Extended-Release Naltrexone Attenuates Inflammatory Signatures in PWH with Opioid Use Disorder

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BACKGROUND

Chronic opioid use among people with HIV (PWH) remains an ongoing public health crisis. The interaction between opioids and HIV may exacerbate HIV-associated immune dysregulation and chronic inflammation, increasing the risk of both AIDS-related and non-AIDS-related morbidity and mortality. Treatment for opioid use disorder (OUD) includes opioid agonists such as buprenorphine or methadone, commonly referred to as treatment-as-usual (TAU), and the long-acting opioid antagonist extended-release naltrexone (XR-NTX). We investigated if OUD treatment regimens impact immune regulation in PWH.

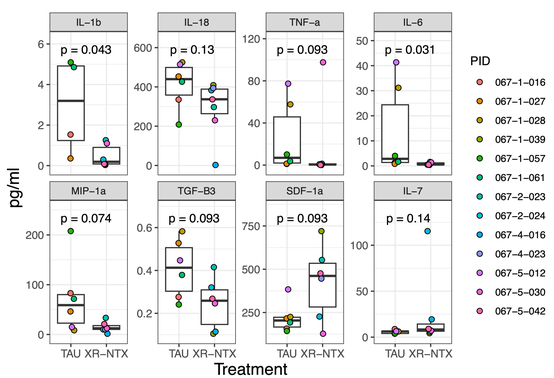
METHODS

Participants from open-label randomized CTN-067 CHOICES trial underwent ART initiation or optimization at enrollment, and treatment for four-to-six months with TAU (n=6) or XR-NTX (n=9). Blood samples were analyzed 6-month post-treatment initiation and included plasma-based cytokine analysis and peripheral blood mononuclear cell (PBMC) transcriptomic and epigenetic analysis using bulk RNA-seq and single-cell RNA/ATAC sequencing.

Characteristics	XR-NTX (N = 9)	TAU (N = 6)
Age (years)	51	53
Sex at birth (% male)	7 (77.8%)	4 (66.7%)
HIV Viral load - Study baseline (cps/ml)	3905	1950
HIV Viral load - Month 6 (cps/ml)	20	114
CD4+ T cell count - Study baseline (cells/mm3)	209	253
CD4+ T cell count - Month 6 (cells/mm3)	329	407

RESULTS

Figure 1. Plasma cytokine milieu from XR-NTX-treated individuals showed significantly lower levels of the pro-inflammatory cytokines IL-6 and IL-1β, with trends toward decreased IL-18, MIP-1α, TNF-α, and TGF-β3 when compared to TAU. PID: participant identification.



PWH with opioid use disorder (OUD) treated with the opioid antagonist naltrexone showed decreased inflammatory signatures. This reduction was most pronounced in monocytes and associated with decreased TNF signaling and reduced chromatin accessibility at targets of the transcription factor NF-κB

Figure 2. Functional enrichment analysis of bulk RNA-seq data revealed a downregulation of inflammatory response pathways and upregulation of TGF-β signaling in participants treated with XR-NTX.

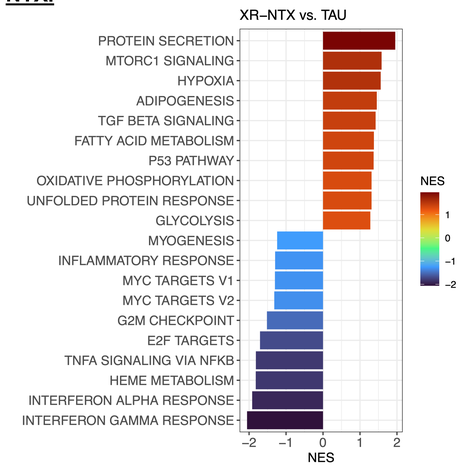


Figure 3. CD4+ and CD8+ T cells show a higher expression of OPRM1 which encodes the μ(*mu*)-opioid receptor. Naltrexone is known to act as an antagonist of TLR4, which is expressed at high levels in different myeloid populations.

