Syphilis Co-infection Is Associated with T-Cell Remodeling and Persistent CD8⁺ Activation During Antiretroviral Therapy in People Living With HIV

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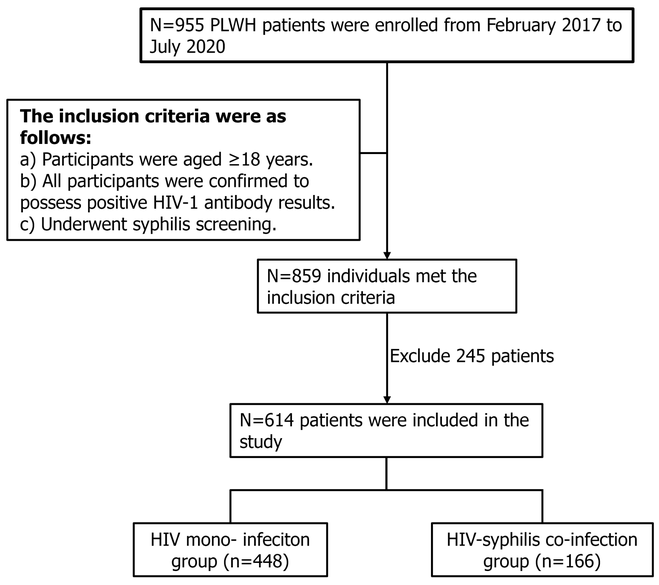
Background

Co-infecting pathogens can establish complex immunological interactions that reshape host immune landscapes and influence the trajectory of chronic infections. Syphilis is a frequent co-infection in people living with HIV (PLWH), but its long-term effects on immune reconstitution and T-cell functional remodeling during antiretroviral therapy (ART) remain poorly characterized.

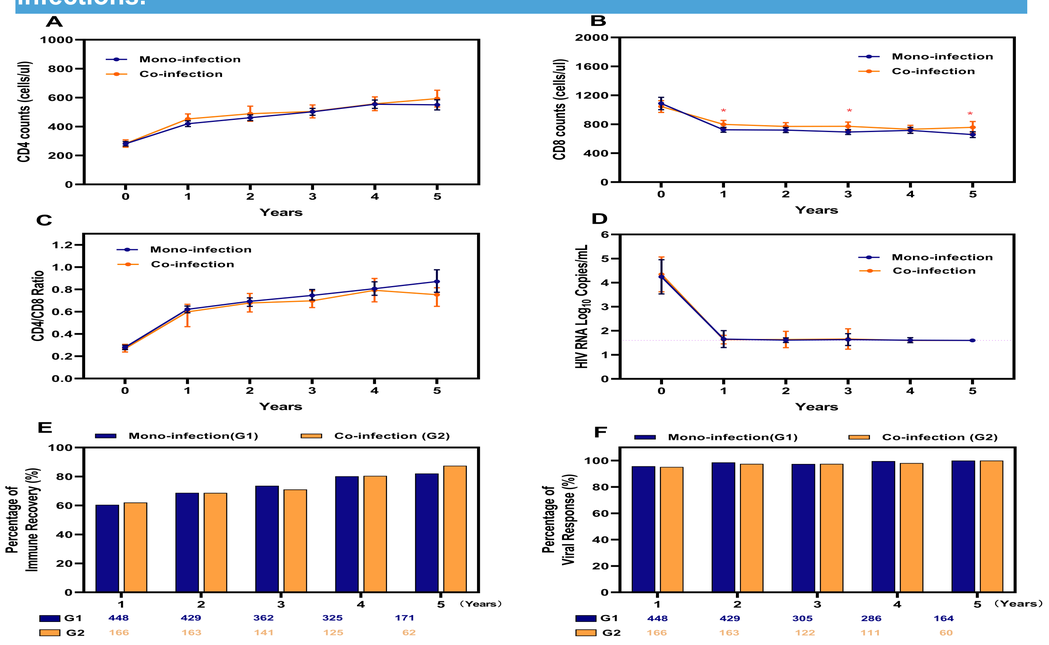
Methods



This was a multicenter retrospective study based on prospectively collected specimens, with a long-term follow-up of up to five years. A total of 614 PLWH were included, of whom 166 (27.0%) had syphilis co-infection. Virological outcomes, CD4⁺ /CD8⁺ T-cell recovery, and long-term ART responses were analyzed. Detailed longitudinal immunophenotyping and functional assays were also performed at baseline and after ART initiation.

