

Sex and Gender Differences in ARV-based Prevention Research

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Objective of talk

- Highlight any efficacy differences by sex/gender from past trials
- Safety and tolerability differences
- Differences in study product adherence trends
- Present potential underlying factors and implications.

Who we're enrolling in these trials?

	Sex	Avg. Age	Married/Stable partner	Adherence (as per drug levels)
CAP 004	Women	24	88%	40%*
iPrEx	Transgender women, MSM	27		51%
Partners PrEP	Serodiscordant couples	36	98%	81%
TDF-2	Men & women	25	6%	79%
FEM-PrEP	Women	24	31%	26%
VOICE-SA	Women	25	8%	March 2013
VOICE-Ug	Women	28	50%	March 2013
VOICE-Zim	Women	28	94%	March 2013
FACTS	Women		2015	

Slide from Mitchell Warren

In looking at sex & gender differences, it helps to view how field has evolved

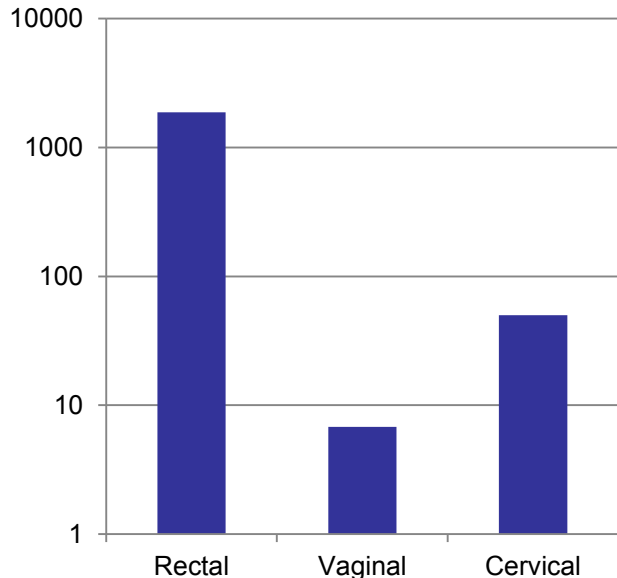
In early 2011

Study	Population	N	Results
CAPRISA 004 <i>South Africa</i>	Women	889	39% [CI = 6-60] efficacy coitally-dependent vaginal TFV gel
iPrEx <i>Brazil, Ecuador, Peru, South Africa, Thailand, US</i>	MSM, transgender women	2499	44% [CI = 15-63] efficacy daily oral FTC/TDF
FEM-PrEP <i>Kenya, S Africa, Tanzania</i>	Women	1950	Futility of daily oral FTC/TDF 6% [CI = -52-41]

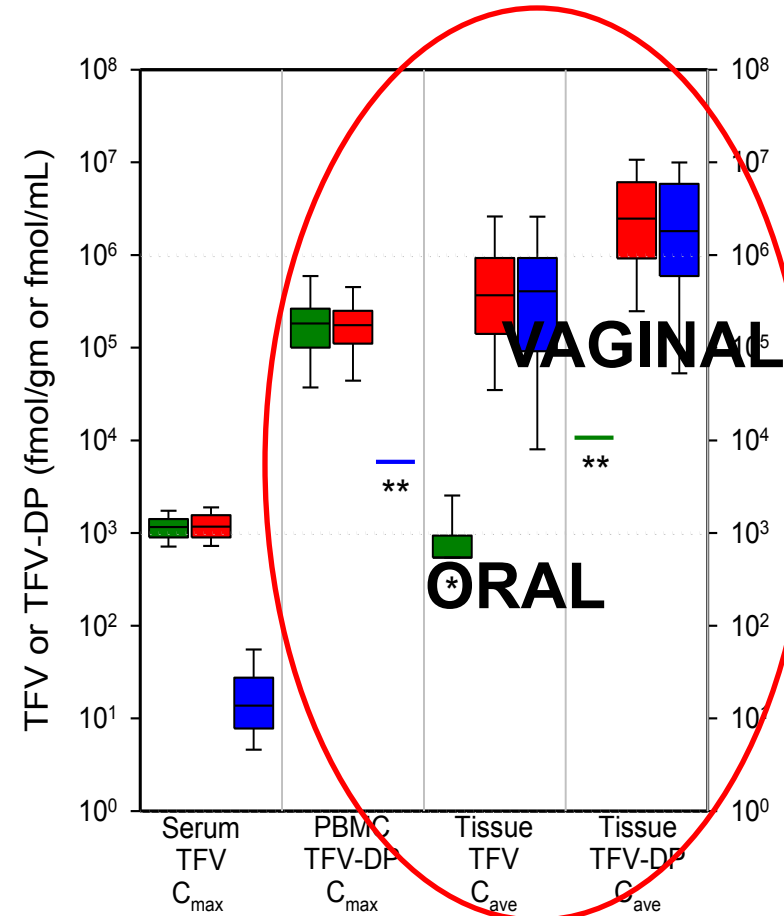
What has biology got to do with it?

