

HIV/AIDS at 30: Back to the Future
BHIVA / Wellcome Trust Multidisciplinary Event to mark World AIDS Day 2011

British HIV Association **BHIVA** Supported by **wellcome**trust

**HIV/AIDS at 30:
Back to the Future**
*Multidisciplinary Event
to mark World AIDS Day*

1500–2045
Thursday 1 December 2011
Wellcome Collection Conference Centre
London

In support of World AIDS Day

In partnership with   HIV 

British HIV Association (BHIVA) 2011

HIV/AIDS at 30: Back to the Future
BHIVA / Wellcome Trust Multidisciplinary Event to mark World AIDS Day 2011

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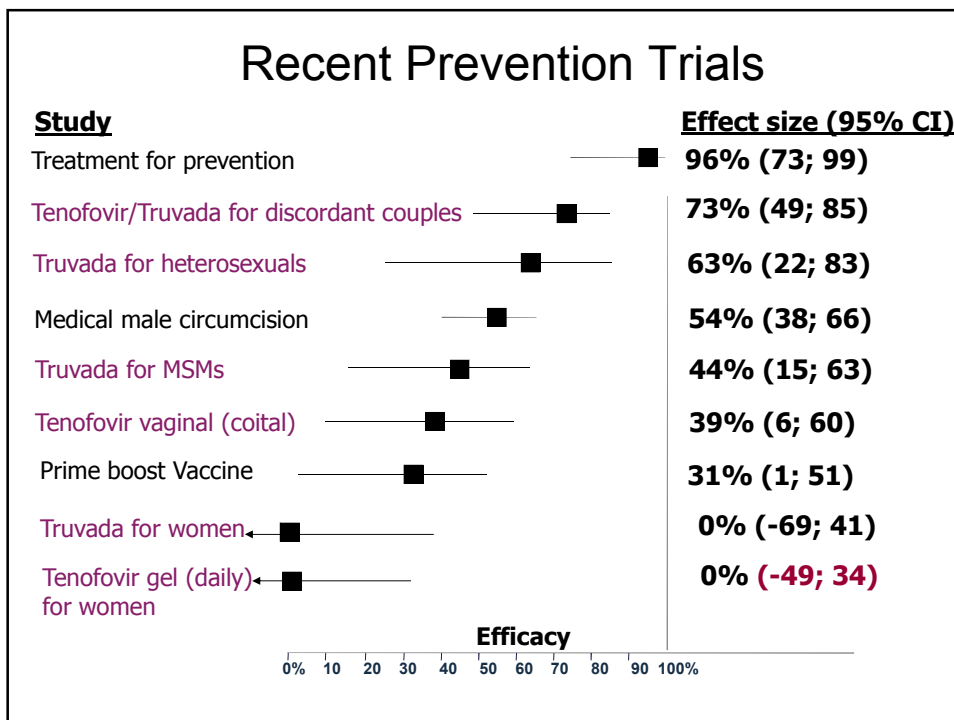
Dr Sheena McCormack
MRC Clinical Trials Unit, London

Thursday 1 December 2011, Wellcome Collection Conference Centre, London

Prevention – looking ahead Sheena McCormack

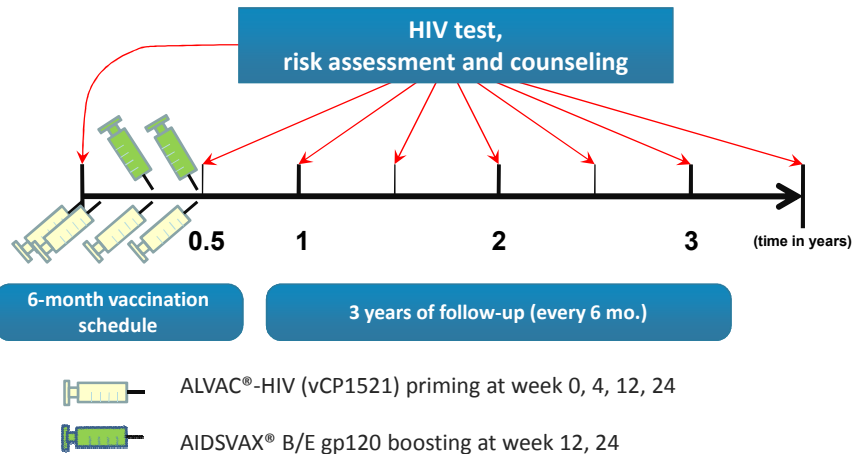


- Summary of recent prevention trials
 - Success, but not consistent
- Focus on
 - HIV vaccines
 - Anti-retrovirals (except MTCT)
- Relevance to the UK setting
 - Integration
 - behaviour



HIV vaccines – building on RV144

RV-144 Vaccination and Follow-up



Lessons learnt from RV144

Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

Supachai Rerks-Ngarm, M.D., Punnee Pitisuttithum, M.D., D.T.M.H., Sorachai Nitaysaphan, M.D., Ph.D., Jaranit Kaewkungwal, Ph.D., Joseph Chiu, M.D., Robert Paris, M.D., Nakorn Premsri, M.D., Chawetsan Namwat, M.D., Mark de Souza, Ph.D., Elizabeth Adams, M.D., Michael Benenson, M.D., Sanjay Gununathan, M.D., Jim Tartaglia, Ph.D., John G. McNeil, M.D., Donald P. Francis, M.D., D.Sc., Donald Stablein, Ph.D., Deborah L. Bix, M.D., Supamit Chunsuttiwat, M.D., Chirasak Khamboonruang, M.D., Prasert Thongcharoen, M.D., Ph.D., Merlin L. Robb, M.D., Nelson L. Michael, M.D., Ph.D., Prayura Kunasol, M.D., and Jerome H. Kim, M.D., for the MOPH-TAVEG Investigators*

ABSTRACT

- Highest protection 6-12m
- More confident if consistent with time, **but it's not**
- Ab titres high at 6m and low by 12 but this does not mean they are the correlate of protection
- Limited T cell responses (17%) and no effect on VL
- Combination the right approach, need better immunogens and shorter schedules

