Cytokine and toll-like receptor expression in the female genital tract correlates inversely with sexually transmitted infections and non-Lactobacillus dominant microbiome.

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INTRODUCTION

Background: Inflammatory cytokine expression in the female genital tract (FGT) is influenced by external factors like sexually transmitted infections, commensal microbiota, intravaginal practices and risk of HIV acquisition. However, few studies have focused on expression of the cytokine receptors through which they signal.

Objective: quantified expression levels of several cytokine receptors and Toll-like receptors and correlate their expression to vaginal microbiota and sexually transmitted infection profiles.

RATIONALE

Literature has focused on cytokine concentrations, but few data are available on cytokine receptor expression in the FGT. This could have implications for how inflammation might have negative HIV implications.

What are the different downstream effects of cytokine receptors (e.g. on the barrier)?
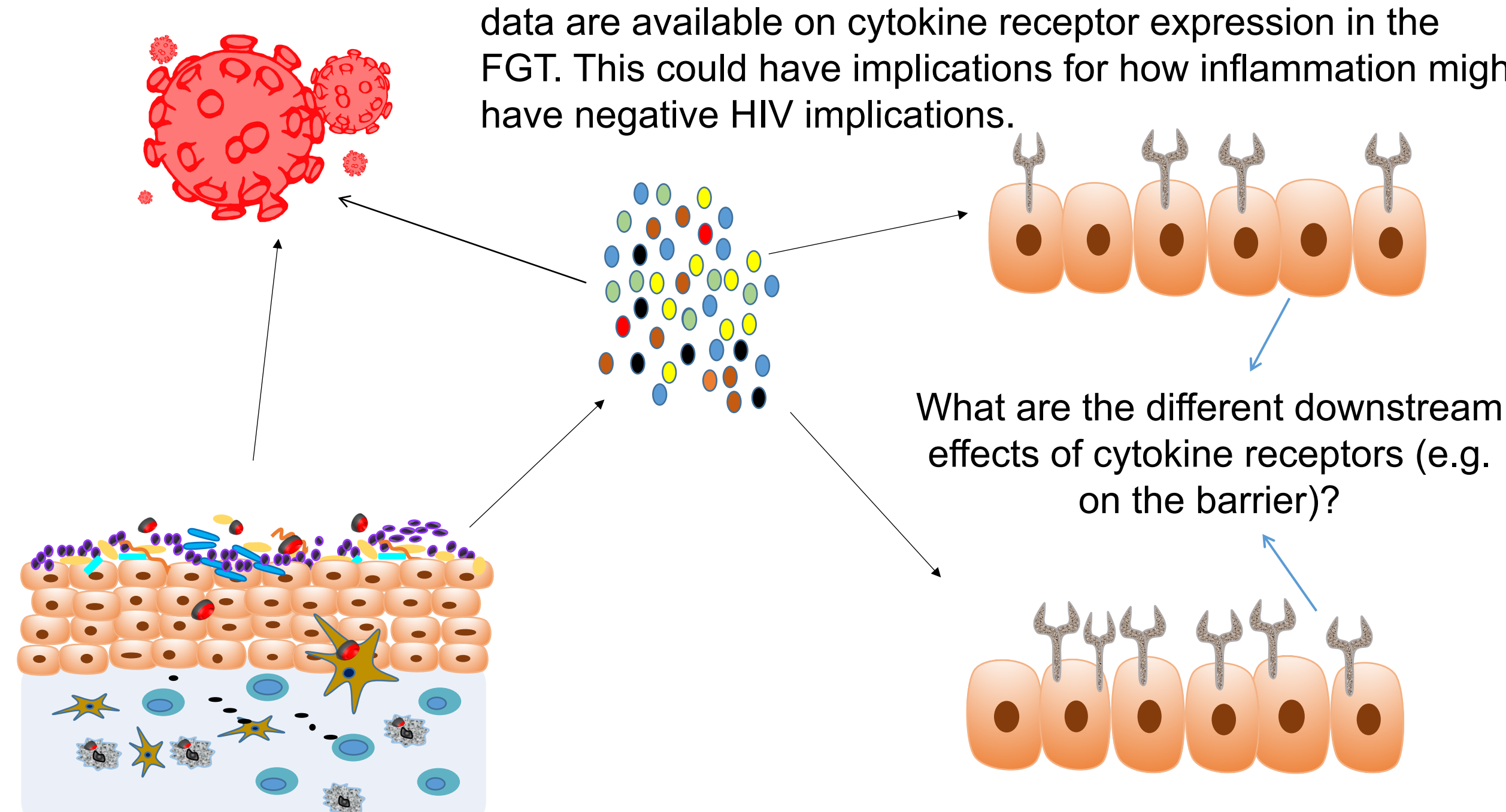
PARTICIPANT RECRUITMENT, SAMPLE COLLETION AND PROCESSING