- Vaginal tenofovir gel achieves 1000x greater vaginal tissue concentrations than oral tenofovir
- Oral tenofovir results in >10x higher concentrations in rectal tissue than cervical and vaginal tissue

Tissue tenofovir concentrations at 24 hours after a single dose of oral FTC/TDF



Patterson et al. Sci Transl Med 2012



MTN-001 Hendrix et al CROI 2011

Time has changed our thinking....

- Vaginal tenofovir gel achieves 1000x greater vaginal tissue concentrations than oral tenofovir
- Oral tenofovir results in >10x higher concentrations in rectal tissue than cervical and vaginal tissue
- Thus, plausible interpretations of results through early 2011 (i.e., CAPRISA 004 → iPrEx → FEM-PrEP) the was that a) oral PrEP might be less effective in women than in MSM and b) topical PrEP may be better than oral PrEP for women

These interpretations lost coherence in the 2nd half of 2011, with results from Partners PrEP & TDF2 and lack of HIV protection from TFV gel in VOICE?

Evidence of efficacy in women...

- Partners PrEP gender subgroup analysis:

Women: 45 total infections: 8 TDF, 9 FTC/TDF, 28 placebo

WOMEN	Efficacy	95% CI	P-value
TDF	71%	37-87%	p=0.002
FTC/TDF	66%	28-84%	p=0.01

- Compare to FEM-PrEP: 33 FTC/TDF, 35 placebo*
- TDF2 results among women also show protection, with smaller sample size: efficacy **49%**, **p=0.1**
 - 7 FTC/TDF infections vs. 14 placebo
 - In as-treated analysis, 3 vs. 13 infections, efficacy 75%, p=0.02

Plasma Tenofovir levels and HIV protection

- Objective adherence measures from trials show:

	% with tenofovir detected		HIV-1 protection: detection versus no detection of tenofovir	
	Seroconverters	Non-seroconverters	Protection	p-value
iPrEx	9%	51%	92%	<0.001
Partners PrEP FTC/TDF arm	25%	81%	90%	0.002

Donnell et al CROI 2012 Abstract 30
Grant et al N Engl J Med 2010



Seat belt has no value
unless you buckle up

We seem now to agree that oral PrEP....

- PrEP has efficacy for men and women to a comparable degree, although seemingly efficacy in women is more fragile to adherence
- Because two trials in young women failed to demonstrate efficacy; we still need to figure:
 - how we do trials in these women
 - how they perceive these trials (motivation for trial participation)
 - how we all devote efforts to their huge HIV prevention needs,
 - whether/not young women will use PREP if offered
- Seems, so much more to learn on a social sciences front about
 - Women's perceptions when they test HIV negative
 - Societal, cultural & structural contexts in which they participate in our trials
 - Gender dynamics in these populations. To what extent do these impact trial outcomes (***keep your condom & I will keep my money***)