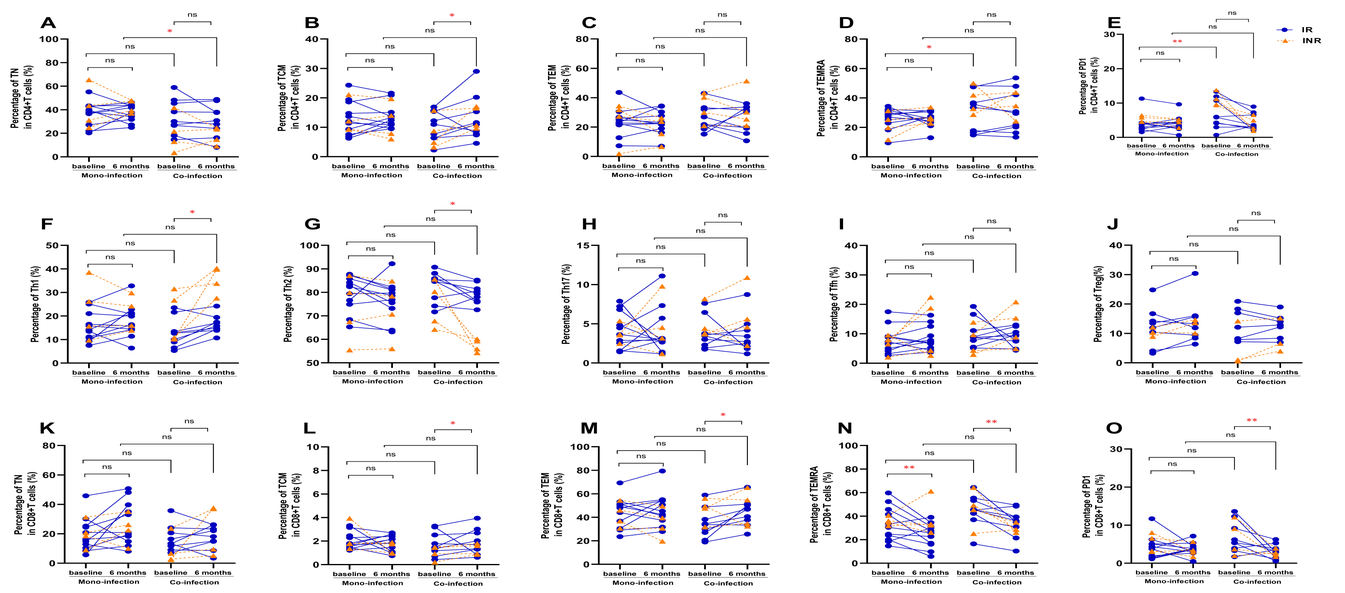
Resuluts

1.Comparable long-term immune recovery and viral response following ART were found between HIV mono-infected and HIV/syphilis co-infected patients, except for higher CD8⁺ T cell levels in the co-infected group, as shown by demographic and laboratory characteristics confirming ART effectiveness despite co-infections.



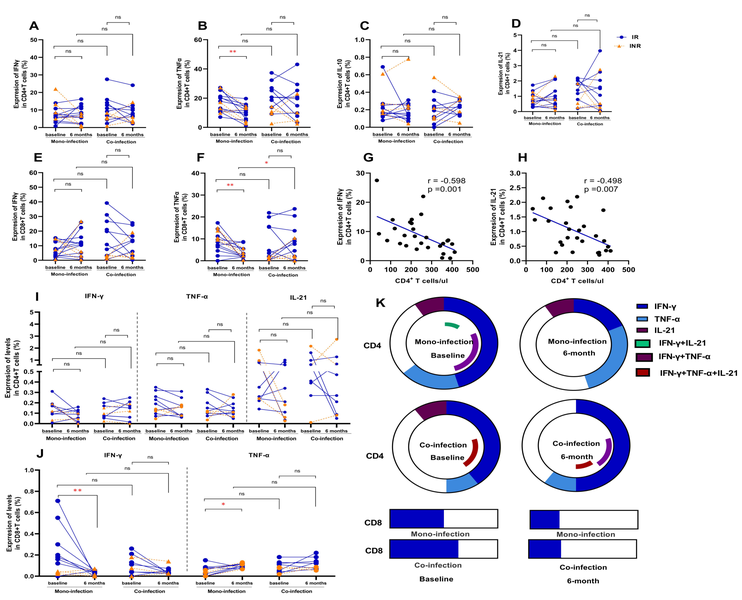
(A) Longitudinal changes in CD4+ T-cell counts (cells/μL). Both groups showed a gradual increase during ART. (B) Longitudinal changes in CD8+ T cell counts (cells/μL). A gradual decline was observed in both groups, with a more pronounced decrease in the mono-infection group. (C) Longitudinal changes in the CD4/CD8 ratio, demonstrating an upward trend in both groups. (D) Longitudinal changes in plasma HIV RNA viral load (log_{10} copies/mL). (D) Longitudinal changes in plasma HIV RNA viral load (log10 copies/mL). (E) Proportion of individuals achieving immune recovery (IR) following 5 years post-ART. Immune recovery (IR) defined as a sustained CD4⁺ T cell counts of ≥350 cells/μL in individuals undergoing continuous ART with persistent viral suppression. (F) Proportion of individuals achieving viral response at 5-year post-ART. Viral response (VR) defined as HIV-1 RNA level below 40 IU/mL detected by real-time polymerase chain reaction (PCR). * 0.01<p < 0.05.

