# The impact of periodic presumptive treatment for vaginal infections on the microbiome among women participating in the Preventing Vaginal Infections trial

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## Background

- Bacterial vaginosis (BV) is the most common vaginal infection globally, affecting hundreds of millions of women each year
- BV frequently recurs following successful treatment and is associated with HIV-1 and STI acquisition, and adverse reproductive health outcomes
- Innovative treatment and prevention approaches are needed to reduce the burden of disease caused by BV and its associated complications
- In the Preventing Vaginal Infections trial (#NCT01230814), a randomized controlled trial of monthly periodic presumptive treatment (PPT) with intravaginal metronidazole 750mg + miconazole 200mg, reduced BV by 35% compared to placebo (RR=0.65;95% CI 0.48-0.87) *[McClelland et al. JID, 2015]*

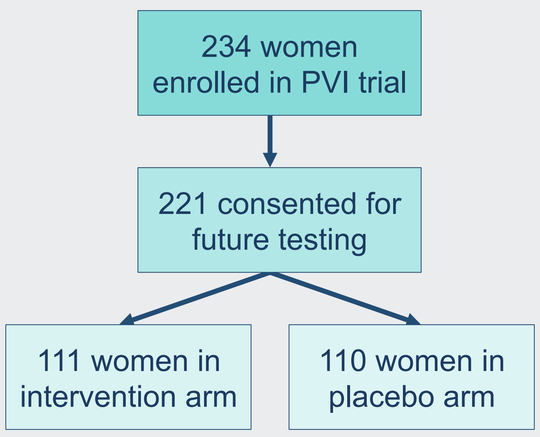
***Objective: Assess the effect of the intervention on detection of select bacterial species in the vaginal microbiome***

## Methods

- HIV-negative, non-pregnant women were enrolled from 4 sites:
  - Nairobi, Kenya (two sites)
  - Mombasa, Kenya
  - Birmingham, USA
- Eligible participants had a vaginal infection at screening:
  - Bacterial vaginosis
  - Vulvovaginal candidiasis
  - *Trichomonas vaginalis*
- Participants were enrolled between 2011-2012 and randomized to PPT or matching placebo for 5 consecutive nights each month for 12 months
- Vaginal fluid specimens were collected every other month using Dacron swabs and tested using species-specific quantitative PCR (qPCR) assays that target the 16S rRNA gene
- Relative risks [RR] were generated using generalized estimating equations with a log link and exchangeable correlation structure to separately assess the effect of the intervention on species detection

## Results

**Figure 1. Study population for analysis**




Specimens were tested for the following bacterial species by qPCR:

BV-associated species
- BVAB1
- BVAB2
- BVAB3 (*Mageebacillus indolicus*)
- *Atopobium vaginae*
- *Leptotrichia/Sneathia*
- *Megasphaera species*
- *Gardnerella vaginalis*

*Lactobacillus species*
- *L. crispatus*
- *L. jensenii*
- *L. iners*

**Table 1.** Participant characteristics at enrollment by study arm

| | Placebo n=110 | Intervention 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 in the past week | 2 (1-4) | 2 (1-3) |
| # of partners in the past week | 1 (1-2) | 1 (1-2) |
| New partner in the past week | 23 (21) | 22 (20) |
| Ever had anal sex | 13 (12) | 12 (11) |

Data presented as N(%) or median (IQR)

