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BHIVA 'Best of CROI' Feedback Meetings

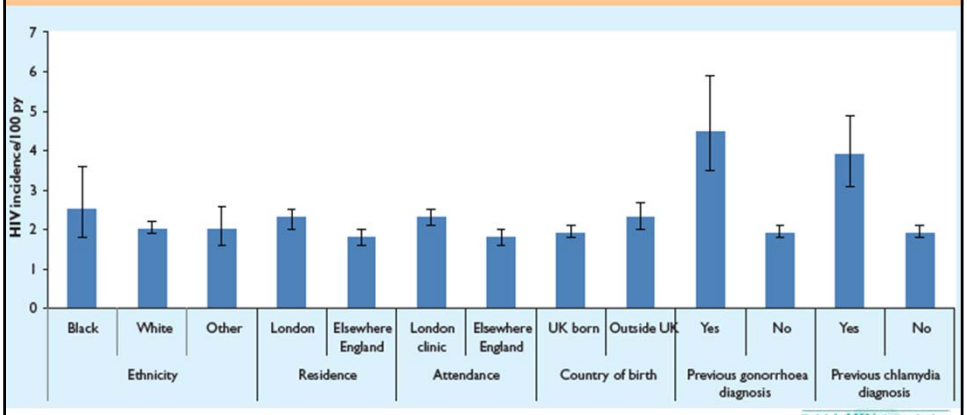
London | Birmingham
Haydock | Wakefield | Newcastle
Edinburgh | Cardiff

HIV Transmission, Prevention and Testing

- Epidemiology
- Pre-exposure Prophylaxis (PrEP)
- New approaches to HIV Testing
- Attitudes to Treatment as Prevention
- Mother to child transmission
- "Functional cure"

UK MSM: Poster 1072 HPA
HIV incidence in the open cohort of 38,000 MSM attendees of Sexually Transmitted Infection clinics across England: 2008-2011

Figure 2 HIV incidence among MSM attending STI clinics by sub-groups, England, 2008-2011



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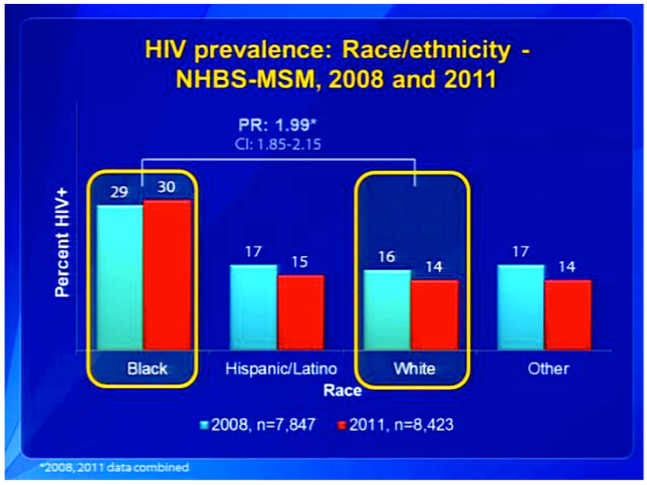
Prevalence survey USA 2008 / 2011



From Oral 90: HIV Prevalence and Awareness of Infection in 2008 and 2011 among MSM: 20 US Cities Cyprian Wejnert

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Oral 28: Hormonal Contraception and Risk of HIV: An analysis of data from the Microbicides Development Programme Trial
Angela Crook MRC Clinical Trials Unit, London CROI 2013

	Baseline covariate adjusted model†	**Baseline covariate adjusted model†**	**Time-updated Covariate adjusted model†**	**Model for 52 weeks baseline contraception** with censoring and IPW
HC	Baseline	Current	Current	
DMPA	1.36 (1.06-1.76)	1.32 (1.00-1.73)	1.36 (1.04-1.79)	1.40 (1.02-1.92)
Net En	1.17 (0.85-1.61)	1.06 (0.76-1.48)	1.14 (0.81-1.59)	1.29 (0.87-1.92)
OC	0.95 (0.67-1.36)	0.83 (0.59-1.16)	0.85 (0.61-1.19)	0.91 (0.56-1.48)
No HC	1.0	1.0	1.0	1.0

†Models adjusted for age, centre, randomisation, HSV-2 result, chlamydia result, vaginal discharge, frequency of sex, condom use (at the last sex act)

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Pre-exposure prophylaxis for HIV in women: daily oral tenofovir, oral tenofovir-emtricitabine, or vaginal tenofovir gel in the VOICE Study (MTN 003)

