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Factors associated with treatment failure following male-partner treatment for BV

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We acknowledge the **Boonwurrung** and the **Wurrundjeri clans** of the **Kulin Nation** who are the custodians of the land and waters, and pay our respects to Elders past and present.

WUNUNGU AWARA
MONASH INDIGENOUS STUDIES CENTRE

WANGAILATHA WANGU NGA KIYAWATHA FROM THE TATI TATI, MUTTI MUTTI,
WADI WADI AND LATJI LATJI NATIONS, ROBINVALE, NORTHERN VICTORIA.

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GEDI COMMITTEE

Disclosure & Disclaimer

Funding

National Health and Medical Research Council of Australia

Terminology used

When I refer to women and men in this presentation, I am including people with a vagina or penis, respectively. However, I acknowledge that people may use other terms to describe their gender.

People in our trials are asked to nominate their gender, which is reflected in the results.

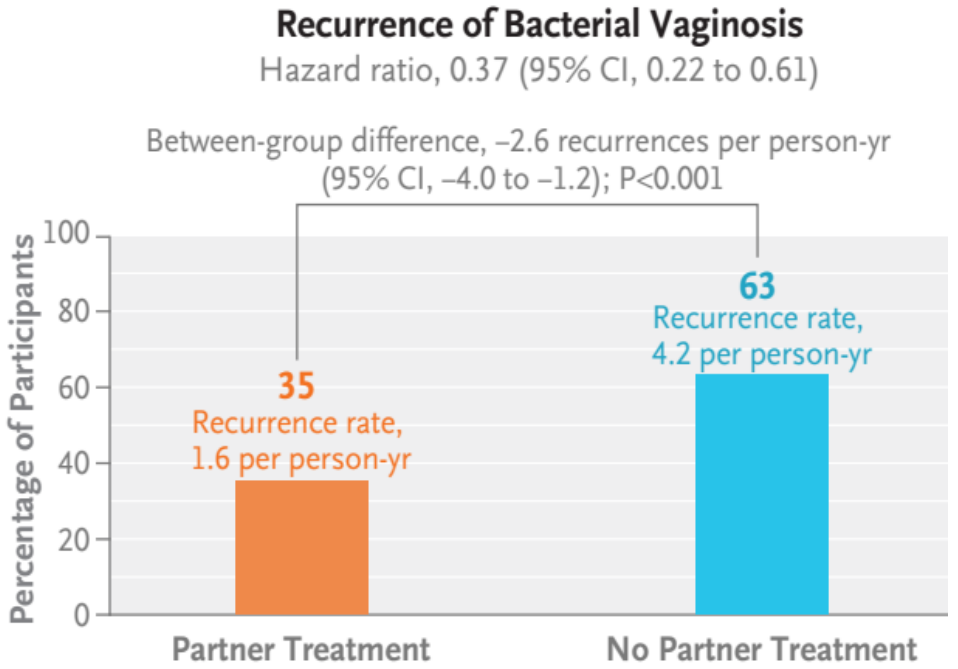
Bacterial vaginosis

- BV is the most common vaginal dysbiosis affecting reproductive aged women globally and is associated with substantial obstetric & gynaecologic sequelae and negative impacts on quality of life and relationships[1,2,3]
- Treatment is with broad-spectrum antibiotics
- Over 50% experience BV recurrence within 6 months after first-line antibiotics, which rises to 60-80% among women with an ongoing regular sexual partner[4]
- We hypothesised that reinfection was responsible for significant proportion of repeat BV positivity after treatment[5]
- Conducted a RCT of concurrent male and female partner treatment[6]

Our RCT showed that partner treatment had a dramatic effect in reducing the number of women with repeat BV positivity

Sexual transmission is a significant driver of BV recurrence

- There was a smaller group of women who had a repeat BV diagnosis in the intervention group, with 35% recurring within 12 weeks

