Acute Bacterial STIs Enhance HIV-1 Reservoir Reactivation and Immune Dysregulation in ART-suppressed PLWH

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BACKGROUND

- The persistent HIV-1 reservoir in CD4+ T cells remains the major obstacle to cure, yet the mechanisms regulating reservoir reactivation and immune surveillance are not fully understood
- Sexually transmitted infections (STIs) induce mucosal inflammation and systemic immune activation that may alter reservoir dynamics and compromise HIV-specific immune responses.
- **Our objective** was to analyze how acute bacterial STIs influence HIV-1 reservoir reactivation and immune cell dysfunction in ART-suppressed PLWH.

METHODS

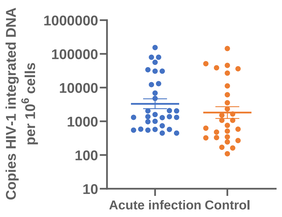
- Comparative, observational, cross-sectional study comprising PLWH with acute bacterial STI (*Chlamydia trachomatis or Neisseria gonorrhoeae*) (n=27) and uninfected controls (n=26).
- HIV-1 reservoir size was quantified by ddPCR.
- Proviral reactivation was assessed in purified CD4+ T cells by measuring p24-gag expression.
- CD4+ memory subsets and SAMHD1 phosphorylation were evaluated by flow cytometry.
- Immune exhaustion, senescence, and activation markers were assessed on CD4+ and CD8+ T cells by multiparametric flow cytometry.
- Plasma levels of cytokines were quantified by multiplex bead-based immunoassay.

RESULTS

1) **Table 1.** Baseline characteristics of participants. Acute bacterial STIs included proctitis (*C. trachomatis* 52%, *N. gonorrhoeae* 48%) and urethritis (*C. trachomatis* 68%, *N. gonorrhoeae* 32%).

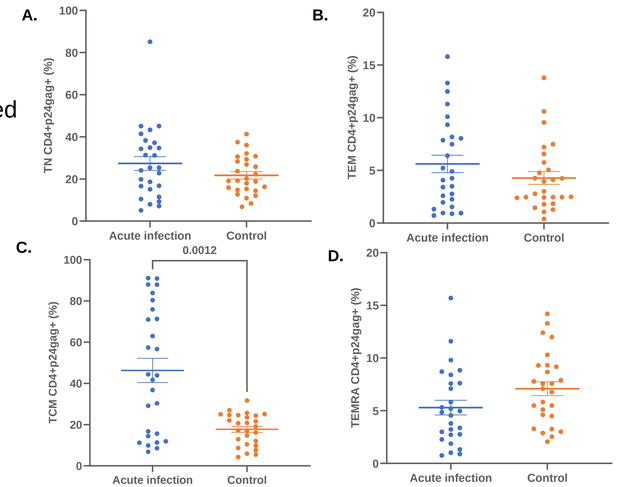
	PLWH-Acute infection (n=27)	PLWH-Control (n=26)	p value
Demographic characteristics			
Age, median (IQR)	39 (30-42)	42 (33-49)	0.33
Male, n (%)	27 (100)	26 (100)	1
HIV Infection			
Time HIV-1 infection (years), median (IQR)	8 (6-14)	9 (6-14)	0.96
CD4/CD8 ratio, median (IQR)	0.98 (0.7-1.2)	0.88 (0.6-1.04)	0.31
CD4 count (cells/mL), median (IQR)	769 (561-1128)	818 (647-892)	0.92
CD8 (cells/mL), median (IQR)	765 (552.5-1169)	934 (557-1159)	0.70
Time with ART (years), median (IQR)	7 (9-9)	8 (6-12)	0.55

2) **Figure 1.** No significant differences were observed in HIV-1 proviral reservoir size between groups.

