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## BACKGROUND

- The Evidence for Contraceptive Options and HIV Outcomes (ECHO) trial found no substantial difference in HIV acquisition risk between women randomised to injectable depot medroxyprogesterone acetate (DMPA-IM), copper intrauterine device (IUD) or the levonorgestrel (LNG) implant.
- ECHO did not determine whether these contraceptives increase HIV risk relative to *other* contraceptive methods or to *no* contraception.
- We investigated the impact of DMPA-IM, copper IUD and LNG implant on cervicovaginal inflammatory profiles previously associated with HIV acquisition, among a sub-cohort of ECHO participants.

## METHODS

- We analysed lateral vaginal wall specimens at baseline and at months 1 and 3 after contraceptive initiation from participants at the Setshaba Research Centre and MatCH Research Unit in South Africa (Fig 1).

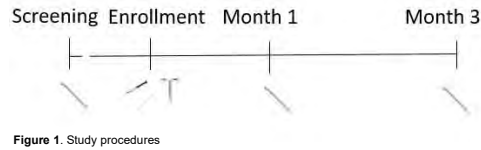
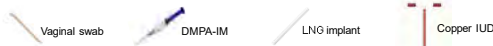


Figure 1. Study procedures

- Samples from 167 participants were analysed.
  - n=53 (DMPA-IM)
  - n=59 (LNG implant)
  - n=55 (Copper IUD)
- Eleven cytokines (MIP-1 $\alpha$ , MIP-1 $\beta$ , MIP-3 $\alpha$ , IP-10, RANTES, IL-6, IL-8, IL-1 $\beta$  and TNF- $\alpha$  and IFN- $\alpha$ ) and an antimicrobial peptide (SLPI) were measured using Luminex.
- Marker concentration changes over time by contraceptive method were assessed using Wilcoxon signed rank test and generalized linear modelling with adjustment for multiple comparisons using a false discovery rate step-down procedure.

## LEGEND



## RESULTS

- The median age was 24 years (range 18-35).
- There were no baseline differences in age, marital, cohabitation or educational status, clinical exam findings or laboratory results (*Chlamydia trachomatis* and *Neisseria gonorrhoeae*) between contraceptive groups.
- At baseline, younger women had significantly higher IL-8, IL-6 and IL-1 $\beta$  concentrations. There was a consistent but non-significant trend toward higher concentrations of all other cytokines among younger women.
- Women with lower body mass index ( $\leq 30$  vs.  $>30$ ) had consistently but non-significantly higher concentrations of all cytokines. Similarly, herpes simplex virus type 2 seropositive women had lower concentrations of all cytokines except MIP-1 $\beta$ , though only MIP-1 $\alpha$  reached statistical significance.

## Copper IUD and LNG implant use were associated with increased cervicovaginal inflammation.

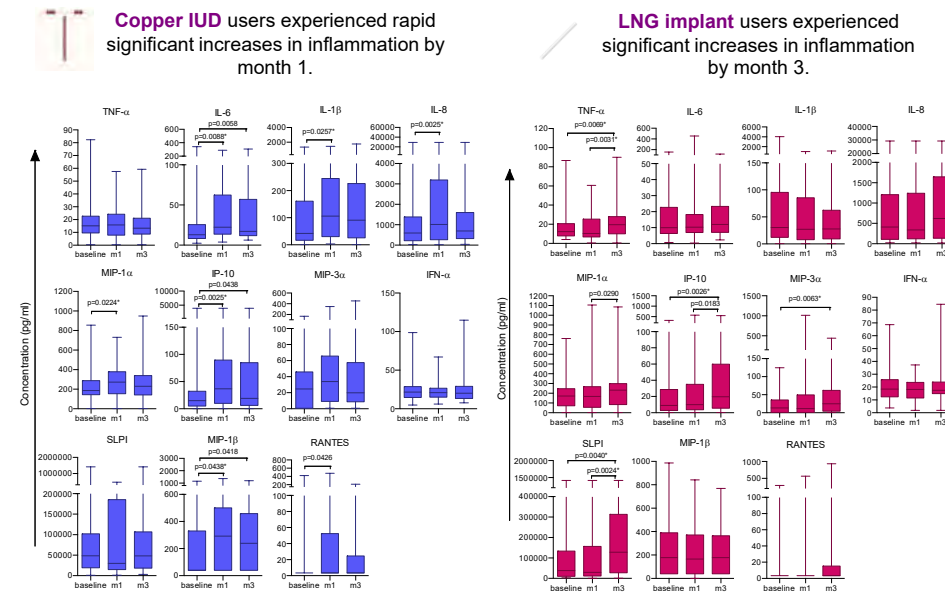


Figure 2. Analysis of cytokine concentrations at months 1 and 3 after contraceptive initiation using Wilcoxon signed rank test. \* $p < 0.05$  after adjusting for multiple comparisons.

Table 1. Change in marker concentrations from baseline to month 1 adjusted for site and age

Cytokine	Standardized coefficient $\beta$	P-value	Standardized coefficient $\beta$	P-value	Standardized coefficient $\beta$	P-value
TNF- $\alpha$	0.58	0.566	-1.70	0.095	-1.15	0.256
IL-8	1.13	0.265	-0.13	0.896	-0.32	0.751
MIP-1 $\alpha$	1.46	0.151	1.11	0.271	-0.46	0.850
IL-6	3.10	0.003	0.75	0.455	0.04	0.965
IP-10	1.98	0.054	-0.35	0.731	0.51	0.812
IL-1 $\beta$	1.76	0.085	0.40	0.889	-1.22	0.227
MIP-3 $\alpha$	1.06	0.295	-0.54	0.589	-0.15	0.883
IFN- $\alpha$	-0.82	0.418	0.08	0.935	-1.51	0.136
SLPI	0.46	0.647	-1.88	0.099	-0.62	0.541
MIP-1 $\beta$	2.83	0.007	-0.04	0.972	0.04	0.968
RANTES	2.43	0.019	1.36	0.180	1.57	0.122

Table 2. Change in marker concentrations from baseline to month 3 adjusted for site and age

Cytokine	Standardized coefficient $\beta$	P-value	Standardized coefficient $\beta$	P-value	Standardized coefficient $\beta$	P-value
TNF- $\alpha$	-0.21	0.836	-0.94	0.351	2.47	0.015
IL-8	0.61	0.546	0.90	0.373	0.67	0.503
MIP-1 $\alpha$	0.73	0.485	0.80	0.427	1.78	0.078
IL-6	2.94	0.004	0.26	0.798	1.09	0.277
IP-10	1.18	0.240	-0.97	0.335	3.31	0.001
IL-1 $\beta$	1.74	0.085	0.23	0.815	-1.43	0.165
MIP-3 $\alpha$	0.89	0.378	-0.06	0.936	2.39	0.019
IFN- $\alpha$	-0.26	0.777	-1.42	0.157	-0.53	0.586
SLPI	0.26	0.794	-0.41	0.686	3.28	0.001
MIP-1 $\beta$	2.48	0.015	-0.26	0.792	-0.24	0.807
RANTES	1.91	0.059	-0.29	0.773	2.04	0.044

## CONCLUSIONS

- Copper IUD and LNG implant use were associated with increased cervicovaginal inflammatory markers that have been associated with HIV acquisition.
- Recent studies have demonstrated important interactions between inflammation, the microbiome, contraception and HIV risk. Microbiome data will be integrated into these results in future analyses.
- Continued research to understand these effects is important for safe contraceptive use and to inform novel contraceptive development.

