# MTN-024/IPM 031 Study Results

## Phase 2a Safety Study of a Vaginal Matrix Ring Containing Dapivirine in a Postmenopausal Female Population

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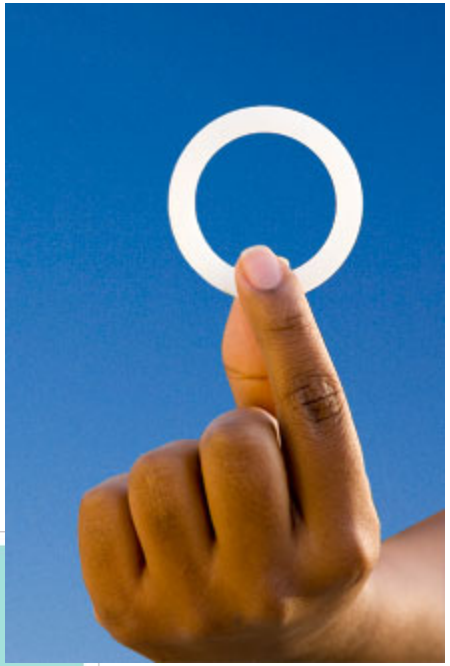
Pitt CRS

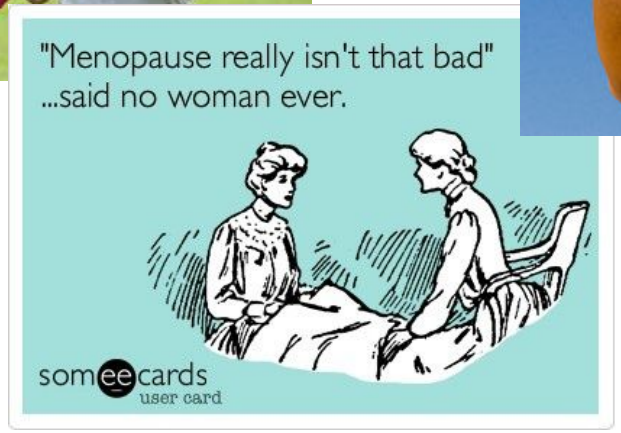
INTERNATIONAL PARTNERSHIP FOR MICROBICIDES

MTN microbicide trials network

# MTN-024/IPM 031 Team

- NIH/DAIDS
- Network Leadership
- MTN CORE Representatives
- BRWG
- BSWG
- SCHARP/SDMC
- FHI 360
- IPM
- CWG
- Sites:
  - UAB CRS
  - Case Western CRS
  - Pitt CRS




"Menopause really isn't that bad"
...said no woman ever.
someecards
user card

# Dapivirine

- NNRTI active against HIV-1 regardless of co-receptor tropism of virus
- Well-tolerated, good safety profile, promising anti-HIV-1 activity *in vitro* and *ex vivo*
- Dapivirine VR (25 mg) studied in efficacy and long-term safety trials (MTN-020 and IPM 027)
- Phase 3 results in next presentations!

- **Important to study in all age groups, including adolescents and menopausal women**

# MTN-024/IPM 031

- Phase 2a, two-arm, placebo-controlled, double-blind randomized trial
- 96 women
- Healthy, HIV-negative, postmenopausal women aged 45-65 (inclusive)
- Three US sites
  - University of Alabama at Birmingham, Case Western, and Pittsburgh

# Study Duration

- Approximately 13 weeks per enrolled participant, 12 months planned accrual

MTN-024/IPM 031 was the first clinical trial of a dapivirine vaginal ring in postmenopausal women

| Group | N | Group Description |
|---|---|---|
| A | 72 | Dapivirine VR, containing 25 mg dapivirine |
| B | 24 | Placebo VR |

**Randomized 3:1**

# Primary Objective and Endpoints: Safety

**To assess the safety of dapivirine (25 mg) in HIV-uninfected postmenopausal women**

*Grade 2 or higher genital, genitourinary and reproductive system adverse events judged to be related to study product **and** Grade 3 or higher adverse events*

*Defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009) and Addendum 1, Female Genital Grading Table for Use in Microbicide Studies*

