Women with HIV have a lower frequency of monocyte reservoir reactivation compared to men with HIV

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BACKGROUND

There are known sex differences in HIV infection, latency, and immune responses[1]. Women are overrepresented in some cohorts of immune controllers of HIV, raising questions about whether sex differences in immune responses track with features like spontaneous viral control[2]. Previous studies addressed sex differences in the CD4 T cell reservoir and report that though men and women have similar HIV DNA levels in CD4s, there are sex-based differences in latency and reactivation[3,4]. Therefore, we sought to assess if there were sex-differences in latency and reactivation in the monocyte reservoir in a large cohort of people with HIV (PWH).

METHODS

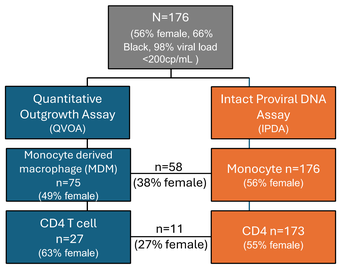


Figure 1. Participant overview and sample workflow. Biospecimen data were obtained from participants enrolled in a study in Baltimore, MD. Blue boxes illustrate samples used in QVOA, orange IPDA, the lines connecting the boxes illustrate the number of participants with sufficient sample for both assays.

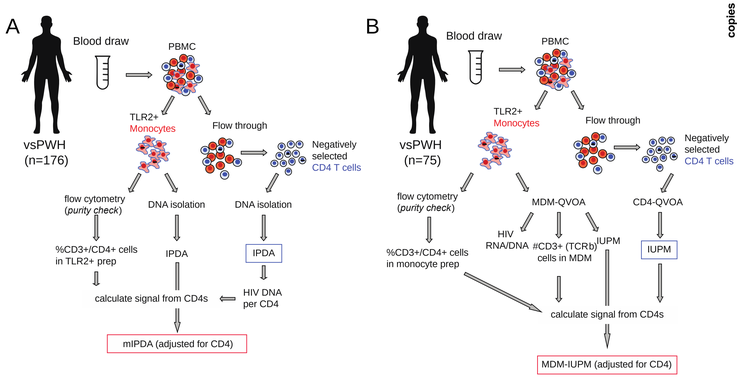
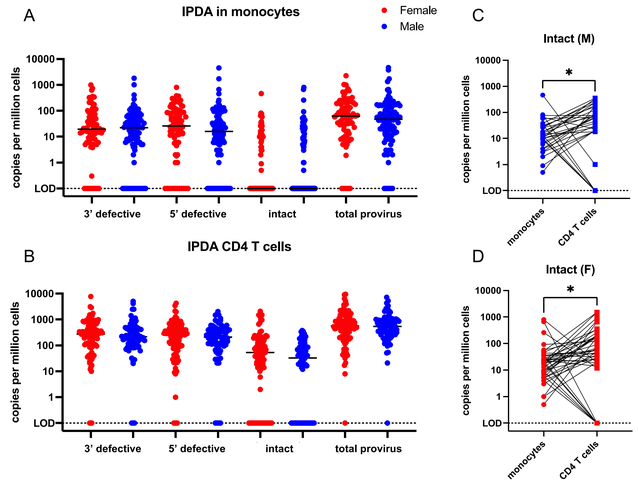


Figure 2. IPDA and MDM-QVOA methodology. (A) We performed IPDA as described[4-6] to measure genetically intact and defective (3′ deleted/ hypermutated and 5′ deleted) proviral DNA with minor modifications made for monocyte assessment[5,6]. Red and blue boxes indicate data reported in Fig 3. (B) The MDM-QVOA assay was completed as previously described[6]. The red and blue boxes indicate data reported in Fig 4.

The latent HIV reservoir in monocytes is less **likely to reactivate in women with HIV**, *despite* having **equivalent levels of HIV DNA** compared to men with HIV.

RESULTS



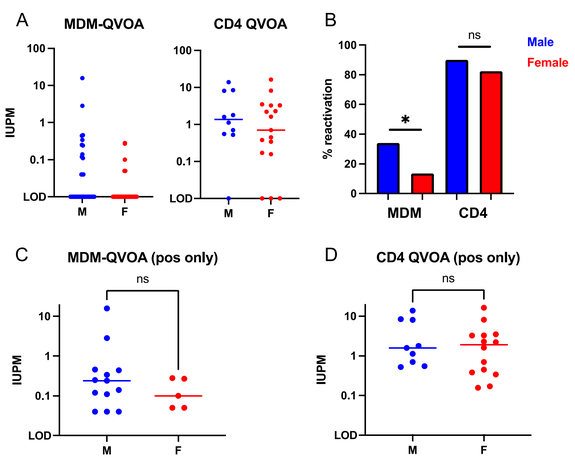


Figure 3. IPDA measures in monocytes and CD4 T cells from virally suppressed men and women with HIV. 94% of PWH had detectable provirus in monocytes (median[md]= 58 copies[cp]/1e6) with 42% having detectable intact provirus (md=17cp/1e6) vs. 99% (554cp/1e6) and 73% (69cp/1e6) in CD4s, respectively. No sex differences were observed in the frequency of PWH that had detectable provirus or with the absolute quantities observed in monocytes (A) or CD4s (B). When comparing participants with intact reservoirs in monocytes, both men (C) and women (D) had larger reservoirs in CD4s. However, 12% of men and 17% of women, had larger intact reservoirs in monocytes compared to CD4s and there were no differences in CD4:monocyte intact ratio (not shown).

Figure 4. QVOA measures in monocyte-derived macrophages (MDM) and CD4 T cells from virally suppressed men and women with HIV. 24% of PWH had reactivatable monocyte reservoirs as measured by MDM-QVOA, while 85% had reactivatable CD4 reservoirs (A). The frequency of reactivation was significantly lower in women compared to men with HIV (13% vs 32%, $\chi 2=4.4$, P=0.036, B). Of the participants with reactivatable reservoirs, the infectious units per million (IUPM) values did not differ between sexes in either MDM (C) or CD4 T cells (D).

CONCLUSIONS

Long–lived cellular reservoirs of latent HIV are a critical obstacle to viral eradication. Our findings demonstrate that approximately 44% of vsPWH harbor intact HIV DNA in monocytes, 24% of which are replication competent. We report for the first time, that monocyte reservoirs in women with HIV are less likely to reactivate (13% vs 32%, $\chi 2=4.4$, P=0.036) despite having equivalent levels of HIV DNA compared to men with HIV. Though we did not observe reactivation differences in CD4 T cells in our cohort, as has been previously described[3,4], it was not the main objective of the study and therefore significantly fewer CD4-QVOAs were completed. This study complements our previous work where we demonstrate that the monocyte reservoir is stable and persistent in a small cohort of long-term virally suppressed PWH[5]. Future directions include studying reactivation conditions in male and female MDM, eg. estrogen and innate sensing, to determine why women are less likely to reactivate compared to men. *This sex-related difference in HIV reactivation has significant implications for the design and measurement of curative interventions in women with HIV.*

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