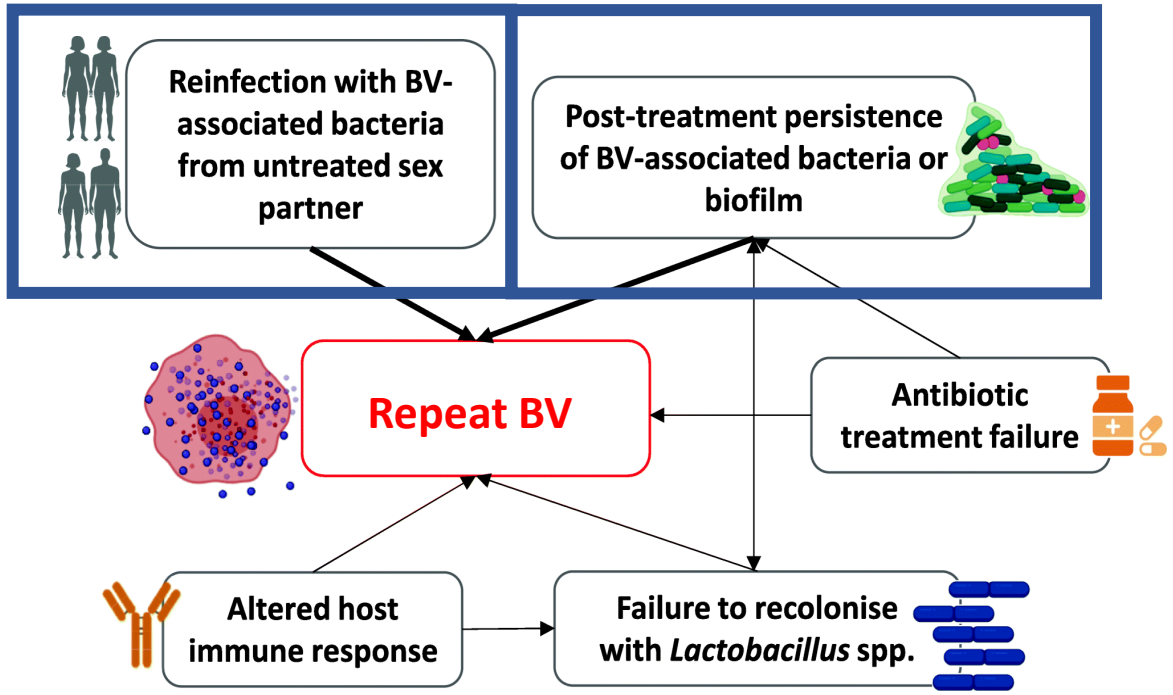


[1]Peebles STD 2019, Cohen PlosMed 2012, Koumans Int J Gynaecol Obstet. 1999, Brotman JID 2010; [2]Bilardi PLoS one 2013; [3]Koumans CID 2002, Oduyebo Cochrane 2009; [4]Bradshaw JID 2006, Sobel JID 1993; [5]Vodstrcil BMC Med 2021; [6]Vodstrcil NEJM 2025

Bacterial vaginosis

Mechanisms driving repeat BV are complex and multifactorial

- Knew that reinfection would not be the only driver of having a repeat BV diagnosis following treatment
- Hypothesised that there were two main pathways responsible for repeat BV infections after treatment



Vodstrcil *et al* BMC Medicine 2021

Bacterial vaginosis – Treatment failure

What drove repeat BV after the intervention?

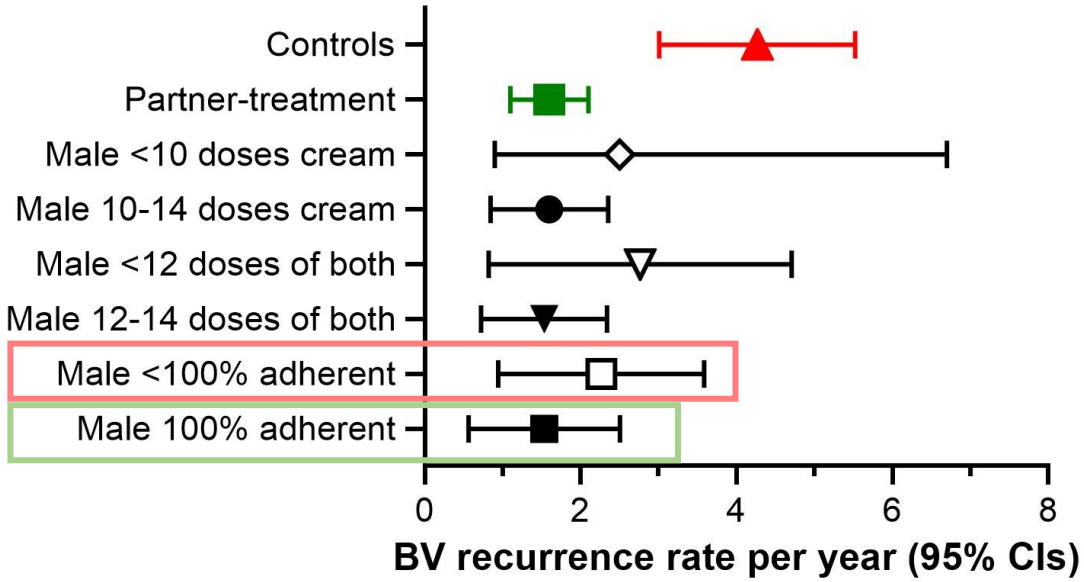
?Reinfection was not prevented in all women:

- Poor adherence in men was linked to treatment failure in women, with lowest rates of repeat BV among women whose male partner was 100% adherent to combination therapy
- Treatment may not eradicate male carriage of BV-associated bacteria, leading to reinfection
- Sex during treatment or new/additional partners may cause reinfection or infection with new BV-associated bacteria

For others, persistent infection may be driving treatment failure

Open symbols = less adherent

Closed symbols = more adherent



Vodstrcil et al *NEJM* 2025

Study objectives

Objectives:

Among a cohort of couples receiving concurrent female and male-partner treatment for BV, our objective was to determine factors associated with repeat BV at week 4

Study endpoint:

Repeat BV diagnosis within 4 weeks of concurrent partner treatment (defined as Amsel + Nugent)

Pooled analysis – Three cohorts

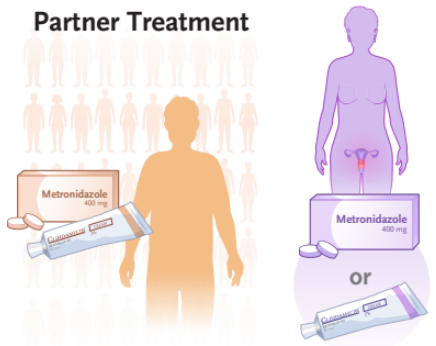
Pilots 1 & 2:

March 2018 – March 2019

single-site, single-arm, open-label

All couples received concurrent Rx

P1 – Follow up days 8, week 2, 3 & 4
P2 – Follow up day 8 & week 4, 8 & 12



N=49

Plummer et al PLoS One 2018
Plummer et al mBio 2021

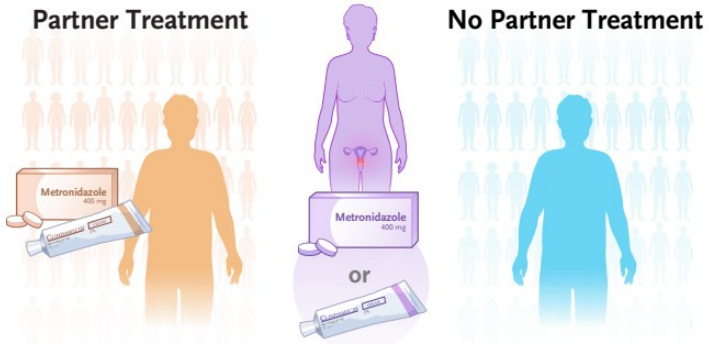
Step Up RCT – Intervention group:

April 2019 – November 2023

multi-centre, randomised, open-label, phase 3 trial

Couples randomised to concurrent treatment or standard-of-care

Follow up at day 8 & week 4, 8 & 12



N=69

Vodstrcil et al NEJM 2025

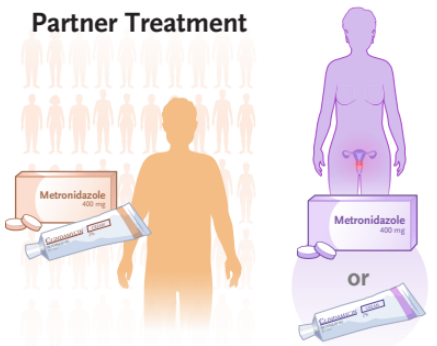
Open-label extension study:

December 2023 – May 2025

single-site, single-arm, open-label

All couples received concurrent Rx

Follow up at day 8 & week 4



N=70

Unpublished – Asha Doolabh honours student

Step Up pooled data - Methods

Participants and eligibility

Women ≥18 years of age were eligible for inclusion if they:

i. had symptomatic BV and met the diagnostic criteria of 3 to 4 Amsel criteria and a Nugent score = 4 to 10;

ii. had a regular male partner for the 8 weeks prior to enrolment & had no other partners at enrolment

Men were eligible if they:

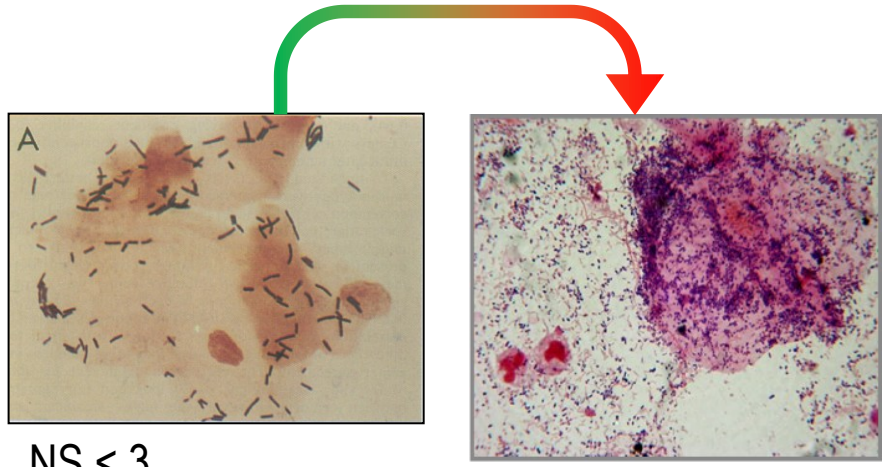
i. enrolled within a week of their partner;

