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Letter to Editor

Clinical effects of Gag mutations as predictors of second-line failure

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Dear Editor,

In low- and middle-income countries, expanding access to diagnostic testing and antiretroviral therapy (ART) is a key strategy in achieving the UNAIDS 2030 goal of eliminating the AIDS epidemic as a public-health threat by 2030[1]. In patients experiencing virological failure of ritonavir-boosted protease-inhibitor (PI/r)-based second-line HAART, a sizable percentage do not harbour mutations within the protease (PR) gene (PI DRMs), indicating that resistance is mediated by other factors[2]. Data on this issue remain scarce in the context of India's expanding ART programme.

Using a validated in-house genotyping method, 129 HIV-1-positive individuals who were failing PI-based treatment and were attending YRG CARE were retrospectively analysed[3]. Out of 129 individuals, 95 (73 %) lacked PI mutations, whereas 34 (26 %) possessed them. In patients without PI mutations, the second-line treatment duration was shorter (17 months, $p < 0.0001$) and the baseline CD4 T-cell count was lower at 210 cells/μL (IQR 114–800, $p = 0.1001$). Common NRTI mutations observed among failures were M184I/V (94 % vs 80 %, $p < 0.05$) and K65R (6 % vs 10 %, $p < 0.05$), which were significantly higher in the cohort without PI mutations. Substrate-cleft mutations V82A/T/F/S (15 %), V32I (6 %), flap mutations M46I/L (20 %), I54T/L/M (18 %), and mutations in other conserved residues N88D/S (4 %) and L90M (4 %) were the most common PI drug-resistance mutations found among participants with PI mutations. Protease (PR) gene mutations were absent in 73 % of patients who did not respond to PI/r-based second-line HAART. This finding aligns with other research highlighting Gag mutations as an alternative pathway to PI resistance[4,5].

This study advances understanding of PI treatment failure by emphasizing the role of Gag gene mutations and supports the integration of Gag analysis into routine resistance genotyping to better elucidate mechanisms of virological failure.

ABBREVIATIONS

ART - Antiretroviral Therapy, **DRMs** - Drug Resistance Mutations, **HAART** - Highly Active Antiretroviral Therapy, **PI** - Protease Inhibitor

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SSM: Writing – original draft, Methodology Writing – review & editing, Analysis. SS: Supervision, Investigation, Formal analysis. PB: Investigation, Conceptualization. All authors read and approved the final manuscript.

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AVAILABILITY OF DATA AND MATERIALS

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CONSENT FOR PUBLICATION

Not applicable.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

The authors declare that they have not used generative AI (a type of artificial intelligence technology that can produce various types of content including text, imagery, audio and synthetic data. Examples include ChatGPT, NovelAI, Jasper AI, Rytr AI, DALL-E, *etc*.) and AI-assisted technologies in the writing process before submission.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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