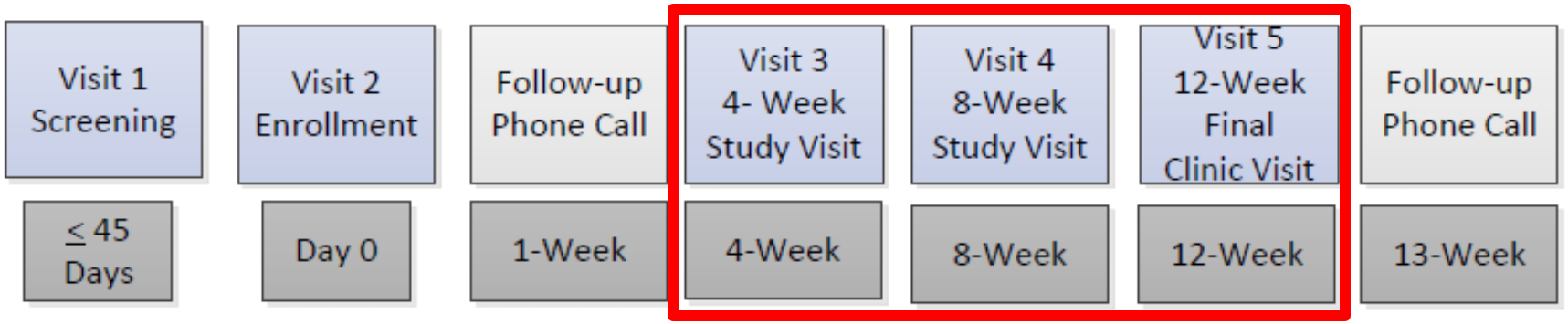
# Secondary Objectives and Endpoints: Acceptability, Adherence and PK

| Acceptability | Adherence | Pharmacokinetics |
| --- | --- | --- |
| The proportion of participants who find the study VR to be as acceptable as other HIV prevention methods | Adherence measures of daily study product use based on self-report over the study product use period | Assessments of dapivirine concentrations in plasma, vaginal fluid and cervical tissue |

# Exploratory Objectives and Endpoints: Acceptability, Adherence and PK

| Acceptability | Adherence | Vaginal Microenvironment |
| --- | --- | --- |
| Participant's self-report on multiple components of acceptability via attitudinal questions | Residual amount of dapivirine measured in returned VRs and dapivirine concentrations in plasma, vaginal fluid, and cervical tissue | Changes in pH, microflora and biomarkers |

# Study Visit Schedule and PK Specimen Collection




| Visit | Specimens Collected for PK |
|---|---|
| **Visit 3:** 4-Week | • Plasma (n=96)<br>• Vaginal fluid via swab (n=45) |
| **Visit 4:** 8-Week | • Plasma (n=96)<br>• Vaginal fluid via swab (n=45) |
| **Visit 5:** 12-Week | • Plasma (n=96)<br>• Vaginal fluid via swab (n=45)<br>• Cervical tissue (n=15) |


RESULTS

# Screening/Enrollment

| Site | Total No. Screened | Screen Failures | Total No. Enrolled |
|---|---|---|---|
| Birmingham, AL | 61 | 29 | 32 |
| Cleveland, OH | 76 | 44 | 32 |
| Pittsburgh, PA | 63 | 31 | 32 |
| **TOTAL** | **200** | **104** | **96** |

# Study Termination by Arm

| | DPV | Placebo |
|---|---|---|
| **Participants Enrolled** | 72 | 24 |
| **Participants Terminated at Scheduled Exit Visit** | 70 (97%) | 22 (92%) |
| **Participants Terminated Prior to Scheduled Exit Visit** | 2 | 2 |

Reasons for termination include:

- Investigator decision due to noncompliance (1)
- Unable to contact participant (1)
- Unable to adhere to visit schedule (2)

Overall retention was 97%

# Demographics by Arm

| | DPV | Placebo | All Arms |
|---|---|---|---|
| **Mean Age in Years (SD)** | 57.2 (4.3) | 55.3 (3.0) | 56.8 (4.1) |
| **45-49 Years (n,%)** | 1 (1%) | 0 (0%) | 1 (1%) |
| **50-54 Years (n,%)** | 21 (29%) | 12 (50%) | 33 (34%) |
| **55-59 Years (n,%)** | 26 (36%) | 11 (46%) | 37 (39%) |
| **60-65 Years (n,%)** | 24 (33%) | 1 (4%) | 25 (26%) |
| | | | |
| **Race** | | | |
| **Black or African American (n,%)** | 22 (31%) | 8 (33%) | 30 (31%) |
| **White (n,%)** | 48 (67%) | 15 (63%) | 63 (66%) |
| **Other (n,%)** | 2 (3%) | 1 (4%) | 3 (3%) |
| | | | |
| **Mean Age of Menopause (SD)*** | 49.4 (4.1) | 49.5 (5.2) | 49.5 (4.3) |

