

# Feasibility of Estrogen Ring and/or Probiotics for Improving Vaginal Health in African/Caribbean/Black Women: Results from a Prospective, Randomized, Open-label, Phase I Trial (CTN 308)

Jenna Ratcliffe\*<sup>1</sup>, Junic Wokuri\*<sup>2</sup>, Christina L. Hayes<sup>1</sup>, Gregor Reid<sup>3</sup>, Rupert Kaul<sup>4,5</sup>, Jesleen Rana<sup>2</sup>, Muna Alkhaifi<sup>2</sup>, Wangari Tharao<sup>2</sup>, Fiona Smaill<sup>6</sup>, & Charu Kaushic<sup>1</sup>

<sup>1</sup>McMaster Immunology Research Centre and Department of Medicine, McMaster University, Hamilton, ON, Canada.

<sup>2</sup>Women's Health in Women's Hands Community Health Centre, Toronto, ON, Canada.

<sup>3</sup>Departments of Microbiology & Immunology and Surgery, Western University, and Canadian Research and Development Centre for Human Microbiome and Probiotics, The Lawson Health Research Institute, London, ON, Canada.

<sup>4</sup>Departments of Immunology and Medicine, University of Toronto, Toronto, ON, Canada.

<sup>5</sup>Department of Medicine, University Health Network, Toronto, ON, Canada.

<sup>6</sup>Department of Pathology and Molecular Medicine and Michael G. DeGroote Institute for Infectious Disease Research, McMaster University, Hamilton, ON, Canada.

\*Co-first authors contributed equally to this work.

