Risk of sexually transmitted infections among women randomized to DMPA-IM, the copper IUD, and levonorgestrel implant in the ECHO trial

Evidence for Contraceptive Options & HIV Outcomes

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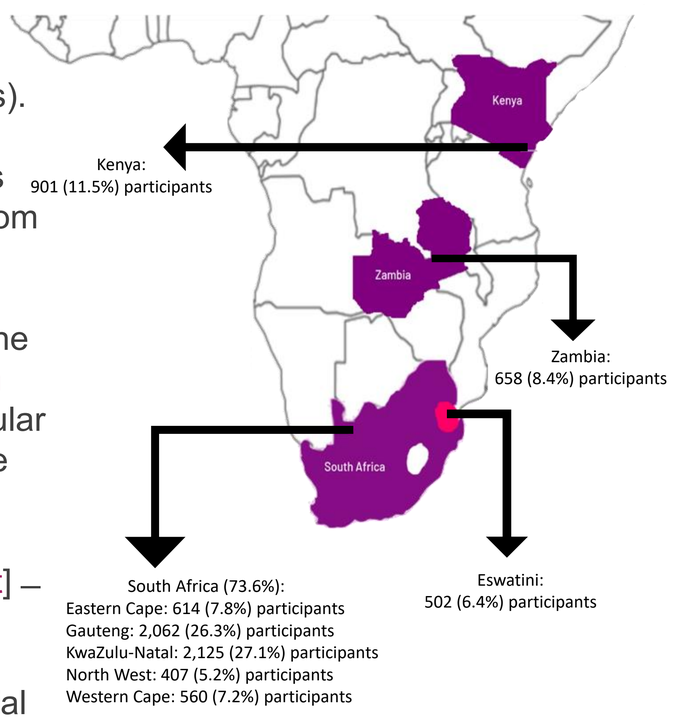
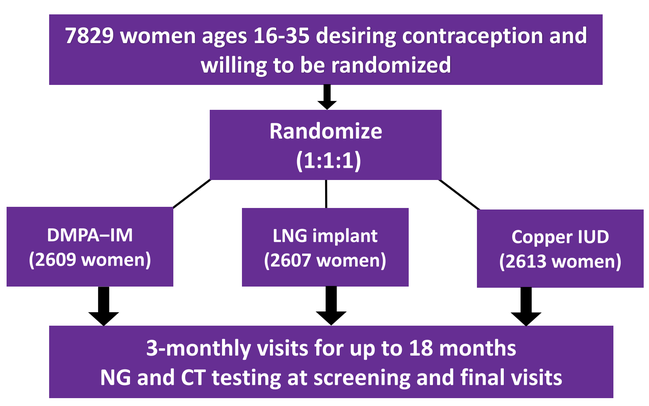
Background

Women and girls in need of contraception are at risk of HIV and sexually transmitted infections (STIs). Yet, the evidence base on STI risk associated with contraceptive use is limited, and no data are available from randomized controlled trials.

To address this gap, we assessed the relationship between three common contraceptive methods – intramuscular depot medroxyprogesterone acetate [DMPA-IM], a copper intrauterine device [copper IUD], and a levonorgestrel implant [LNG implant] – and acquisition of two STIs – N. *gonorrhoeae* [NG] and *C. trachomatis* [CT] in a randomized trial of HIV incidence among HIV-seronegative women.



Methods



- Nucleic acid amplification testing for *N. gonorrhoeae* and *C. trachomatis* conducted at screening, final visit, and at interim visits if clinically indicated.
- STI treatment based on syndromes and laboratory results.

- **Point prevalence** estimated using log binomial regression to assess pairwise comparisons:
  - Exposures: DMPA, copper IUD, LNG implant
  - Outcomes: N. *gonorrhoeae, C. trachomatis*
- **As randomized**: method assigned at randomization, comprising intention to treat (ITT) analysis with adjustment for study site.
- **Continuous use (CU):** limited to participants who continued to their randomized method throughout follow-up. For NG, adjusted for study site, HIV status at final visit, total number of pelvic exams; for CT, adjusted for study site, age group, and CT positivity at screening
  - Method discontinuation:
    - DMPA: >119 days between injections
    - Copper IUD: Spontaneously expelled and not replaced within 28 days; removed and not reinserted same day; received >28 days after randomization
    - LNG implant: If removed and not reinserted same day

Results

- Participant characteristics were similar across randomized study arms.
- Participants who continuously used their randomized method through their final visit were also similar across randomized study arms.