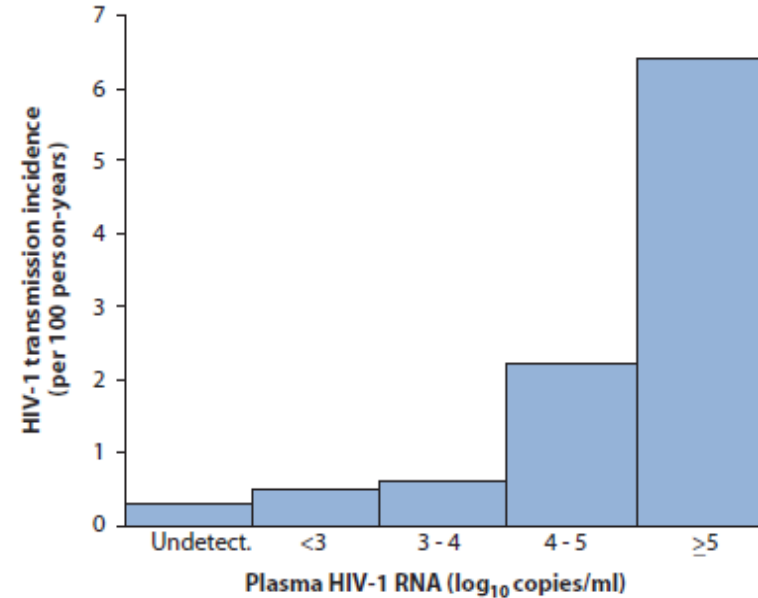
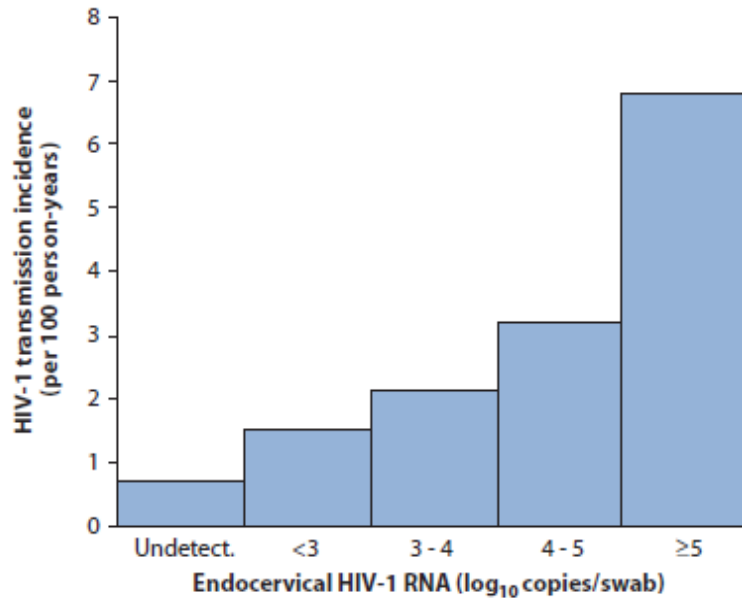
Jury still out for topical PrEP (*Microbicides*)

- Two trials of tenofovir gel have conflicting results (VOICE & CAPRISA)
 - Is it that human behavioral may conform more to using a product when its needed than daily?
 - FACTS 001 will be critical to this understanding
- IPM 027 (*The Ring Study*) & MTN 020 (*ASPIRE*) will be critical to understanding the future of HIV prevention
 - Less user-dependent modalities

Treatment as Prevention Research

- Genital & Plasma HIV shedding correlates with HIV transmission risk

A Female-to-male HIV-1 transmission



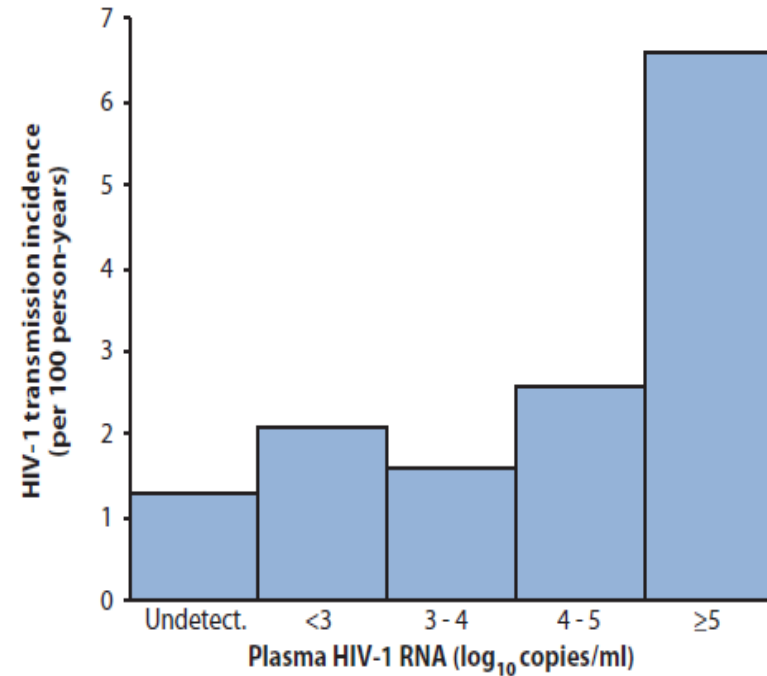
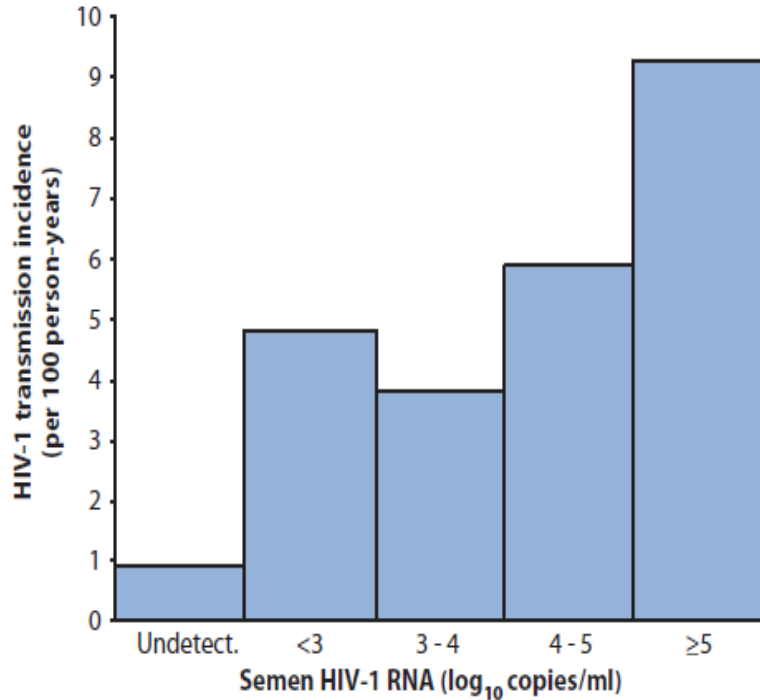
	Log ₁₀ endocervical HIV-1 concentration (copies/swab)				
	Undetectable	<3	3-4	4-5	≥5
# Genetically linked HIV-1 seroconversion events	7	2	18	14	5
# Non-transmitters	717	94	581	313	54
Person-years	1093.0	143.6	905.1	475.6	81.0
HIV-1 seroincidence	0.6	1.4	2.0	2.9	6.2
95% confidence interval	0.3-1.3	0.2-4.9	1.2-3.1	1.6-4.9	2.0-13.8