*N = 81 (menopausal age not evaluable for some participants due to hysterectomy or ablation)

# Demographics by Site

| | Birmingham, AL | Cleveland, OH | Pittsburgh, PA | All Arms |
|---|---|---|---|---|
| **Mean Age in Years (SD)** | 57.8 (4.2) | 56.5 (4.0) | 56.0 (4.0) | 56.8 (4.1) |
| **45-49 Years (n,%)** | 0 (0%) | 0 (0%) | 1 (3%) | 1 (1%) |
| **50-54 Years (n,%)** | 8 (25%) | 12 (38%) | 13 (41%) | 33 (34%) |
| **55-59 Years (n,%)** | 14 (44%) | 13 (41%) | 10 (31%) | 37 (39%) |
| **60-65 Years (n,%)** | 10 (31%) | 7 (22%) | 8 (25%) | 25 (26%) |
| | | | | |
| **Race** | | | | |
| **Black or African American (n,%)** | 10 (31%) | 15 (47%) | 5 (16%) | 30 (31%) |
| **White (n,%)** | 21 (66%) | 16 (50%) | 26 (81%) | 63 (66%) |
| **Other (n,%)** | 1 (3%) | 1 (3%) | 1 (3%) | 3 (3%) |
| | | | | |
| **Mean Age of Menopause (SD)*** | 48.6 (3.7) | 49.6 (5.2) | 50.0 (3.6) | 49.5 (4.3) |

*N = 81 (menopausal age not evaluable for some participants due to hysterectomy or ablation)

# Safety Data: Primary Endpoint

| Participants who experienced a Grade 2 Genitourinary AE by Arm | | |
|---|---|---|
| | **DPV** | **Placebo** |
| **Number of ppts with Grade 2 GU AE/n** | 6/72 (8%) | 3/24 (13%) |
| **P-value* as compared with Placebo** | **.69** | - |

** P-value is calculated using Fisher's exact test (not corrected for multiple comparisons)*

# Safety Data: Primary Endpoint

| Participants who experienced Grade 3 or Higher AEs by Arm | | |
|---|---|---|
| | **DPV** | **Placebo** |
| **Number of ppts with at least 1 grade 3 or higher AE/n** | 4/72 (6%) | 0/24 (0%) |
| **P-value* as compared with Placebo** | **.57** | **-** |

** P-value is calculated using Fisher's exact test (not corrected for multiple comparisons)*

**Only one grade 3 AE (vaginal pain) was deemed related to study product**

# Safety Data: Product Holds

| Participants who experienced Product Holds by Arm | | |
|---|---|---|
| | DPV | Placebo |
| Number of ppts with at least 1 product hold/n | 3/72 (4%) | 2/24 (8%) |

- There were 6 protocol-required product holds for 5 women, all due to AEs which resolved
- Two women in the DPV arm declined to re-start product

# Safety Data: All AEs

**AEs were reported for 60 of 96 enrolled participants**

| All AEs Regardless of Relationship | | | |
|---|---|---|---|
| | DPV (46 of 72 ppts) n (%) | Placebo (14 of 24 ppts) n (%) | All Arms (60 of 96 ppts) n (%) |
| **Grade 1** | 85 (72.6%) | 20 (57.1%) | 105 (69.1%) |
| **Grade 2** | 28 (23.9%) | 15 (42.9%) | 43 (28.3%) |
| **Grade 3** | 4 (3.4%) | 0 | 4 (2.6%) |
| **Grade 4** | 0 | 0 | 0 |
| **Death** | 0 | 0 | 0 |
| **Total** | 117 | 35 | 152 |

# Safety Data: Attribution

| | DPV | | Placebo | | All Arms | |
|---|---|---|---|---|---|---|
| | Not related | **Related** | Not related | **Related** | Not related | **Related** |
| **Grade 1** | 35 (41.2%) | **50 (58.8%)** | 8 (40.0%) | **12 (60.0%)** | 43 (41.0%) | **62 (59.0%)** |
| **Grade 2** | 22 (78.6%) | **6 (21.4%)** | 11 (73.3%) | **4 (26.7%)** | 33 (76.7%) | **10 (23.3%)** |
| **Grade 3** | 3 (75.0%) | **1 (25.0%)** | 0 | **0** | 3 (75.0%) | **1 (25.0%)** |
| **Grade 4** | 0 | **0** | 0 | **0** | 0 | **0** |
| **Death** | 0 | **0** | 0 | **0** | 0 | **0** |
| **Total** | 60 (51.3%) | **57 (48.7%)** | 19 (54.3%) | **16 (45.7%)** | 79 (52.0%) | **73 (48.0%)** |

