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Age and viral replication, not vertical HIV acquisition, drive inflammation and T-cell dysfunction in heavily treatment experienced: data from the Prestigio Registry

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Heavily treatment-experienced (HTE) individuals carry a high inflammatory burden, which is potentially increased in those with vertical HIV transmission (VT), due to lifelong viral exposure. We assessed inflammation and T-cell activation/exhaustion/senescence in HTE with VT or horizontal transmission (HT). Interleukin-6 (IL-6) was lower in VT and positively correlated with age. T-cell dysfunction was greater in HTE than people without HIV (PWOH), mainly driven by viremic VT and HT. Age and viral replication, rather than transmission mode, underlie immune dysregulation in HTE.

HTE people with HIV (PWH) are defined as those who harbour a multidrug resistant virus [1]. Antiretroviral resistance to multiple drug classes is strictly dependent on suboptimal treatment exposure which may lead to active HIV replication [2].

Lack of viral control has been independently associated with high levels of inflammation [3] which is an established cause of clinical progression [4]. Of note, residual inflammation persists even in the setting of viral suppression and is linked to the development of noninfectious comorbidities [5].

In keeping with these findings, recent data from our group data have demonstrated that plasma inflammatory burden follows a hierarchical distribution, with the highest levels observed in viremic HTE individuals, intermediate levels in aviremic HTE, and the lowest levels in virologically suppressed PWH without evidence of drug resistance [6]. These results highlight an excess risk of noninfectious comorbidities in HTE, regardless HIV RNA load.

PWH with vertical transmission (VT) are known to experience adherence challenges increasing their risk of developing antiretroviral drug resistance [7,8]. Further, life-long exposure to HIV in this population may fuel systemic inflammation [9] and contribute to the pathogenesis of comorbidities at a younger age [10].

Taken together, these observations lead us to hypothesize that HTE with vertical HIV acquisition feature higher inflammation and T-cell dysfunction than HTE with horizontal transmission (HT).

HTE individuals with either VT and HT were enrolled from the Prestigio Registry [11]. All had documented resistance to nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, and/or integrase strand transfer inhibitors. Participants were further classified according to virological status at sampling as suppressed (viral load, VL $<$ 50 cp/ml) or viremic (VL $>$ 200 cp/ml), as illustrated in Fig. 1a. Demographic and clinical characteristics of the study population were recorded. Propensity score was used to match VT and HT for sex, HIV duration, $CD4^+$ T-cell nadir and HIV RNA load at plasma sampling.

A broad range of plasma cytokines and chemokines [GM-CSF, interferon gamma (IFN-), IFN-, interleukin (IL)-2, IL-4, IL-5, IL-6, IL-9, IL-10, IL-12p70, IL-17A, tumour necrosis factor alpha (TNF-)] was assessed by cytometric bead array; sCD14 was measured by ELISA samples, following the manufacturer's instructions.

T-cell dysfunction was measured by the surface expression of senescence (CD57), activation (HLA-DR/CD38) and exhaustion (PD-1/TIGIT) markers on $CD4^+$ and $CD8^+$ T-cells using flow cytometry. Eight people without HIV (PWOH), matched for age and sex, were included as controls to provide a baseline for comparison. They were selected to reflect the age distribution of both study groups (four matched to the younger VT group, median 31 years, and four to the older HT group, median 50 years). Overall, the age of the control group did not differ significantly from either PWH group ($P = 0.3$).

Kruskal–Wallis and Mann–Whitney tests were used for comparisons. Fisher's exact test for categorical variables (expressed as percentages). Spearman's correlation was used to correlate age at sampling and inflammation markers. Data were analysed with GraphPad Prism 10.2.1.

Sixteen VT and 16 HT individuals were enrolled (Table S1, Supplemental Digital Content, http://links.lww.com/QAD/D750). In each group, 8/16 had undetectable viral load (HIV RNA $<$ 50 copies/ml) and 8/16 had detectable viral load (HIV RNA $>$ 200 copies/ml). 62.5% were female in both groups. VT were younger than HT

