

Assessing Phenotypic Effect of Integrase Strand Transfer Inhibitor (INSTI)-Based Resistance Substitutions Linked to Failures on Cabotegravir



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Key Findings

- ◆ Clinical isolates with resistance-associated mutation (RAM) patterns similar to observed CAB INSTI resistance patterns showed meaningful increases in half-maximal inhibitory concentration (IC₅₀) fold changes, which strongly reduced sensitivity to EVG and, to a lesser extent, BIC
- ◆ These data suggest that CAB-associated resistance will negatively affect the efficacy of EVG-based regimens, including E/C/F/TDF and E/C/F/TAF, and may negatively affect the efficacy of BIC-based regimens, including B/F/TAF
 - Limitations of this study include not assessing the impact of minority RAM variants, which may emerge at greater frequencies under drug pressure and can affect drug susceptibility
 - Real-world outcomes with INSTI-based regimens have yet to be determined

Conclusions

- ◆ These data reinforce the 2023 recommendations by the DHHS to test for INSTI drug resistance after CAB treatment or PrEP failure¹
- ◆ These data also highlight the need for careful selection of subsequent treatment regimens in people with CAB resistance, as INSTI agents may not be effective

Introduction

- ◆ INSTI-based regimens are recommended by international HIV guidelines as initial and switch therapy in people with HIV (PWH)¹⁻³
- ◆ With novel antiretroviral agents (such as long-acting, injectable CAB) becoming available, there is a need to understand how the resistance profiles of novel agents might affect subsequent treatment options
- ◆ INSTI resistance patterns including, but not limited to, Q148K/R, N155H, R263K, G118R, E138A/K and G140A/S mutations (alone or in combination) have been documented in CAB virologic failures and/or PrEP seroconversions⁴⁻¹²

References: 1. DHHS. <https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf> (accessed July 28, 2023). 2. Gandhi RT, et al. JAMA 2023;329:63-84. 3. European AIDS Clinical Society. https://www.eacsociety.org/media/guidelines-11.1_final_09-10.pdf (accessed July 28, 2023). 4. Swindells S, et al. N Engl J Med 2020;382:1112-1123. 5. Overton T, et al. Lancet 2021;396:1994-2005. 6. Jaeger H, et al. CROI 2021, Oral 401. 7. Overton T, et al. CROI 2022, Oral 479. 8. Orkin C, et al. N Engl J Med 2020;382:1124-1135. 9. Orkin C, et al. IAS 2021, Oral OAB0302. 10. Ramgopal MN, et al. CROI 2023, Oral 191. 11. Eshleman SH, et al. J Infect Dis 2022;225:1741-1749. 12. Marzinke MA, et al. Antimicrob Agents Chemother 2023;67:e0005323. 13. Landovitz RJ, et al. N Engl J Med 2021;385:595-608. 14. Delany-Moretlwe S, et al. Lancet 2022;399:1779-1789. 15. Margolis DA, et al. Lancet 2017;390:1499-1510. 16. Biktarvy USPI, Gilead Sciences, October 2022. 17. Tsiang M, et al. Antimicrob Agents Chemother 2016;60:7086-7097. 18. Stribild USPI, Gilead Sciences, September 2021.