Grade 3 AEs:

- Multiple sclerosis relapse (not related)
- Elevated blood pressure (not related)
- Persistent vomiting (not related)
- Vaginal pain (related)

# Pharmacokinetics: Dapivirine

| Plasma DPV (pg/mL) | Median (IQR) | Mean (95% CI) |
|---|---|---|
| Week 4 (n=69) | 268 (213, 325) | 273 (250, 297) |
| Week 8 (n=70) | 288 (217, 325) | 289 (259, 318) |
| Week 12 (n=69) | 262 (227, 351) | 298 (264, 333) |

| Vaginal fluid DPV (ng/mg) | Median (IQR) | Mean (95% CI) |
|---|---|---|
| Week 4 (n=33) | 34 (26, 61) | 64 (401, 88) |
| Week 8 (n=34) | 45 (32, 78) | 79 (46, 111) |
| Week 12 (n=33) | 41 (22, 81) | 72 (44, 101) |

# Pharmacokinetics: Dapivirine

- No change in median DPV concentrations in plasma and vaginal fluid over 12 weeks

- DPV was detectable in cervical tissue in only 5/10 women
  - Median DPV 0.6 ng/mg

# Cervical biopsies

| | DPV detectable (n=5) | DPV undetectable (n=5) |
|---|---|---|
| **Plasma DPV (pg/mL)** | mean=318.6<br>median=270.0 | mean=257.8<br>median=265.0 |
| **Vaginal fluid DPV (ng/mg)** | mean=105.9<br>median=73.5 | mean=35.7<br>median=39.3 |
| **Cervical tissue biopsy weights (mg)** | mean=13.8<br>median=15.6 | mean=11.2<br>median=11.5 |

- Median biopsy weights were 36% lower in women with undetectable levels
- Plasma and vaginal fluid DPV levels lower but not statistically significant

# Residual drug levels

- Median residual drug levels was 21.1 mg across all visits
  - **Consistent with adherence to VR use**
  - No difference between women with detectable vs undetectable cervical tissue DPV levels
- Undetectable DPV in cervical tissue due to small biopsies rather than lack of absorption?

# Compared to published DPV PK data

- MTN-024/IPM 031 plasma DPV at 28 days:
  - Median 268.0 pg/mL, Mean 272.5 pg/mL
- Reproductive age women:
  - IPM 024: Mean plasma DPV 217.5 pg/mL at 28 days (Nel A et al, AIDS 2014. 28:1479-87)
  - IPM 013: Mean plasma DPV 260 pg/mL at 28 days (Nel AM et al, J AIDS Clin Res 2014. 5:355)
    - Mean plasma DPV 270.4 after 2nd 28-day ring use period
  - MTN-013/IPM 026: Median plasma DPV 175 pg/mL at 28 days (Chen BA et al, JAIDS 2015. 70:242-9)

**DPV levels not lower compared to reproductive age women**

# Conclusions

- VRs were safe and well-tolerated in postmenopausal women
- Majority of AEs (N=152) were mild (69%) or moderate (28%)
- About half of AEs (52%) were unrelated
  - Only one grade 3 AE (vaginal pain) was related

# Conclusions

- No difference in related grade 2 genitourinary AEs or grade 3 or higher AEs by arm
- However, 2 women declined to restart VR after their AEs resolved
  - 1 additional woman was discontinued due to noncompliance with protocol after an AE of Grade 3 vaginal pain

# Conclusions

- Median plasma and vaginal fluid DPV concentrations constant over 12 weeks
- Residual DPV levels consistent with adherence
- Undetectable DPV in cervical tissue may be due to smaller biopsies
- Further studies are needed to assess biological differences in the postmenopausal genital tract