Next steps

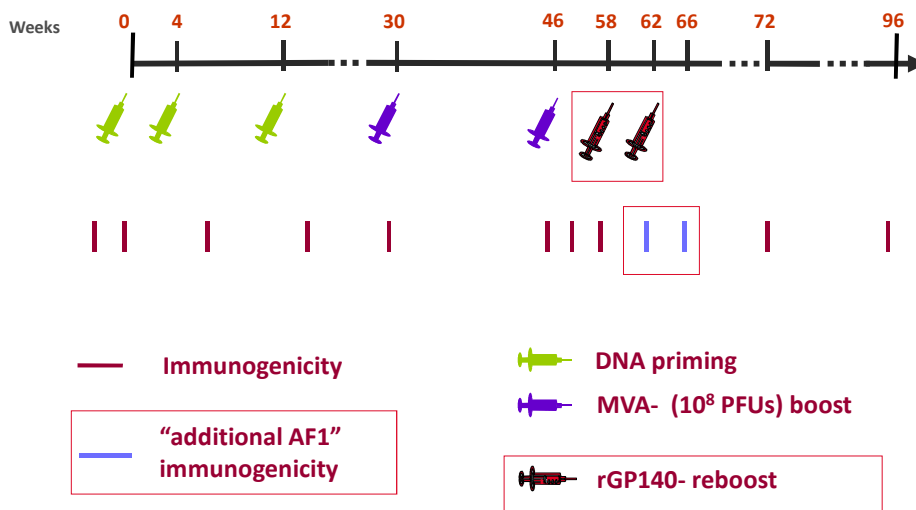
Globally over the next 5years:

- Walter Reed (MHRP) plan to repeat the trial
- HVTN will investigate various combinations of DNA (VRC), NYVAC (Sanofi) and protein (Novartis) in SA, in a multi-stage, multi-arm Phase IIb trial

UK HIV Vaccine Consortium and partners:

- Currently investigating **mucosal routes** for adjuvanted rgp140, and **transcutaneous** for DNA
- Plan to assess impact of **adjuvanted rgp140** in ppts already immunised with **DNA and MVA** in Tanzania
- Plan to assess DNA, MVA and rgp140+GLA in a **long (separate) or short (combined) schedule**

Schema: TaMoVac 01 with AfrEVacc amendment



Anti-retrovirals – looking ahead



Sponsored by
NIH/NIAID/DAIDS

Co-Funding by
Bill and Melinda Gates
Foundation

Drug Donated By
Gilead Sciences

CAN A PILL A DAY
**PREVENT
HIV?**


FOR INFORMATION ON THIS NEW AND
EXCITING **HIV PREVENTION STUDY**

SMS "Info" at no cost to 30060 or
e-mail MCVHP@hiv-research.org.za


All participants will be compensated for their time and transport.



The iPrEx Study




- MSM and Trans Women
- **Comprehensive Prevention Package**
- Randomized 1:1 **Daily Oral PREP**
- **FTC/TDF vs Placebo**
- **Followed Monthly**



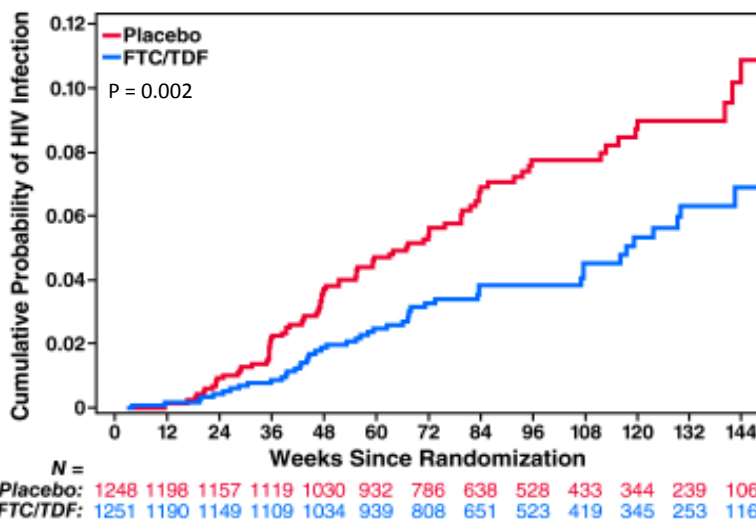
Fully enrolled as of December 2009

Sites	11
Participants	2499



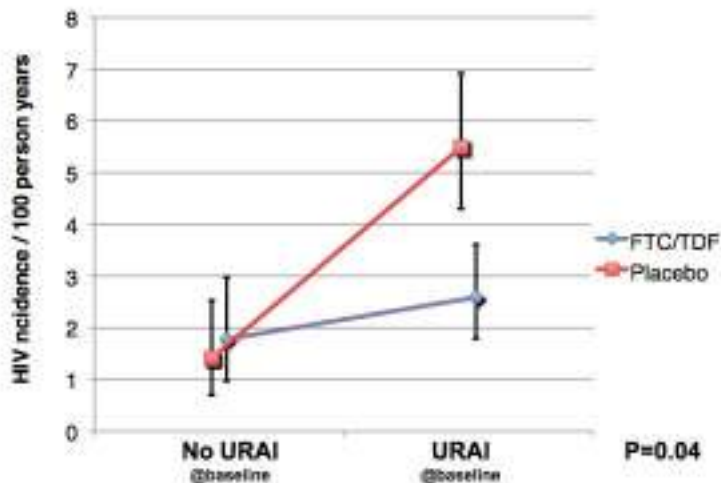
New England Journal of Medicine, online Nov 23, 2010

**Efficacy (MITT) 44% (15-63%) Through May 1, 2010
Durable Through 144 Weeks in the Final Analysis**



HIV Incidence by URAI and Group

Bars are Standard Error of the Incidence Estimate

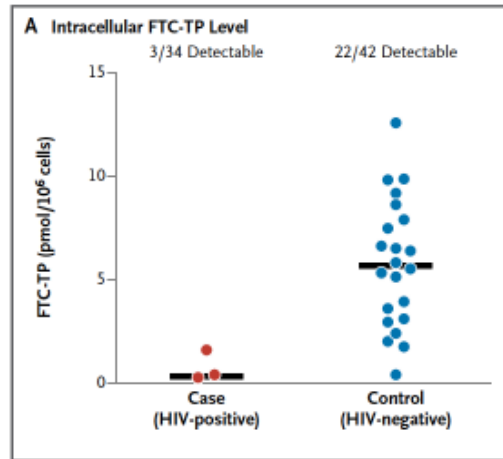


N	1014	1485
Efficacy	-25%	52%
95% CI	-174 - 44	28 - 68

Grant et al, CROI 2011

Drug Levels

- Cases matched to controls by site and time on study
- Drug Detection Correlated with Seronegative Status (OR 12.9, $P < 0.001$)
 - 92% reduction in HIV risk
 - 95% if controlled for Unprotected Receptive Anal Intercourse