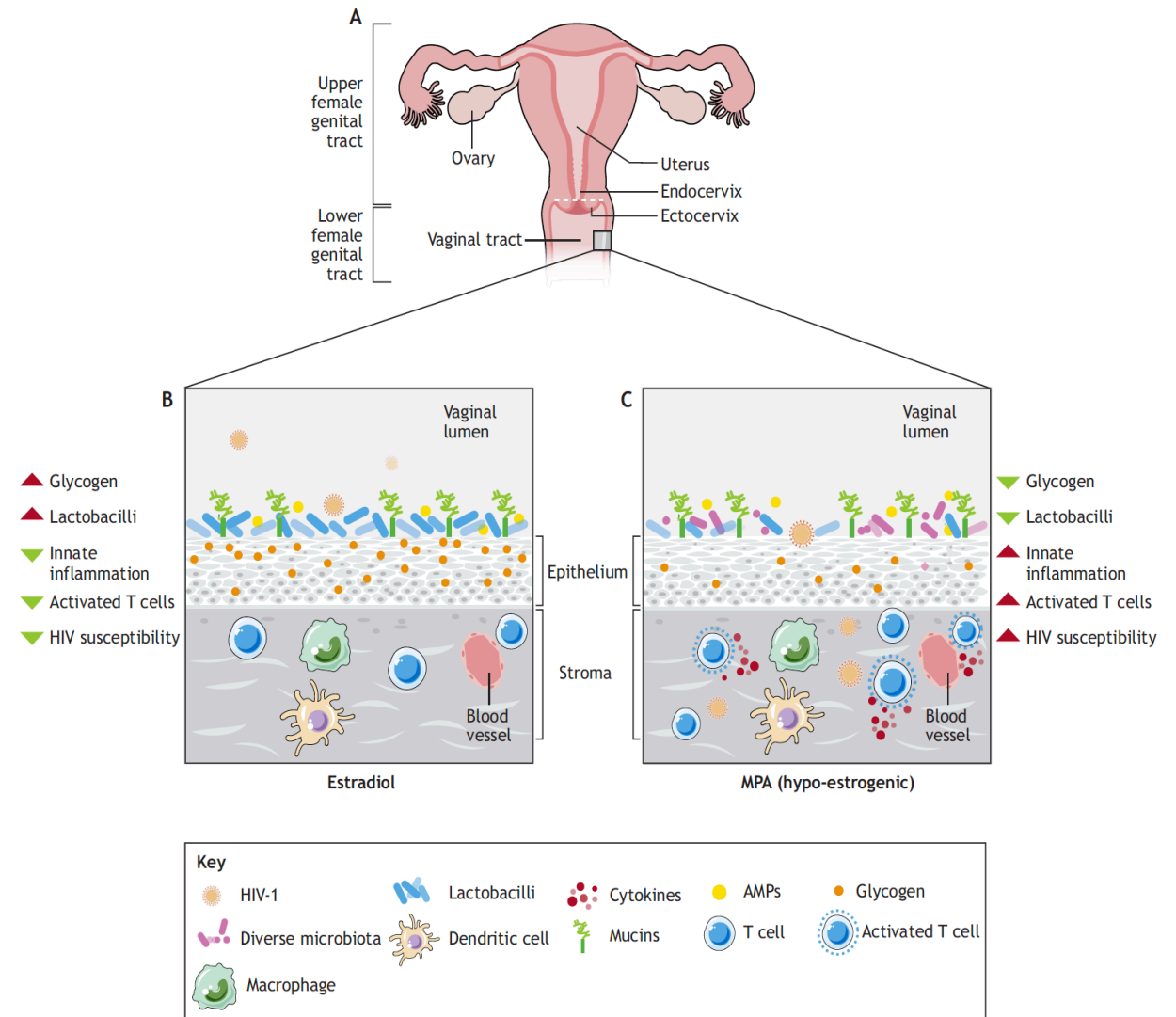


Women's Health  
in Women's Hands



## Female sex hormones & the vaginal microbiota impact the immune milieu and barrier function of the lower female genital tract, which affects susceptibility to BV and HIV infection.<sup>1</sup>

Bacterial vaginosis (BV) is a common clinical condition characterized by a *Lactobacillus* diminished polymicrobial vaginal microbiota, inflammation of the lower female reproductive tract, and elevated risk of HIV infection. Multiple studies have shown that African/Caribbean/Black (ACB) women have a higher prevalence of polymicrobial microbiota compared to Caucasian and Asian women. With the aim of reducing BV and susceptibility to HIV infection, we propose to enhance vaginal *Lactobacillus* colonization in ACB women using a combination of low dose intravaginal estrogen and probiotic administration. To determine if administration of probiotics and estrogen is an acceptable intervention to improve vaginal health, a prospective, randomized, open-label, intervention phase I trial (CTN 308) was conducted.




### Reference

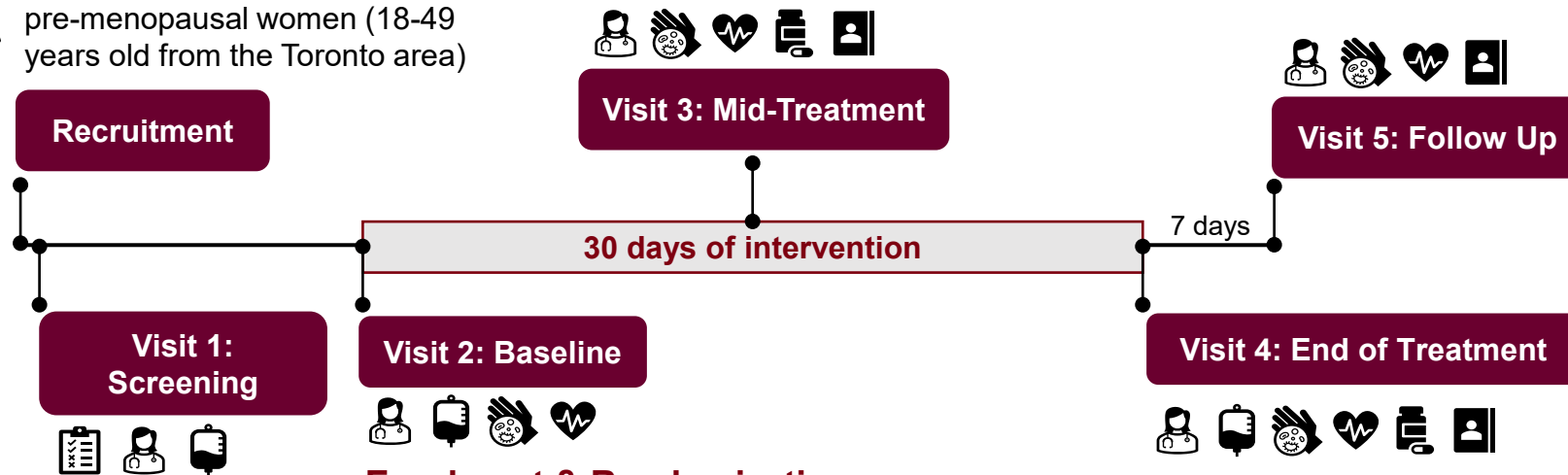
<sup>1</sup>Wessels, J. M., Felker, A. M., Dupont, H. A., & Kaushic, C. (2018). The relationship between sex hormones, the vaginal microbiome and immunity in HIV-1 susceptibility in women. *Dis Model Mech*, 11(9). <https://doi.org/10.1242/dmm.035147>

