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Persistent APOBEC activity in children with longstanding HIV infection: characterization and correlation with clinical outcome

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Introduction

- This study aims to characterize APOBEC-associated mutational signatures in young individuals with longstanding HIV infection and prolonged exposure to antiretroviral therapy, and to evaluate their potential associations with clinical outcomes

Study Design

- An observational study was conducted on 47 individuals with childhood-acquired HIV-1 infection, for whom HIV-DNA samples collected between March 2021 and July 2025 at the Ospedale Pediatrico Bambino Gesù were available.

Methods

- HIV-DNA extraction was performed on PBMCs using the High Pure PCR Template Preparation Kit (Roche Diagnostics). Total HIV-DNA quantification was carried out in 42 (89.4%) using a home-made droplet digital PCR (ddPCR) assay (Scutari et al., 2023);
- Next-generation sequencing (NGS) was performed with DeepChek® HIV Full PR/RT/INT Drug Resistance kit (ABL Diagnostics) on the MiSeq platform (Illumina).
- The prevalence of drug resistance mutations (DRMs) and signature APOBEC-related mutations (APO-Ms) (frequency higher than 5%) was evaluated through the DeepChek and HIVdb Stanford tools.

Results

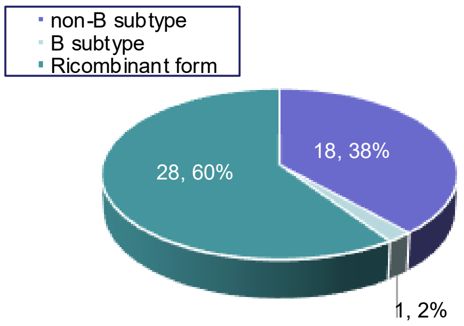
- Participants had a median age of 19 years (IQR: 14-25) and were mainly male (53.2%). Among them, 41 cases (87.2%) acquired the HIV-1 infection through vertical transmission.
- Among the 47 individuals, 26 (55.3%) had received early therapy, defined as initiation within the first year of life and an AIDS event was observed in 34% (16/47) individuals.
- Notably, early-treated individuals had a significantly lower HIV reservoir compared with those treated later, as reflected by lower median total HIV-DNA levels (387 [123–697] vs 1262 [367–1712] copies/10^6 CD4+ T cells; p=0.027)

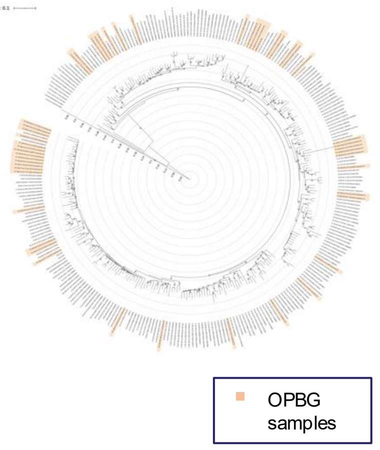
	Overall (N=47)
Age years, Median (IQR)	19 (14-25)
Male, N(%)	25 (53.2)
Italian, N(%)	21 (44.6)
Risk Factor, N(%)	
Mother-to-child	41 (87.2)
AIDS events, N (%)	16 (34)
CD4+ T-cells at study enrollment, cells/mm³, median (IQR)	798.8 (559-1050)
Total HIV-1 DNA, copies/million CD4+ T-cells, median (IQR)[1]	551 (181-1340)
VL HIV-RNA	
HIV-RNA undetectable or <40 copies/mL, N(%)	33 (70.2)
HIV-RNA detectable, N(%)	14 (29.8)
Viral load, copies/mL, median (IQR)	170 (142-17133)
ART start after diagnosis, N(%)	
Early (<1 year)	26 (55.3)
Late (>1 year)	21 (44.7)

[1]Data was aviable for 42 individuals

HIV-1 characterization

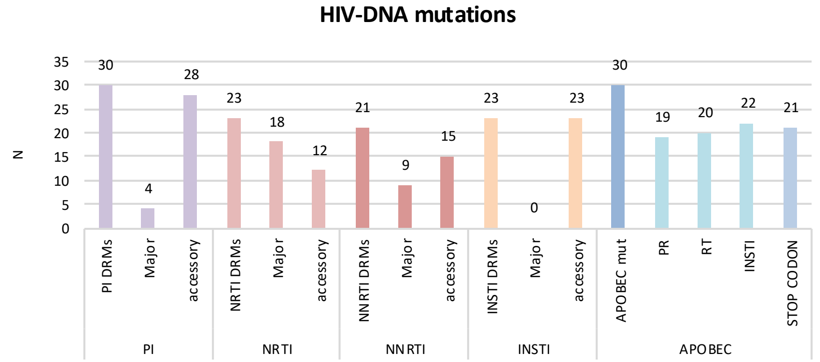
- Participants were infected mostly by recombinant forms (CRF) (28;60%), followed by pure non-B forms (18;38%) and B subtype (1;2%)
- The most frequent subtype was BF, accounting for 15 out of 47 cases (32%), followed by subtypes C and A1, each representing 8 cases (17%)