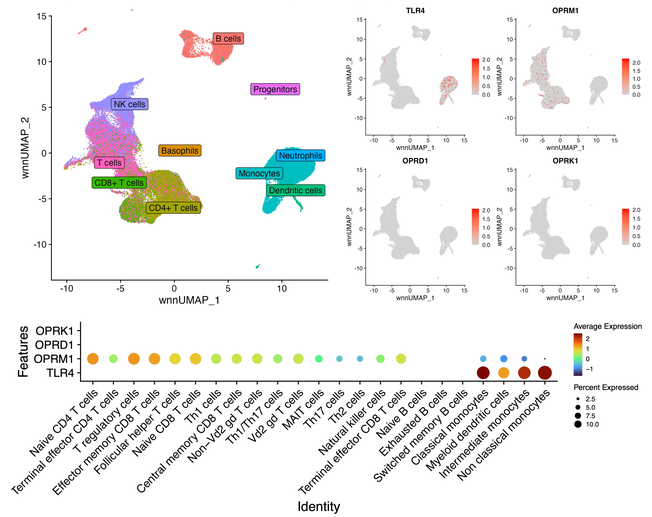


Figure 4. At single-cell level, downregulation of inflammatory pathways in XR-NTX-treated PWH was observed in several innate (monocytes) and adaptive (T and B cells) immune subsets, with reduced expression of NF-κB and interferon-related pathways.

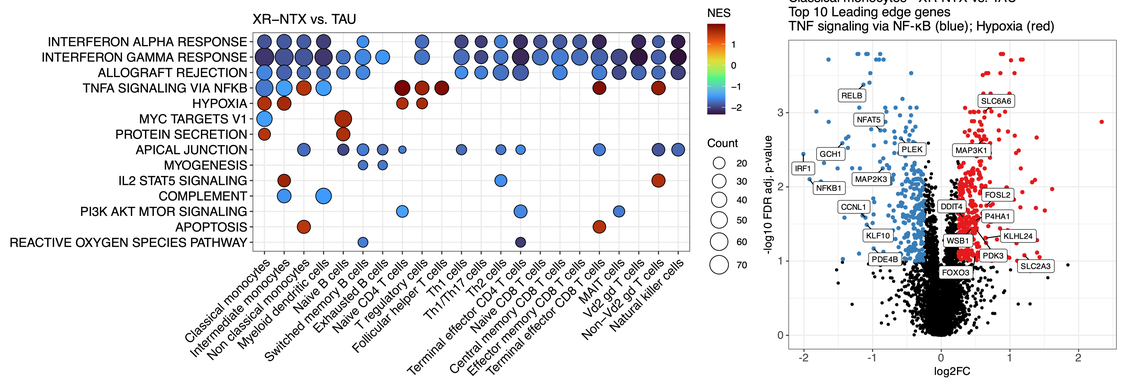
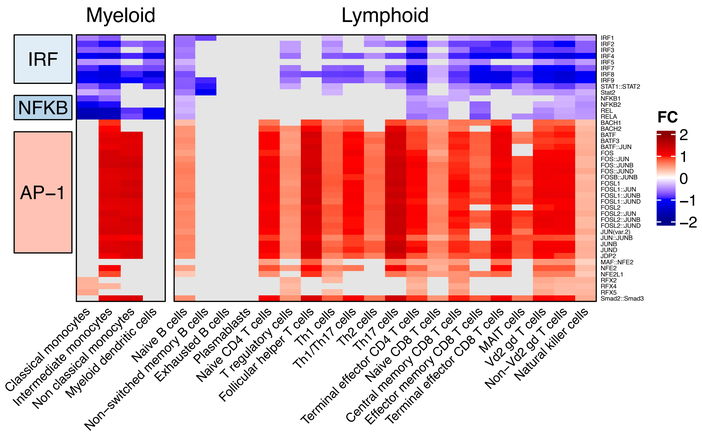


Figure 5. Chromatin accessibility in monocytes revealed closed NF-κB transcription factor binding sites in XR-NTX-treated participants, along with IRF targets, suggesting epigenetic remodeling consistent with reduced inflammation.



CONCLUSIONS

- Taken together, these findings indicate that XR-NTX treatment attenuates the inflammatory signatures contributing to the amelioration of immune function in PWH with OUD receiving ART.
- The transcription factor NF-κB, an upstream regulator of inflammation, is repressed in monocytes at gene expression and epigenetic level. These observations suggest that NF-κB have a central role in the overall decrease of inflammatory signatures in XR-NTX treated PWH.
- These highlight XR-NTX as a promising therapeutic strategy to reduce chronic inflammation and improve disease management in PWH with OUD.

FINANCIAL SUPPORT

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NIH National Institute of Allergy and Infectious Diseases

PLAIN LANGUAGE SUMMARY

People with HIV and opioid use disorder who were treated with naltrexone showed lower inflammation compared with standard care. This may work together with HIV treatment to improve immune homeostasis and to decrease inflammation.