# Adherence and Acceptability

Ariane van der Straten


INTERNATIONAL PARTNERSHIP FOR MICROBICIDES

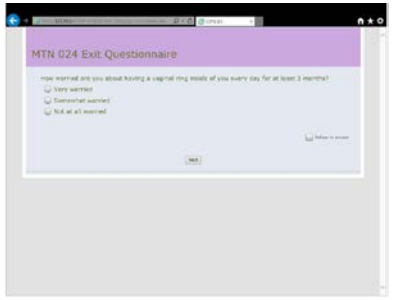
MTN microbicide trials network

# Behavioral Study Objectives

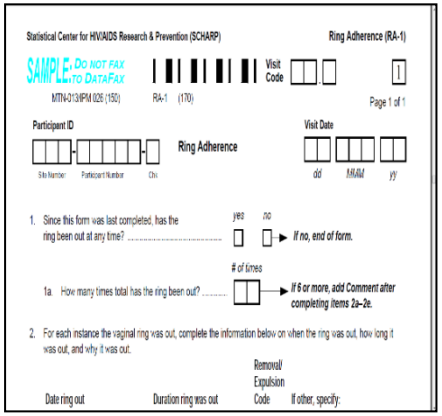
- To assess adherence to 3 months of vaginal ring use
- To assess acceptability of a monthly vaginal ring in U.S. postmenopausal women

# Behavioral Assessments

- CASI: Baseline, Monthly, PEV




- CRFs: Baseline, Monthly, PEV


Statistical Center for HIV/AIDS Research & Prevention (SCHARP)

Ring Adherence (RA-1)

SAMPLE: DO NOT FAX TO DATAFAX

Visit Code

MTN-013/IPM 026 (150) RA-1 (170)

Page 1 of 1

Participant ID

Ring Adherence

Visit Date

Site Number Participant Number Chk dd MMM yy

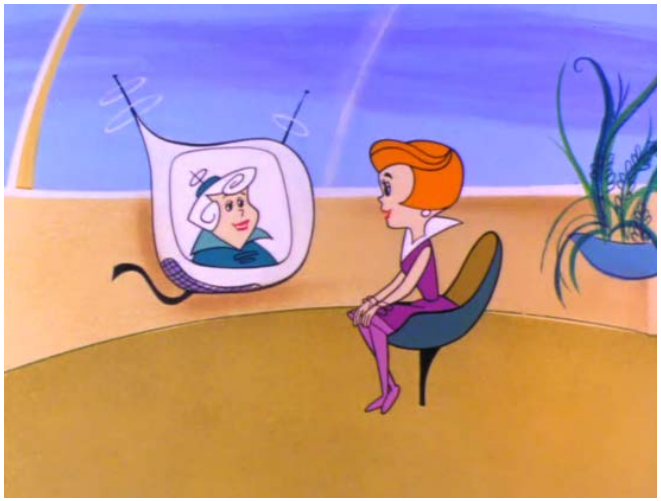
1. Since this form was last completed, has the ring been out at any time? yes no ► If no, end of form.

1a. How many times total has the ring been out? # of times ► If 6 or more, add Comment after completing items 2a–2e.

2. For each instance the vaginal ring was out, complete the information below on when the ring was out, how long it was out, and why it was out.

Date ring out | Duration ring was out | Removal/ Expulsion Code | If other, specify:

- In-depth-Video Interviews at PEV
  - F2F interaction with trained social scientist
  - Allows standardization of interviewing approach
  - Administered immediately after CASI at M3
  - Explored ring acceptability & use experience



# Behavioral Objectives and Measures

- Adherence (self-reported monthly CRF):
  - "Ring never out"
  - **Per protocol adherent**: ring never out except for study-instructed removals (i.e., product holds, study procedures)
  - Non-adherent: ring out for non study-related reasons
    - Ring expulsions (involuntary)
    - Ring removals (voluntary)
- Preference: ring vs male condoms
- Acceptability (baseline and Month-3 CASI, IDIs):
  - Likes/dislikes, change over time
  - Worries/concerns (at baseline and month-3)
  - Ring use experiences (e.g. during sex, problems)

# Analysis

- Analysis blinded & behavioral data combined across study groups
- Descriptive data summarized as mean/median (continuous variables) and tabulated (categorical variables)
- McNemar test for change between baseline & Month-3
- Qualitative interviews: audio-recorded, transcribed, coded thematically and analyzed using NVivo

| Baseline Characteristics | | TOTAL N=96 |
|---|---|---|
| Study site | Cleveland, OH<br>Birmingham, AL<br>Pittsburgh, PA | 33%<br>33%<br>33% |
| Mean age, years (range) | | 56.8 (46-65) |
| Has a primary sex partner | | 61% |
| Sexual intercourse in past 30 days | | 66% |
| More than high school education | | 83% |
| Race | White | 66% |
| | African American/Black | 31% |
| | Other | 3% |
| | Hispanic | 1% |
| Menopause symptom scale, mean (range) | | 7.8 (0-22) |
| History of vaginal product use ** | | 76% |
| History of tampon use | | 83% |

