Feasibility and safety 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).

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Introduction

Women are at twice the risk of HIV-1 infection compared to men, due in part to a number of biological factors:

- A reduced abundance of *Lactobacillus* and increased diversity of the vaginal microbiota (dysbiosis) is associated with increased risk of infection
  - Dysbiosis is more prevalent in African/Caribbean/Black (ACB) women compared to women of other ethnicities, which has been associated with higher risk of HIV-1 infection
- Female sex hormones can alter the immune milieu of the vaginal mucosa, which impacts local inflammation, integrity of the vaginal barrier, and consequently the susceptibility to HIV-1 infection
  - Estrogens can reduce vaginal inflammation as well as promote *Lactobacillus* colonization, which can result in enhanced protection towards infection

Therefore, innovation of therapeutic and prevention strategies that target both sex hormone and vaginal microbiota factors may be able to enhance vaginal health and reduce risk of HIV infection.

Study Objective

A prospective, randomized, open-label, phase I clinical trial (CTN 308; clinicaltrials.gov NCT03837015) was conducted to assess the **safety, tolerability, and feasibility of administering low dose, intravaginal estradiol alone or in combination with a *Lactobacillus*-based probiotic to premenopausal ACB women in order to promote vaginal health and resilience towards HIV infection.**

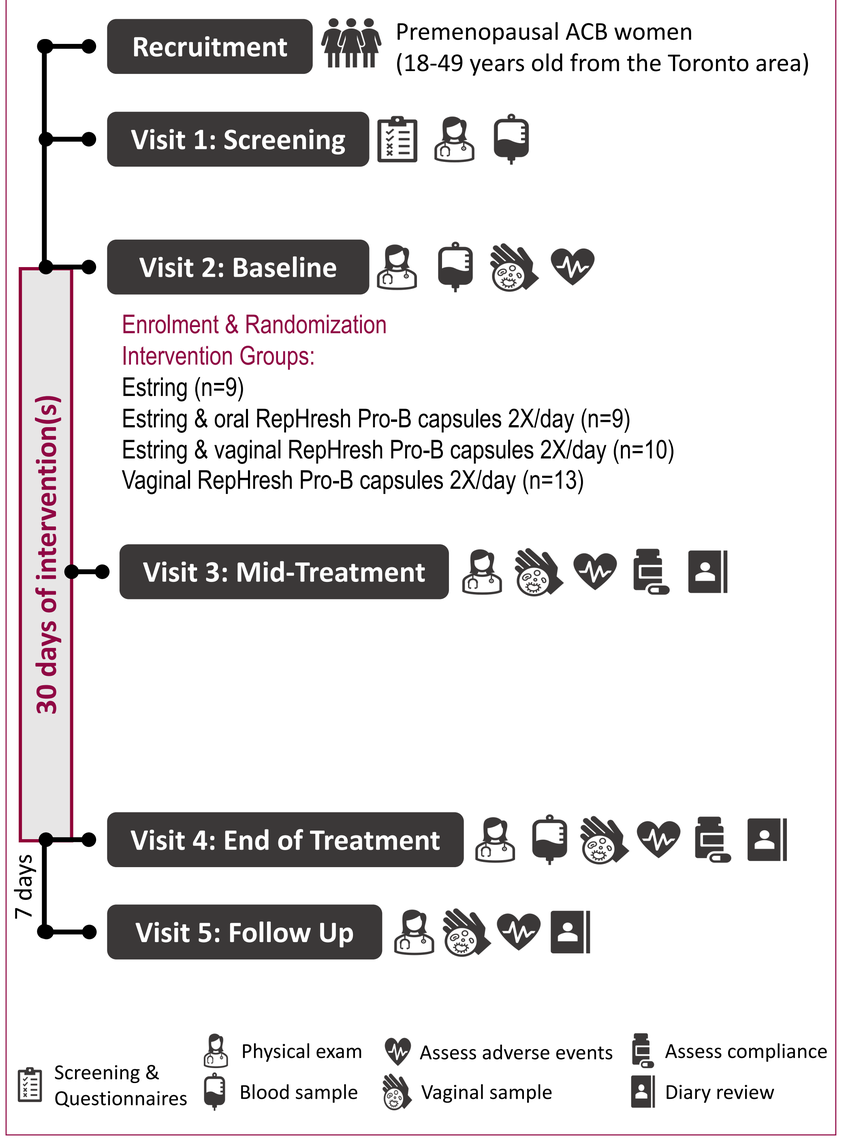
Study Design

Interventions

Estring: intravaginal, low dose (7.5µm/day) estradiol ring

RepHresh ProB: *L. rhamnosus* GR-1 (1x10^7 CFU) & *L. reuteri* RC-14 (1x10^7 CFU) capsules

Study Protocol



Results

STUDY PARTICIPATION

Enrolment & retention rates met study targets of 80%.

Table 1. Summary of CTN 308 participation.

Study Participation	
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. IP = intervention protocol.

ADHERENCE

Most participants that completed the study were highly adherent to the intervention protocol (IP), regardless of intervention(s) and probiotic administration route.