Adolescent girls and young women
Age: 14-24 years
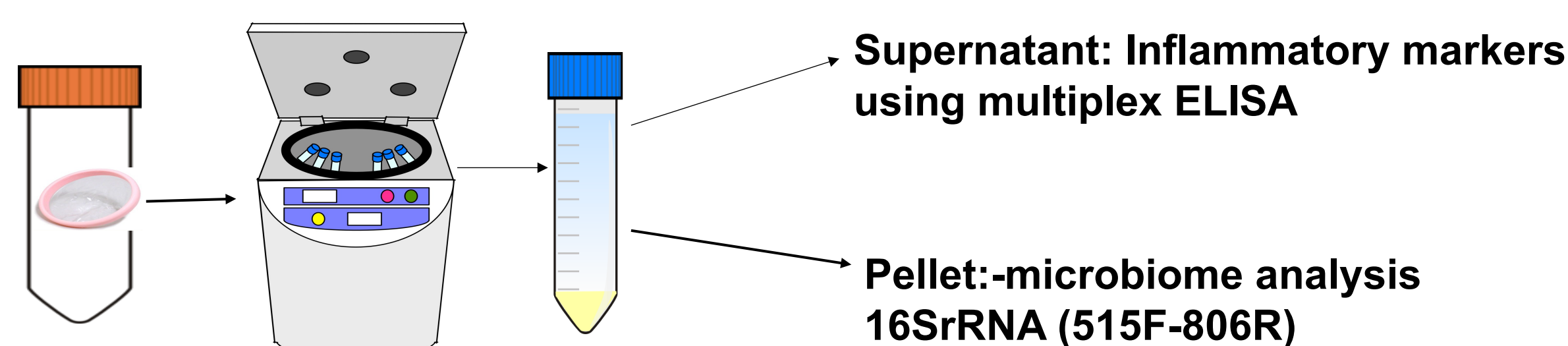
Non-sex worker
N=34