** female condoms, contraceptive vaginal ring or sponge, cervical barrier, douche

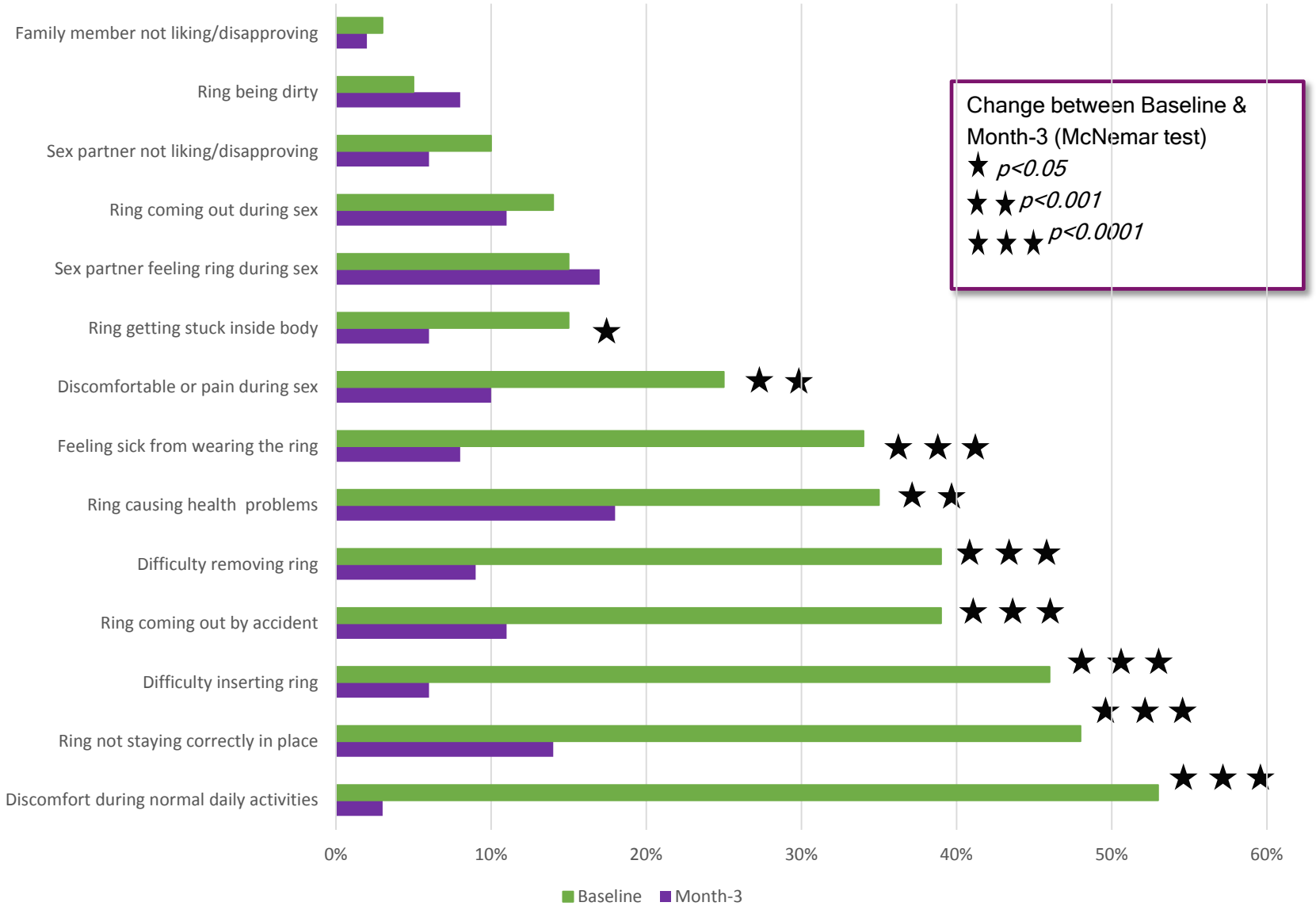
| Cumulative Ring Adherence | %Total (N=96) |
|---|---|
| “Ring never out” | 74% (71) |
| Per protocol adherence | 81% (78) |
| Ring never out for >12h | 91% (87) |
| Reasons for ring out | **(N=94)** |
| Full expulsion* | 6% (6) |
| Removals** | 17% (16) |
| Partial expulsions (put back in place without removals)*** | 16% (15) |