	Log ₁₀ plasma HIV-1 concentration (copies/ml)				
	Undetectable	<3	3-4	4-5	≥5
# Genetically linked HIV-1 seroconversion events	1	1	5	20	19
# Non-transmitters	233	147	584	587	191
Person-years	335.4	219.7	898.8	918.2	297.0
HIV-1 seroincidence	0.3	0.5	0.6	2.2	6.4
95% confidence interval	0.01-1.7	0.01-2.5	0.2-1.3	1.3-3.3	3.9-9.8

Baeten et.al. *Sci Transl Med* 3, 77ra29 (2011);

Male to female HIV transmission

B Male-to-female HIV-1 transmission



	Log ₁₀ semen HIV-1 concentration (copies/ml)				
	Undetectable	<3	3-4	4-5	≥5
# Genetically linked HIV-1 seroconversion events	4	8	9	7	4
# Non-transmitters	307	113	158	79	26
Person-years	488.2	180.2	253.3	130.6	47.4
HIV-1 seroincidence	0.8	4.4	3.6	5.4	8.4
95% confidence interval	0.2-2.1	1.9-8.6	1.6-6.6	2.2-10.7	2.4-20.2

	Log ₁₀ plasma HIV-1 concentration (copies/ml)				
	Undetectable	<3	3-4	4-5	≥5
# Genetically linked HIV-1 seroconversion events	1	1	5	12	13
# Non-transmitters	49	30	194	287	117
Person-years	75.2	48.5	305.7	464.5	197.1
HIV-1 seroincidence	1.3	2.1	1.6	2.6	6.6
95% confidence interval	0.03-7.2	0.05-11.0	0.5-3.8	1.3-4.5	3.6-11.0

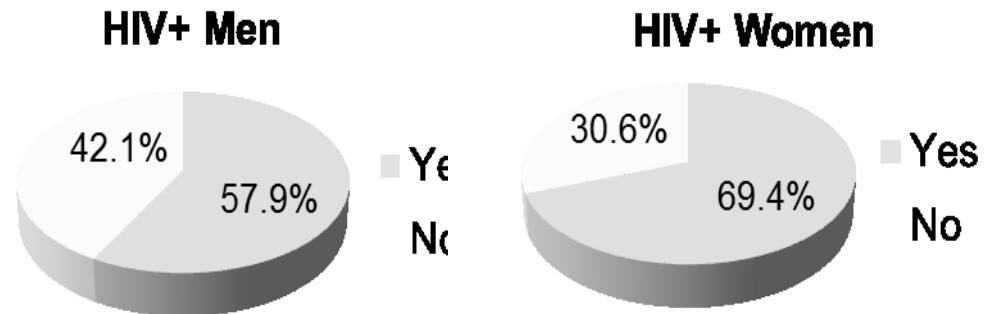
From these data.....