# CTN 308: a Prospective, Randomized, Open-Label, Intervention Phase I Trial

**Interventions:** **Estring<sup>®</sup>**: intravaginal low dose estradiol ring (7.5µg/day)  
**RepHresh<sup>™</sup> Pro-B<sup>™</sup>**: 1x10<sup>7</sup> cfu of *Lactobacillus rhamnosus* GR-1 & 1x10<sup>7</sup> cfu *Lactobacillus reuteri* RC-14 probiotics per capsule

## Study Design:








 African/Caribbean/Black (ACB) pre-menopausal women (18-49 years old from the Toronto area)



### Enrolment & Randomization

#### Intervention Groups:

- Estring<sup>®</sup> (n=9)
- Estring<sup>®</sup> & oral RepHresh<sup>™</sup> Pro-B<sup>™</sup> capsules 2X/day (n=9)
- Estring<sup>®</sup> & vaginal RepHresh<sup>™</sup> Pro-B<sup>™</sup> capsules 2X/day (n=10)
- Vaginal RepHresh<sup>™</sup> Pro-B<sup>™</sup> capsules 2X/day (n=13)

-  Screening
-  Physical exam
-  Blood sample
-  Vaginal sample
-  Assess adverse events
-  Assess compliance
-  Diary review

## Intervention Feasibility Assessments:

- Enrolment rate
- Retention rate
- Intervention protocol (IP) adherence rates
- Diary completion rate
- BV prevalence at baseline (microscopic evaluation of vaginal fluid)

**Enrolment and retention rates met study targets of 80%.**

**Table 1. Summary of CTN 308 participation.**

<b>Study Participation</b>	
Recruited participants	63
Enrolled participants	51
Enrolment Rate	81%
Completed/Retained participants	41
Retention Rate	80%
Terminated participants	10
Termination rate	20%
Lost to follow up	1 (2%)
Withdrew consent	6 (12%)
IP non-adherence	3 (6%)

Data shown as number of participants (% of total participants) or rate as a percentage.