New England Journal of Medicine, online Nov 23, 2010

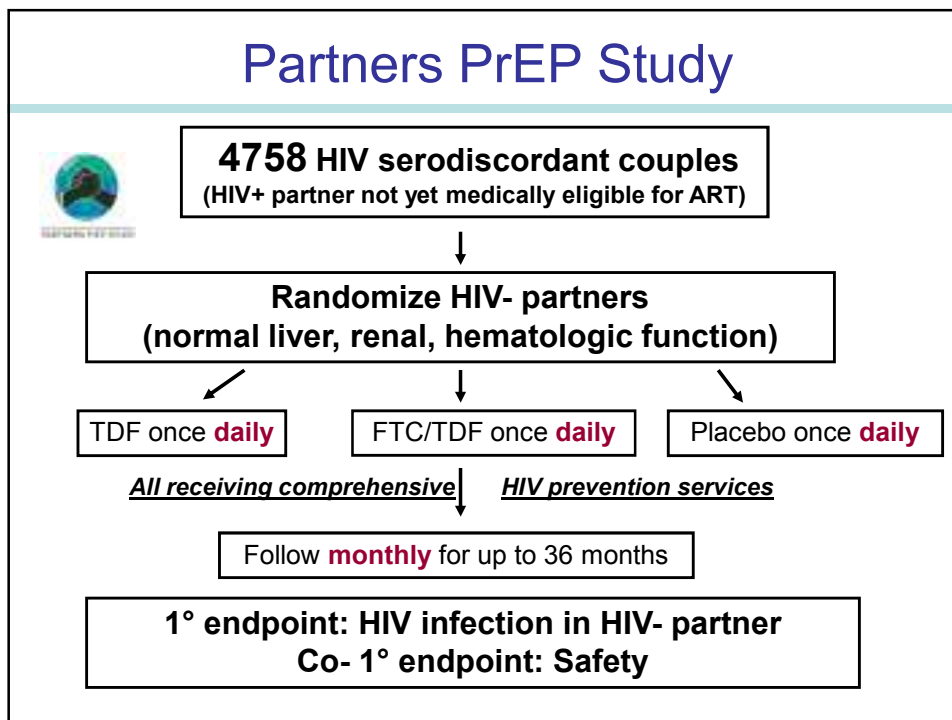
Partners PrEP Study: Sites



Eldoret,
Kisumu,
Nairobi,
Thika,
Kenya

Jinja,
Kabwohe,
Kampala,
Mbale,
Tororo,
Uganda

Partners PrEP Study



Primary efficacy results

- Primary analysis: modified intention-to-treat (mITT)
 - excluding infections present at randomization (3 TDF, 3 FTC/TDF, 6 placebo)

	TDF	FTC/TDF	Placebo
Number of HIV infections	18	13	47
HIV incidence , per 100 person-years	0.74	0.53	1.92
HIV protection efficacy, vs placebo	62%	73%	
95% CI	(34-78%)	(49-85%)	
p-value	0.0003	<0.0001	
Z-score, vs. $H_0=0.7$	-2.17	-2.99	

ITT analysis results similar

Subgroup analysis - gender

- Both TDF and FTC/TDF significantly reduced HIV risk in both men and women

Women: 42 total infections: 8 TDF, 9 FTC/TDF, 25 placebo

Men: 36 infections: 10 TDF, 4 FTC/TDF, 22 placebo

	Efficacy	95% CI	P-value	Interaction p-value
TDF				
Women	68%	29-85%	p=0.01	p=0.54
Men	55%	4-79%	p=0.04	
FTC/TDF				
Women	62%	19-82%	p=0.01	p=0.24
Men	83%	49-94%	p=0.001	



Women

CAPRISA 004

- Before and after sex tenofovir vaginal gel
- 98 infections; 39% (95% CI: 6-60%) reduction in HIV

FEM-PREP

- Daily oral Truvada
- Closed for fertility after 56 infections (95%CI: -69-41%)

Partners in PrEP

- Daily oral tenofovir: 34 infections; 68% (95% CI: 29-85%)
- Daily oral Truvada: 33 infections; 62% (95% CI: 19-82%)

VOICE

- Daily oral tenofovir discontinued for fertility
- Daily vaginal tenofovir discontinued: 92 infections (95%CI: -49-34%)
- Daily oral Truvada continues

Next steps

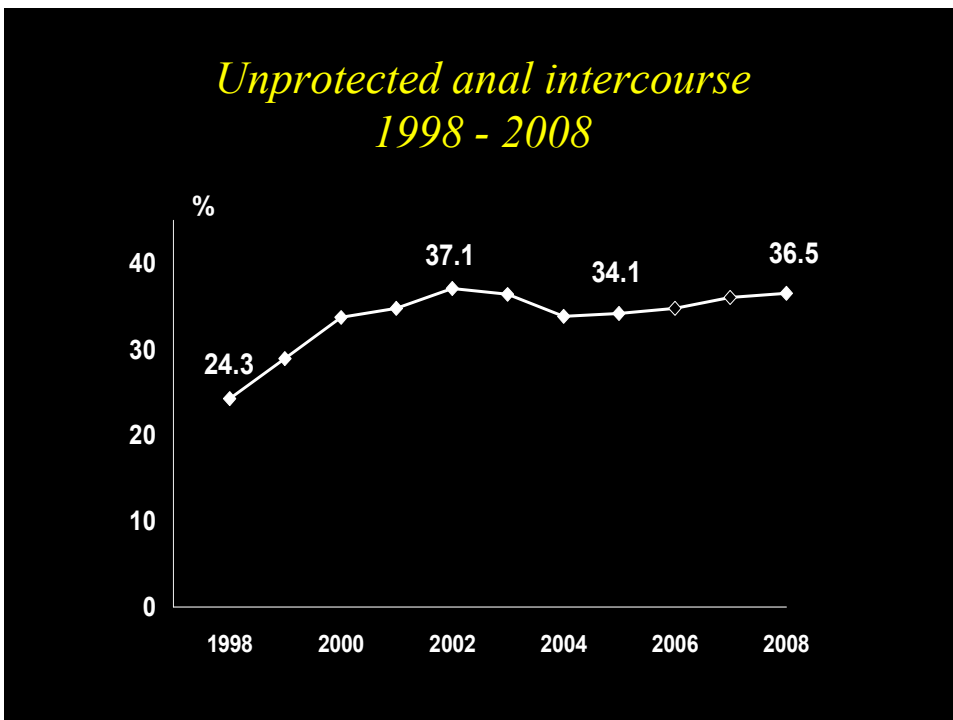
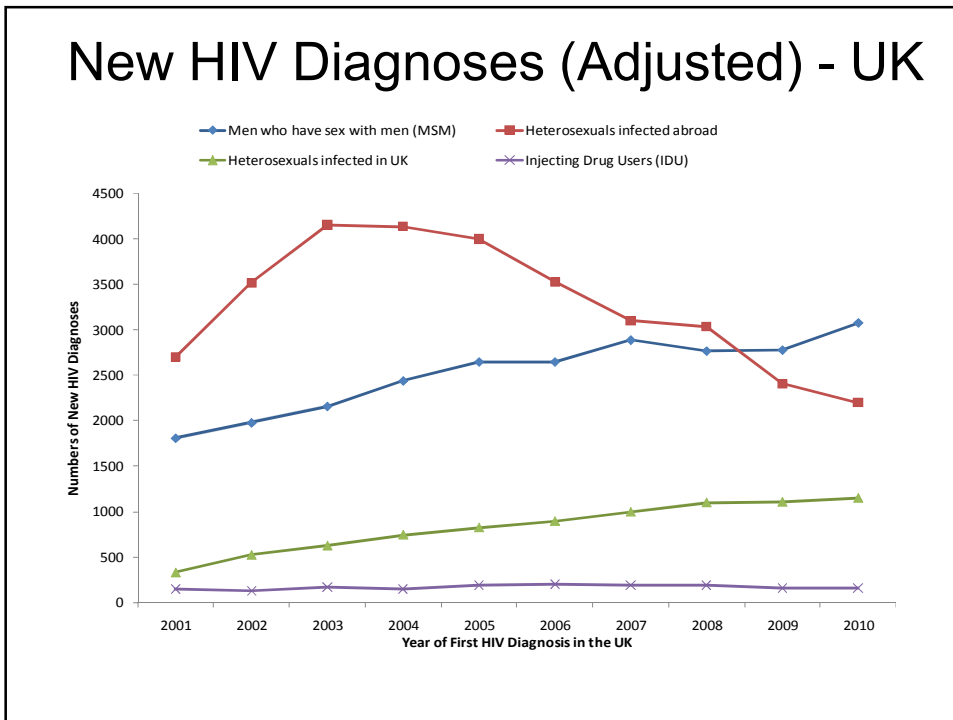
SSA:

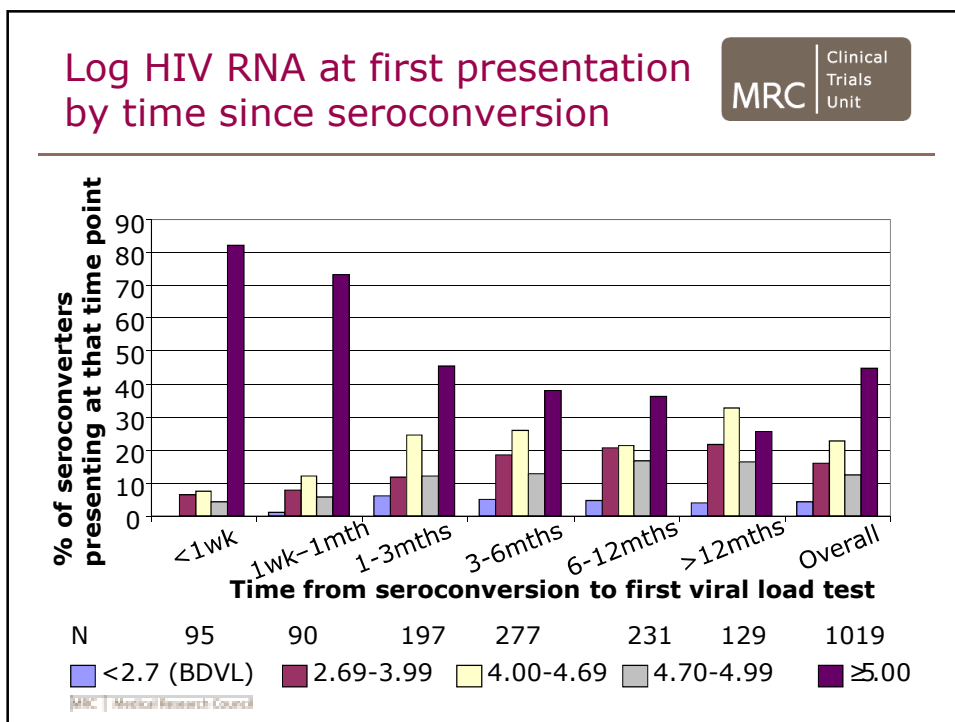
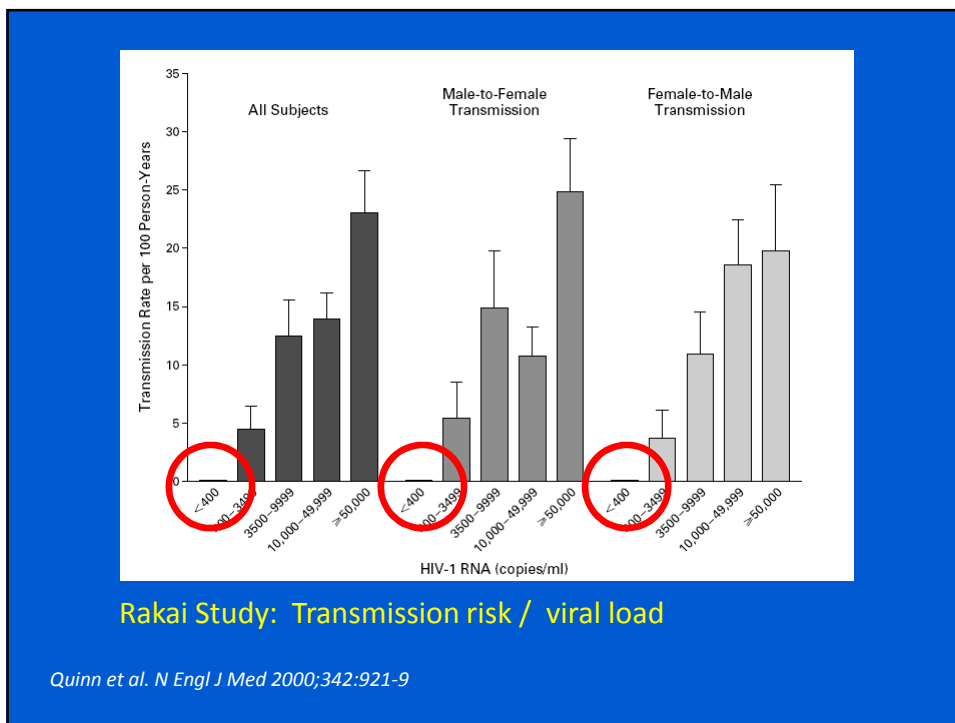
- FACTS 001 placebo-controlled trial to continue with before and after regimen in SA and Kenya
- Two trials of dapivirine ring compared to placebo
- Oral PrEP much more challenging

US and Europe:

- Demonstration projects in MSM in the US; CDC guidelines
- Clinical trials/cohort studies in MSM in Europe
 - ✓ Ipergay: double dose before sex, single dose after compared to placebo
 - ✓ PROUD
- Pre-conception PrEP will probably continue

**Embedding Open-label PrEP trial
in expansion of
UK HIV Prevention Programme**





Partners Identified

- 70 Partners (of 32 new HIV +ve MSM) were identified in total
- In 3 cases the number of partners were not fully documented.