Transactional group
N=19

Female sex worker
N=43

➢ Duration of sample collection: 1.5-2 hours
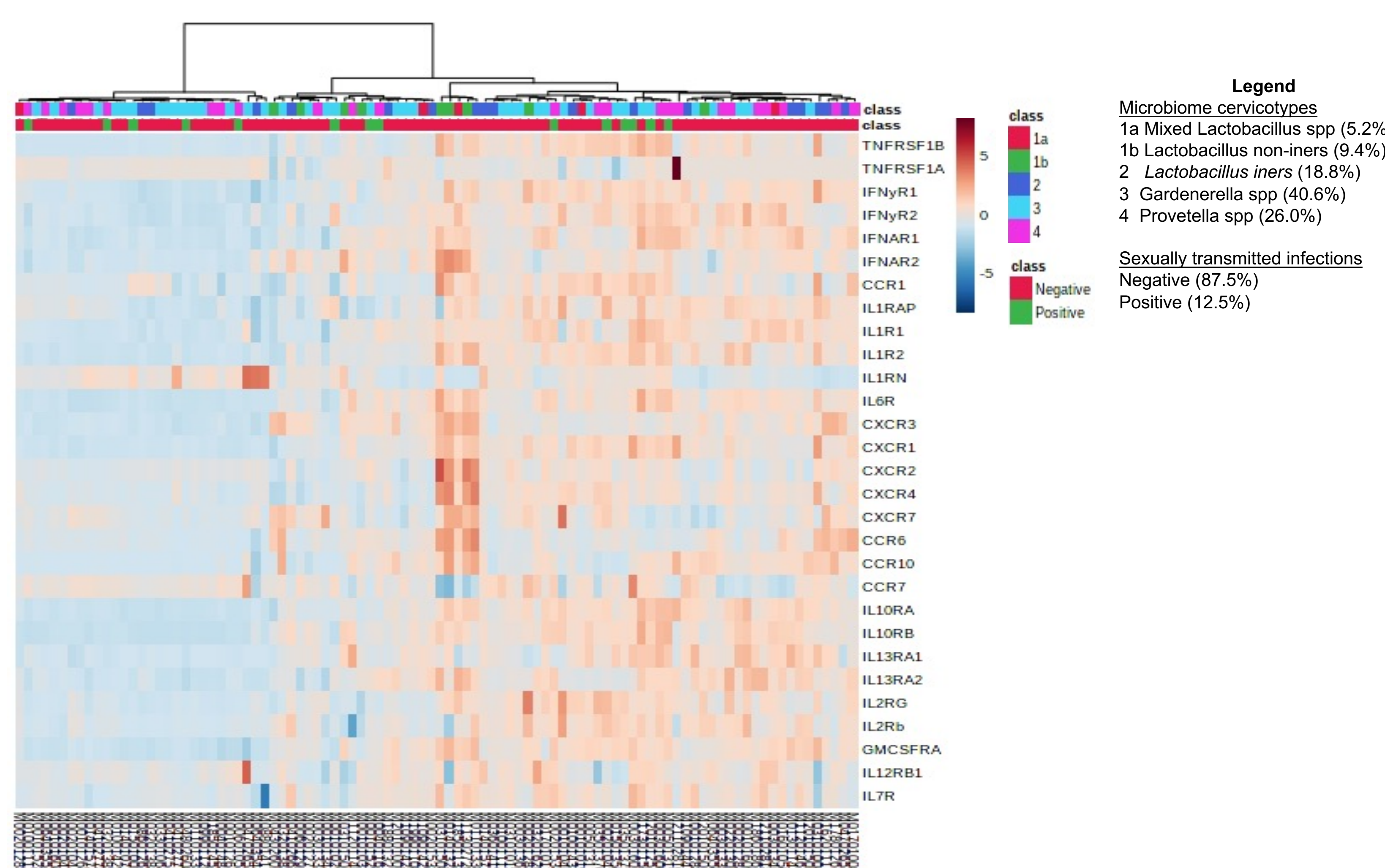➢ Amount of fluid; 50-250ul

Supernatant: Inflammatory markers using multiplex ELISA

Pellet:-microbiome analysis 16SrRNA (515F-806R)

RESULTS

Subject characteristics

|	CASUAL	TRANSACTIONAL	FSW
N	34	19	43
Age*	20 (16,22)	18 (17,20)	20 (19,23)
HIV status	5.9% (2)	5.3%(1)	9.3%(4)
STI infection	14.7%(5)	10.5%(2)	16.3% (7)
Completed primary school	67.64% (23)	78.94% (15)	76.74% (33)
Non-optimal microbiota	58.8% (20)	63.2% (12)	74.4% (32)
Douching	55.88% (19)	31.57% (6)	60.46% (26)
Unprotected exposure (Y/N)	26.5% (9)	36.8% (7)	44.2% (19)
DMPA	11.8% (4)	10.5% (2)	32.6% (14)

Table 1. Approximately 75% of the participants had attained the minimum level of education. Unprotected sex events were more prevalent among the casual group and the transactional.