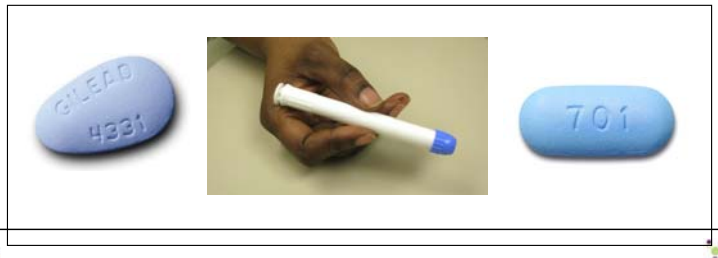
Marrazzo JM, Ramjee G, Nair G, Palanee T, Mkhize B, Nakabiito C, Taljaard M, Piper J, Gomez K, Chirenje M, for the VOICE Team

Study funding: U.S. NIH NIAID, NICHD & NIMH UM1AI068633; UM1AI068615

VOICE
VAGINAL + ORAL INTERVENTIONS TO CONTROL THE EPIDEMIC

The VOICE Study

- Phase 2B, randomized, double-blind, placebo-controlled, five-arm trial of daily use of the following for prevention of HIV acquisition in women:
  - Vaginal tenofovir (TFV) 1% gel (40 mg)
  - Oral tenofovir (TDF, 300 mg)
  - ~~Oral tenofovir / emtricitabine (TDF / FTC; 300 mg / 200 mg)~~



VOICE Design

5,029 HIV- women

Vaginal sex in prior 3 months
Not pregnant or breastfeeding
Willing to use effective contraception

Randomized to once daily use

Oral TDF | Oral FTC/TDF | Oral Placebo | Vaginal TFV | Vaginal placebo

Monthly visits

Comprehensive HIV prevention counseling, condoms, contraception, pregnancy test, STI evaluation & treatment, provision of study product

1° endpoints: HIV infection, safety

Primary Efficacy Results (mITT)

	TDF*	FTC/TDF	TFV Gel
HIV protection efficacy vs. placebo			
HR **95% CI**	1.49 (0.97, 2.3)	1.04 (0.7, 1.5)	0.85 (0.6, 1.2)
P-value	0.07	>0.2	>0.2

*Censored on date when sites were informed to take women off of TDF and TDF placebo pills

VOICE – adherence and drug levels

- Adherence measures within study:
- Self-reported adherence: 90-91%%
- By pill-count: 86-92%
- By detectable tenofovir: 25-30%
- 50-58% had no detectable level at any point
- Non-detection associated with being unmarried, age less than 25 and a primary male partner of less than 28
  - All associated with higher rates of HIV acquisition

- *Therefore:*
- *Need to understand our patients' perception of risk of HIV acquisition*
- *Need greater education at population levels about risks and risk taking*

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Other PrEP information

- *#997 (Bekker et al)*
- iPrEx: efficacy of TVD in younger MSM 28% vs 56% in older
- *#1001 (Marcus et al)*
- iPrEx: no evidence of sexual risk compensation
  - No difference in STIs, PHI, UPAI
  - After stopping Rx or if "suspected" taking active treatment
- *#996 (Hosek et al)*
- "Project PrEpare Study"
  - Adherence to PrEP low if sexual risk behaviour low
  - Adherence to PrEP completely varied (high to low) if risk behaviour high
- *#1003 (Heffron et al)*
- Preference for daily versus intermittent PrEP in heterosexuals
  - 45% versus 50%
  - But in 50% sex typically unplanned….

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Other PrEP: potential new agents

- GSK744LAP
  - Potent integrase inhibitor
  - Can be given im or s/c
  - Pharmacokinetics support 3 monthly injections
  - Macaque rectal challenge model:
    - All of 8 protected versus 0 controls ($p<0.0001$)
- TDF intravaginal ring
  - Converted to TFV-DP intracellularly
  - High levels in upper and lower vagina and cervix
    - Not rectum or inguinal lymph nodes
  - Prevented infection in all (n=6) in macaque study

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Aggressive testing in Texas

#P1063 *(Giordano et al)*

- Rapid universal screening for HIV (RUSH) in ED
- Data presented 2009-2012
- Opt out , no written consent
- Blood tests on those having blood drawn anyway (40%)
- 203159 tests ,3653+ve 669 new +ve 0.33%
- Only 51% of new diagnoses linked to care
- no association with age sex or race