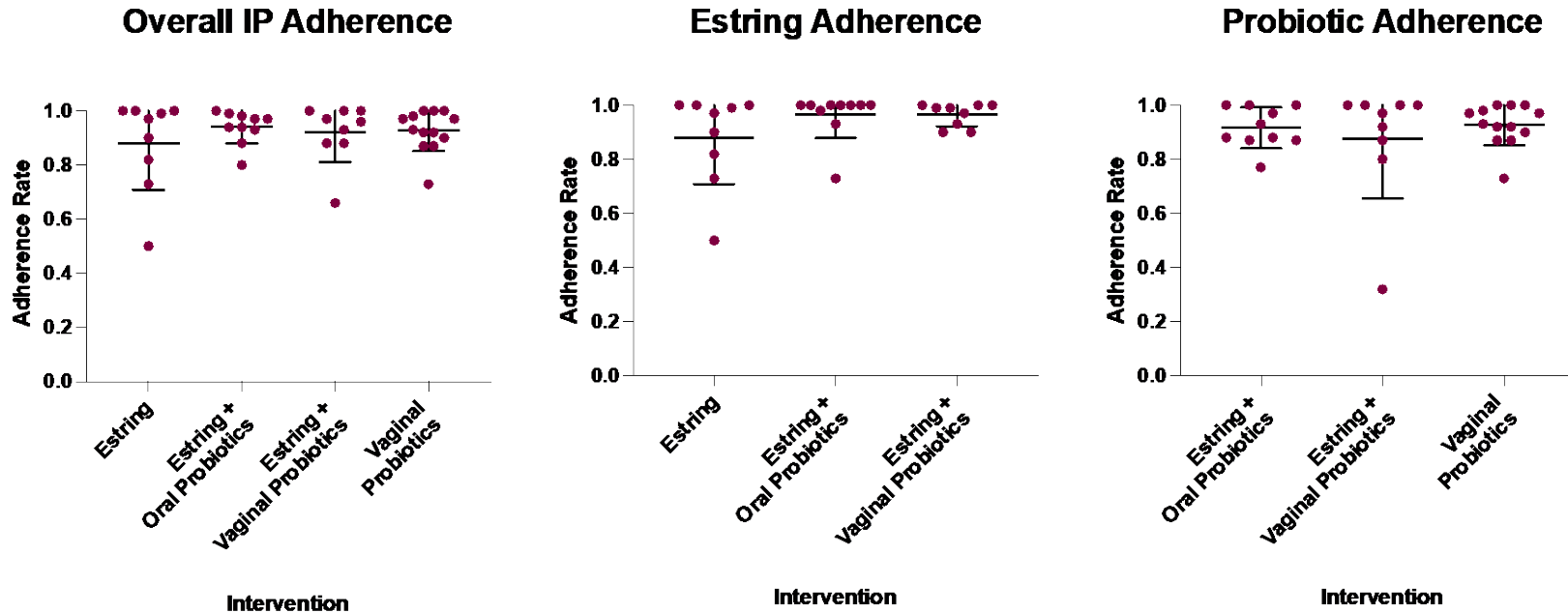
**1 in 5 participants had BV at study baseline, which was similar to the proportion of participants that reported 1 or more previous incidences of BV.**

**Table 2. BV status at study baseline and BV history.**

<b>BV Status</b>	<b>Enrolled Participants</b>	<b>Completed Study Participants</b>
BV+ status at baseline visit	10 (20%)	9 (22%)
Undetermined	1 (2%)	1 (2%)
<b>Reported BV History</b>		
>1 previous BV occurrences	6 (12%)	5 (12%)
1 BV previous occurrence	6 (12%)	5 (12%)
0 BV previous occurrences	39 (76%)	31 (76%)

Data shown as number of participants (% of total participants).

Participants that completed the study were highly adherent regardless of intervention(s) and probiotic route of administration.



**Figure 1. CTN 308 IP adherence rates.** The overall adherence rate (Estring and probiotics combined) was calculated, as well as Estring and probiotic use adherence rates individually. Each data point represents a participant; black lines depict the mean  $\pm$  standard deviation. No significant differences between intervention groups or probiotic administration routes were observed by ANOVA with Tukey's post-hoc test ( $p \geq 0.19$ ).

## Summary

- 81% of screened participants enrolled in the study
- 80% of enrolled participants completed the study
- Approximately 1 in 5 enrolled participants had BV
- Adherence to the interventions was high among all groups, with few participants terminating due to non-compliance

## Conclusion

**Enrolment, retention and adherence rates indicate that low dose intravaginal estrogen and/or twice daily probiotics are acceptable interventions.**