- 35 Traceable partners
- 29 Untraceable partners
- 6 partners already HIV +ve

Partners Tested

- 27/35 (77%) were documented as being tested.
- N.B All 35 informed of Diagnosis

- 7/27 tested HIV +Ve
(Royal Free, 56DS and Italy)

- Provider referral appropriately offered in 3 cases not applicable in the all other cases.

Prevention Programme

- ICP: audit of **Testing** and **Behavioural Interventions** in clinics (HPA), national community organisations through CHAPS, Pan-London clinic & community (Ergoclear)
- **Risk score**: questions in development (HPA to pre-pilot); THT's 'Clever Dick-Smart Arse'
- **Web-tool**: awaiting outputs from above, and Pilot
- **PrEP pilot** (and trial)
- **Pharmacology** WkGp: in vivo dosing, ex vivo challenge of alternative regimens and for PEP recommendations
- **Modelling Cost-effectiveness**: UCL with LSHTM
- Overall coordination/dissemination: currently through PrEP eWG

PROUD

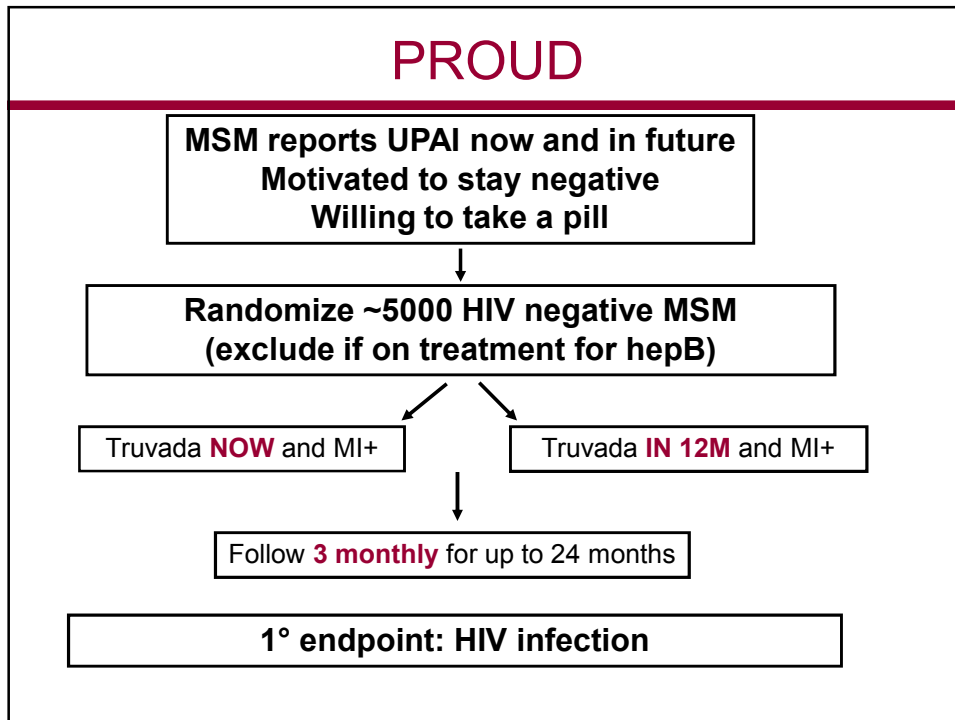
Pre-exposure Option for preventing HIV in the UK: an open-label randomisation to an immediate or Deferred offer

Why a Trial?

- We want '**real-life**' **efficacy**
 - When individuals know they are using an effective alternative to condoms
 - Placebo controls behaviour, so **need non-placebo** control group
- Propose randomise to immediate offer vs deferred to 12m
 - Mimic clinic routine as much as possible
 - Measure **net benefit**, i.e. cannot reliably separate behaviour and biology
- We want **to offer more than daily**

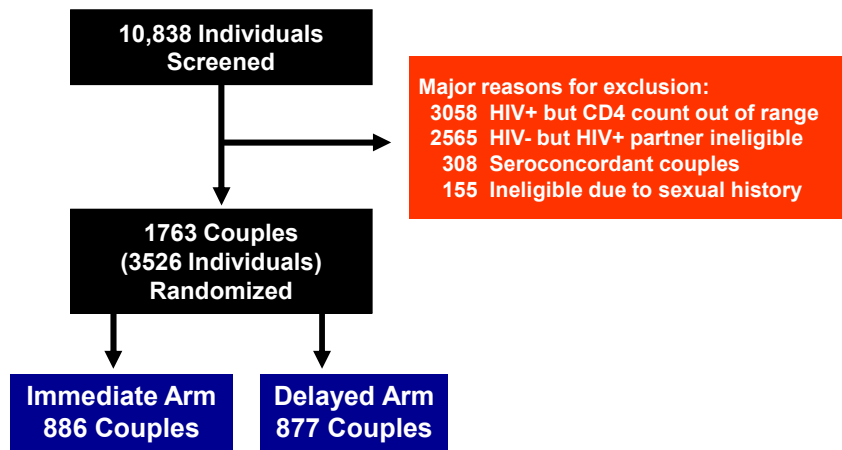
Why a Pilot?