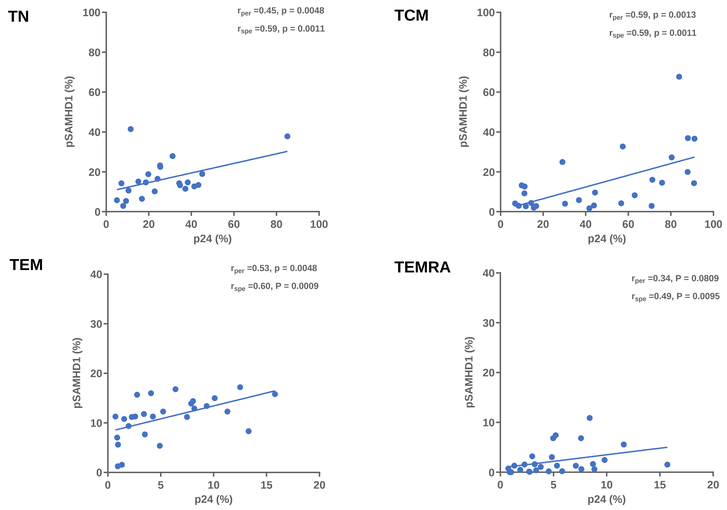


Acute bacterial STIs may act as transient but biologically meaningful triggers of HIV reservoir destabilization, promoting viral reactivation and immune dysfunction despite suppressive ART

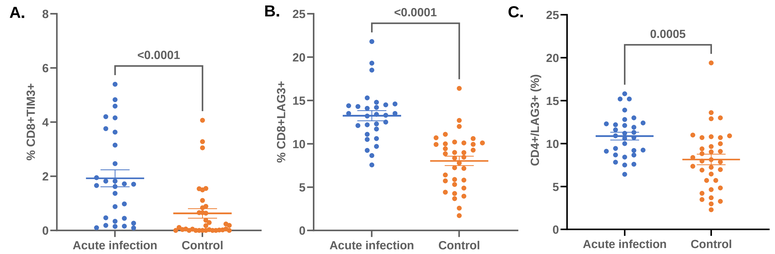
3) **Figure 2.** Central memory CD4+ T cells (TCM) in the STI-positive group exhibited significantly higher proviral reactivation capacity (2.5-fold, p=0.0012) **(C)**



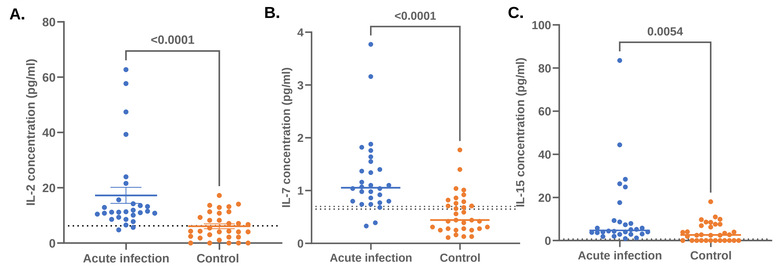
4) **Figure 3.** Replication levels positively correlated with SAMHD1 phosphorylation in all CD4+ T-cell memory subsets



5) **Figure 4.** STI-positive individuals showed higher levels of CD8+TIM-3+ (2.8-fold; p<0.0001), CD8+LAG-3+ (1.7-fold; p<0.0001) and CD4+LAG-3+ (1.3-fold; p=0.0005) T cells compared to controls.



6) **Figure 5.** Plasma quantification revealed increased levels of IL-2 (p<0.0001), IL-7 (p<0.0001), and IL-15 (p=0.0054) in STI-positive group.



CONCLUSIONS

- In ART-suppressed PLWH, acute bacterial STIs did not expand the HIV-1 reservoir but significantly boosted proviral reactivation in central memory CD4+ T cells, a key compartment for long-term viral persistence.
- SAMHD1-mediated antiviral restriction was impaired in both naïve and effector memory CD4+ T cells, likely lowering their intrinsic defense and increasing susceptibility to new infection events, which could facilitate reseeding of the reservoir.
- Elevated immune checkpoint expression and cytokines indicate a pro-inflammatory milieu that may drive both immune dysfunction and viral reactivation.
- These findings highlight acute STIs as transient but biologically meaningful events capable of destabilizing reservoir latency.
- It is important a rigorous STI management in PLWH to limit immune exhaustion and support HIV cure strategies.

STIs can reactivate dormant HIV and weaken immune defenses in people on effective treatment

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