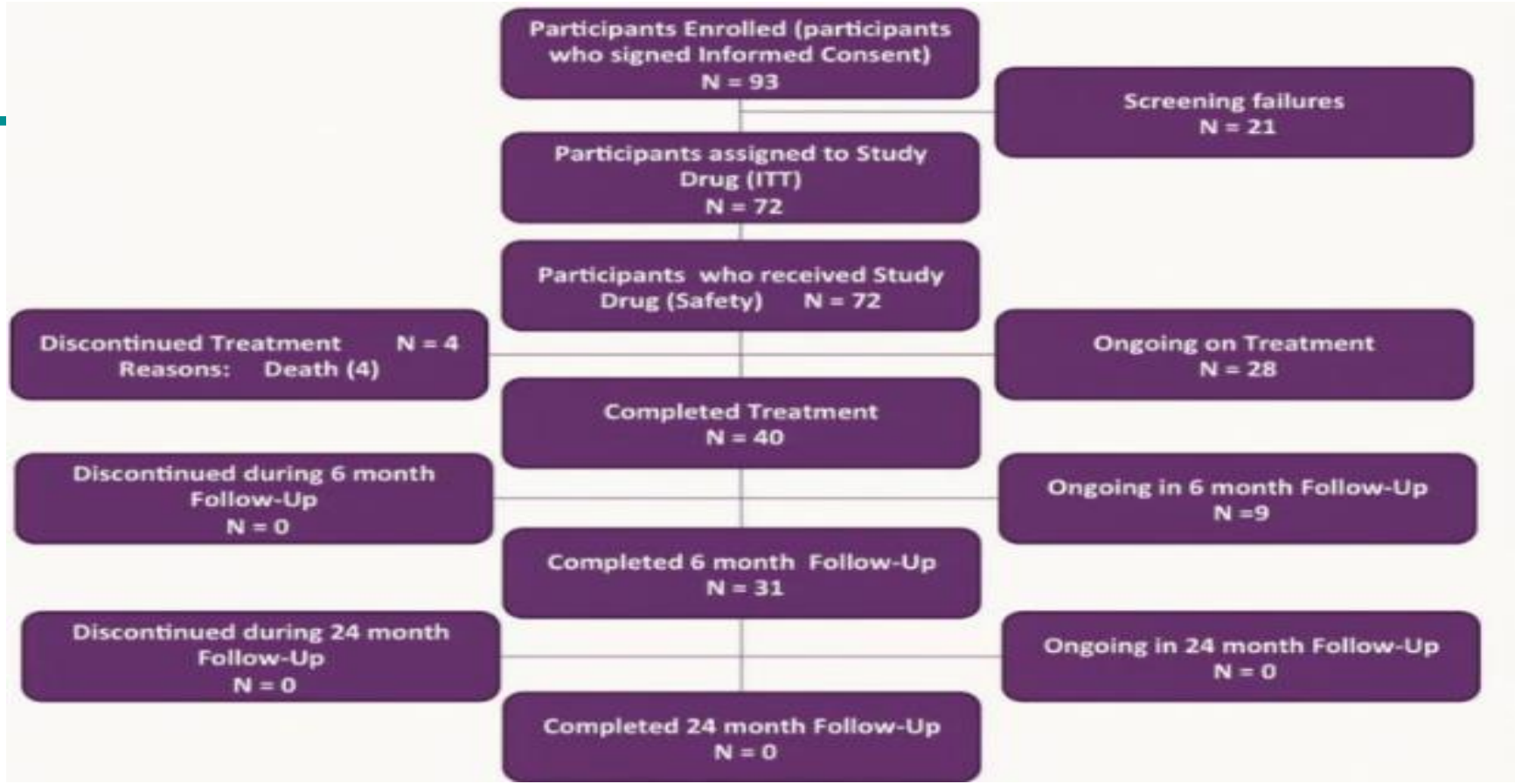
Gandhi et al, AM J Respir Crit Care Med 2010; 181: 80-6

Nix-TB Trial

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

*Amended from 600 mg bid strategy

Francesca et al., Abstract 80LB



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Francesca et al., Abstract 80LB

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

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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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

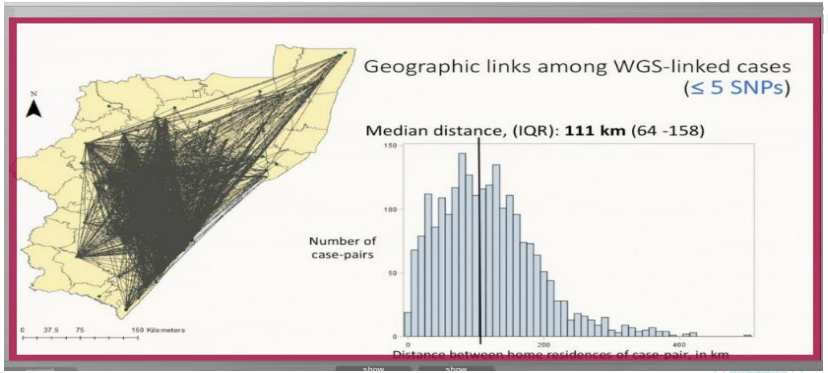
Transmission of Extensively Drug-Resistant Tuberculosis in South Africa

N. Sarita Shah, M.D., M.P.H., Sara C. Auld, M.D., James C.M. Brust, M.D., Barun Mathema, Ph.D., Nazir Ismail, Ph.D., Pravi Moodley, M.D., Koleka Mlisana, M.D., Ph.D., Salim Allana, M.B., B.S., M.D., Angela Campbell, M.A., Thuli Mthiyane, M.Sc., Natashia Morris, M.Sc., Primrose Mpangase, B.A., Hermina van der Meulen, Shaheed V. Omar, Ph.D., Tyler S. Brown, M.D., Apurva Narechania, M.A., Elena Shaskina, Ph.D., Thandi Kapwata, M.Sc., Barry Kreiswirth, Ph.D., and Neel R. Gandhi, M.D.

