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BACKGROUND

People with HIV (PWH), even those who start ART early and restore CD4 counts, remain at higher risk for TB and infection-related cancers.

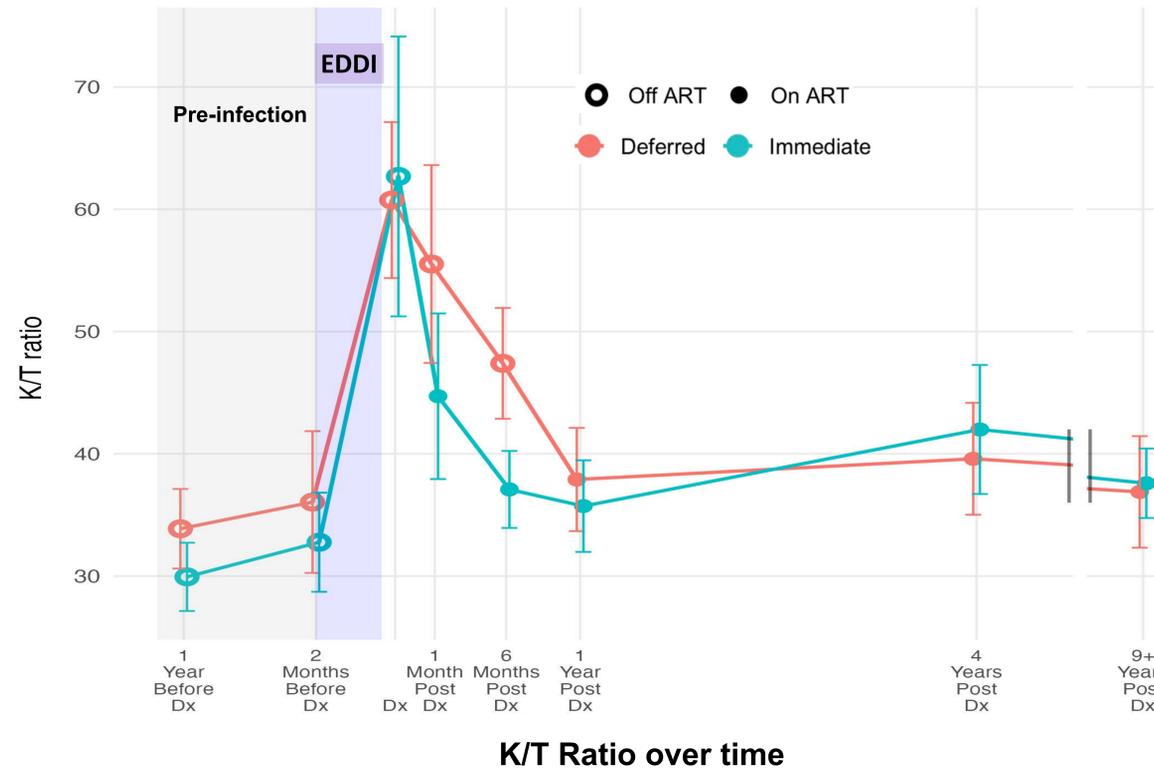
HIV induces IDO, an enzyme in the kynurenine pathway (KP), which leads to increases in kynurenine/tryptophan (K/T) ratios and related metabolites. Elevated K/T is associated with immuno-suppressive effects, including decreased T cell proliferation, and increased Treg/Th17.

Whether KP effects underlie the persistent immunosuppression in treated PWH is unclear, as studies to date compare PWH to imperfectly matched individuals without HIV. To address this, we used data from the Sabes/MERLIN study. This acute infection cohort provides a rare opportunity to directly compare each participant's post-acquisition K/T to their K/T values before HIV acquisition.

METHODS

2109 Peruvian MSM and transgender women without HIV were followed (2013-2016) with monthly tests for HIV (serology and RNA). 216 participants with incident acute (HIV-seronegative, RNA+) or recent (HIV-seropositive, w/ RNA-negative test in past 3 months) HIV infection were randomized to start ART immediately or defer for 24 weeks (or when Peruvian ART initiation threshold was met). EDDI (estimated date of HIV acquisition) was calculated using a published algorithm and all HIV test results with associated test uncertainty.

Plasma from 88 participants was analyzed before, at and after HIV Dx. We measured K/T (nM/μM) ratios by liquid chromatography-tandem mass spectrometry and cytokines by MSD. We used paired t tests and segmented linear mixed-effects models for time effects and Pearson's correlation for relationship of K/T to CD4/CD8, VL, HIV DNA and cytokines.



K/T ratio before and after HIV acquisition in early treated participants who were consistently suppressed for up to 10 years on ART. Plotted data are from GEE model with interaction term for ART arm.

K/T rapidly increased after HIV acquisition and then declined. It remained higher than pre-infection values even after 9 years on ART. Higher levels of K/T, which is immunosuppressive, may be linked to increased risk of TB and cancers in PWH, even in those who start ART early.

RESULTS

- K/T at the two pre-Dx timepoints did not differ (p=0.46).
- Compared to baseline values, K/T increased significantly (~2-fold) at HIV Dx (p<0.001) and then decreased.
- K/T remained elevated at 4 and 9+ years compared to preinfection

P value	Baseline vs Year 4	Baseline vs Year 9+
Deferred arm	0.02	0.25
Immediate arm	<0.001	<0.001
Overall	<0.001	0.002

RESULTS (continued)

- K/T did not differ by randomization arm except at 1 and 6 months after diagnosis (p=0.04 and p<0.001, respectively), prior to ART initiation in the deferred arm.
- Associations with K/T ratios were as follows:
 - VL. Significant positive associations with logVL at peak (p=0.02, both arms) and at months 1 and 6 (p=0.003, p=0.001) in the deferred arm
 - CD4/CD8. Significant negative associations at 1 & 6 months (p<0.01 for both), and 1 year (p=0.02) but not at 4 or 9+ years.
 - IP-10. Not associated with K/T before HIV acquisition but significant positive associations were seen at diagnosis, 1 & 6 months (p values < 0.01), 1 year (p = 0.03) and a trend at 4 years (p=0.07).
 - TNFα, MIP-1α, IL-7, IL-12p70, IFNγ, or IL-10 were not associated with K/T at any timepoint (except for TNFα at Dx, p=0.05).
- An individual's K/T values after acquisition (1y, 4y) were correlated with their pre-acquisition (enrollment, 2 months before diagnosis) values (p<0.01), consistent with a potential genetic influence on K/T levels.

CONCLUSIONS

In this exploratory analysis, K/T remains elevated after HIV acquisition even in virally-suppressed, early-treated individuals and thus may drive persistent immune dysfunction in PWH through other soluble mediators (e.g.IP-10), or effects on Treg and Th17 cells. Further studies are warranted.

We gratefully acknowledge all study participants and MSD & Gilead Sciences for ART donation
 Grants; NIH/NIAID R01AI176531, NIDA RO1 DA040532 & R01 DA032106