Unsupervised clustering of microbiome and STI infection by gene expression
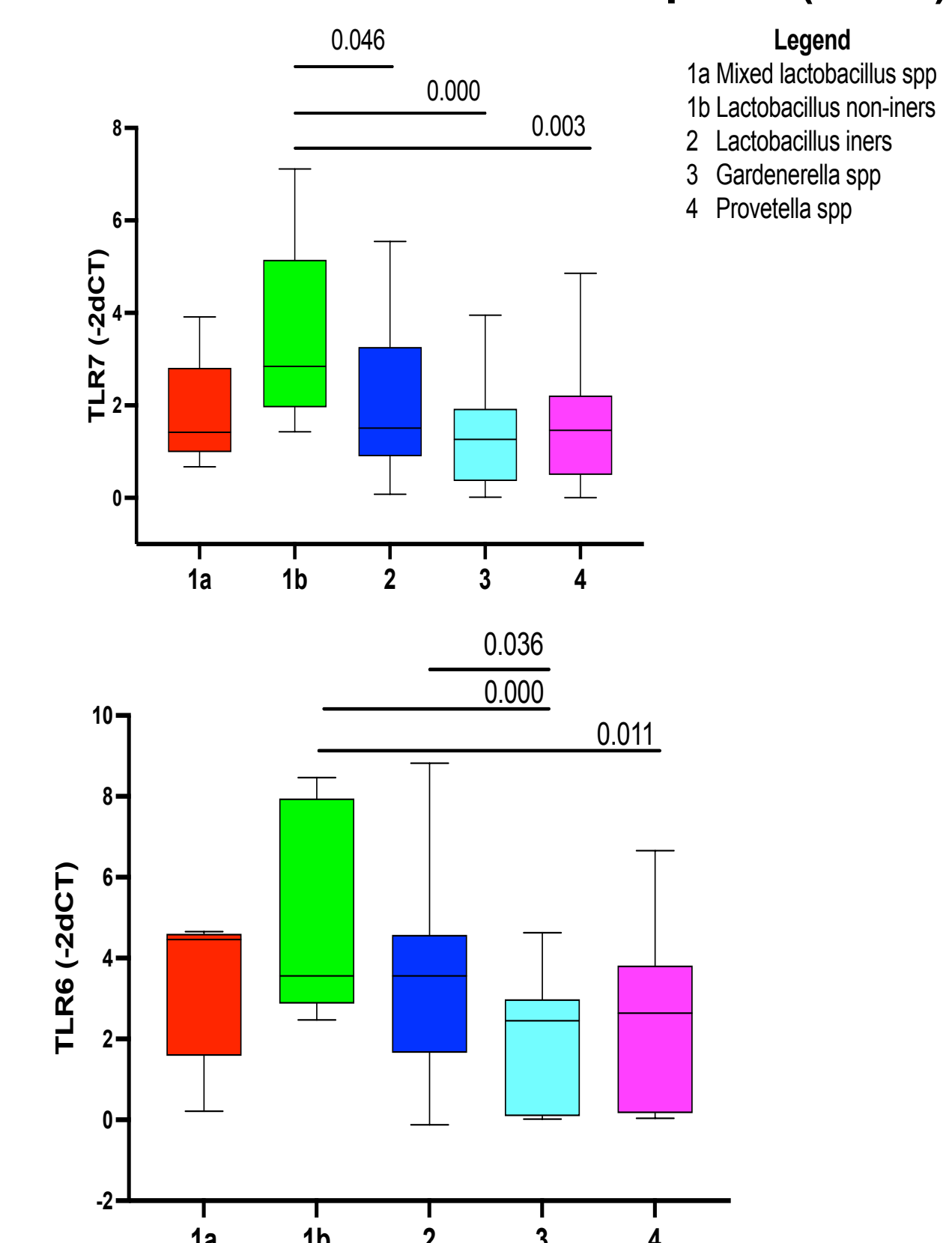

Legend
Microbiome cervicotypes
1a Mixed Lactobacillus spp (5.2%)
1b Lactobacillus non-iners (9.4%)
2 *Lactobacillus iners* (18.8%)
3 Gardenerella spp (40.6%)
4 Provetella spp (26.0%)

Sexually transmitted infections
Negative (87.5%)
Positive (12.5%)

Figure 1: Cytokine receptor expression was significantly upregulated among women with lactobacillus dominant microbiome (CST 1a,1b and 2) while it was down regulated in women who had a diverse microbiome (CST3 and 4).