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

70% genomically 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



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Shah et al. , Abstract 77

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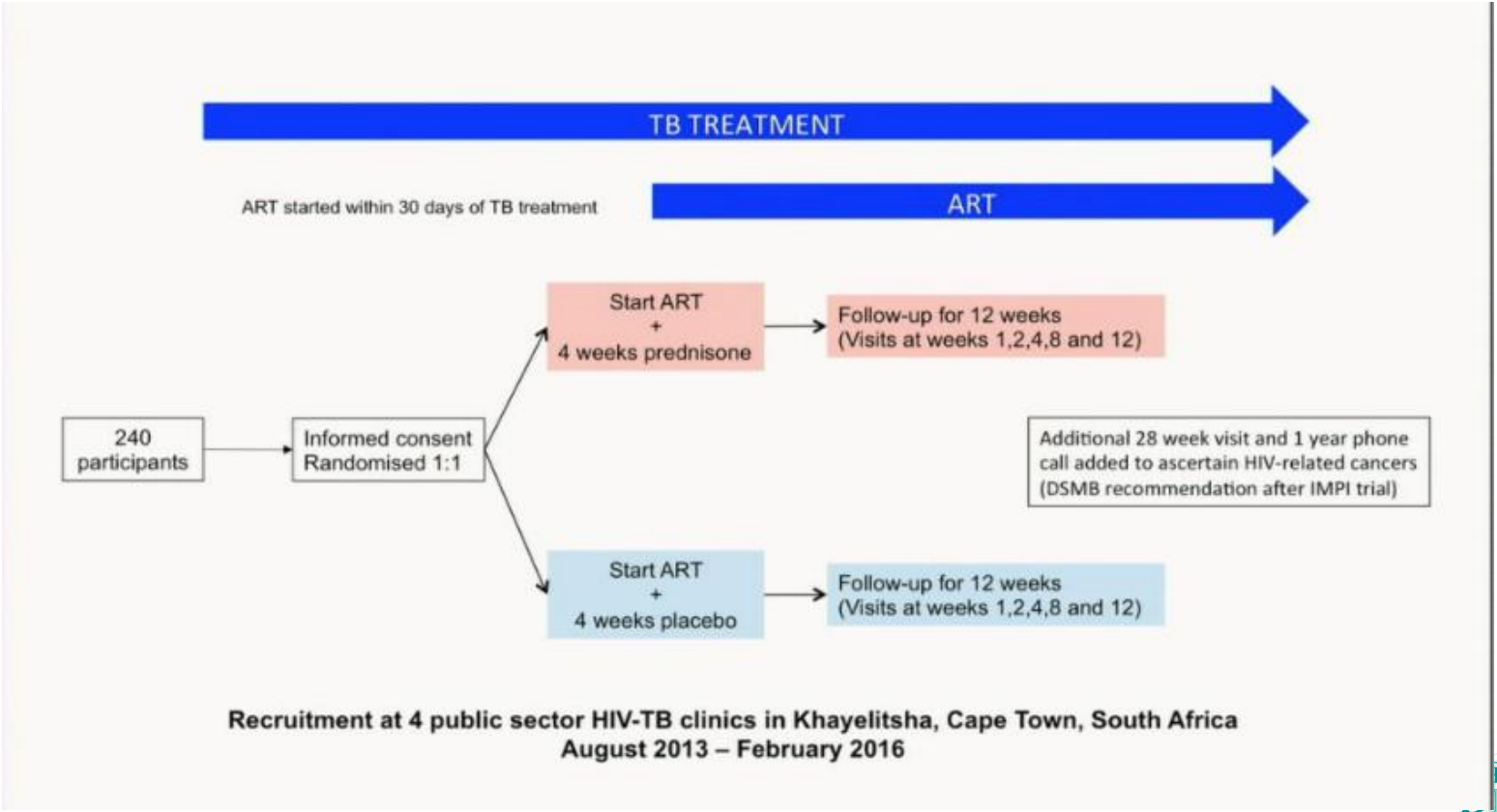
RCT of prednisolone to prevent paradoxical TB IRIS



Meintjes et al., Abstract 81LB

Endpoints

- **Primary endpoint = Paradoxical TB-IRIS**
  - International Network for the Study of HIV-associated IRIS (INSHI) case definition [1]
  - Adjudicated by an independent expert committee
  - By intention to treat

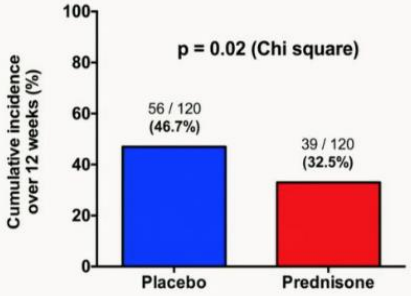
- **Secondary endpoints included**
  - Time to TB-IRIS
  - Mortality
  - Hospitalisation
  - Interruption of ART or TB treatment for adverse events

- **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

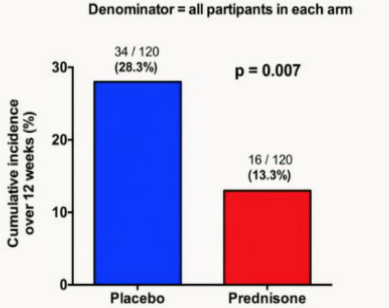
Meintjes et al., Abstract 81LB

Primary endpoint: Paradoxical TB-IRIS



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

Open-label corticosteroids for TB-IRIS treatment



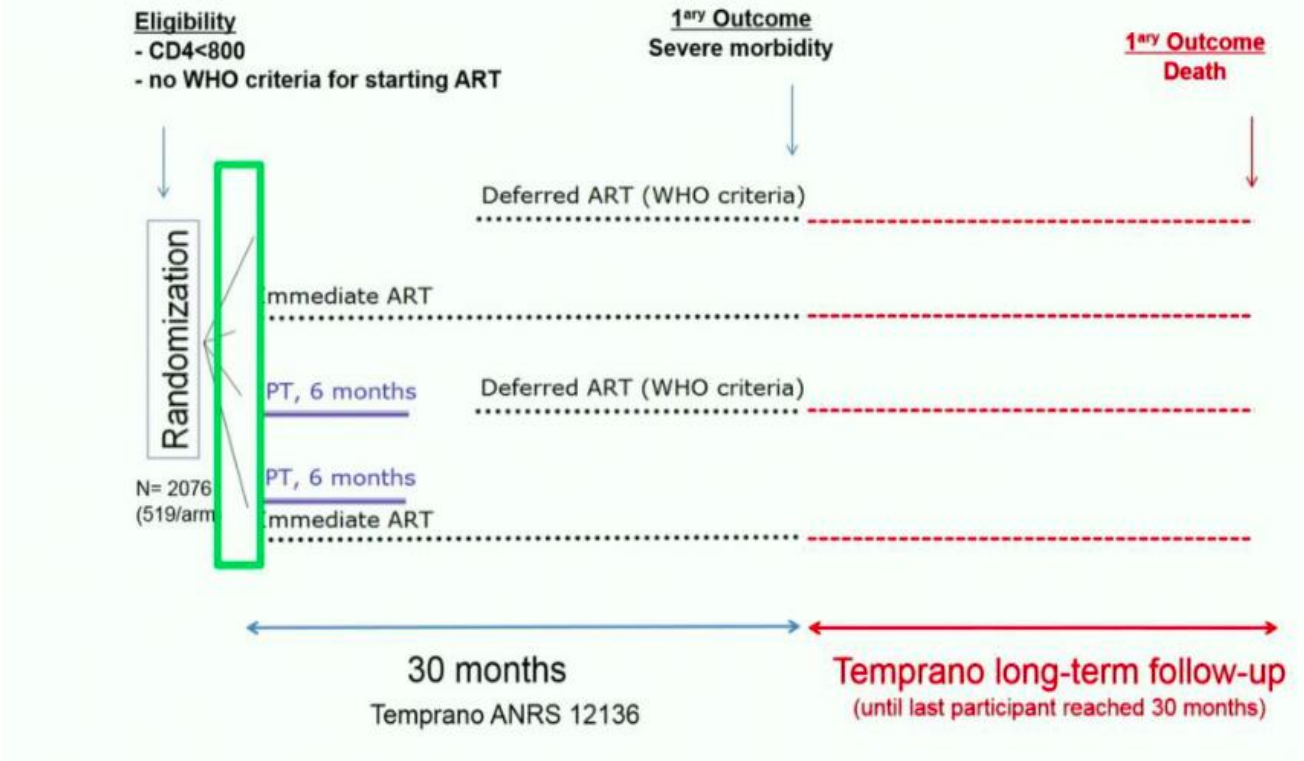
Relative risk = 0.47 (95%CI = 0.27 – 0.83)