**Figure 2a.** BV–associated species prevalence by visit – Placebo arm

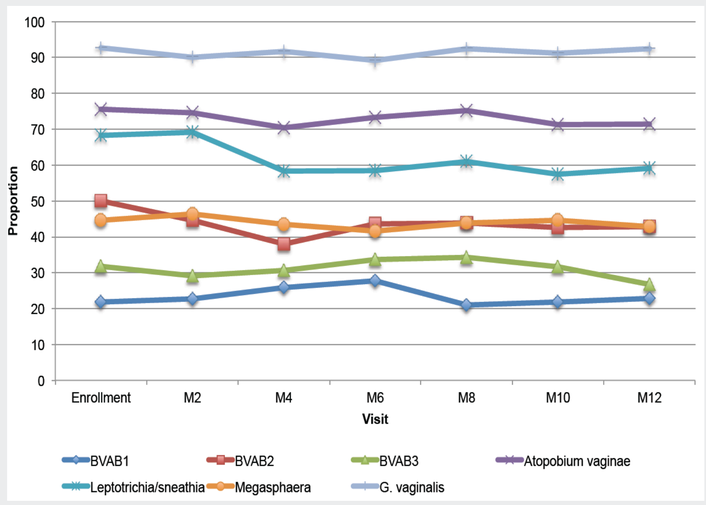



**Figure 2b.** BV–associated species prevalence by visit – Intervention arm

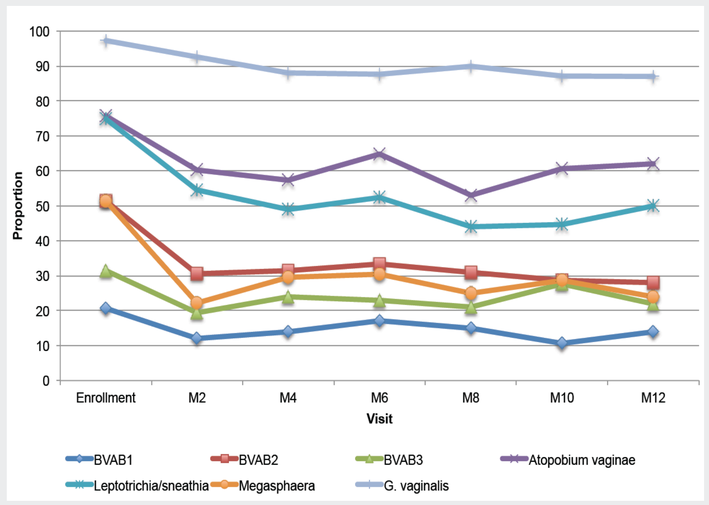



**Figure 3a.** *Lactobacillus* species prevalence by visit – Placebo arm

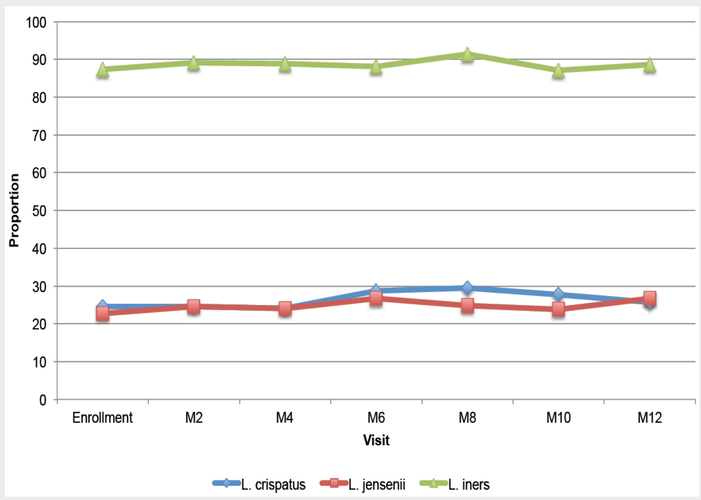



**Figure 3b.** *Lactobacillus* species prevalence by visit – Intervention arm

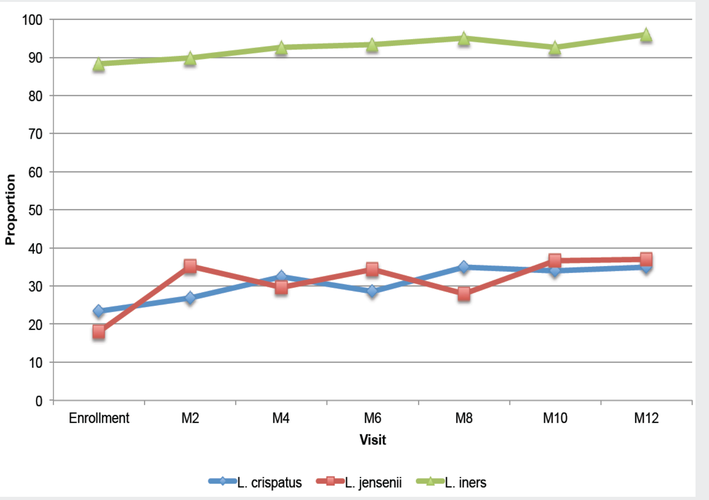



**Table 2**. Prevalence and relative risk of bacterial species during follow-up by study arm

| Bacteria | Placebo[1] N=630 | Intervention[1] N=616 | RR[2] | (95% CI) | p-value | aRR[3] | (95% CI) | p-value |
|---|---|---|---|---|---|---|---|---|
| *L. crispatus* | 168 (27) | 196 (32) | 1.21 | (0.91, 1.59) | 0.19 | 1.20 | (0.92, 1.57) | 0.19 |
| *L. jensenii* | 158 (25) | 196 (32) | 1.32 | (0.97, 1.79) | 0.07 | 1.32 | (0.97, 1.77) | 0.07 |
| *L. iners* | 650 (89) | 574 (93) | 1.05 | (0.99, 1.12) | 0.13 | -- | -- | -- |
| **BVAB1** | **149 (24)** | **85 (14)** | **0.60** | **(0.39, 0.93)** | **0.02** | **0.63** | **(0.46, 0.88)** | **0.006** |
| **BVAB2** | **268 (43)** | **189 (31)** | **0.72** | **(0.55, 0.95)** | **0.02** | **0.76** | **(0.58, 0.98)** | **0.03** |
| BVAB3 | 195 (31) | 141 (23) | 0.75 | (0.54, 1.03) | 0.08 | 0.78 | (0.58, 1.06) | 0.11 |
| ***Atopobium vaginae*** | **458 (73)** | **368 (60)** | **0.82** | **(0.71, 0.94)** | **0.005** | **0.84** | **(0.74, 0.96)** | **0.03** |
| ***Leptotrichia/Sneathia*** | **382 (61)** | **304 (49)** | **0.81** | **(0.68, 0.97)** | **0.02** | **0.82** | **(0.69, 0.98)** | **0.03** |
| ***Megasphaera*** | **276 (44)** | **165 (27)** | **0.61** | **(0.46, 0.82)** | **0.001** | **0.66** | **(0.50, 0.86)** | **0.003** |
| *G. vaginalis* | 574 (91) | 547 (89) | 0.97 | (0.92, 1.04) | 0.41 | 0.96 | (0.92, 1.01) | 0.16 |

[1]Data presented are N (%). [2]Relative risk (RR) from generalized estimating equations with a log link and exchangeable correlation structure and clustered by participant. [3]aRR with adjustment for study site. Convergence not achieved for *L. iners* model with adjustment for site.

## Conclusions

- Use of monthly PPT for one year significantly reduced colonization with several bacterial species strongly associated with BV, including BVAB1, BVAB2, *A. vaginae*, *Leptotrichia/sneathia* and *Megasphaera*
- *L. crispatus* and *L. jensenii* colonization was higher in the intervention arm compared to placebo, but the difference was not statistically significant
- *Gardnerella vaginalis* and *L. iners* were frequently detected in both study arms
- The role of PPT to improve vaginal health should be considered

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