* *mostly due to bowel movement & when checking with fingers*

** *mostly due to physical discomfort, ring feeling out of place, worries/not liking the ring & to clean it.*

*** *mostly due to urinating, bowel movement, exercising, when checking with finger*

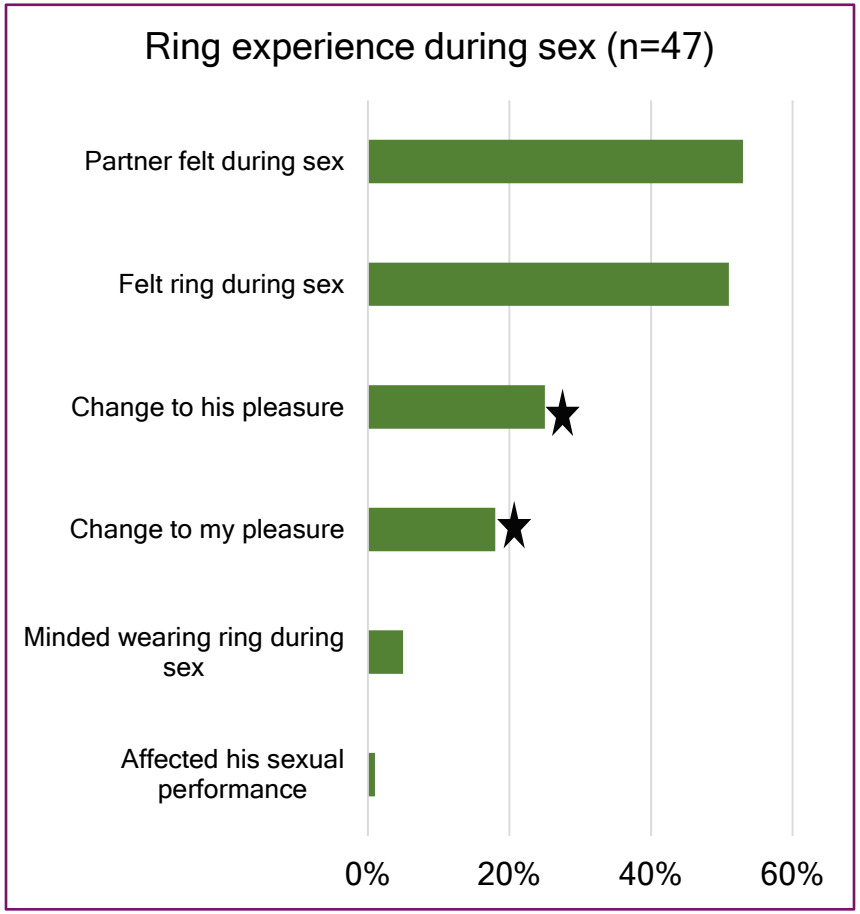
# Worries About the Ring

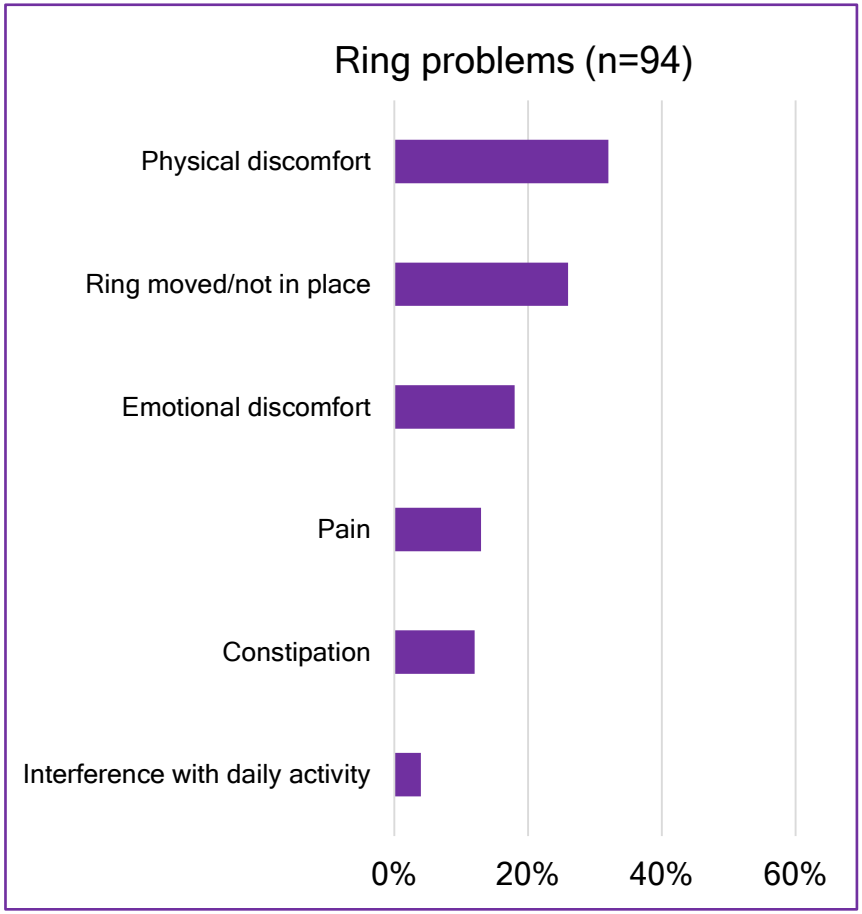


# Overall Acceptability

- 99% responded that “ring is very/easy to use”
- 97% responded they were very/comfortable with the ring inside every day
- 85% agreed the ring is easy to insert
- 80% agreed the ring is easy to remove
- 36% reported change in vagina
  - 20% vaginal wetter (3/4 not at all bothered by it)
  - 10% vaginal drier (1/3 not at all bothered; 2/3 a little bothered)
  - 6% other changes (i.e., vaginal irritation from condoms)

# Ring Use Experiences




★60% of those was “increased pleasure”

# 93% Very Much/Liked the Ring (Month-3 CASI)

*It's something women can do themselves*