In patients at high risk of paradoxical TB-IRIS and improving on TB treatment, prednisone 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

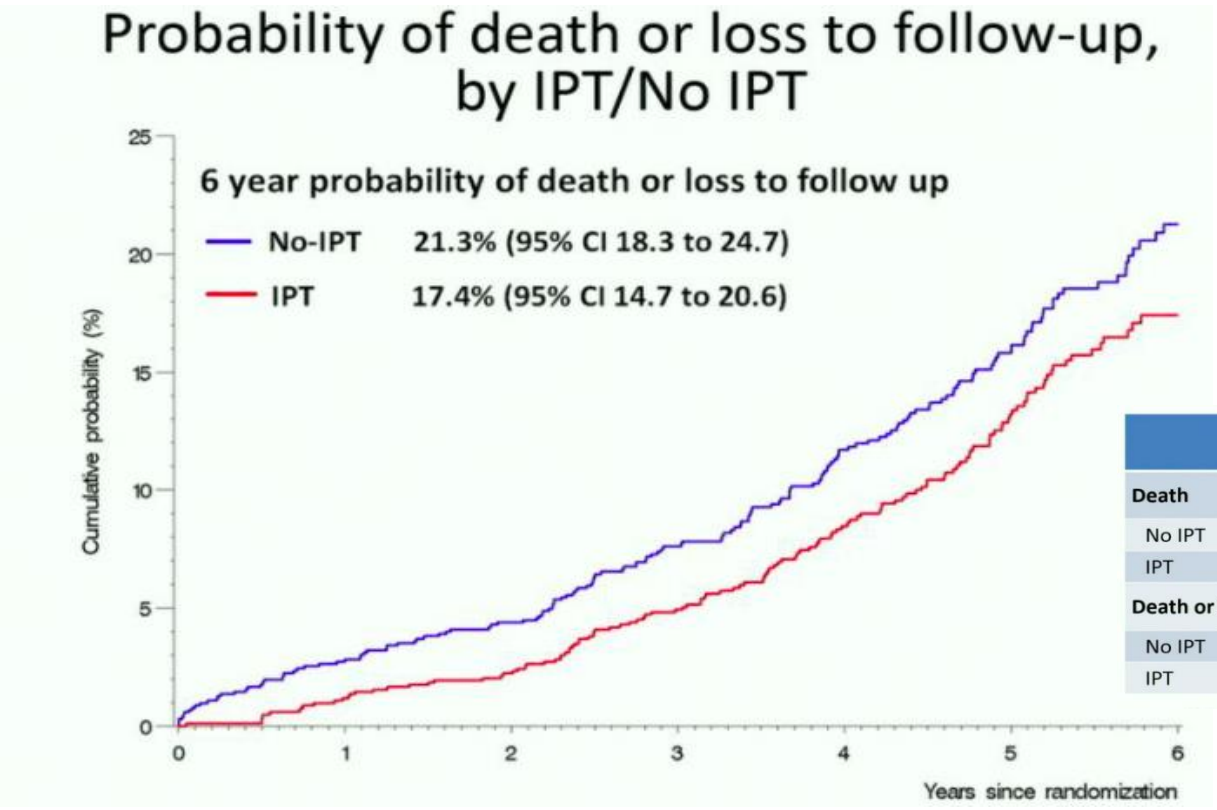
Meintjes et al., Abstract 81LB

Temprano/ANRS 12136: Long-term follow-up study (A Abadje)



Anani D. et al, Abstract O78

Temprano: Long-term follow-up study



	N	n	Rate /100 PY	Hazard Ratio*	95% CI	p
Death						
No IPT	1026	52	1.1			
IPT	1030	34	0.7	**0.63**	**(0.41-0.97)**	*0.04*
Death or Loss to follow-up						
No IPT	1026	162	3.5			
IPT	1030	131	2.7	**0.78**	**(0.62-0.98)**	*0.03*

Anani D. et al., Abstract O78

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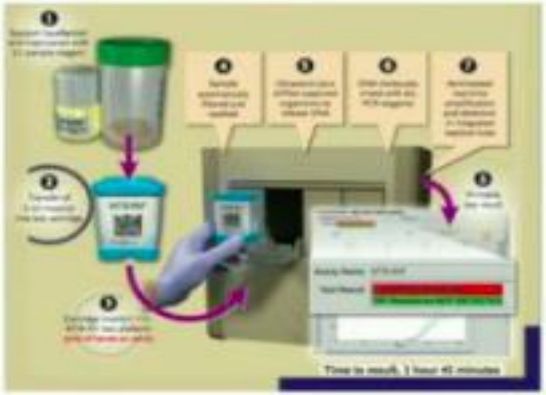
A Multi-centre diagnostic accuracy study of the Expert Ultra for TB diagnosis