- **Major uncertainties** to assess:
 - level of **real** interest among MSM in taking PrEP
 - **acceptability of deferred** offer and visit schedule
 - whether **behavioural diaries** feasible
 - whether **instructions** for use are clear
 - level of **adherence**
- **Opportunity to optimise integration** with other initiatives in clinics and community

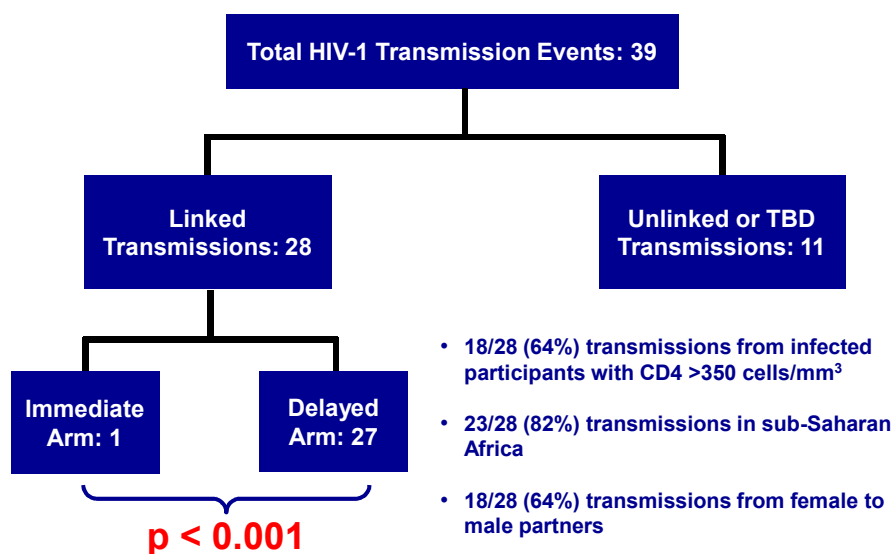


Treatment as prevention?

HPTN 052 Enrollment



HPTN 052: HIV-1 Transmission



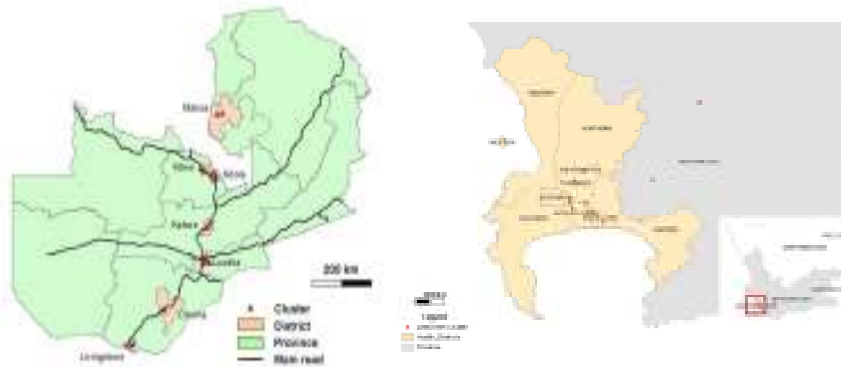
The PopART hypothesis

- Universal voluntary HIV testing with appropriate combination prevention offered to all those testing HIV–ve in addition to immediate ART for all those testing HIV+ve will have a substantial impact on HIV incidence at population level

Study arms

- Arm A (8 clusters): Full PopART intervention including immediate ART irrespective of CD4 count
- Arm B (8 clusters): Full PopART intervention *except* that ART initiated according to current national guidelines (CD4 < 350)
- Arm C (8 clusters): (Enhanced) standard of care

Location of study clusters



Looking ahead

Long term:

- A vaccine?

Medium term:

- ARV for prevention
 - Behaviour – need a better understanding of risk over time and in response to BI; PrEP is not for everyone
 - Biology does matter – pharmacodynamics and challenge helpful, but limited to perfect use and fixed challenge

Now:

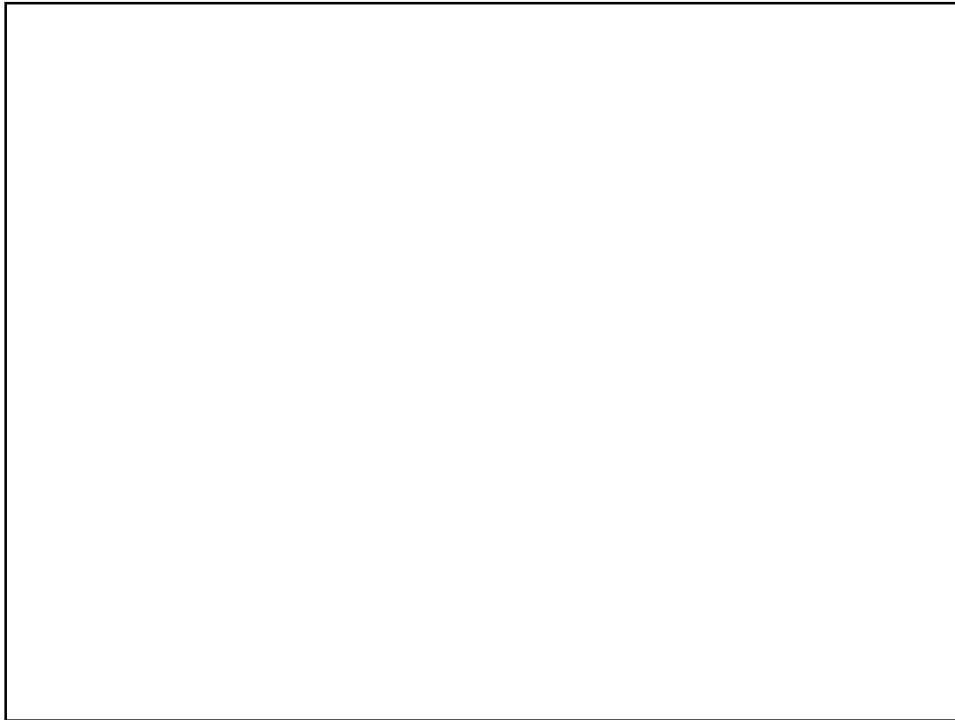
- We can identify HIV positive individuals that contribute to onward transmission...
- We can improve further on the basics
 - Increasing awareness of risk eg dipping, tops
 - Appropriate frequency of testing
 - Partner notification and other ways to reach undiagnosed

Thanks for slides to

- Merlin Robb and Mary Marovich from MHRP
- Jonathan Weber from Imperial
- Sarah Joseph from CTU
- Bob Grant and Dave Glidden from iPrEx
- Connie Cellum and Jared Baeton from Partners
- Slim Karim from CAPRISA
- Tony Nardone and Noel Gill from HPA
- Jonathan Elford from City
- Sarah Fidler from Imperial
- Kholoud Porter from CTU
- Raj Gill from Dean Street
- Mike Cohen from UNC
- Richard Hayes from LSHTM