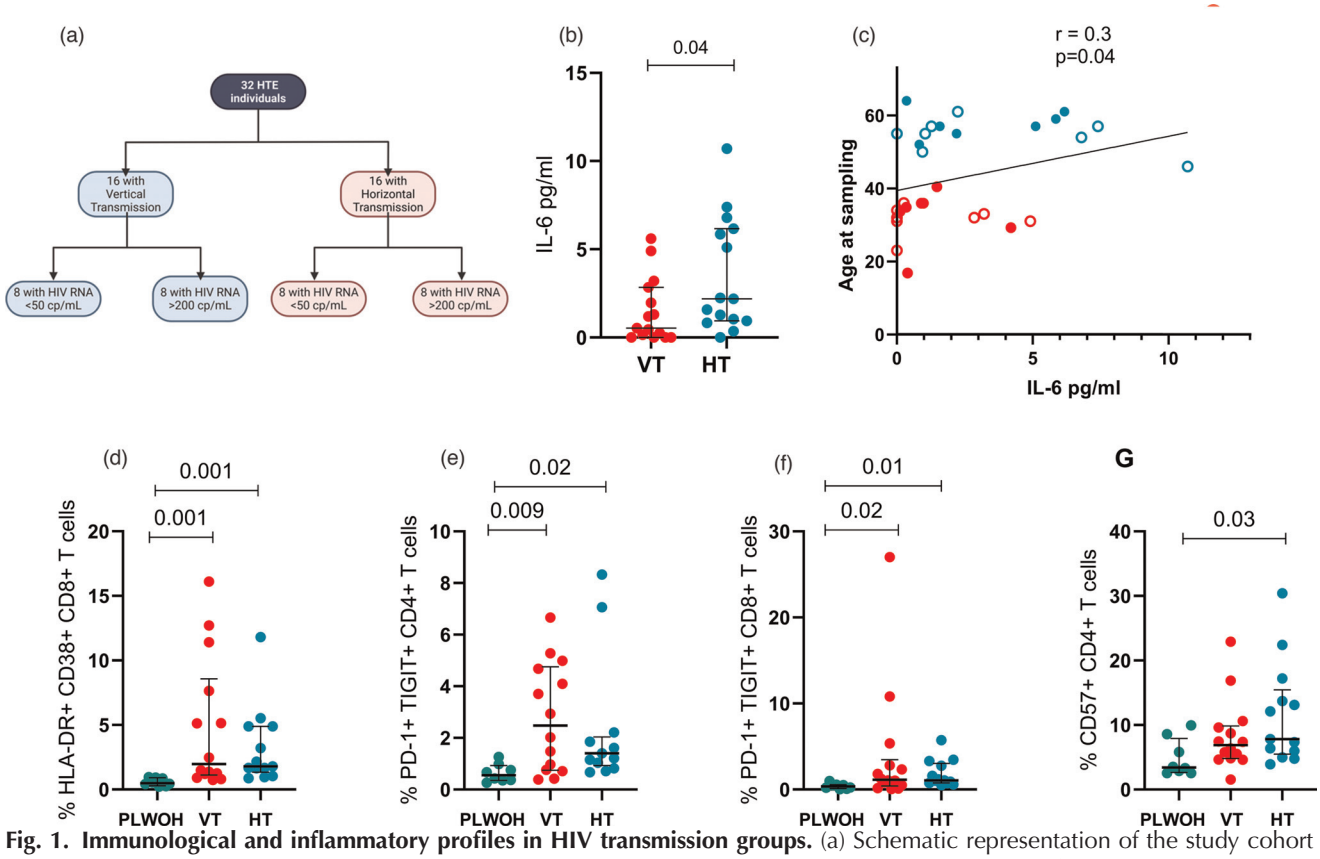

Fig. 1. Immunological and inflammatory profiles in HIV transmission groups. (a) Schematic representation of the study cohort including 32 HIV transmission-exposed (HTE) individuals divided into two groups based on the route of HIV acquisition: vertical transmission (VT, $n=16$) and horizontal transmission (HT, $n=16$). Each group was further stratified by HIV RNA levels (<50 or >200 copies/ml). (b) Plasma IL-6 concentrations (pg/ml) in VT and HT individuals. Each dot represents one individual; lines indicate median and interquartile range. Statistical significance was determined using the Mann–Whitney *U* test. (c) Correlation between plasma IL-6 levels and age at sampling in HTE individuals. Spearman's correlation coefficient (r) and p-value are shown. (d–g) Frequency of activation, exhaustion and senescence markers on $CD4^+$ and $CD8^+$ T-cells in VT, and HT groups compared to PWOH. Statistical analysis: Kruskal–Wallis test, multiple comparisons.

individuals (31 years, IQR 27–33 vs. 56, IQR 54–59; $P<0.0001$), yet duration of HIV infection was comparable in the two groups (31 years, IQR 27–33 vs. 30 years, IQR 25–32; $P=0.7$). The total duration of virologic suppression (VL < 50 cp/ml; $P=0.7$) and detectable viremia (VL > 200 cp/ml; $P=0.8$), expressed in years, was similar between VT and HT individuals (Table S1, Supplemental Digital Content, http://links.lww.com/QAD/D750). Among comorbidities, hypertension was more frequent in individuals with horizontal HIV transmission compared to those with vertical transmission (Table S1, Supplemental Digital Content, http://links.lww.com/QAD/D750). No statistically significant difference was observed in $CD4^+$ T-cell nadir and absolute count at the time of sampling between VT and HT.