ii. confirmed they had no other partners at enrolment;

iii. had no contraindications to either antibiotics used for the intervention

For the pooled analysis:

Women were eligible if they returned for a week 4 study visit, or returned a vaginal smear for Nugent scoring via the post



NS < 3

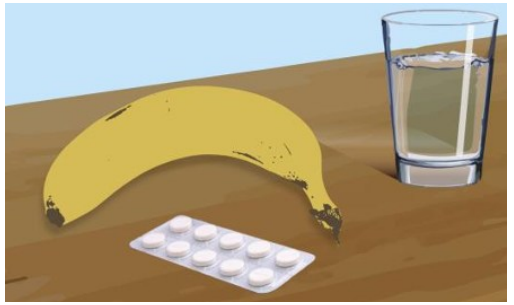
NS = 7-10

All participants provided written informed consent prior to baseline procedures. Alfred Health HREC 506/18

Step Up pooled data - Methods

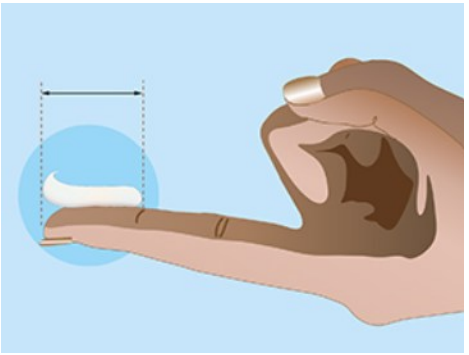
Treatment

- Female participants received first-line treatment
  - Oral metronidazole 400mg bid 7 days, minority given intravaginal clindamycin 7 nights
- Male partners: Combination therapy 7d twice a day
  - Oral metronidazole 400mg tablets & applied 2% clindamycin cream topically to the glans penis and upper shaft (under the foreskin if uncircumcised)



Measurements

- BV assessment at week 4 (clinic visit: Amsel & Nugent; home pack: Nugent)
- Adherence assessed at day 8
- Behavioural and sexual practices measured at each timepoint



Analyses

- Cumulative rates of repeat BV per person-year and Poisson 95% confidence intervals (CIs) stratified by study-group
- Cox regression to generate hazard ratios and 95% CIs for the time-to-event analyses of key risk factors

All analyses were conducted in Stata (version 19.0)

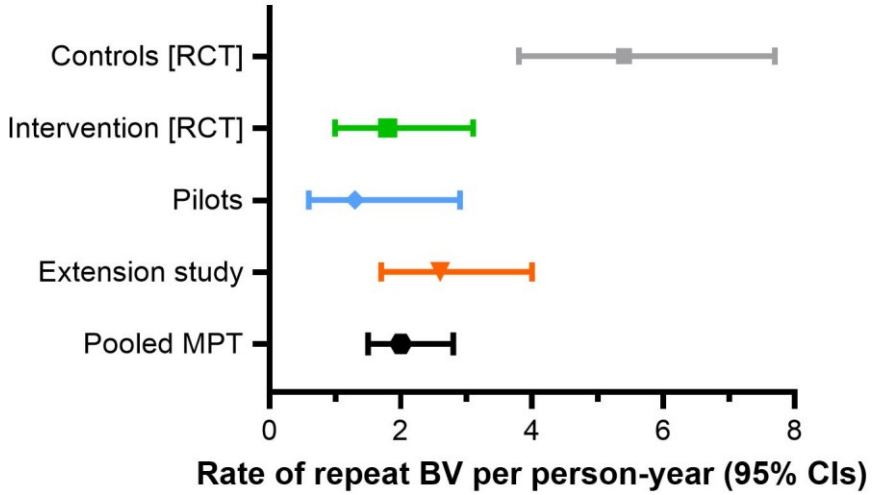
Results – Study population

	Pilots N=49 n (%)	RCT N=69 n (%)	Extension N=70 n (%)
Female av age ± stdev	29 ± 7	29 ± 6	27 ± 6
Male av age ± stdev	31 ± 8	30 ± 9	29 ± 6
Intrauterine device use			
not using an IUD	35 (71)	50 (72)	46 (66)
using an IUD (mainly LVN-IUD)	14 (29)	19 (28)	24 (34)
Male circumcision status			
uncircumcised	40 (82)	55 (80)	56 (80)
circumcised	9 (18)	14 (20)	14 (20)
Prior history of BV	39 (80)	60 (89)	55 (82)
median no. of prior BV diagnoses [IQR]	2 [1-4]	3 [1-5]	2 [1-4]
median duration relationship (months) [IQR]	9 [3-12]	15 [7-50]	10 [5-27]

