Inflammatory Signatures among People with HIV Initiating DTG/3TC vs. BIC/F/TAF in the CoRIS Cohort

662

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BACKGROUND

- Two-drug regimens (2DRs) may offer an alternative strategy to reduce long-term toxicities associated with antiretroviral therapy (ART). Dolutegravir plus lamivudine (DTG+3TC) is recommended as initial therapy in ART guidelines, among other 3DRs, with some requirements (HBsAg negative, HIV-viral load < 500,000 copies/mL, not recommended after PrEP failure) [1,2].
- Persistent immune activation underlies the increased risk of comorbidities during HIV treatment. So far, existing evidence on whether initiation of two-drug therapy differs from three-drug regimens in this regard is limited.
- We investigated the effects of DTG/3TC vs. BIC/F/TAF on inflammatory signatures in a prospective cohort of people with HIV (PWH) initiating ART.

METHODS

- Observational retrospective study. We included PWH who initiated DTG/3TC or BIC/F/TAF within the Spanish CoRIS cohort from January 2016 to December 2023 and had available plasma samples at month 0 (before ART initiation) and month 24 (±6).
- We matched participants starting each regimen 1:1 by propensity score (PS). The covariates included age, sex, baseline CD4/CD8 ratio and baseline HIV-1 RNA.
- Proteomic profiling was performed by Proximity Extension Assay using an inflammation-specific panel (Olink Target 96 Inflammation).
- Differences between groups and timepoints were analyzed by Welch two sample t-test and paired t-test, respectively. Gene Set Enrichment Analysis (GSEA) was performed to investigate differential pathways between groups. P-values were adjusted by false discovery rate.

RESULTS

- We selected 174 PS-matched participants. After sample quality control, we analyzed 148 participants and 78 proteins. **Table 1** shows the characteristics of the two groups. The groups were comparable except for nadir and baseline CD4+, which were lower in the B/F/TAF group.
- Differential expression analysis showed overexpression of 11 proteins in the BIC/F/TAF group at baseline. Notably, after two years of ART, these signals were no longer detectable (**Figure 1**). When compared separately, the expression of different sets of inflammatory proteins strongly decreased in both groups. Proteins such as CXCL9, CXCL11, and CD6 —associated with pathogen response— were underexpressed in both groups after two years of ART. Functional evaluation of differentially expressed proteins supported the relevance of biological processes such as cell adhesion, activation of T cells, and general activation of immune response.

References: [1]Gandhi RT, et al. Antiretroviral Drugs for Treatment and Prevention of HIV in Adults: 2024 Recommendations of the International Antiviral Society–USA Panel. JAMA. 2025;333(7):609–628. [2] EACS Guidelines versión 12.0, October 2023.

After two years, the expression of some inflammatory proteins significantly decreased in both treatments.

Despite higher baseline inflammation in the BIC/F/TAF group, this therapy effectively neutralized the initial disparity.

Table 1. Characteritics of Population after Propensity Score Matching

	BIC+FTC+TAF (n = 86)	DTG+3TC (n = 88)	p-value
Age, median (IQR)	37.3 (29.4, 46.3)	35.2 (28.3, 42.3)	0.33
Male sex at birth, n (%)	78 (91%)	83 (94%)	0.36
Transmission category, n (%)			0.38
Homo/bisexual (HSH)	60 (70%)	69 (78%)	
Injecting drug user (UDI)	0 (0%)	1 (1%)	
Heterosexual contact (HSM)	22 (26%)	15 (17%)	
Country of origin, n (%)			0.019
Western Europe	50 (58%)	43 (49%)	
Africa	7 (8%)	8 (9%)	
Latin America	28 (33%)	32 (36%)	
Virologic failure ever, n (%)	1 (1%)	0 (0%)	0.31
Active smoking, n (%)	35 (42%)	28 (39%)	0.68
Nadir CD4, median (IQR)	353.5 (214.0, 470.0)	407.0 (291.0, 555.0)	0.024
Baseline CD4, median (IQR)	369.0 (230.0, 510.0)	442.0 (314.0, 652.0)	0.005
Baseline CD4/CD8, median (IQR)	0.5 (0.2, 0.6)	0.5 (0.3, 0.7)	0.09
Two-year CD4, median (IQR)	633.5 (448.0, 839.0)	737.0 (533.0, 929.0)	0.047
Two-year CD4/CD8, median (IQR)	0.8 (0.5, 1.1)	0.8 (0.6, 1.1)	0.34

The results of the GSEA analysis (**Figure 2**) support the observation of less inflammation in the DTG+3TC-treated group, with lower expression of genes involved in immune activation, cell adhesion and adaptive response. This suggests that the treatment may reduce the activation of immune cells and their migration into the tissues, which would translate into an anti-inflammatory effect.