### Impact of alpha diversity on cytokine and chemokine receptor expression
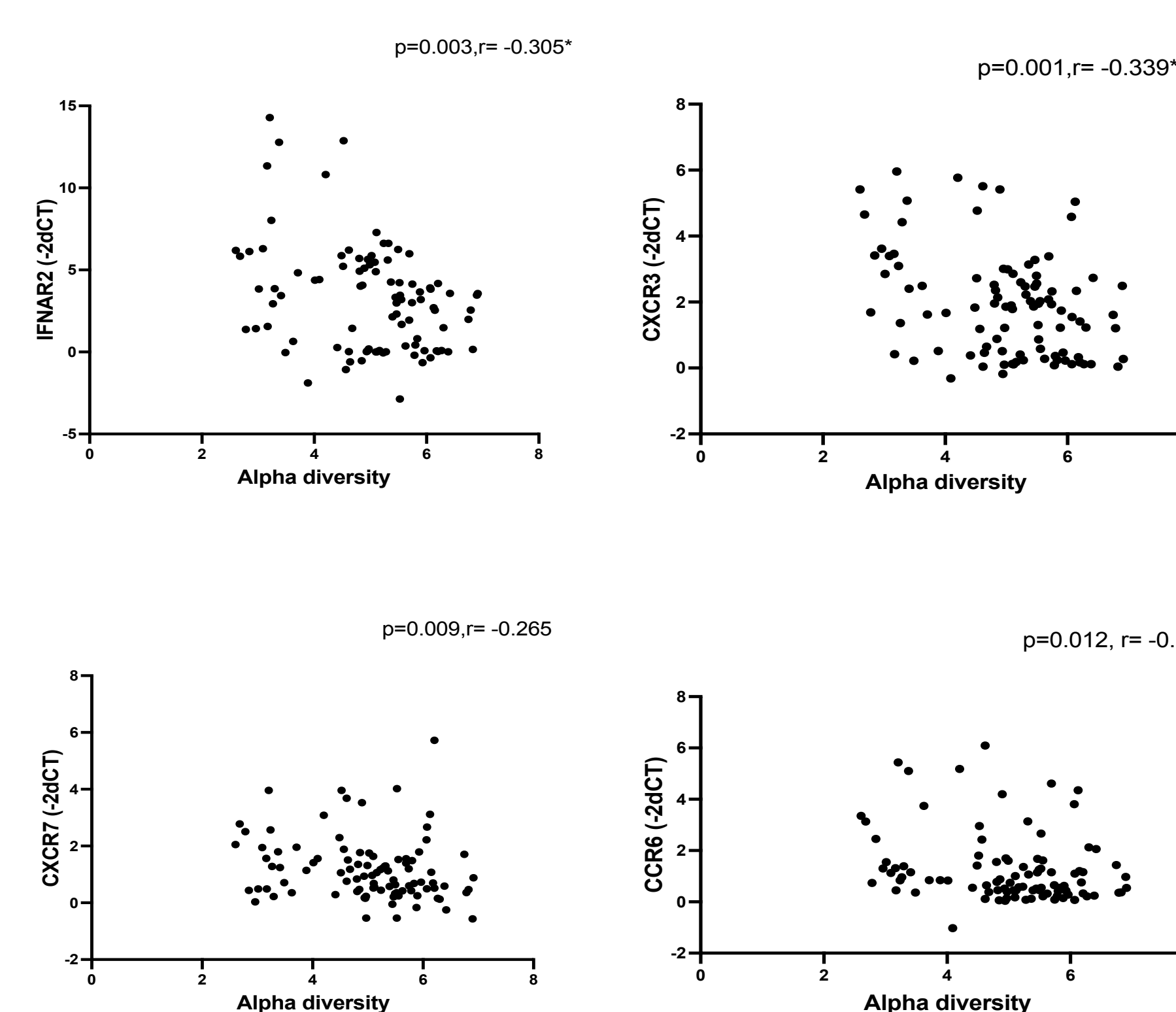
Figure 2a: Participants with diverse intra-individual microbiome diversity had decreased expression of cytokine and chemokine receptors.

Impact of microbiome on Toll like receptors (TLRs)

Legend
1a Mixed lactobacillus spp
1b Lactobacillus non-iners
2 Lactobacillus iners
3 Gardenerella spp
4 Provetella spp

Figure 2b: Participants with Lactobacillus non-iners dominant microbiome had increased expression of TLR6, TLR7 and TLR2.

