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### Long-term effectiveness of bictegravir/emtricitabine/tenofovir alafenamide in people with HIV and resistance-associated mutations

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**Resistance-associated mutations (RAMs) limit treatment options for HIV. We evaluated virologic outcomes in people with HIV harboring RAMs who switched to bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) in a real-world cohort during 4 years of follow-up. Virologic suppression was sustained across RAM subgroups, including M184V/I with additional nucleoside reverse transcriptase inhibitor (NRTI)-RAMs. Stratification by genotypic susceptibility score (GSS) suggests robust effectiveness. B/F/TAF demonstrates durable long-term suppression in different resistance profiles, supporting its use in this population.**

## Introduction

Resistance-associated mutations (RAMs) represent a therapeutic challenge in HIV management, potentially limiting antiretroviral treatment options for people with HIV (PWH). The fixed-dose combination of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) has demonstrated high rates of virologic suppression in both clinical trials [1–5] and real-world settings [6–10], including among PWH harboring RAMs. Nevertheless, virologic outcomes may vary according to the type and complexity of resistance patterns. Nucleoside reverse transcriptase inhibitor (NRTI)-RAMs, including M184V/I, thymidine analog mutations (TAMs), L74V, and K65R, may compromise the antiviral activity of individual regimen components, potentially affecting overall treatment effectiveness.

Clinical evidence from the GS-US-380-4030 study demonstrated that 89% of PWH with preexisting M184V/I achieved viral suppression at 48 weeks after switching to B/F/TAF, supporting the Food and Drug Administration (FDA) approval in 2024 for use in individuals with documented M184V/I resistance [11,12]. However, the long-term effectiveness of B/F/TAF in PWH with complex resistance profiles remains unclear. Real-world evidence is needed to understand virologic outcomes in PWH who have documented RAMs and prior treatment failures.

In Argentina, where an estimated 140 000 people are living with HIV, the epidemic is characterized by a predominance of cisgender men, with sexual transmission as the main route of acquisition, and a substantial proportion of PWH receiving care in the public health system (65%). Second-generation integrase strand transfer inhibitor-based regimens, primarily dolutegravir-based and bictegravir-based combinations, are recommended for initial therapy and as a switching strategy [13,14].

This study aimed to evaluate virologic outcomes in treatment-experienced PWH harboring RAMs who initiated B/F/TAF therapy, and to assess the relationship between the genotypic susceptibility score (GSS) and sustained virologic suppression over time.

## Methods

This was a sub-analysis of BICTARG study [15], an observational, retrospective, real-world cohort that evaluated the effectiveness of B/F/TAF in PWH who had previous antiretroviral treatment experience and initiated therapy between October 2019 and December 2021 in Argentina. Historical genotypic resistance tests performed prior to switching to B/F/TAF were reviewed to identify preexisting RAMs. We included participants with documented RAMs, including M184V/I, TAMs,

L74V, and K65R. Participants were stratified by B/F/TAF GSS into three groups: group 1 (GSS 1.0–1.75), group 2 (GSS 2.0–2.75), and group 3 (GSS 3.0), representing reduced, intermediate, and full susceptibility, respectively. The primary endpoint was virologic suppression (plasma HIV-1 RNA <50 copies/ml), with virologic suppression rates (VSR) assessed at months 36 and 48, calculated among participants with available data (missing = excluded). Clinical follow-up and antiretroviral therapy provision were maintained throughout the study period, including during the COVID-19 pandemic, via pharmacy support, home delivery of medication, and telemedicine [16].

## Results

Among the 2632 treatment-experienced PWH who received B/F/TAF, 202 (7.7%) had historical RAMs, including 117 (58% of those with RAMs; 4.4% overall) with at least one NRTI-RAM. Participants were predominantly of Latin ethnicity (99%), with a median age of 44 years (IQR 18–85), and 69% were men. At B/F/TAF initiation, 34% had a detectable viral load (>50 copies/ml).

At 36 months, virologic suppression was achieved in 93% of PWH with any RAM and in 92% of those with at least


**Fig. 1. Panel a: proportion of people with HIV and resistance-associated mutates maintaining HIV-1 RNA less than 50 copies/ml at 36 months.** Panel b: proportion of people with HIV and resistance-associated mutations maintaining HIV-1 RNA less than 50 copies/ml at 48 months. Panel c: virologic suppression rates according to genotypic sensitivity score among people with HIV harboring resistance-associated mutations.

one NRTI-RAM. Among individuals with a single M184V/I, the VSR was 83%. Participants with M184V/I plus one TAM achieved 92% virlogic suppression, whereas those with M184V/I plus two or more TAMs reached 100%. Complete suppression (100%) was also observed among participants with M184V/I plus L74V; M184V/I plus L74V and TAMs; and M184V/I plus K65R (Fig. 1, panel a).

At 48 months, VSR remained high: 100% in PWH with a single M184V/I mutation, 100% with M184V plus TAMs, and 100% with M184V/I plus L74V (Fig. 1, panel b).

When stratified by GSS, VSR at 36 months was 100% in group 1 ($n = 14$), 96% in group 2 ($n = 88$), and 90% in group 3 ($n = 100$); at 48 months, corresponding rates were 100, 96, and 92%, respectively (Fig. 1, panel c).

## Discussion

This study provides important real-world evidence from Argentina, supporting global findings and contributing novel data on treatment durability and long-term effectiveness over a 4-year follow-up.

Studies evaluating B/F/TAF in PWH with RAMs have consistently demonstrated its high effectiveness in achieving VSR. A pooled analysis of six clinical trials reported that switching to B/F/TAF in PWH with virologic suppression who harbored M184V/I plus other RAMs achieved 97–100% VSR at the last visit (up to 180 weeks), demonstrating that this mutation does not compromise its effectiveness [3].

Real-world evidence has supported these findings through retrospective cohort studies. High rates of virologic suppression through 48–96 weeks have been reported in PWH with M184V/I alone or in combination with other RAMs, such as TAMs, L74V, and K65R [7,8]. A retrospective cohort from Hospital Universitario La Paz (Spain) including 506 treatment-experienced PWH, of whom 13.6% had preexisting NRTI-RAMs, reported 88.4% VSR in the intention-to-treat analysis and 93.8% per-protocol at 48 weeks among those with NRTI-RAMs, with no significant differences compared with individuals without NRTI resistance [9].

Our real-world study of 202 PWH with preexistent RAMs provides evidence with longer follow-up. We observed high VSR at 36 months and up to 100% at 48 months in PWH with single M184V/I or M184V/I combined with other RAMs, including in individuals with low GSS. These results provide additional evidence supporting the effectiveness of B/F/TAF in this particular population.

This study has several limitations. The retrospective design may be subject to unmeasured confounding factors and information bias. The prolonged follow-up period led to missing data, which may have influenced the estimation of long-term outcomes. We were unable to evaluate differences in VSR by calendar year during follow-up, as this analysis was not performed. In addition, the high proportion of participants with virologic suppression at baseline may limit generalizability and could have led to an overestimation of treatment effectiveness. Data on previous antiretroviral regimens have been described elsewhere [15].

In conclusion, real-world data from Argentina provide additional evidence for the use of B/F/TAF in PWH with certain RAMs. Sustained virologic suppression across different resistance profiles over 4 years suggests that this regimen is a reliable treatment option in routine clinical practice.

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### Conflicts of interest

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