Participant Baseline Characteristics by Intention to Treat (ITT) and Continuous Use (CU) Analyses

	ITT (N=7829) n (%)	CU (N=6361) n (%)
Age		
≤ 24 years old	4967 (63.4)	3986 (62.7)
25+ years old	2862 (36.6)	2375 (37.3)
Nulligravid	1462 (18.7)	1048 (16.5)
Earns Own Income	1697 (21.7)	1403 (22.1)
Highest Education Level		
None/Some/All Primary School	772 (9.8)	670 (10.6)
Some/All Secondary School	5815 (74.3)	5087 (80.0)
Attended Post-Secondary School	1242 (15.9)	1004 (15.8)
No Previous Contraceptive	586 (7.5)	485 (7.6)
STI Testing Frequency at Screening Visit		
C. trachomatis	7815 (99.8)	6352 (99.9)
N. gonorrhoeae	7816 (99.8)	6353 (99.9)

Results Cont.

Point Prevalence of NG and CT at Screening and Final Visits by Study Site

	N. Gonorrhoeae		*C. Trachomatis*	
	Screening (N=7816) % (CI*)	Final (N=7268) % (CI*)	Screening (N=7815) % (CI*)	Final (N=7269) % (CI*)
Total	4.7 (4.3, 5.2)	4.8 (4.4, 5.4)	18.2 (17.3, 19.0)	15.4 (14.6, 16.2)
Study Site				
Kingdom of Eswatini	4.6 (3.1, 6.8)	7.1 (5.1, 9.8)	16 (13.1, 19.5)	17 (14.0, 20.8)
Kenya	3.0 (2.1, 4.3)	3.3 (2.3, 4.8)	9.3 (7.6, 11.4)	11.4 (9.5, 13.7)
Zambia	2.9 (1.9, 4.5)	5.7 (4.1, 7.8)	4.7 (3.3, 6.7)	8.5 (6.6, 11.0)
South Africa (by province)				
Eastern Cape	6.3 (4.6, 8.5)	4.3 (3.0, 6.3)	22.3 (19.2, 25.9)	14.7 (12.1, 17.8)
Gauteng	4.8 (3.9, 5.8)	4.3 (3.5, 5.3)	19.6 (18.0, 21.4)	16.3 (14.7, 18.1)
KwaZulu-Natal	4.6 (3.8, 5.6)	4.6 (3.8, 5.7)	21.0 (19.3, 22.8)	18.4 (16.7, 20.1)
North West	4.2 (2.6, 6.7)	3.9 (2.4, 6.4)	20.1 (16.6, 24.4)	12.0 (9.2, 15.8)
Western Cape	8.6 (6.6, 11.3)	8.8 (6.5, 11.9)	28.3 (24.8, 32.3)	17.3 (14.2, 21.2)

* CI: 95% confidence interval

- The risk of NG and CT was considerable in this population of sexually active women at both the screening and final visits, even in the context of routine prevention counseling and syndromic management.
- Generally higher prevalence of NG and CT was observed in South Africa compared to other study regions.

Point Prevalence of NG and CT at Screening and Final Visits by Age Group (ITT analysis)

	Screening % (95% CI)	Final % (95% CI)
≤ 24 Years Old		
N. gonorrhoeae	5.4 (4.8, 6.0)	5.8 (5.2, 6.5)
C. trachomatis	21.5 (20.4, 22.6)	19.6 (18.5, 20.8)
25 + Years Old		
N. gonorrhoeae	3.6 (3.0, 4.3)	3.2 (2.6, 4.0)
C. trachomatis	12.4 (11.3, 13.7)	8.2 (7.2, 9.3)

- At screening and final visit, the prevalence of NG and of CT were significantly higher in women ages ≤24 years than those who were ages 25 years and older.
- There was no evidence of effect modification by age group.

Pairwise Comparisons of Point Prevalence (PR) Ratios of NG and CT at Final Visit by Randomized Method (ITT analysis)

	N. gonorrhoeae		*C. trachomatis*	
	PR (95% CI)	P value	PR (95% CI)	P value
Copper IUD vs LNG Implant	1.2 (0.9, 1.5)	0.175	0.9 (0.8, 1.0)	0.178
DMPA-IM vs Copper IUD	**0.7 (0.5, 0.9)**	**0.002**	0.9 (0.8, 1.0)	0.144
DMPA -IM vs LNG Implant	0.8 (0.6, 1.0)	0.085	**0.8 (0.7, 0.9)**	**0.005**

- DMPA-IM showed a 30% lower risk of NG detection at the final visit, compared with the copper IUD.
- DMPA-IM also showed a 20% lower risk of CT detection at the final visit, compared with the LNG implant.
- The CU analysis was consistent with ITT results.

Implications

- Post-randomization sexual behavior differences may have influenced the results (*additional analyses to inform this question are ongoing).*
- Any true decreased risk must be evaluated along with all potential risks and benefits of the contraceptive methods.
- The high NG and CT final visit prevalence, despite routine prevention counseling and syndromic management, particularly among women ≤ 24 years, warrants greater focus on NG and CT testing and treatment in this population, and in partners of this population.

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