Periodic presumptive treatment for vaginal infections may reduce chlamydia and gonorrhea incidence: a secondary analysis from the Preventing Vaginal Infections trial

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Disclosures

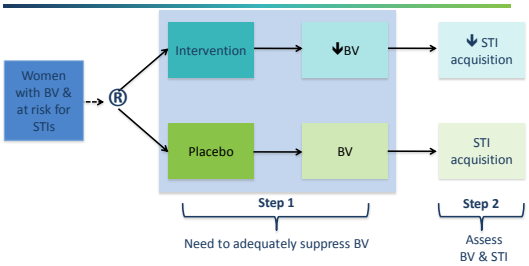
- Dr. Balkus has received honoraria from Symbiomix, Inc for consulting and donated reagents from Hologic/Gen-Probe
- Dr. McClelland has received honoraria for invited lectures and consulting as well as donated study product for this trial from Embil Pharmaceutical Company and currently receives research funding from Hologic/Gen-Probe
- Dr. Schwebke has received consultancy payments from Akesis, Hologic, Symbiomix, and Starpharma, and has grants/pending grants from Akesis, BD Diagnostic, Hologic, Cepheid, Quidel, Symbiomix, Starpharma, and Viamet
- All other authors declare that they do not have a commercial or other association that might pose a conflict of interest

Background

- ~211 million new *C. trachomatis* (CT) and *N. gonorrhoeae* (GC) infections globally each year
  - Development of innovative strategies for STI prevention is a global public health priority
- Vaginal microenvironment plays an important role in mediating STI susceptibility
  - Several prospective studies reported an association between abnormal vaginal microbiota/bacterial vaginosis (BV) and STIs[1]
  - Open-label trial of US women with asymptomatic BV by Nugent score reported a lower incidence of STIs while on suppressive therapy compared to standard of care[2]
- Preliminary evidence in support of the hypothesis that improving vaginal health through treatment of asymptomatic BV could reduce STI incidence

[1]Brotman *et al. JID* (2010); Allsworth et al. AJOG (2011); Martin *et al. JID* (1999)
[2]Schwebke *et al. AJOG* (2007)

BV & STIs: Causal relationship?



Preventing Vaginal Infections (PVI) trial demonstrated a 35% reduction in BV over 12 months among women who received monthly period presumptive treatment (PPT) with intravaginal metronidazole + miconazole versus placebo

McClelland *et al. JID* (2015)

PVI secondary analysis objective & outcomes

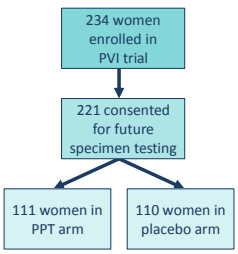
Objective:

- Assess the effect of the PVI trial intervention (PPT) on incident bacterial STIs during follow-up

Hypothesis:

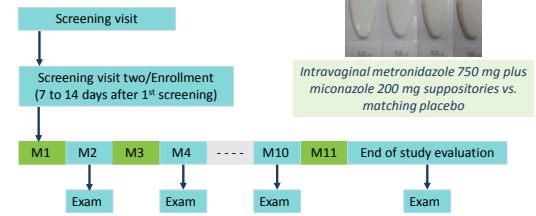
- Incidence of bacterial STIs will be lower in the PPT arm versus placebo

PVI trial design & analysis population



- HIV-negative, non-pregnant women enrolled at 4 sites between 2011-2012:
  - Nairobi, Kenya (two sites)
  - Mombasa, Kenya
  - Birmingham, USA
- Eligible participants had a vaginal infection detected at screening:
  - Bacterial vaginosis
  - Vulvovaginal candidiasis
  - *Trichomonas vaginalis*

PVI study schedule



Intravaginal metronidazole 750 mg plus miconazole 200 mg suppositories vs. matching placebo

- Study product dispensed at monthly treatment visits
- Women with self-reported vaginal discharge or odor received open label treatment with oral metronidazole and fluconazole plus study product

Taking advantage of stored specimens

Genital fluid collected using Hologic/Gen-Probe Aptima kits

- Baseline exam visits for *C. trachomatis* and *N. gonorrhoeae*
- Baseline and follow-up exam visits for *T. vaginalis* testing at the end of the study

Analytic methods

- Calculated incidence of CT, GC and combined bacterial STI outcome (CT and/or GC)
  - Follow-up time censored following the first incident infection
- Constructed Poisson regression models to assess the effect of the intervention on:
  - Combined bacterial STI outcome (CT and/or GC)
  - CT and GC, as separate outcomes
- All statistical tests were assessed using a 2-sided α of 0.05

