Elevated genital cytokines in HIV-infected women using copper and levonorgestrel IUDs

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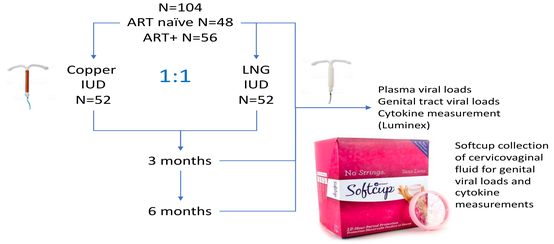
INTRODUCTION

Women living with HIV (WLHIV) and receiving antiretroviral therapy (ART) must balance potential impact of contraception on HIV outcomes and their risk of transmitting HIV to their partners or infants when selecting family planning. Intrauterine devices (IUDs) have long-lasting contraceptive efficacy but are not widely used in contexts with high HIV prevalence. The copper IUD (C-IUD) is safe for use vis a vis HIV infection as it does not influence HIV disease progression in WLHIV not using ART. However, less is known regarding effect on transmission.

Because IUDs may increase genital inflammatory cytokine concentrations in WLHIV and this may further vary by ART use, we compared the effect of the C-IUD versus the levonorgestrel intrauterine system (LNG-IUS) on genital cytokines in WLHIV, grouped by reported ART use (ART+) or no ART use (non-ART) at study entry.

STUDY DESIGN

2IUD cytokine sub-study



The 2IUDnCT trial randomized WLHIV by ART group to C-IUD or LNG-IUS insertion in a 1:1 ratio. Plasma was collected for plasma viral loads (pVL) measurement. Softcups were used to collect cervicovaginal secretions (1-hour insertion) to measure cytokines and genital tract viral loads (gVL; primary outcome). Measures were collected at baseline (before insertion), 3- & 6-months post-insertion.

Baseline median genital cytokine concentrations differ by ART status in WLHIV

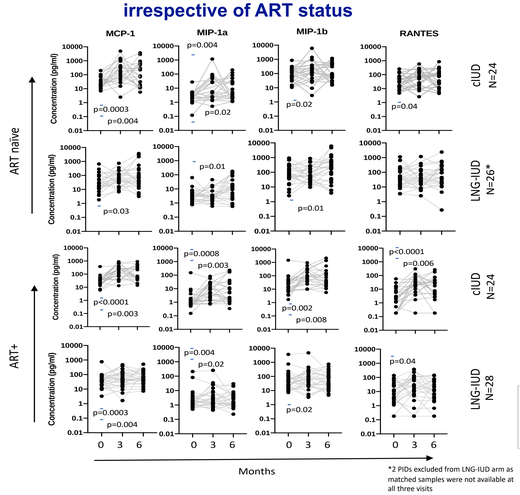
Cytokine class	Cytokine	ART- Median	IQR	ART+ Median	IQR	P-value
Inflammatory	IL-1a	822,8	282,5-1379	415,9	159,3-893,7	0,0200
	IL-1b	913,7	189,2-1681	106,1	35,25-422,4	<0.0001*
	IL-6	50,13	12,49-125,1	10,58	5,04-25,35	0,0001*
	IL-12p70	77,43	59,9-100,6	67,11	40,21-95,43	0,1784
	TNF-a	38,21	12,51-73,32	39,15	27,22-63,55	0,3081
Chemokine	Eotaxin	4,17	0,37-10,77	7,83	6,04-10,08	0,0029*
	IL-8	1664	733,6-3142	838,3	356,1-2154	0,0480
	IP-10	2184	258,1-6928	355,4	97,05-1361	0,0068
	MCP-1	21,72	14,26-65,78	36,72	19,73-55,22	0,1022
	MIP-1a	3,14	1,9-4,97	1,22	0,80-2,57	<0.0001*
	MIP-1b	74,25	43,56-218,5	24,86	12,22-57,55	<0.0001*
	RANTES	35,26	13,83-99,47	3,72	1,58-13,86	<0.0001*
Growth factor	FGFBasic	19,39	14,24-25,82	39,25	33,72-44,56	<0.0001*
	G-CSF	1964	511,4-4951	804,3	334,0-2876	0,0597
	GM-CSF	66,29	51,32-83,72	108,6	74,68-131,3	<0.0001*
	IL-7	4,89	3,63-8,84	3,71	2,36-5,66	0,0030
	IL-9	4,91	3,30-6,67	18,28	13,05-25,22	<0.0001*
	PDGF-bb	29,14	16,9-41,8	13,84	9,81-20,12	<0.0001*
	VEGF	2423	1309-3854	1013	531,1-1778	<0.0001*
Adaptive	IFN-g	49,37	27,12-77,43	23,83	17,61-30,57	<0.0001*
	IL-2	0,02	0,02-2,81	2,42	0,40-3,73	<0.0001*
	IL-4	0,84	0,52-1,38	1,15	0,86-1,51	0,0050
	IL-5	0,52	0,07-3,77	1,04	0,04-3,40	0,9312
	IL-13	2,72	1,91-3,57	0,99	0,70-1,39	<0.0001*
	IL-15	2,59	0,01-6,43	2,7	0,14-9,57	0,0719
	IL-17	26,48	13,81-38,00	19,59	14,59-27,83	0,4880
Anti-inflammatory	IL-10	16,32	14,16-20,50	10,72	7,91-14,4	<0.0001*
	IL-1ra	58085	9439-101878	10889000	1101338-10889000	<0.0001*