- 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

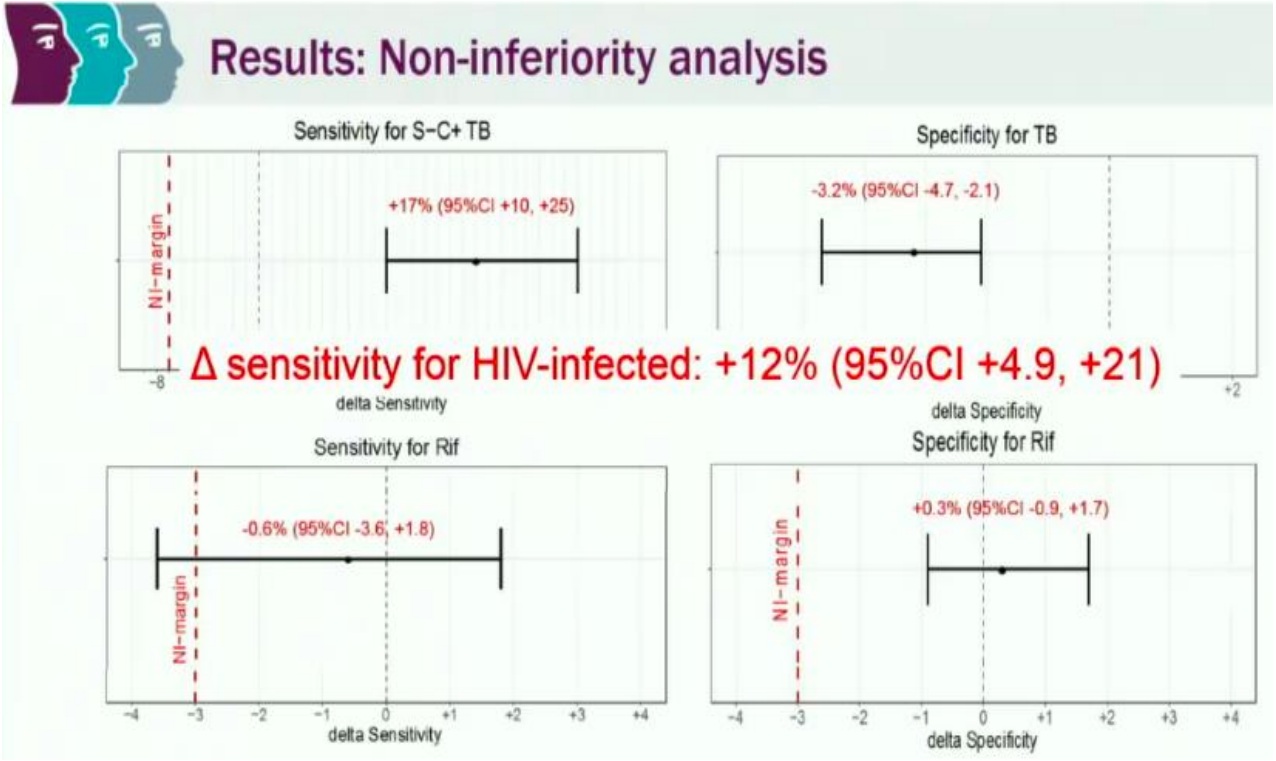
- Imperfect sensitivity for paucibacillary disease (HIV, early disease, children etc.)
- Imperfect sensitivity for RIF-resistance detection in case of heteroresistance
- Imperfect specificity for RIF-resistance detection due to silent mutation detection
- Cross-reactivity with some NTMs

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



Rothwell, Abstract O76LB

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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

Standardized incident ratios decreased for some cancers

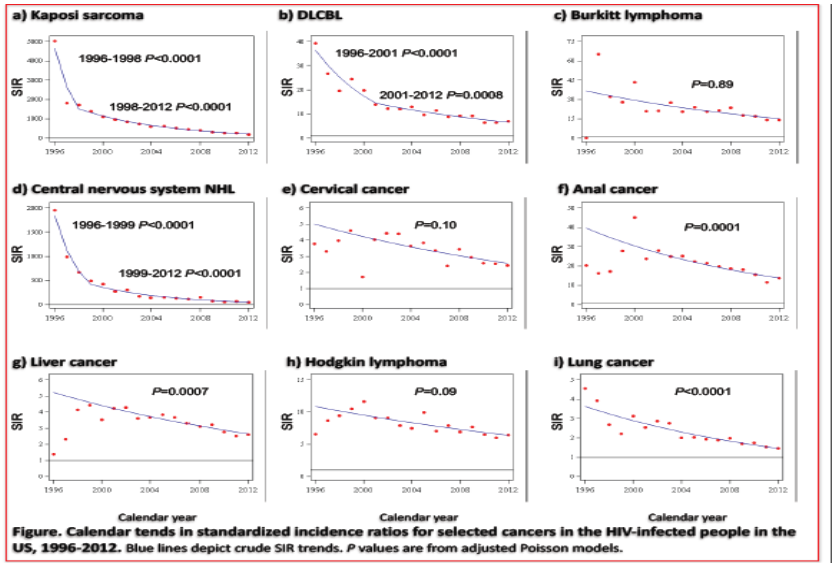

Figure. Calendar tends in standardized incidence ratios for selected cancers in the HIV-infected people in the US, 1996-2012. Blue lines depict crude SIR trends. *P* values are from adjusted Poisson models.

ADCs, AIDS-defining cancers; CI, confidence interval; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; HPV, human papillomavirus; KS, Kaposi sarcoma; NADCs, non-AIDS-defining cancers; NHL, non-Hodgkin lymphoma; OCP, oral cavity/pharynx; SIR, standardized incidence ratio; VRNADCs, virus-related non-AIDS-defining cancers; VUNADCs, virus-unrelated non-AIDS-defining cancers.