2. Syphilis Co-infection Alters CD4⁺ and CD8⁺ T Cell Subset Responses During Early ART in HIV-infected Individuals.



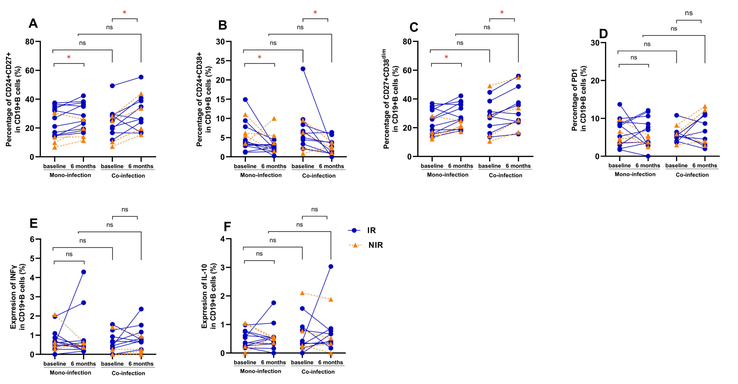
(A–J) Frequencies of CD4⁺ subsets: TN (CD45RA⁺ CCR7⁺), TCM (CD45RA⁻ CCR7⁺), TEM (CD45RA⁻ CCR7⁻), TEMRA (CD45RA⁺ CCR7⁻), Th1 (CXCR3⁺), Th2 (CXCR3⁻ CCR6⁻), Th17 (CCR6⁺), Tfh (CXCR5⁺), Treg (CD25⁺ CD127^{low}), and PD-1 expression at baseline and 6 months. (K–O) Frequencies of CD8⁺ subsets: TN, TCM, TEM, TEMRA, and PD-1 expression at baseline and 6 months. Peripheral blood samples were analyzed by flow cytometry. Blue lines with circles indicate immune recovery (IR); orange lines with triangles indicate immune non-recovery (INR). Because the number of INR patients was relatively small, statistical analyses were not performed to avoid potential Type II errors due to insufficient statistical power. * 0.01 < p < 0.05, **0.001 < p < 0.01, ns, no significant.

3. HIV/Syphilis Co-infection is Associated with Sustained TNF-α Expression in CD8⁺ T Cells Despite ART



(A-D) CD4⁺ T-cell responses to polyclonal stimulation (PMA/ionomycin): frequencies of IFN-γ, TNF-α, IL-10, and IL-21 producers at baseline and 6 months. (E–F) CD8⁺ T-cell responses to polyclonal stimulation: frequencies of IFN-γ and TNF-α producers at baseline and 6 months. (G–H) Correlations of CD4⁺ IFN-γ⁺ and IL-21⁺ cells with baseline CD4 counts. (I–J) HIV peptide-specific stimulation: frequencies of cytokine-producing CD4⁺ (IFN-γ, TNF-α, IL-21) and CD8⁺ (TNF-α, IFN-γ) T cells. (K) Positive rates of HIV peptide-specific responses in CD4⁺ (IFN-γ, TNF-α, IL-21) and CD8⁺ (TNF-α, IFN-γ) T cells. All values represent percentages within parent CD4⁺ or CD8⁺ T-cell populations. Blue lines with circles denote immune recovery (IR); orange lines with triangles denote non-IR (NIR). * 0.01 < p < 0.05, **0.001 < p < 0.01, ns, no significant.

4. Similar B Cell Subset Dynamics During Early ART in HIV and HIV/Syphilis Co-infected Patients



(A–C) Distribution of CD19⁺ B-cell subsets: memory regulatory (CD24⁺ CD27⁺), regulatory (CD24⁺ CD38^{hi}), and memory (CD27⁺ CD38^{dim}) at baseline and 6 months. (D) PD-1 expression on CD19⁺ B cells at baseline and 6 months. (E–F) IFN-γ and IL-10 expression in CD19⁺ B cells at baseline and 6 months. Blue lines with circles indicate immune recovery (IR); orange lines with triangles indicate non-IR (NIR). * 0.01 < p < 0.05, ns, no significant.

Conclusion

This study highlights that while syphilis co-infection does not impair virological suppression or CD4⁺ T cell recovery during ART, it is associated with sustained CD8⁺ T cell activation, altered immune phenotypes, and persistent pro-inflammatory cytokine production. These findings underscore the importance of routine STI screening, tailored management of syphilis recurrence, and close monitoring of immune function in co-infected PLWH. Future multicenter, long-term, and multi-omics studies are warranted to elucidate the mechanisms underpinning persistent immune activation in this population and to explore potential immunomodulatory strategies.

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