Impact of study group on cytokine and chemokine receptor expression
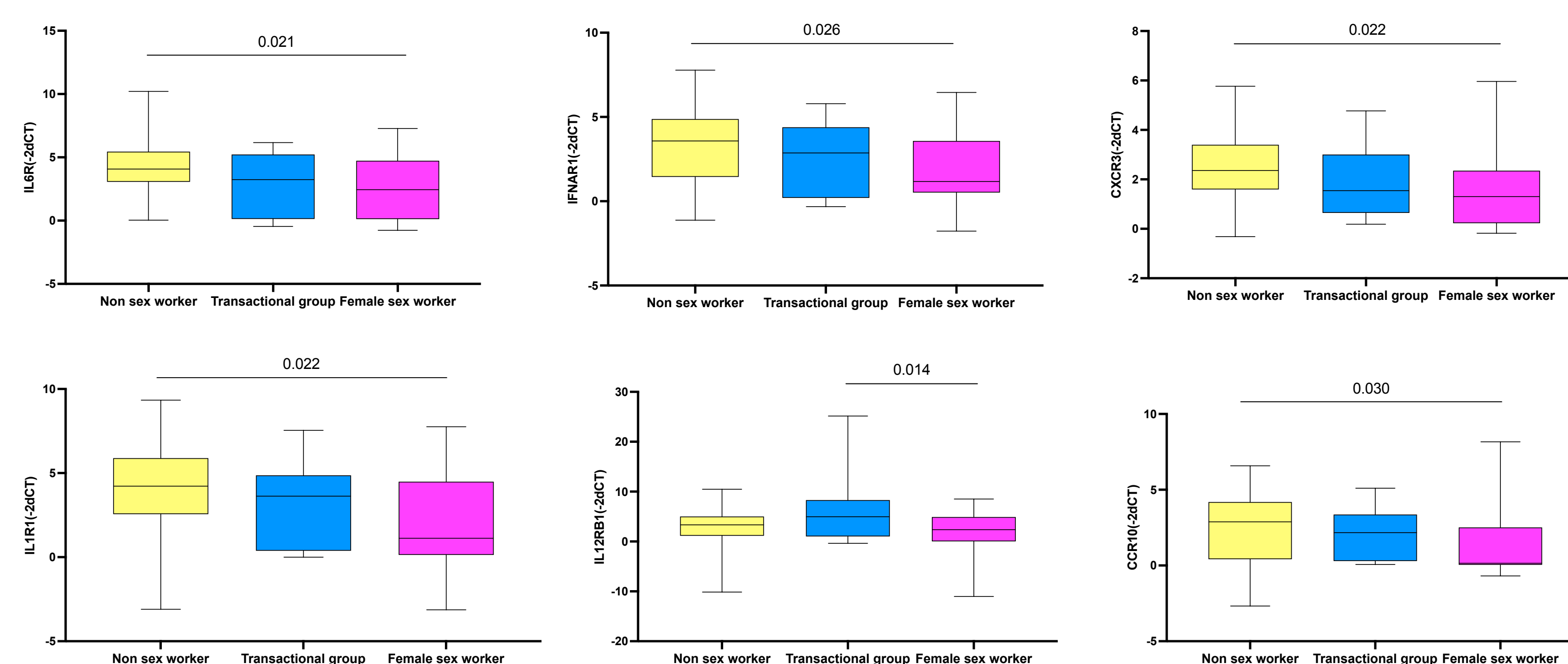
Figure 3: Study participant in the non-sex worker group had high expression of IL6R,IFNAR1,CXCR3,IL1R1 and CCR10 whereas those in the transactional group had increased expression of IL12RB1

CONCLUSION

➢ Decreased cervicovaginal cytokine receptor and TLR expression was observed in AGYW with an STI and/or non-optimal vaginal microbiota.
➢ This may represent a mechanism used to avoid immune detection.
➢ Understanding the regulation of cytokines and their receptors in tandem may be key to understanding mucosal signaling that leads to increased risk of HIV infection and adverse reproductive health outcomes.

REFERENCES

➢ McKinnon, L. R. *et al*. Genital inflammation undermines the effectiveness of tenofovir gel in preventing HIV acquisition in women. *Nat. Med.* (2018).
➢ Ye, C. J. *et al*. Intersection of population variation and autoimmunity genetics in human T cell activation. *Science* **345**, 1254665 (2014).