RCT universal vs targeted HIV screening in ED

University of Cincinnati #P 1062 *(Lyons et al)*

- 4692 in Universal testing arm
  - 1915 consented (41%)
  - 1911 tested (41%)
- 4880 in Targeted testing arm
  - 1454/3067 consented (47%)
  - 1451 tested (30%)
- Higher proportion consenting in Targeted arm
- New positives: 6 (0.31%) and 3 (0.22%) in each arm
- Parallel seroprevalence study: 0.36%

- *Supports "routine" rather than targetted testing, but much lower consent rates than in UK testing pilots*

Home Testing for HIV
Plenary #162 *(Myers)*

- FDA approved home testing (Determine HIV Combo) in 2012
- Previously unpublished “trial” of 5055 patients across 20 sites in the US
  - 82% “high prevalence”; 18% “low”
  - Test failure rate: 1.1%
  - HIV prevalence rate: 2.12%
  - Sensitivity: 91.67% (specificity: 99.8%)

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Home Testing for HIV
Plenary #162 *(Myers)*

- Concerns with Home Testing: (already being used; often to test sexual partners)
- Propensity for self-harm and violence
  - Not observed
- Lost Opportunities
  - Screening for other STIs
- False reassurance
- Cost
  - $40; only 17-18% in US and Europe prepared to pay
- Risk compensation
- Linkage to care

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Home Testing for HIV
Poster #1064 *(Katz et al)*

- Modelling of impact of introduction of home-testing to MSM population in Seattle
  - Assumed “window period” of 3 months for HTK
  - “window period” of 2 months for laboratory kit
  - HIV prevalence of 18.6%
- If all MSM replaced clinic testing with home testing, HIV prevalence increased to 27.4%
- If increased frequency of testing with home testing, HIV prevalence increased to 22.3%
- HIV prevalence would only remain the same if there was a reduction in window-period to 2 months and increased testing rates

- ***“All models are wrong, but some are useful”***

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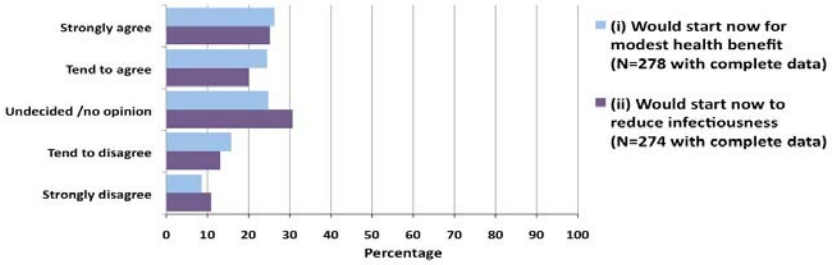
Treatment as Prevention: who wants it?

- Poster 1038 Rodger, A et al ASTRA UK
- Attitudes to early ART among 286 ART naïve individuals



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Treatment as Prevention: who wants it?

- Poster #550
- Acceptance of ART in the Delay Arm after Notification of Interim Study Results: Data from HPTN 052
- Circa 20% chose NOT to accept ART

Reasons for Decline	N=101 30 Jun 2012 (1 Year of Follow-up) [N (%)]	N=73 31 Dec 2012 (1.5 Years of Follow-up) [N (%)]
Believes CD4 is too high	58 (57%)	42 (58%)
Not ready to begin ART (including) • Feels healthy • Doesn't want to take/commit to ART • Fear of side effects • Family problems • Mentally unprepared • Mobile lifestyle • In denial	28 (28%)	20 (27%)
Wants to discuss decision with family/friends	5 (5%)	3 (4%)
Plans to begin at a later date	3 (3%)	2 (3%)
Still deciding	1 (1%)	1 (1%)
Other/unknown reasons (including) • Lost-to-follow-up • Religious belief • Wants guaranteed drug supply after study • Spouse did not allow	6 (6%)	5 (7%)

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Prevention of Mother to Child transmission

Mother to child transmission in UK and Ireland

- *#P906 (Townsend at al)*
- 12,340 pregnancies
- Transmission 2.2% in 2000
- Falling to 0.5% in 2010-11
  - Diagnosis and use of ART/earlier initiation of ART
- 5 transmissions on cART despite undetectable VL
  - 4 likely postnatal
  - 1 perinatal
- ***Need for ongoing support after delivery***

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Prevention of Mother to Child transmission