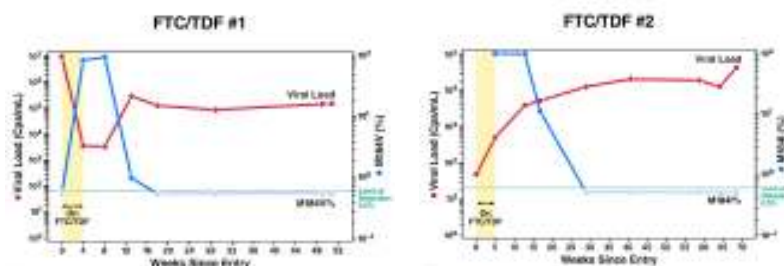
And to the UK PrEP eWG

Charles Lacey (charles.lacey@hymns.ac.uk); Clutterbuck, Daniel; Sullivan, Ann; Natha, Macky; Alan McOwan (alan.mcowan@chelwest.nhs.uk); Hart, Graham; Elford, Jonathan; Boffito, Marta; Alan Winston (a.winston@imperial.ac.uk); D.J.Back@liverpool.ac.uk; Noel Gill; Anthony Nardone; catherine.lowndes@hpa.org.uk; David Dunn; Deenan Pillay; Andrew Philips; Yusef Azad; Brian.Gazzard@chelwest.nhs.uk; Yvonne.Stuppel@chelwest.nhs.uk; kay.orton@dh.gsi.gov.uk; Gus@nam.org.uk; steve.taylor@heartofengland.nhs.uk; Iain.Reeves@homerton.nhs.uk; lisa.power@tht.org.uk; roger@nam.org.uk; matthew.hodson@gmfa.org.uk; werner.leber@nhs.net; Ian Williams (ian.williams@ucl.ac.uk); r.gilson@ucl.ac.uk; judith.russell@nhs.net; Nwokolo, Nneka; 'Emma.Devitt@chelwest.nhs.uk'; paul.benn@nhs.net; 'v.cambiano@ucl.ac.uk'; Andrew Copas; 'Alec.Miners@lshtm.ac.uk'; 'carol.emerson@belfasttrust.hscni.net'; 'carolemerson15@hotmail.com'; 'Keith Alcorn'; 'Caspar Thomson'; 'Rob.horne@pharmacy.ac.uk'; 'khoo@liverpool.ac.uk'; 'ford.hickson@sigmaresearch.org.uk'; 'ben.tunstall@tht.org.uk'; 'sal@tradesexualhealth.com'; 'rob.cookson@lgf.org.uk'; 't.doyle@mesmac.co.uk'; 'tomdoyle68@googlemail.com'; 'greg@metrocentreonline.org'; 'Roy.kilpatrick@hivscotland.com'; 'sarah@eddystone.org.uk'; 'deborah.jack@nat.org.uk'; 'p.scott@ergoclear.com'; 'gmburu@aidsalliance.org'; 'akerr@aidsalliance.org'; 'smclean@aidsalliance.org'; 'korr@aidsalliance.org'; 'mt@aidsfreeworld.org'; 'Mariama.kamara@ahpn.org'; 'info@bodyandsoulcharity.org'; 'francis.kaikumba@ahpn.org'; yvonne.gilleece@bsuh.nhs.uk; margaret.kingston@cmft.nhs.uk; christine.bowman@sth.nhs.uk; george.kinghorn@sth.nhs.uk; michael.brady@kch.nhs.uk; valerie.delpech@hpa.org.uk; Rebekah Webb; spetretti@positivelyuk.org; Anne Johnson; gabriel.schembri@cmft.nhs.uk; eleanor.roaf@manchester.nhs.uk; Monica Desai; Sarika Desai; Robin Shattock; r.shattock@imperial.ac.uk; Veronica Nail; Michael Carter; t.barber@nhs.net; nigel.burbridge@heartofengland.nhs.uk; Fabiola Martin; will.nutland@lshtm.ac.uk; Fox, Julie; Linda Lazarus; Helen.Weiss@lshtm.ac.uk; Fisher, Martin; Sarah Fidler; Smith, Alan [Alan.Smith@imperial.nhs.uk]; Nicky.Mackie@imperial.nhs.uk



HIV Resistance - Results

- New HIV infections (91 samples tested)
 - No drug resistance in participants on Truvada
 - 2 with minor variant drug resistance on placebo (1 to tenofovir, 1 to emtricitabine)
- HIV infections already present at enrollment
 - 2 cases of emtricitabine resistance
 - Resistance dropped to undetectable levels within 6 months after stopping PrEP



Liegler et al, CROI 2011

Adverse events

Adverse Event	TDF/FTC		Placebo		P value
	n (%)	Events	n (%)	Events	
Creatinine Elevated	25 (2%)	28	14 (1%)	15	p=0.08
Creatinine Elevation Confirmed on Next Visit	5 (0.4%)	7	0	0	p=0.06
Phosphate, Electrolytes, Total Bill, AST, ALT, AlkP, Glucose, Amylase, HCO ₃ , Hbg, WBC, Platelets					p>0.15



New England Journal of Medicine, online Nov 23, 2010

Safety

- No statistically significant difference in deaths, SAEs, key laboratory AEs

Number of participants with each safety event	Total	TDF	FTC/TDF	Placebo
Death	24 (<1%)	8	7	9
SAE	320 (7%)	108	107	105
Confirmed creatinine AE	49 (1%)	17	20	12
Confirmed phosphorus AE	403 (9%)	138	133	132



Adverse events

Adverse Event	TDF/FTC		Placebo		P value
	n (%)	Events	n (%)	Events	
Diarrhea	46 (4%)	49	56 (4%)	61	p=0.36
Headache	56 (4%)	66	41 (3%)	55	p=0.10
Nausea	20 (2%)	22	9 (<1%)	10	p=0.04
Weight Decreased	27 (2%)	34	14 (1%)	19	p=0.04



New England Journal of Medicine, online Nov 23, 2010

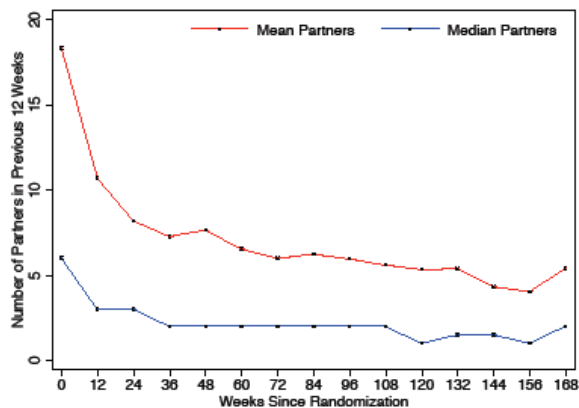
Adverse events

Adverse Event	TDF/FTC		Placebo		P value
	n (%)	Events	n (%)	Events	
Depression	43 (3%)	46	62 (5%)	63	p=0.07
Grade 3 or Grade 4	151 (12%)	248	164 (13%)	285	p=0.51
Death	1 (<1%)	1	4 (<1%)	4	p=0.18
Serious AE	60 (5%)	76	67 (5%)	87	p=0.57