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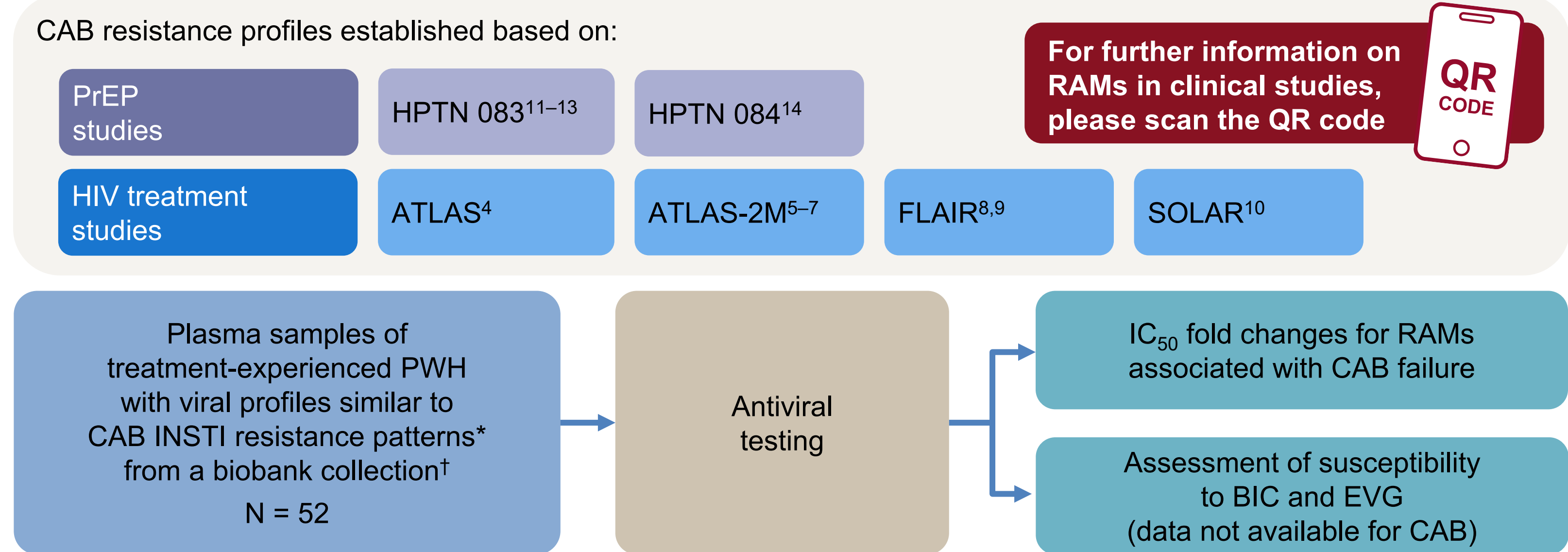
Objective

- ◆ To assess the potential effect of INSTI resistance substitution patterns (comprising Q148K/R, N155H, R263K, G118R, E138A/K and G140A/S mutations) on the antiviral activity of the INSTIs BIC and EVG