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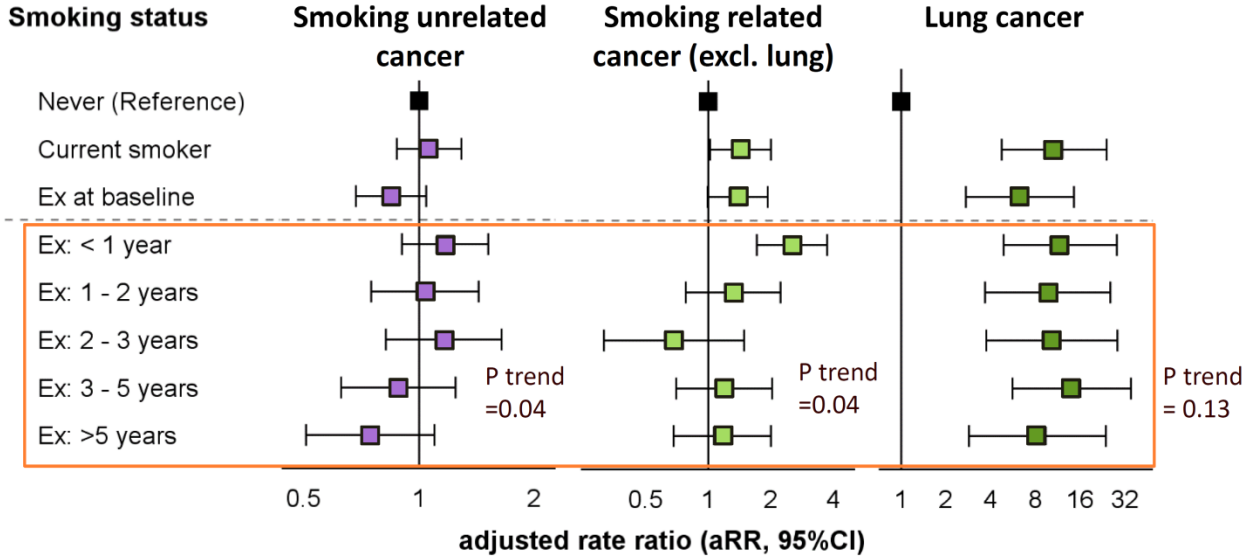
Effect of smoking cessation on cancer incidence

Adjusted rate ratios for specific cancer



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/ul), 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)

Greene, Abstract 22

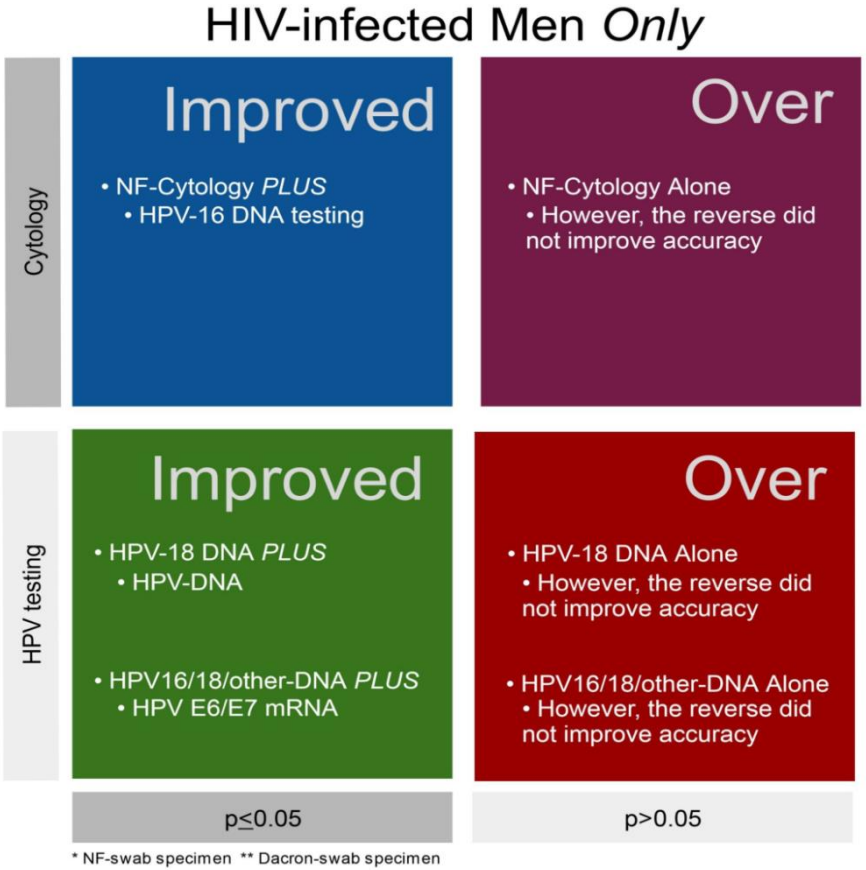
Natural history CIN 2 in HIV+ childbearing age: Women's Interagency HIV Study (WIHS)

- 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?

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

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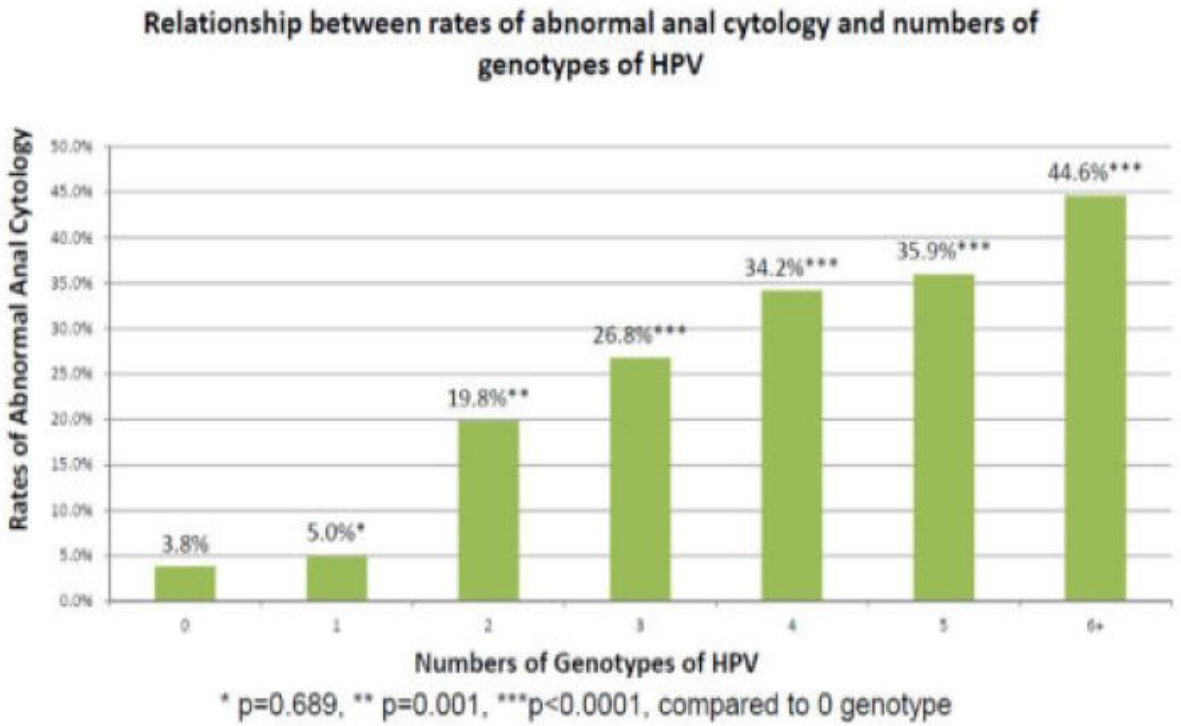
Multiple HPV infections and anal pre-cancer in HIV+ men