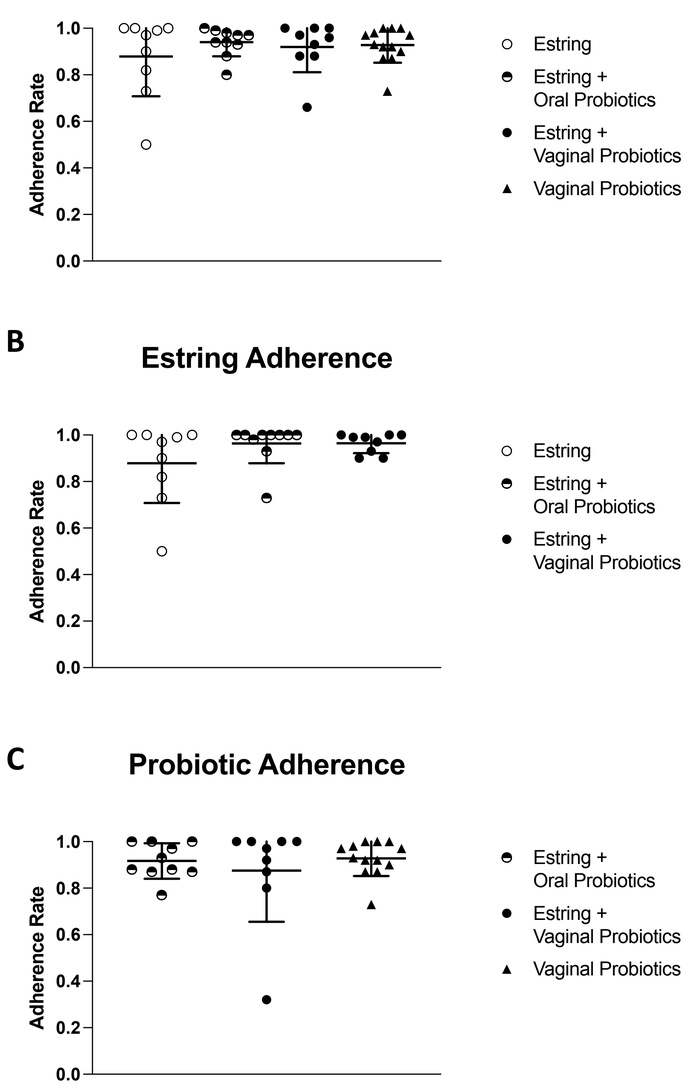


Figure 1. IP adherence rates of participants that completed the study. The adherence rates (A) overall (Estring and Probiotic rates combined), as well as (B) Estring and (C) Probiotic individually were calculated. Each data point represents a participant; black lines depict the mean ± standard deviation. No significant differences between intervention groups or probiotic administration routes were observed (p≥0.19 by ANOVA with Tukey's post-hoc test).

ADVERSE EVENTS (AEs)

The majority of AEs were mild in intensity, a single occurrence, and resolved by study completion.

No serious AEs were reported.

Table 2. Intensity, duration, and frequency of AEs.

# AEs Reported	92		
Participants that Reported an AE	29	(57%)	
AE Intensity			**AEs of Note**
Mild	66	(72%)	20 (22%) Vaginal itching/irritation/burning; 15 (16%) cramps/abdominal pain; 10 (11%) vaginal discharge
Moderate	18	(20%)	
Severe	7	(7%)	3 (6%) participants; 2 (*13%*) cramps/abdominal pain; 2 (*18%*) headache; 2 (*100%*) light headedness
Other	1	(1%)	Pregnancy
AE Duration			
Ongoing at End of Study	6	(7%)	Vaginal itching/irritation/burning, headache, breast tenderness, insomnia, acne
Resolved	86	(93%)	All severe intensity AEs
AE Frequency			
Participants Reported AE 2X	12	(24%)	Vaginal itching/irritation/burning, cramps/abdominal pain, vaginal discharge, headache, vaginal dryness, vaginal odour
Participants Reported AE 3X	4	(8%)	Cramps/abdominal pain, vaginal odour, spotting

Data shown as n (% total AEs or % of enrolled participants or *% of the specific AE*).

No indications of inflammation or infection were observed during any of the pelvic exams.

BLOOD MARKERS

No clinically significant change in blood markers were observed following 30 days of intervention(s).

Quantities of the following blood markers were within a normal range and were not significantly changed between Screening (Visit 1) and End of Treatment (Visit 4):

- Alkaline phosphatase
- Alanine aminotransferase
- Bilirubin
- Cholesterol
- Triglycerides
- Potassium
- Sodium
- Calcium
- Creatine
- Hemoglobin
- Platelets
- White blood cells

Although glucose was found to be *statistically* significantly changed (p=0.01), participants were all within a normal range, and thus, any changes were considered not *clinically* significant (Figure 2).

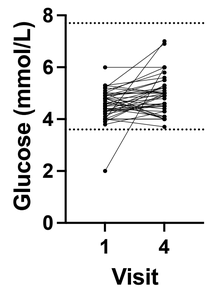


Figure 2. Blood glucose at screening (visit 1) and end of treatment (visit 4). Each set of connected data points represent a participant; dotted lines depict the upper and lower limits of a normal range.

Summary

- High enrolment, retention and adherence rates suggest the interventions are tolerable and practicable
- No serious AEs were reported
- 43% of participants did not experience any AEs
- Most AEs were mild, short-lived, and non-recurring
- AEs of severe intensity were experienced by 6% of participants, all of which resolved by study completion
- Vaginal irritation/itching/burning and cramps/abdominal pain were the most reported AEs
- Blood panels did not reveal any clinically significant changes in blood markers

Conclusion

Administration of low dose intravaginal estrogen and/or twice daily *Lactobacillus* probiotics are safe, acceptable interventions for premenopausal ACB women.

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CIHR IRSC

Women's Health in Women's Hands

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