RESULTS AND DISCUSSION

Relationship between genital cytokines and detectable genital viral load

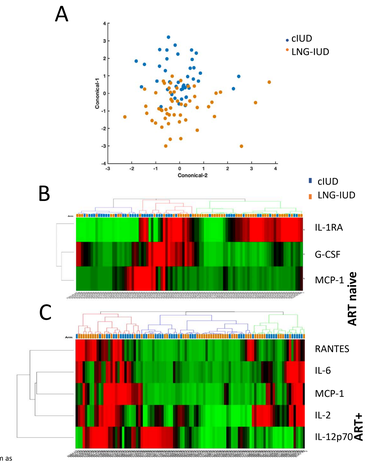
Class	Cytokine	Adjusted R	Adjusted P-value
Inflammatory	TNF-a	0,43	0,007
	IL-6	0,35	0,051
	IL-1b	0,43	0,007
	IL-1a	0,32	0,247
	IL-12p70	0,25	0,817
Growth Factors	VEGF	0,28	0,329
	PDGF-bb	0,30	0,203
	IL-9	0,29	0,241
	IL-7	0,29	0,241
	G-CSF	0,39	0,018
	GM-CSF	0,37	0,039
	FGF-Basic	0,30	0,226
Chemokines	RANTES	0,46	0,004
	MIP-1b	0,33	0,111
	MIP-1a	0,35	0,051
	MCP-1	0,28	0,357
	IP-10	0,40	0,015
	IL-8	0,43	0,007
	Eotaxin	0,25	0,817
Anti-inflammatory	IL-1RA	0,27	0,478
	IL-10	0,36	0,051
Adaptive	IL-5	0,31	0,203
	IL-4	0,40	0,015
	IL-2	0,26	0,542
	IL-17	0,30	0,218
	IL-15	0,25	0,796
	IL-13	0,42	0,007
	IFN-g	0,52	0,000

Both C-IUD & LNG-IUS increased genital tract chemokine & inflammatory cytokines in WLHIV, irrespective of ART status

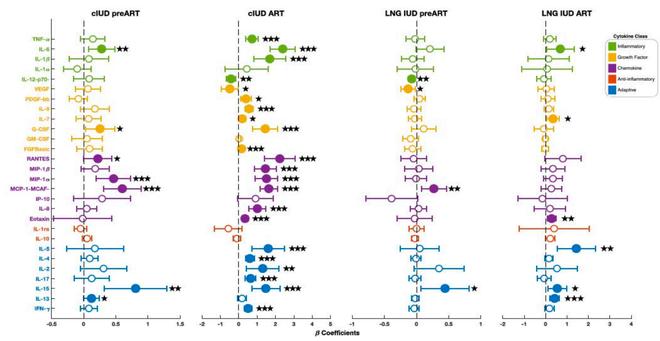


*2 PIDs excluded from LNG-IUD arm as matched samples were not available at all three visits

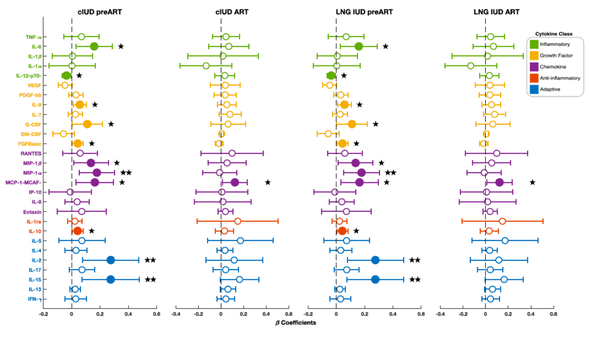
Cytokine signatures only weakly differentiate C-IUD vs LNG-IUS insertion



Changes in genital cytokine concentrations between baseline and 3 months in non-ART and ART+ WLHIV, by arm



Changes in genital cytokine concentrations between baseline and 6 months in non-ART and ART+ WLHIV, by arm



APPROACH AND ANALYSIS

In a secondary analysis of 2IUDnCT (clinicaltrials.gov NCT01721798) comparing safety of C-IUD versus LNG-IUS in WLHIV, menstrual cup cervicovaginal secretions (CVS) were collected in ART- and ART+ women randomized 1:1 to C-IUD or LNG-IUS. Twenty-eight cytokines were measured in 104 age-matched participants with CVS collected at enrolment, then 3m and 6m post-insertion (ART- n=48; ART+ n=56). We compared cytokine clustering by study arm (IUD type) and ART use by Principle Component Analysis (PCA) and Partial Least Squares Discriminant Analysis (PLSDA).

CONCLUSIONS

C-IUD insertion increased genital cytokine concentrations in WLHIV irrespective of ART use. LNG-IUS was initially less inflammatory, particularly in ART- women. Although certain genital cytokines were positively associated with detectable gVL in ART- women, inflammatory profiles specific to either IUC type were not associated with higher proportions of ART+ WLHIV with detectable gVL.

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