Cheng et al., Abstract 594

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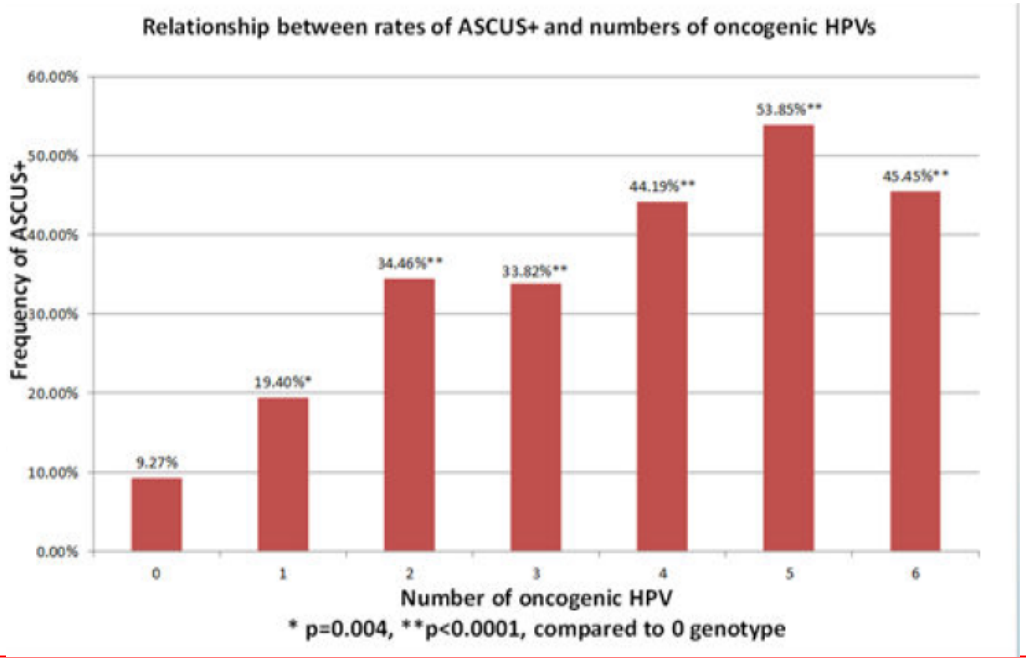


Subjects who have >=5 types of HPV have 20x risk of anal ASCUS+. Multiple anal HPV infections in HIV+ patients warrant aggressive follow-up

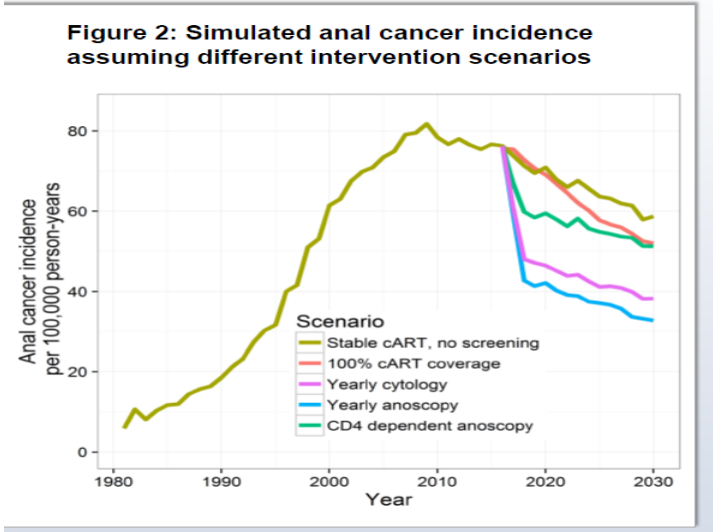
Cheng et al., Abstract 594

HPV related cancers: Screening for anal lesions

What might work…And what doesn't

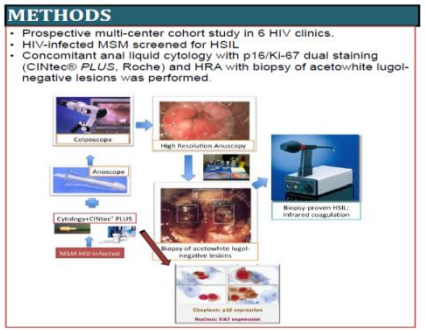
Swiss HIV Cohort: Mathematical model of screening & ART on anal CA incidence

- Yearly anoscopy to prevent most anal CA
- CD4 dependent anoscopy to prevent most/test
- Expanding ART: modest effect



Blaser et al., Abstract 596

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



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

Predictive values for the diagnosis of biopsy-proven HSIL		
	Abnormal anal Cytology (ASCUS, LSIL, or HSIL)	Dual Stain Anal Cytology positivity
Sensitivity (CI95%)	95.6% (91.2-99.9)	42.3% (29.8.2-55.4)
Specificity (CI95%)	58.8% (52.2-65.4)	61.1% (50.8-71.4)
Positive predictive value (CI95%)	39.8% (33.2-46.4)	42.6% (29.8-55.4)
Negative predictive value (CI95%)	95.8% (91.6-99.9	38.9% (28.6-49.2)