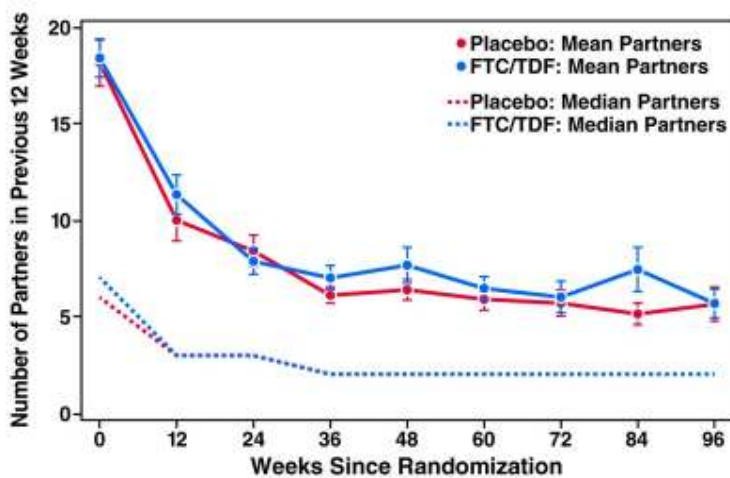
New England Journal of Medicine, online Nov 23, 2010

iPrEx: Number of Partners in Previous 12 Weeks



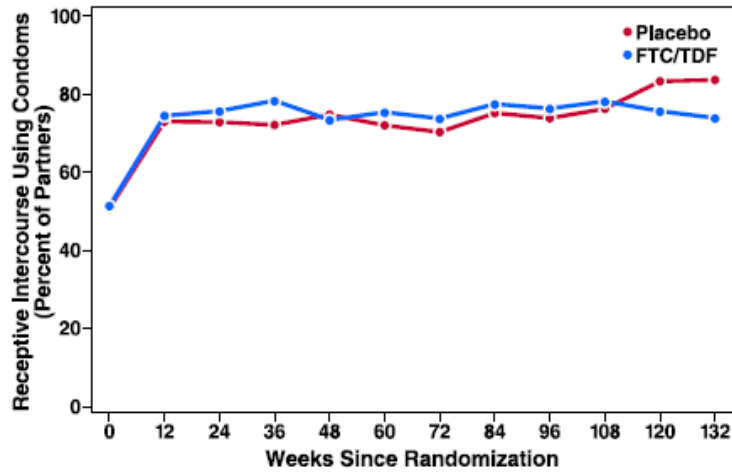
Looks possible in that the median over 12 weeks not that high, and this is all partners whereas we are only asking about receptive AI

Sexual Partners



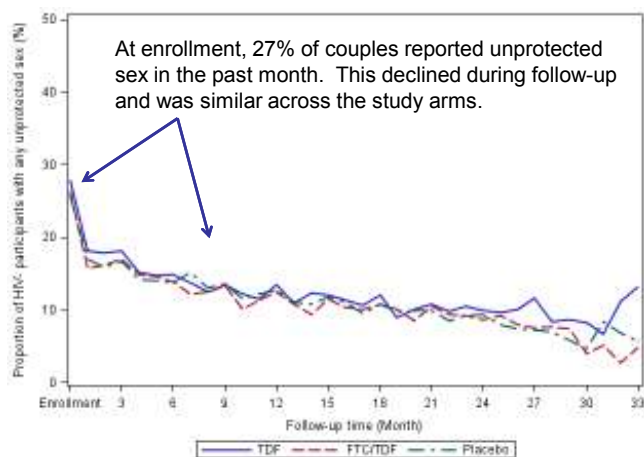
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Condom Use with High Risk Sex



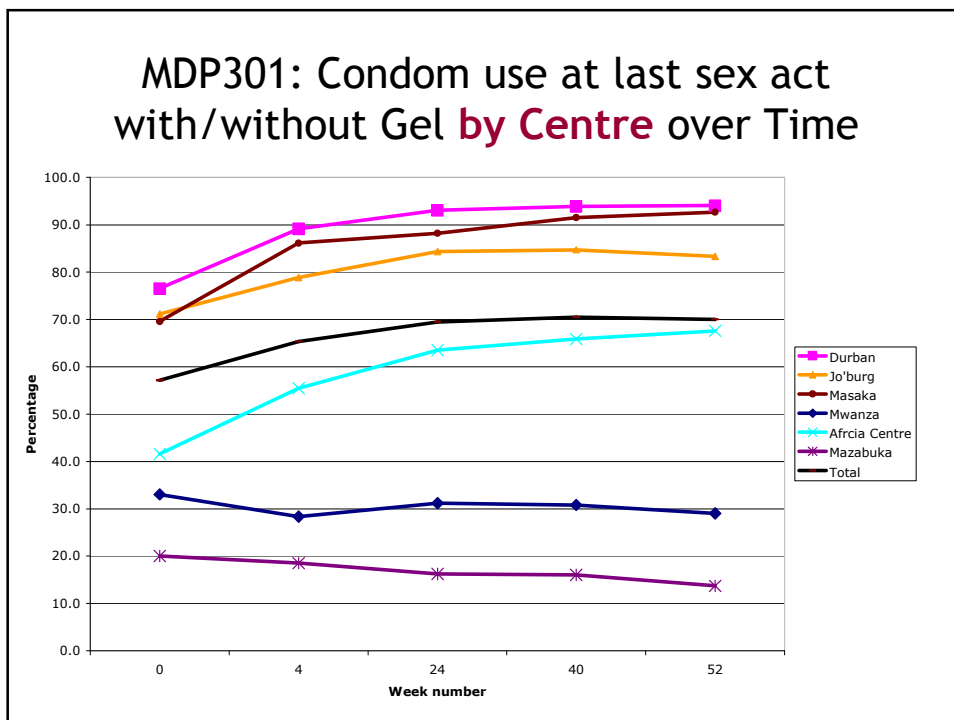
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Sexual behavior



One-third reported an outside partner during the study:
34% TDF, 33% FTC/TDF, 33% placebo





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Supported by

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British HIV Association (BHIVA) 2011