Cohort of women with a high burden of risk factors for BV

Results – Rates of repeat BV by week 4

Study endpoint: BV/no BV by week 4	Controls (RCT) N=68	Pilots N=49	Intervention (RCT) N=69	Extension N=70	Pooled N=188
No. and % who had repeat BV	31, 45.6%	6, 12.2%	13, 18.8%	20, 28.6%	39, 20.7%
Rate of repeat BV post-treatment	5.4 per PY (95%CI: 3.8-7.7)	1.3 per PY (95% CI: 0.6-2.9)	2.1 per PY (95% CI: 1.2-3.5)	2.5 per PY (95% CI: 1.6-3.9)	2.1 per PY (95% CI: 1.5-2.8)



Extension study had a far higher LTFU, as people were aware of the findings, and used it to access partner-treatment.

It is likely that people without symptoms were less likely to return for follow up, biasing our estimate towards failure.

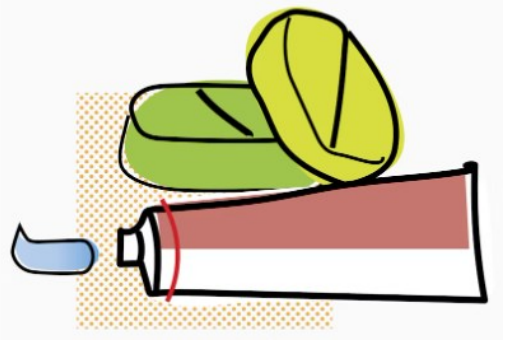
Adherence

Female adherence to treatment was high (monotherapy)

- Metronidazole n=164/174: 93% of women took all 14 doses; or
- Intravaginal clindamycin n=10/13: 77% of women used all 7 doses

Male adherence was mixed (combination therapy)

- Metronidazole n=141/166: 85% took all 14 metronidazole doses
- Topical clindamycin n=107/167: 64% applied all doses, 15 men took <10 doses



Results – Risk of repeat BV for key risk factors

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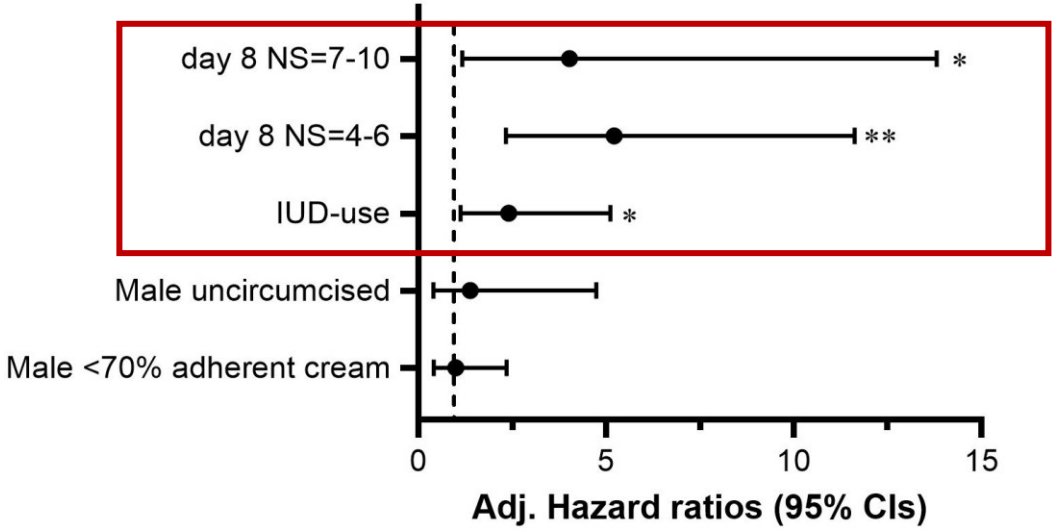
Univariate analyses (adjusted for study group)	n recurred/N (%)	**Rate of repeat BV per person-year** (95%CI)	**Hazard Ratio** (95%CI)	p-value
Age at recruitment (female)	*40/188 (21)*	*2.0 (1.5-2.8)*	1.06 (0.91-1.22)	0.476
Post-treatment (d8) Nugent score				
0-3	14/111 (13)	1.1 (0.6-1.8)	1.0	
4-6	20/53 (38)	4.2 (2.7-6.6)	4.52 (2.26-9.02)	**<0.001**
7-10	4/12 (33)	3.5 (1.3-9.4)	3.56 (1.13-11.22)	**0.030**
Intrauterine device use				
not using an IUD	23/131 (18)	1.7 (0.7-1.5)	1.0	
using an IUD	16/57 (28)	2.9 (1.8-4.7)	1.60 (0.84-3.04)	0.155
Circumcision status				
circumcised	6/37 (16)	1.7 (0.7-3.7)	1.0	
uncircumcised	33/151 (22)	2.1 (1.5-2.9)	1.49 (0.62-3.61)	0.372
Condomless penile-vaginal sex during Rx				
No	34/162 (21)	2.0 (1.4-2.8)	1.0	
Yes	5/22 (23)	2.5 (1.1-6.1)	1.34 (0.52-3.46)	0.832
Male adherence to clindamycin				
Took all clindamycin doses	26/122 (21)	1.9 (1.3-2.8)	1.0	
Took less than 70% of doses	9/45 (20)	2.2 (1.1-4.1)	1.10 (0.51-2.37)	0.808