Serrano-Villar et al., Abstract 595

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Cardiovascular disease

D:A:D

- 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

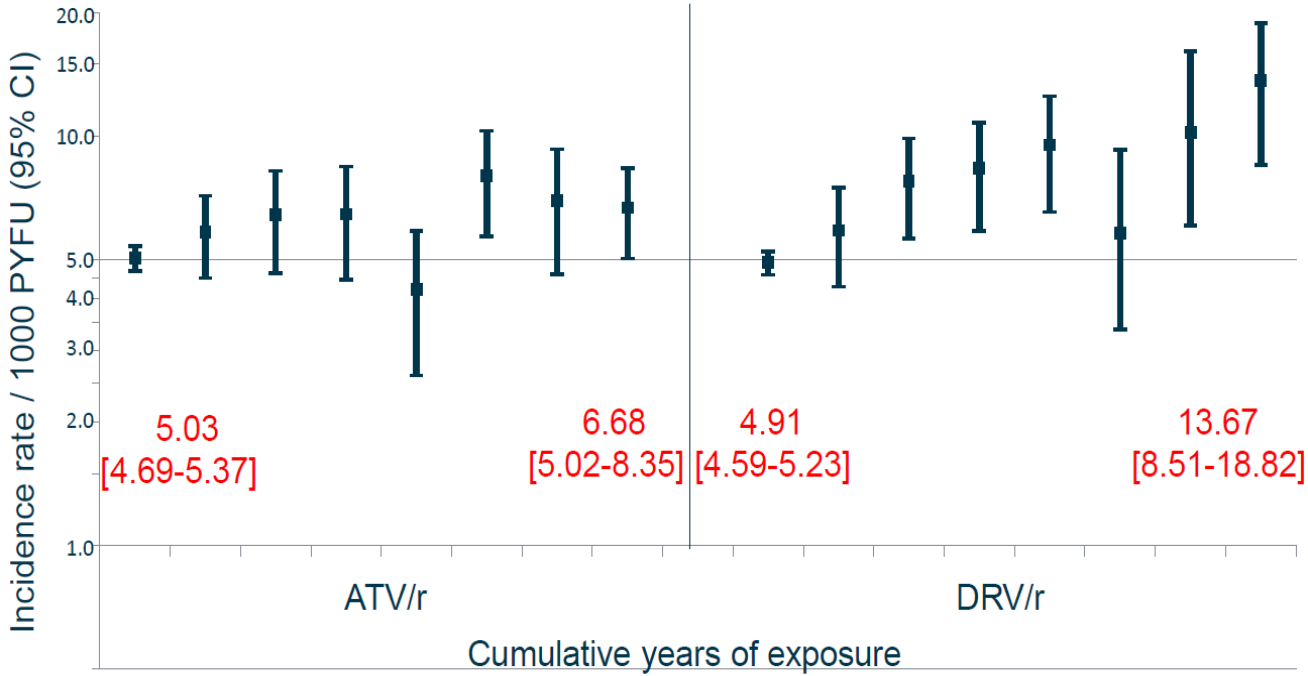
Values fixed at baseline*:

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



	0	0-1	1-2	2-3	3-4	4-5	5-6	>6	0	0-1	1-2	2-3	3-4	4-5	5-6	>6
Events	824	75	49	41	26	46	34	62	909	52	51	44	39	17	18	27
PYFU	163785	12886	7631	6369	6144	5757	4898	9278	185246	8845	6591	5285	4100	2940	1768	1975

Ryom et al., Abstract 128LB

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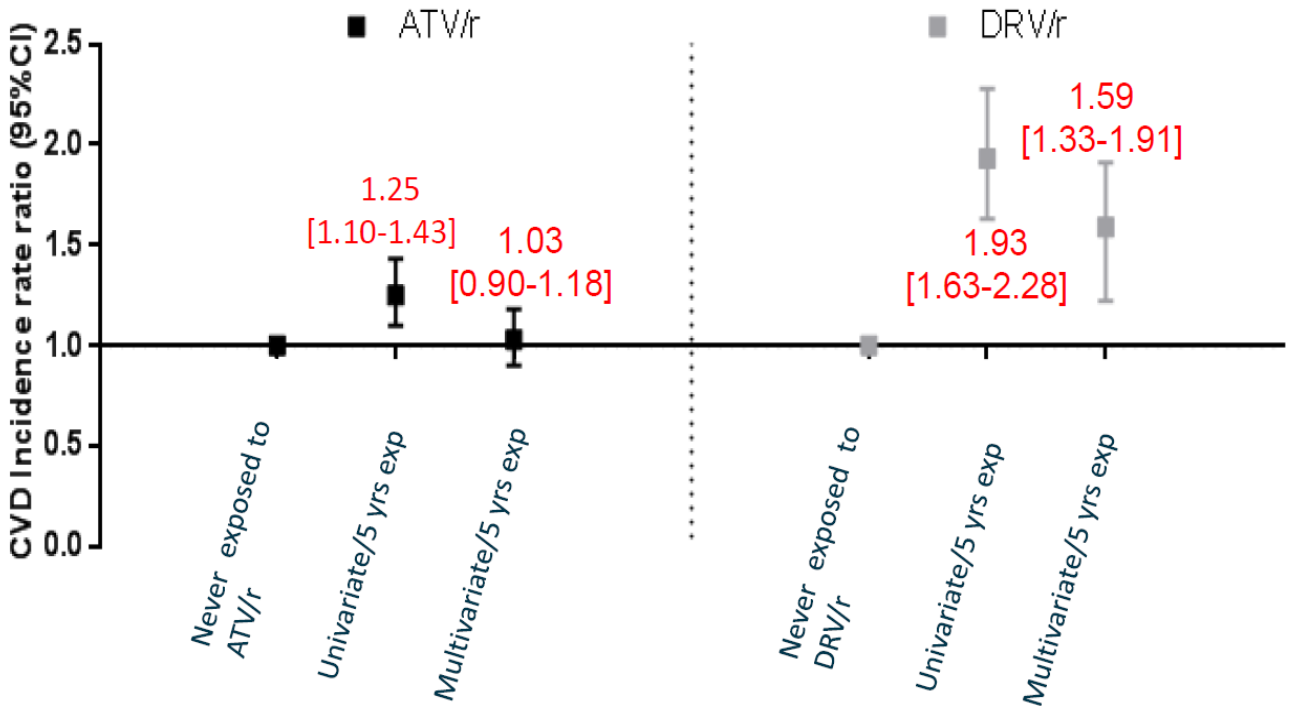
Association Between CVD & Cumulative ATV/r and DRV/r Use