Birth Defects and adverse pregnancy outcomes

- French perinatal cohort study ANRS-EPF #***O81*** *(Sibiude et al)*
  - Power>80% for OR=1.5, 13,000 live births, 1994-2010, Birth defects definition EUROCAT and MACDP
  - Compared with not exposed to this drug during pregnancy, or compared to 2nd or 3rd trimester exposure
- **Efavirenz in 1st trimester n=372 exposed**
  - No assoc with overall birth defects or neural tube defects AOR 1.3(0.9-1.9)
  - **assoc with increased neurological abnormalities AOR =3.2(1.1-9.1) p=0.03**
    - **(4 patients), all exposed at conception**
  - Pachygyria , agenesis of corpus callosum, hydrocephaly, cerebral cyst,
- AZT in 1st trimester n=3,267
  - assoc with overall birth defects 1.4 (1.1-1.8) p=0.002 , specifically with CHD AOR 2.5 (1.6-4.2) p=0.001 increased congenital heart disease esp VSD

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Efavirenz and Adverse Pregnancy Outcomes

- No planned change currently to BHIVA guidelines
- When incorporated into previous meta-analysis, still no efavirenz effect
- No effect of efavirenz on overall birth defects of NTD
- No background rates of abnormalities
- Concerns re “public health” message from this data
  - Risks versus benefits where efavirenz may be main option

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"Functional Cure" in infant

- *#O48LB (Persaud et al)*

- Mother diagnosed at delivery, CD4 600, VL 2,423
- 28mths no ARVs in pregnancy
- baby transferred at 30hrs to tertiary centre
- At 30hrs HIV DNA pos,31 hrs HIV RNA pos 19,000 copies/ml
- treatment AZT/3TC/ NVP started at 31 hours

"Functional cure" 2

- Changed NVP to Kaletra at 7 days
- Viraemia for 19 days
- Typical biphasic decay in VL on HART suggesting 2 different cell types infected (activated CD4 and macrophages)

- At 18mths lost to FU and treatment stopped by carer

- Represented at 23 mths

"Functional cure" 3
Results at 2 and 2.2 yrs

- RNA undetectable, HIV ELISA neg, HIV DNA PCR neg
- HIV specific immune responses Western Blot neg,
- No CD8 specific responses, no immune activation
- Viraemia at 1 copy per ml
- Low level detection of proviral DNA
- Culture of 22million cells unable to detect infectious virus
- HLA Typing CCR5 to look for delta 32 mutation – none
- HLA typing matches mother

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Was this really "functional cure"

- Was this cured or aborted infection?
- What is the definition of "infection"?
- Could this have been maternal cells producing virus?

- Implications for early treatment?

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BHIVA 'Best of CROI' Working Party 2013

- **Dr A Apoola**, *Royal Derby Hospital*
- **Dr D Asboe,** *Chelsea and Westminster Hospital, London*
- **Dr S Bhagani,** *Royal Free Hospital, London*
- **Dr D Chadwick,** *James Cook University Hospital, Middlesbrough*
- **Dr D Churchill,** *Royal Sussex County Hospital, Brighton*
- **Dr P Collini,** *University of Sheffield*
- **Dr S Das,** *Coventry and Warwickshire Hospital*
- **Dr D Dockrell,** *Royal Hallamshire Hospital, Sheffield*
- **Dr T Doyle** *Royal Free Hospital, London*
- **Dr MJ Fisher,** *Royal Sussex County Hospital, Brighton*
- **Dr A Freeman,** *Cardiff University School of Medicine*
- **Dr A Garcia-Diaz,** *Royal Free Hospital, London*
- **Dr M Gompels,** *Southmead Hospital, Bristol*
- **Dr J Greig,** *Royal Hallamshire Hospital, Sheffield*
- **Dr R Gupta,** *University College London*
- **Prof S Khoo,** *University of Liverpool*
- **Prof C Leen,** *Western General Hospital, Edinburgh*
- **Dr R O'Connell,** *Royal London Hospital*
- **Dr EC Ong,** *Royal Victoria Infirmary, Newcastle*
- **Dr C Orkin,** *Bart's and The London NHS Trust*
- **Dr A Palfreeman,** *Leicester Royal Infirmary*
- **Dr M Phillips,** *Manchester Royal Infirmary*
- **Dr K Rogstad,** *Royal Hallamshire Hospital, Sheffield*
- **Prof C Sabin,** *Royal Free and University College London Medical School*
- **Miss K Seden,** *University of Liverpool*
- **Dr J Thornhill,** *Bart's and The London NHS Trust*
- **Dr A Ustianowski,** *North Manchester General Hospital*
- **Miss R Weston,** *Imperial College London*

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