Results – Drivers of repeat positivity

Factors associated with repeat positivity:

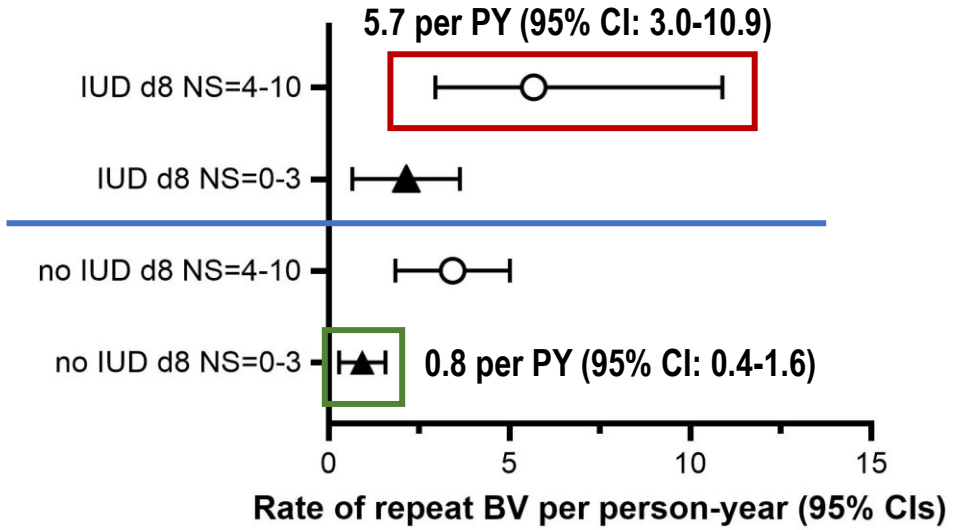
Multivariable Cox regression analysis



*p<0.05
**p<0.001
Model was adjusted for study group

An elevated Nugent score the day after treatment (day 8) (before resuming sex) was associated with a 4 to 5-fold increased risk of repeat BV positivity at week 4

IUD-use was associated with a 2-fold increased risk of repeat BV at week 4



Treatment failure is occurring in some women

Summary

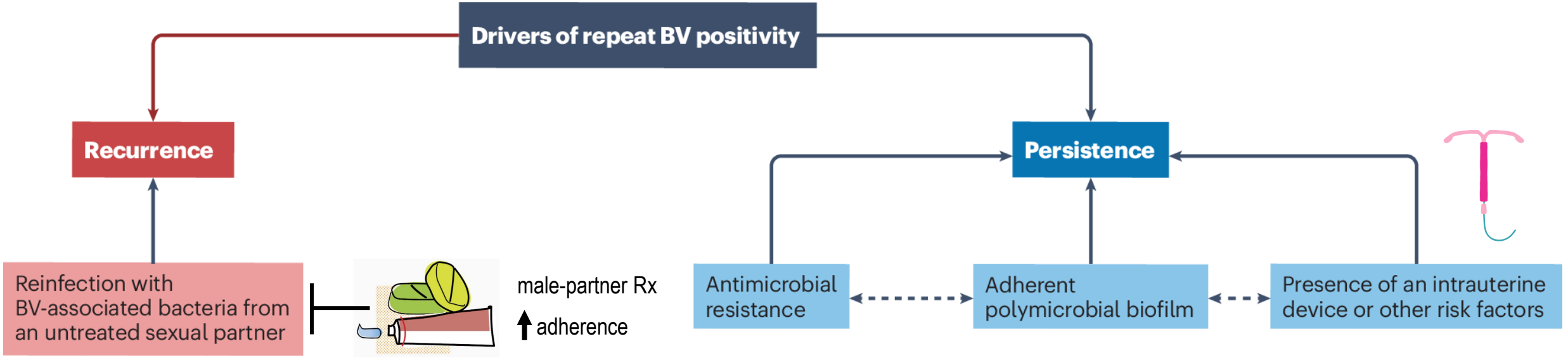
In this pooled study of male partner treatment, the overall rate of repeat BV was 2.1 per person-year (95% CI: 1.5-2.8)