For each analysis, the population under study was restricted to participants who were negative for the STIs or STI of interest at enrollment

Participant characteristics at enrollment

	Placebo n=110		PPT n=111	
Age (years)	29	(23-34)	30	(24-34)
Education (years)	11	(8-12)	10	(8-13)
African or African-American race	106	(96)	111	(100)
Partnership status				
Married or living with a partner	29	(26)	34	(31)
Separated, divorced or widowed	48	(44)	39	(35)
Never married	33	(30)	38	(34)
Number of live births	2	(1-3)	2	(1-3)
Ever engaged in sex in exchange for goods/money/services	60	(55)	59	(53)
#of vaginal sex acts*	2	(1-4)	2	(1-3)
# of partners*	1	(1-2)	1	(1-2)
New partner*	23	(21)	22	(20)
Ever had anal sex	13	(12)	12	(11)

*Data presented as N (%) or median (IQR); *In the past week*

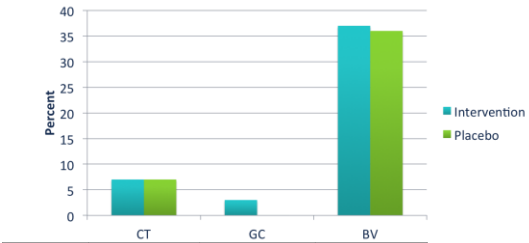
No differences in baseline characteristics by site

Median follow-up time did not differ by arm

PPT: 11.2 months (IQR 11.1-11.6)

Placebo: 11.4 months (IQR: 11.2-11.7)

STIs & BV at enrollment



	CT	GC	BV
Intervention	8 (7%)	3 (3%)	41 (37%)
Placebo	8 (7%)	0 (0%)	40 (36%)

BV = asymptomatic BV by Nugent score (7-10)

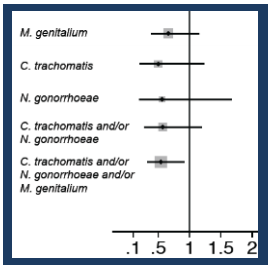
Intervention effect on bacterial STI acquisition

	N	# of events	Person-years	Incidence[1] (95% CI)		IRR[2]	(95% CI)	p-value
Combined STI outcome								
CT and/or GC	203	30	174.3	17.2	(12.0, 24.6)			
Intervention	101	11	88.1	12.5	(6.9, 22.5)	0.57	(0.27, 1.19)	0.13
Placebo	102	19	86.1	22.1	(14.1, 34.6)	1.00	--	--
STIs as separate outcomes								
CT	205	21	179.6	11.7	(7.6, 17.9)			
Intervention	103	7	90.0	7.8	(3.7, 16.3)	0.50	(0.20, 1.23)	0.13
Placebo	102	14	89.6	15.6	(9.3, 26.4)	1.00	--	--
GC	218	14	193.3	7.2	(4.3, 12.2)			
Intervention	108	5	96.3	5.2	(2.2, 12.5)	0.56	(0.19, 1.67)	0.30
Placebo	110	9	96.9	9.3	(4.8, 17.8)	1.00	--	--

[1]Incidence per 100 person-years. Only includes first infection detected.
[2]IRR=incidence rate ratios from Poisson regression models.

Similar effect of PPT on other bacterial pathogens

- Prior analysis assessing the effect of the intervention on detection of *Mycoplasma genitalium* (MG) showed a similar effect[1]
- Combined outcome of CT, GC or MG also showed similar effect and was statistically significant
- BV or BV-associated bacteria could enhance STI acquisition
  - Immunologic response
  - Enzyme and metabolite production



[1]Balkus et al. IDSOG, 2014

Strengths & limitations

Strengths

- Randomized trial data
  - Excellent adherence and retention
  - Novel intervention
- Data from US and African women
- STI testing using highly sensitive assays
- Study population
  - Women with a recent vaginal infection

Limitations

- Limited statistical power

Conclusions

- Monthly PPT may reduce women's risk of bacterial STIs
- Similar effect sizes across STIs, but small sample size precluded detection of significant associations
- Trials designed to assess effect of BV prevention on STIs are necessary to definitively determine if BV increases STI susceptibility
- BV ➔STI could shift asymptomatic BV treatment paradigm

PVI study team

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