VT showed lower IL-6 than HT (0.526 pg/ml, IQR 0–2.85 vs. 2.198 pg/ml, IQR 0.94–6.17; $P=0.04$, Fig. 1b). However, when stratifying according to viremia, VT and HT did not show significant differences in IL-6 levels. The remaining cytokines showed comparable levels between groups, except for a trend to lower IL-10 in VT overall ($P=0.08$) and in those with HIV RNA > 200 cp/ml (0 pg/ml, IQR 0–0 vs. 13.5 pg/ml, IQR 0–28.1; $P=0.06$).

No significant correlations were observed between plasma cytokines and demographic or viro-immunologic parameters, except for IL-6, which was positively associated with age ($r=0.362$, $P=0.04$, Fig. 1c).

No differences were detected between VT and HT in terms of $CD4^+$ and $CD8^+$ T-cell dysfunction. However, compared to PWOH, VT and HT displayed higher activated $CD8^+HLA\text{-}DR^+CD38^+$ (PWOH: 0.4%, IQR 0.2–0.9; VT: 1.9%, IQR 1.1–8.5; $P=0.001$; HT: 1.7%, IQR 1.3–4.8; $P=0.001$, Fig. 1d), exhausted $PD\text{-}1^+TIGIT^+$ $CD4^+$ (PWOH: 0.5%, IQR 0.3–0.9; VT: 2.4%, IQR 0.7–4.7; $P=0.009$; HT: 1.4%, IQR 0.9–2; $P=0.02$, Fig. 1e) and $CD8^+$ (PWOH: 0.3%, IQR 0.1–0.5; VT: 1.1%, IQR = 0.4–3.4; $P=0.02$; HT: 1%, IQR 0.7–3; $P=0.01$, Fig. 1f). Similarly, senescent $CD57^+CD4^+$ T-cells were increased in HT alone compared to PWOH (7.8%, IQR 5.4–15.4 vs. 3.4%, IQR 2.6–7.9; $P=0.03$. Fig. 1g).

These findings were retained in the viremic subgroups of VT and HT who showed higher frequencies of $CD4^+$ and $CD8^+$ T-cells with an activated HLA-DR^+CD38^+ (Fig. S1A, Supplemental Digital Content, http://links.lww.com/QAD/D750; Fig. S1B, Supplemental Digital Content, http://links.lww.com/QAD/D750) and exhausted PD-1^+TIGIT^+ phenotype (Fig. S1C, Supplemental Digital Content, http://links.lww.com/QAD/D750; Fig. S1D, Supplemental Digital Content, http://links.lww.com/QAD/D750) compared to PWOH. In contrast, in the virally-suppressed cohort, only HT displayed higher CD8+ cells with an activated (1.6% IQR 0.9–1.7 vs. 0.4% IQR 0.2–0.9, $P = 0.003$, Fig. S1E, Supplemental Digital Content, http://links.lww.com/QAD/D750) and exhausted phenotype (1% IQR 0.7–1.2 vs. 0.3%, IQR 0.1–0.5, $P = 0.04$, Fig. S1F, Supplemental Digital Content, http://links.lww.com/QAD/D750) compared to PWOH. When stratifying PWOH controls by age, T-cell dysfunction markers were significantly lower in both younger and older PWOH compared to VT and HT, respectively, confirming that PWH display higher levels of T-cell dysfunction overall (Fig. S1G–L, Supplemental Digital Content, http://links.lww.com/QAD/D750).

No link was observed between T-cell phenotype and demographic or viro-immunologic parameters.