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

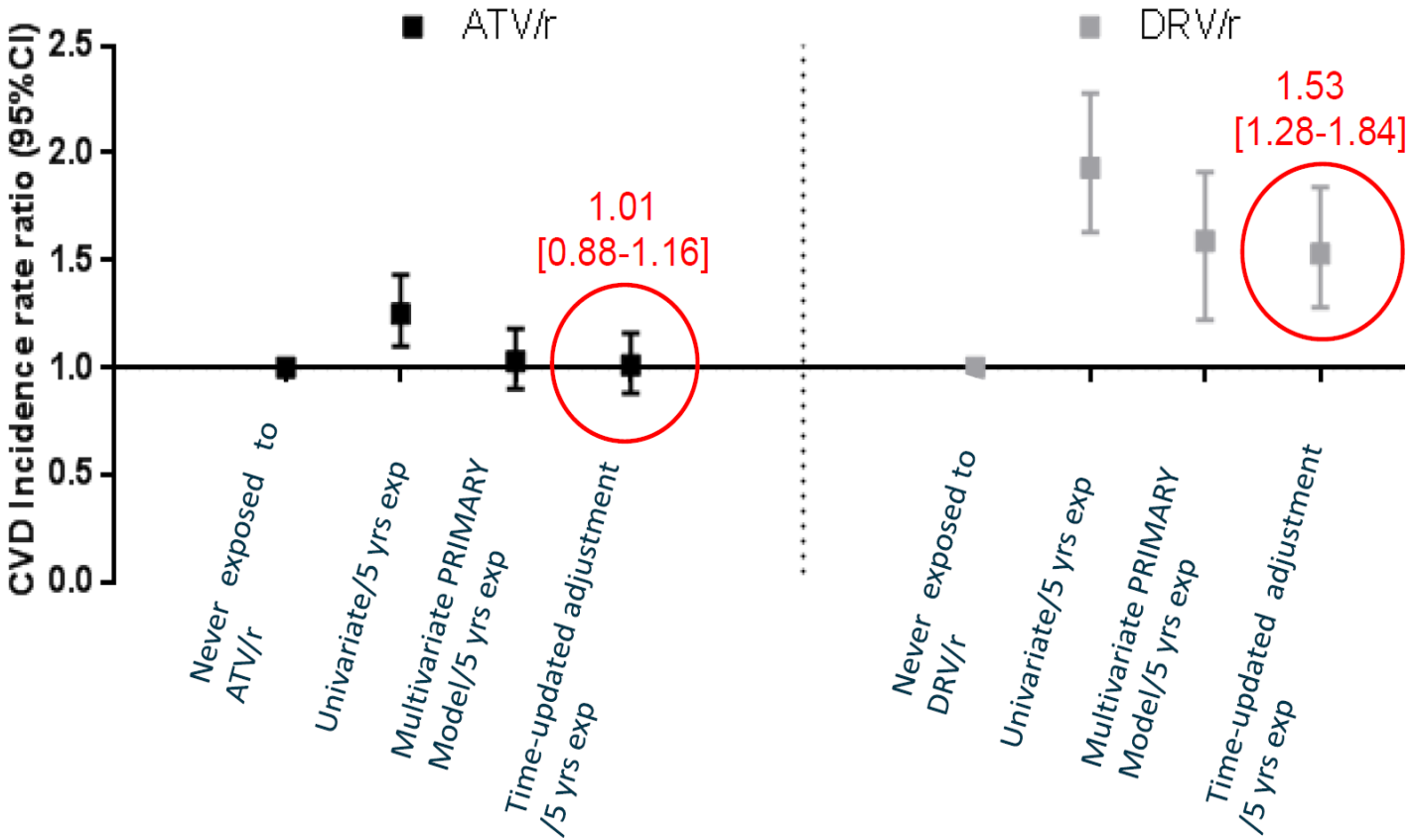


Multivariate models were adjusted for gender, age, race, HIV risk of aquisition, enrollement cohort, baseline date, prior CVD, CD4 nadir, CD4, BMI, diabetes, dyslipidamia, eGFR (all fixed at baseline), cumulative exposure to DRV/r, ATV/r, LPV/r and IDV, recent exposure ABC, prior AIDS, viral load, hepatitis 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



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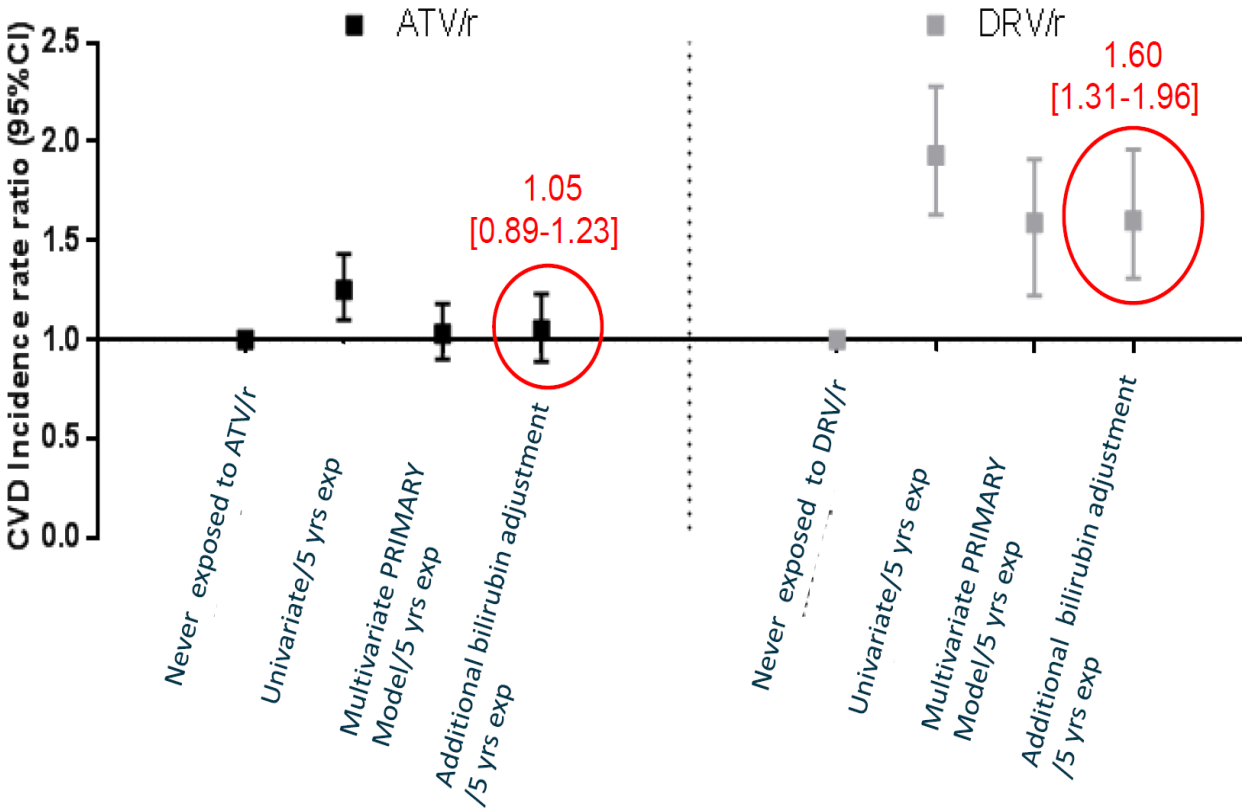
Association Between CVD & cumulative ATV/r and DRV/r Use; Additional Adjustment for Bilirubin Levels (Time-updated)



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
Dr Sanjay Bhagani
Dr David Chadwick
Dr Duncan Churchill
Mr Simon Collins
Dr Alessia Dalla Pria
Dr Sarah Duncan
Dr Julie Fox
Dr Andrew Freedman
Professor Saye Khoo
Professor Clifford Leen
Dr Rebecca Metcalfe
Professor Chloe Orkin
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Dr Rebecca Simons
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