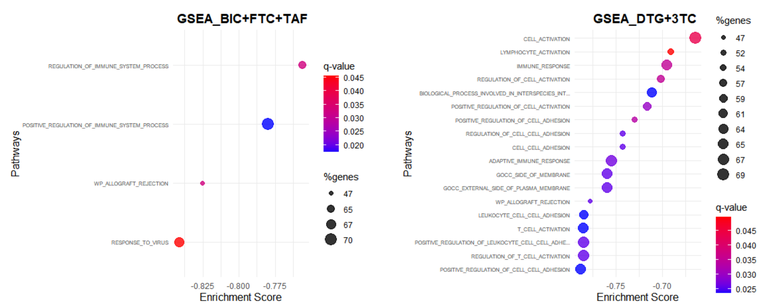
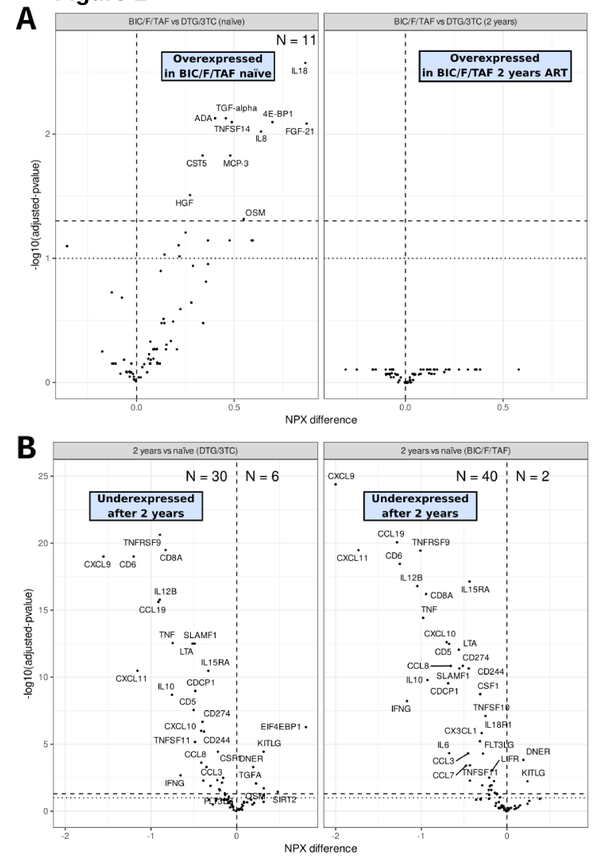


Figure 2: Gene Set Enrichment Analysis (GSEA) results to analyze the main functions in both treatment conditions.
A. For DTG+3TC treatment. B. For BIC+FTC+TAF. The pathways are ranked by enrichment score along the x-axis, with negative values indicating downregulation. Dot size represents the percentage of genes that contribute to enrichment in each pathway, while color indicates the q-value (false discovery rate), with red representing higher significance and blue representing lower significance. Only significantly enriched pathways (q-value ≤ 0.05) are shown.

Figure 1



**The dotted line indicates the threshold of the p-values corrected for false discovery rate.*

CONCLUSIONS

- After 2 years of ART, the expression of different sets of inflammatory proteins significantly decreased in both ART groups. These molecules are involved in relevant inflammation-related functions.
- The higher baseline inflammation in the BIC/F/TAF group, suggests that factors associated with greater inflammation (ie lower CD4 cell count/more advanced HIV disease) may influence regimen selection, but this therapy effectively neutralized the initial disparity.

ADDITIONAL KEY INFORMATION

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