In line with previous studies showing that age has a central role in driving inflammation in treated PWH [12,13], our findings suggest that in the context of HTE, aging rather than the mode of HIV acquisition is closely linked to inflammation. The VT group was substantially younger than the HT group, which likely contributes to some of the observed differences in inflammatory markers. IL-6 emerged as the most robust age-associated marker, consistent with the concept of inflammaging, while TNF- showed only nonsignificant trends in older HT individuals, likely reflecting inter-individual variability in baseline plasma levels as previously described [13]. These observations highlight that age should be carefully considered when interpreting differences between VT and HT groups. VT and HT individuals were matched for duration of HIV infection (median 30 years in both groups; Table S1, Supplemental Digital Content, http://links.lww.com/QAD/D750). While age appears to be the main driver of inflammation in this cohort, long-term HIV exposure may also contribute to the inflammatory burden, suggesting that both aging and cumulative infection could influence immune activation in heavily treatment-experienced individuals.

Of note, although T-cell dysfunction in HTE was mainly driven by uncontrolled viremia, highlighting the key role of viral replication in T-cell homeostatic imbalances [9], aviremic HT showed higher activated HLA-DR^+CD38^+ and exhausted PD-1^+TIGIT^+ $CD8^+$T-cells, which may also mirror their older age.

A limitation of our study is the age difference between the VT and HT groups, which could partially influence some inflammatory marker. Further, our data on T-cell dysfunction in HTE should be detailed in the context of VT and HT in virally-suppressed PWH with no history of viral failure.

Taken together, the present work shows that HTE with vertical HIV acquisition do not feature greater immune dysregulation than HTE with horizontal transmission. Given the key role of age and viral replication in driving inflammatory imbalances in the context of multidrug resistance, our findings highlight the need of complete HIV suppression and careful management of noninfectious comorbidities in HTE of all ages.

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Conflicts of interest

There are no conflicts of interest.

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Stability of the translocator protein 18 kDa density within cognitive circuits in brains of virally-suppressed people with HIV

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[^{11}C]DPA-713 positron emission tomography (PET) has shown higher translocator protein (TSPO) availability, a marker of glial response, in cognitive control and declarative memory brain regions of virally suppressed people with HIV (VS-PWH). Here, 14 VS-PWH completed repeat TSPO PET after ~18 months. Regional TSPO was largely time-stable, with modest variability in some participants that was unrelated to antiretroviral therapy. Further study of a stable, higher TSPO density in select brain regions of VS-PWH is warranted.

We recently reported cross-sectional findings from a [^{11}C]DPA-713 positron emission tomography (PET) study that focused on the relationship between glial dynamics and cognition in virally suppressed people with HIV (VS-PWH) compared to people without HIV (PWoH) [1]. We focused on two well characterized constructs within the National Institutes of Mental Health (NIMH) Research Domain criteria (RDoC) framework [2,3]: cognitive control (CC) and declarative memory (DM). Those RDoC constructs were selected because they are frequently impaired in PWH [4–11], can be reliably assessed using established behavioral and self-report measures, and map onto discrete neural circuits. For example, CC is subserved by regions of lateral prefrontal cortex (lPFC), dorsal anterior cingulate (dACC), and inferior parietal lobe (IPL), while the regions involved in DM include the hippocampus and prefrontal cortex (PFC). VS-PWH had higher TSPO availability, a marker of glial response, compared to PWoH in those CC and DM regions, with higher binding linked to both poorer behavioral performance and greater self-reported symptom burden [1]. Those findings are consistent with most [12–14], but not all [15], prior PET studies in PWH, and highlight the potential contribution of altered glial response to domain-specific cognitive function in VS-PWH. However, our analyses were limited to a single time point, leaving unanswered whether TSPO levels in those regions are stable over time. Here, we evaluate longitudinal TSPO stability from 14 VS-PWH from our original cohort [1] who completed repeat [^{11}C]DPA-713 PET imaging approximately 18 months after baseline (range 12.6–27.7 months).

PET acquisition, reconstruction, kinetic modeling (Logan graphical analysis with metabolite-corrected arterial input), and TSPO (rs6971) genotyping followed our published procedures [1]. Primary outcomes were log-transformed total distribution volume (V_T, ml cm^{-3}) estimates in CC and DM regions. [^{11}C]DPA-713 V_T estimates with partial volume correction derived using the Muller-Gartner algorithm [16] were evaluated as secondary outcomes.

Longitudinal change was assessed using the Reliable Change Index (RCI), which incorporates the baseline standard deviation and test–retest correlation between timepoints. Baseline standard deviation was estimated from the full cohort [1] and test-retest correlation was calculated in the subset with repeat scans. Stability was defined as RCI within $\pm$1.65 [90% confidence interval (CI)], with sensitivity analyses applying a more liberal $\pm$1.28 (80% CI). Based on our prior cross-sectional findings of elevated TSPO in VS-PWH compared to