Failure to achieve an optimal vaginal microbiome after partner-treatment was associated an elevated Nugent score immediately after treatment

- There is a sub-group of women who may not be responding to first-line therapy
  - Persistent BV-associated bacteria/biofilm
  - Failure to recolonise with optimal *Lactobacillus* spp.
  - Host genetics
- One key risk factor is IUD use – IUD users are over-represented in our cohorts compared to use in the general Australian population (4x higher use)
  - Mainly represented hormonal IUD users (i.e., Mirena, Kylena)
  - Copper IUD use is known to be associated with an increased risk of BV & BV recurrence[1]
  - IUD & IUD-strings may provide a nidus for BV-associated biofilm

[1]Achilles AJOG 2018, Peebles CID 2021

Drivers of repeat BV positivity



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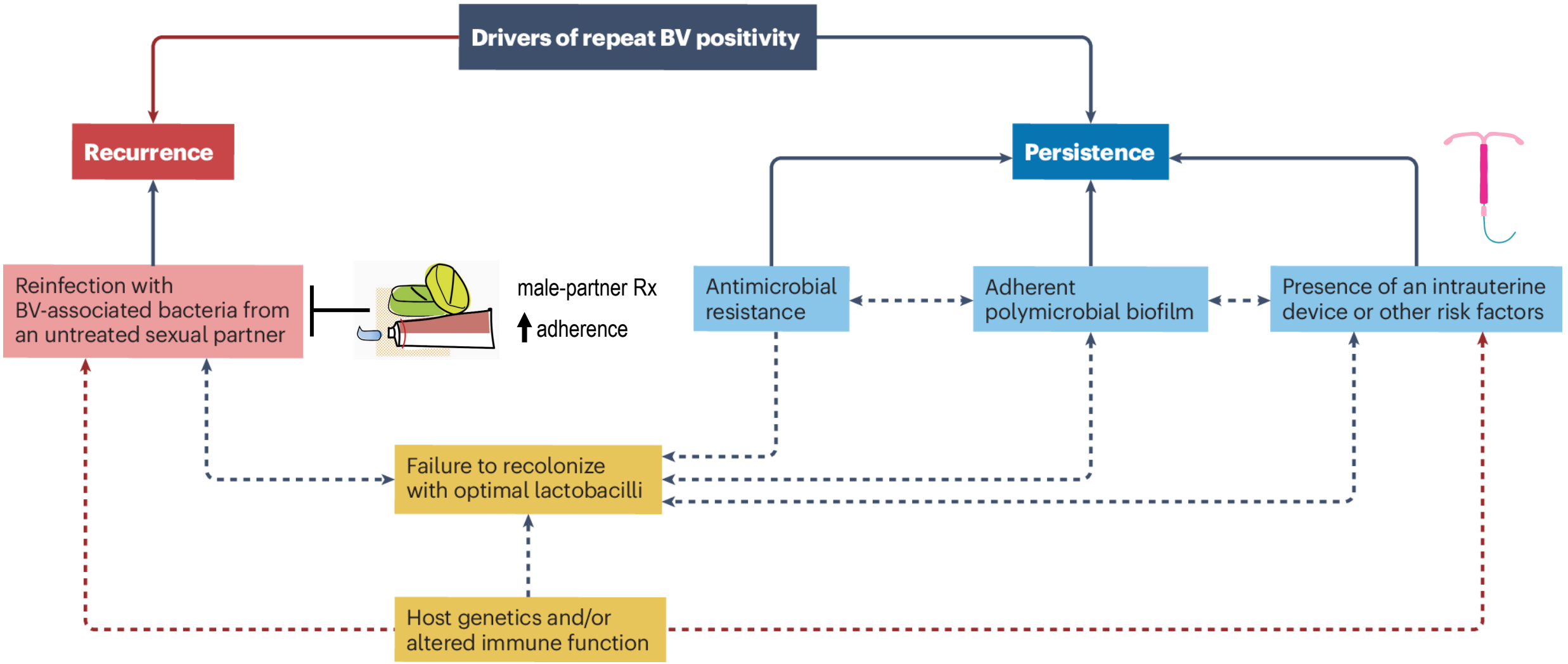
Drivers of repeat BV positivity