- Genital & plasma VL predict transmission risk, in a comparable way by sex
- Unknown: If there is variation in transmission risk by sex
 - *besides adherence, are there other predictors of virologic response to ART by sex?)*
- Key questions remain:
 - Could Treatment as Prevention have varying effects for women compared to men?
 - Do we have enough data to feel confident about comparable ART efficacy for MTF and FTM transmission?
 - How do we get men in for treatment early?
 - Men generally initiate at much lower CD4

But data gap is even greater for early ART in asymptomatic persons....

- Among 772 members of HIV-1 serodiscordant couples in the Partners PrEP Study at the Thika site in Kenya:

Survey question: Would you be willing to start antiretrovirals before your CD4 count reaches 350 if it would lower your chance of giving HIV to your partner?



Top concerns about initiating early ART for HIV-1 prevention :

- Side effects (51.4%)
- Stigma (20.8%)
- Pill burden (19.4%)
- Potential for earlier development of antiretroviral resistance (18.1%)

Changing the conversation

After years of telling people not to get HIV because antiretrovirals are awful, we need to re-brand ART



DIARRRHEA

It might seem like diarrhea is no biggie. That's probably 'cause you never had it like I have. Try shitting your guts out every day for weeks at a time. How about being terrified to go anywhere because you might crap your pants?

Don't get me wrong, I'm really glad to be alive, but

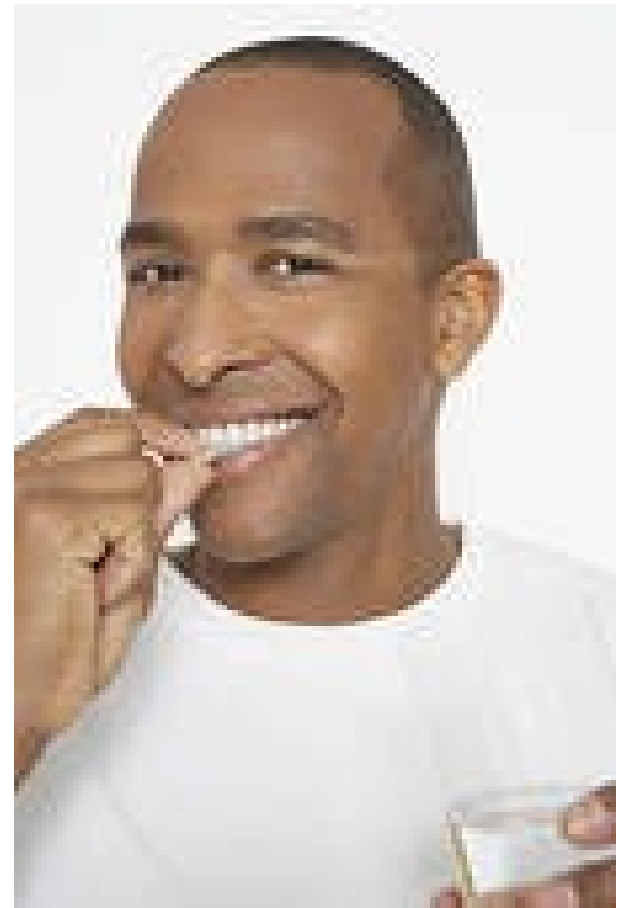
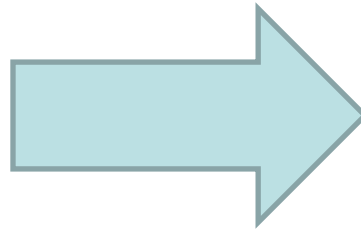
HIV IS NO PICNIC

I don't care how good the sex is or how hot the guy is, nothing is worth what I'm going through now.

stopaids.org

Design: Better World Advertising (www.betterworldadvertising.com)



Willingness to start antiretrovirals

- Soweto, South Africa:

7287 adults tested for HIV

2562 (35%) HIV infected

743 (29%) eligible for ART (CD4<200^{***})

148 (20%) refused

- Most common reason for refusal was feeling well
- *What might this look like for those with CD4>200, >350?*
- *B+ roll-out may only provide half the picture (since motivations for early ART initiation differ*

Reminder: ART for HIV prevention has even greater impact at lower CD4 cell counts

- ART scale-up to those with lower CD4 counts is still insufficient esp. in developing & middle income countries

	Prior to ART initiation		
	Transmissions	Person-Years	Rate
CD4 < 200	8	91	8.8
CD4 200-350	41	1467	2.8
CD4 350-500	24	1408	1.7
CD4 ≥ 500	29	1592	1.8

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PARTNERS PrEP STUDY

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