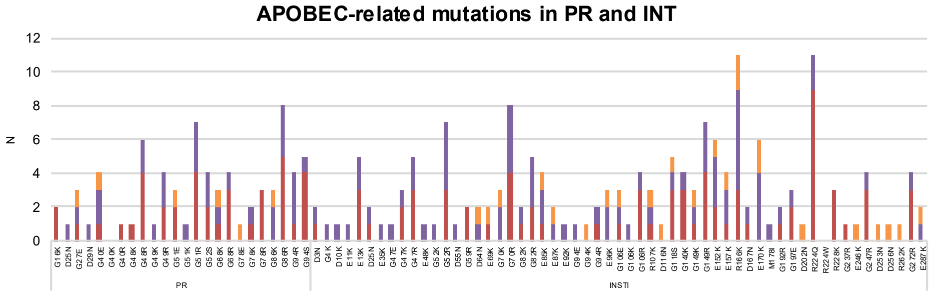


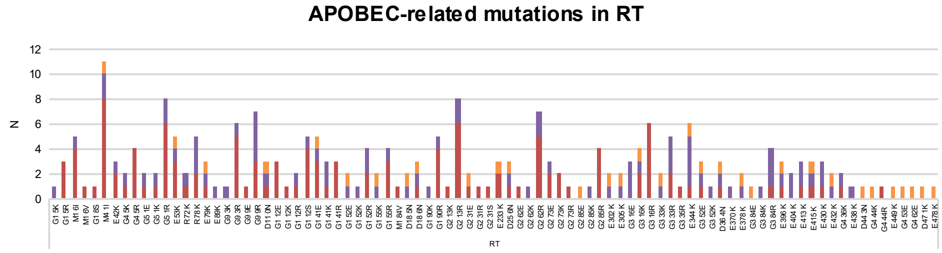
Drug resistance mutation in HIV-DNA

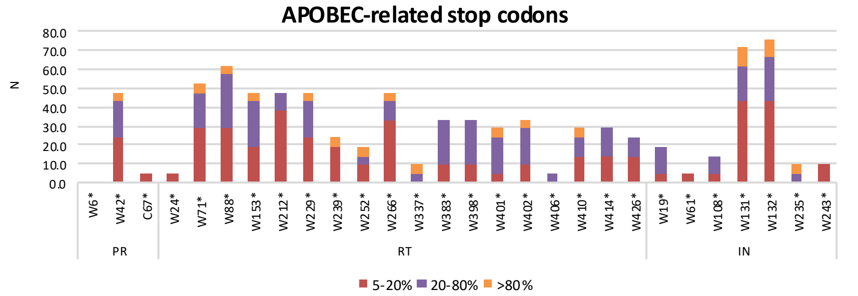
- Overall, 57.4% (27/47) of individuals harboured at least one HIV-1 DRMs: in particular, the NRTI, NNRTI and PI resistance were present in 19.1%, 38.3% and 8.5% of cases, respectively.



- 30/47 individuals (64%) showed at least one APOBEC-related mutation, mainly in the INSTI region (22; 73%), while 21/47 (45%) with at least one APOBEC-related stop codon.







- No significant differences were observed in APOBEC-associated mutations, when stratifying by early treatment initiation (38.5% vs 57.1%, p=0.163) and AIDS-defining events (56.2% vs 41.9%, p=0.893).
- Similarly, no significant differences were found in stop codon frequency with respect to early treatment initiation (42.3% vs 47.6%, p = 0.472) or AIDS-defining events (43.8% vs 45.2%, p = 0.587).

Conclusions

- HIV-DNA sequencing revealed a significant prevalence of drug resistance mutations, as well as APOBEC-related mutations, particularly in the INSTI region.
- Early antiviral treatment was associated with significantly smaller HIV reservoir. The frequency of APOBEC-related mutations or stop codons seems not different in this relatively small cohort, yet their stable presence over the years in these young individuals without clinical progression suggests that studies with larger settings are required to define whether their presence affects the progression of the disease.