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Future directions

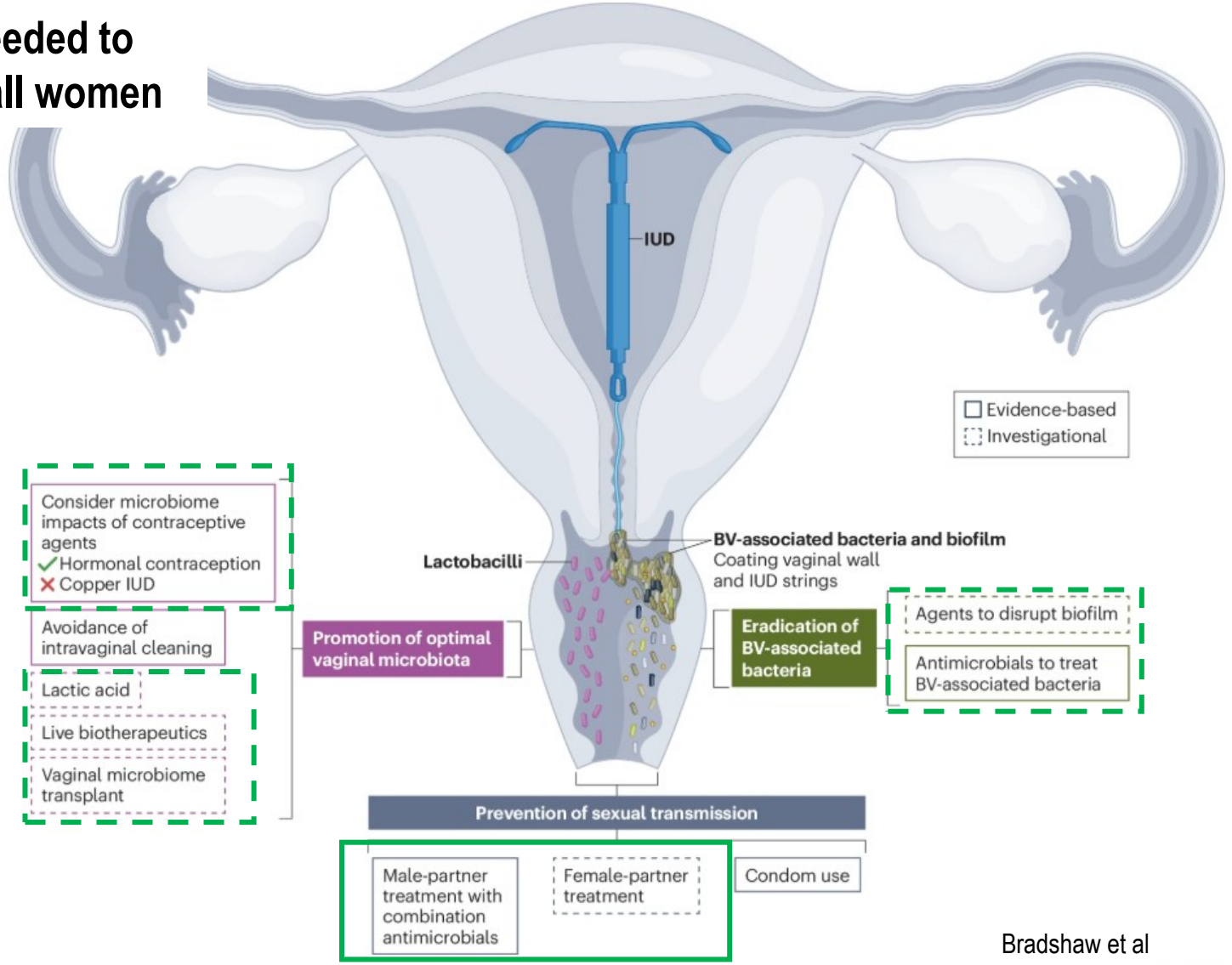
Multi-faceted approaches may be needed to eradicate BV-associated bacteria for all women

- Partner treatment
  - Optimise adherence
  - ?Some men may benefit from a longer duration of therapy
  - ?Female partners (PACT study)

- ?Some women may benefit from longer duration of therapy/combination therapy
- ?Agents to disrupt biofilm

- ?Removal of IUD and re-treatment

- ?Adjunctive therapies to promote an optimal vaginal microbiome



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Colette McGuiness
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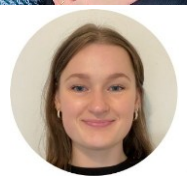

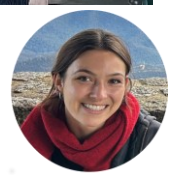

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