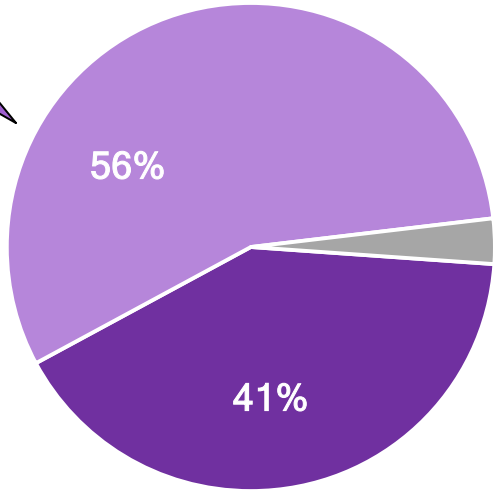
***

*Women are in control of the situation*

*You can forget about it!*

***

*I was blown away that I couldn't feel it once inserted*



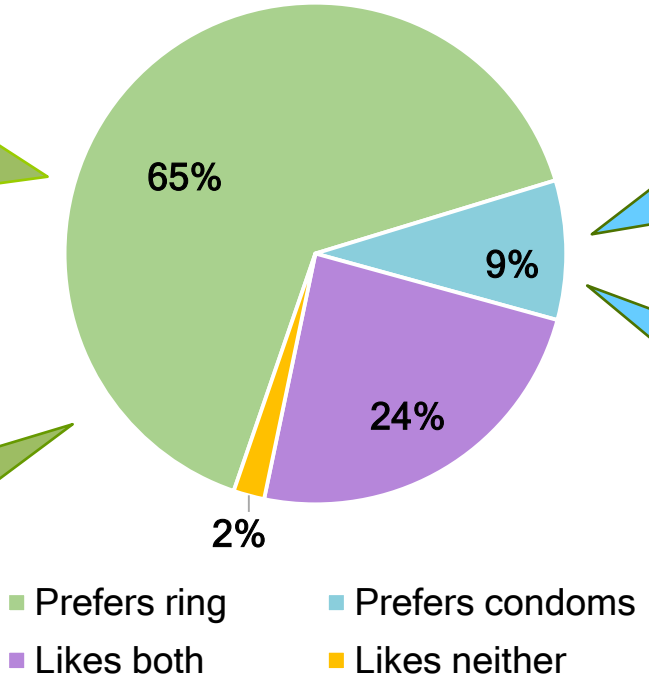

*It would slide down and you'd have some uncomfortable moments*

*I was very aware of it being there*

# Preference: 65% preferred ring to condoms

Once inserted …*it's just like part of you*

*You don't have to tell anybody*




*It feels more protected [with a condom]*

*Used just for sex; can be thrown away after.*

# Conclusions

- The ring was very acceptable among healthy postmenopausal women
- Adherence was high with few removals/expulsions- Confirmed by drug pharmacokinetics
- Worries decreased significantly comparing baseline to Month-3 (end of ring use)
- A majority preferred the ring to condoms
- Vaginal rings are a promising microbicide approach for HIV prevention in postmenopausal women

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