Methods

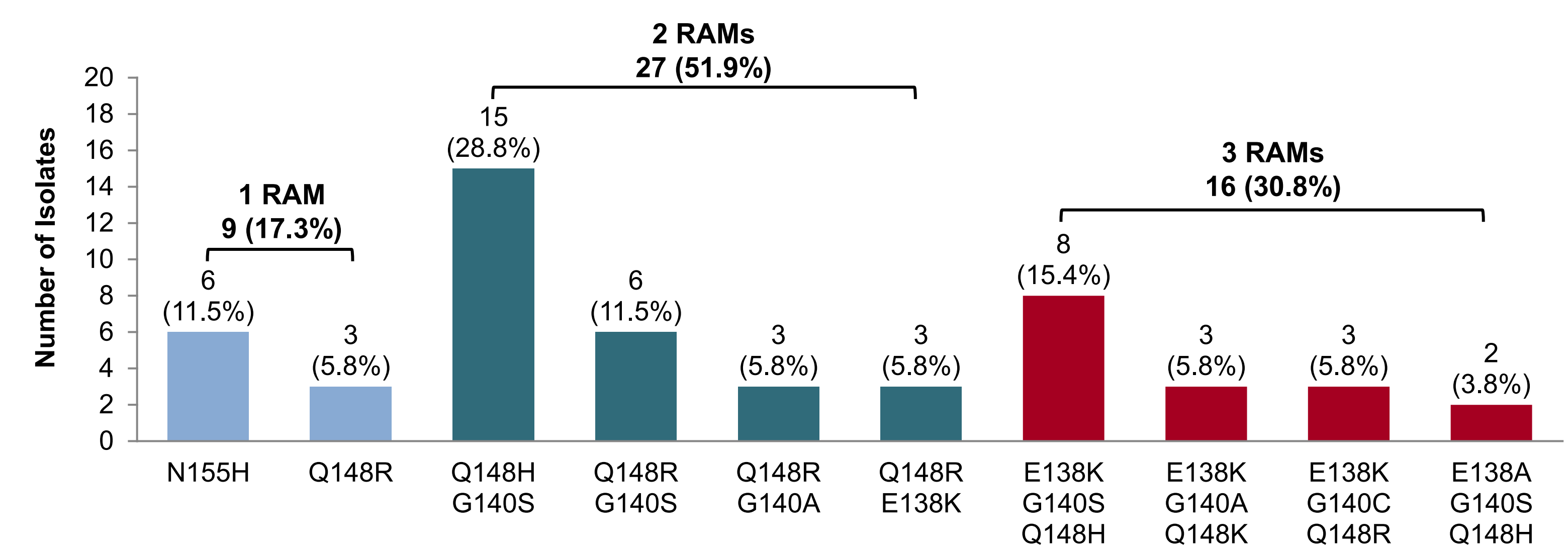
Study Design Schema

- ◆ Antiviral resistance testing was performed using person-derived clinical isolates (N = 52) with viral profiles similar to CAB INSTI resistance patterns⁴⁻¹⁴



*Mutations: E138A/K, G140A/C/S, N155H and Q148K/H/R, alone or in combination; †Information about the clinical samples is limited and clinical data are not available.

INSTI RAMs From Clinical Isolates* (N = 52)

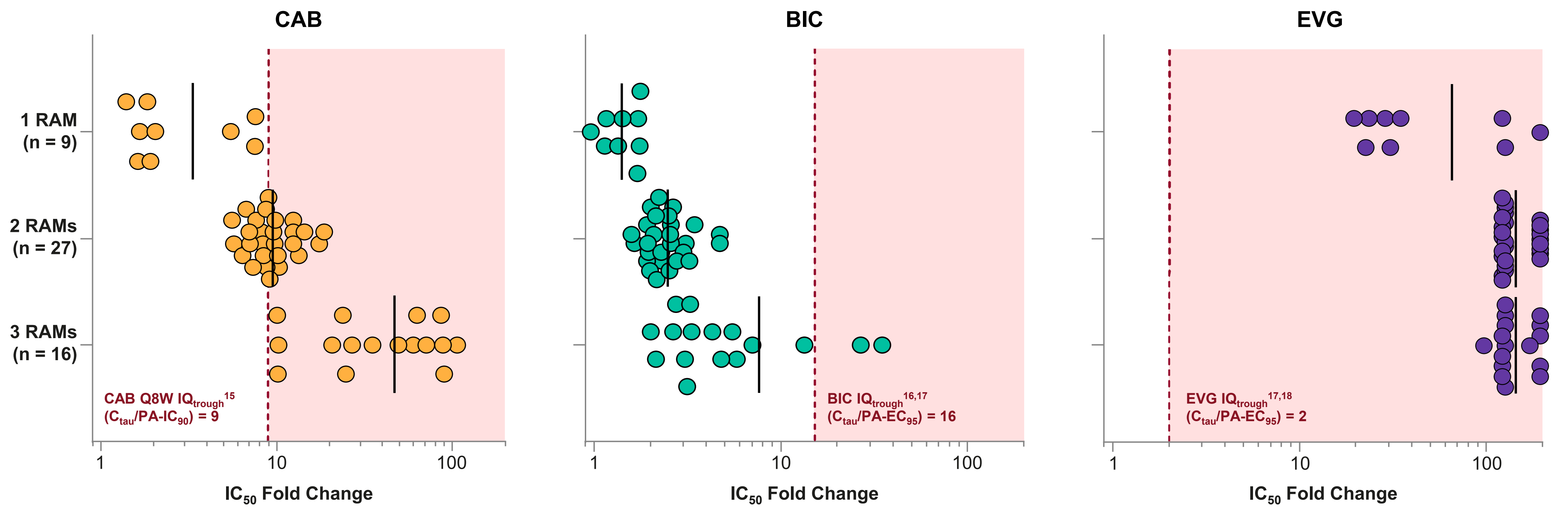


*Information about the samples from the biobank is limited and clinical data are not available.

- ◆ Over half of isolates had 2 RAMs and almost a third of isolates had 3 RAMs

Results

IC₅₀ Fold Changes for Clinical Isolates* With RAM Patterns Associated With CAB Failure



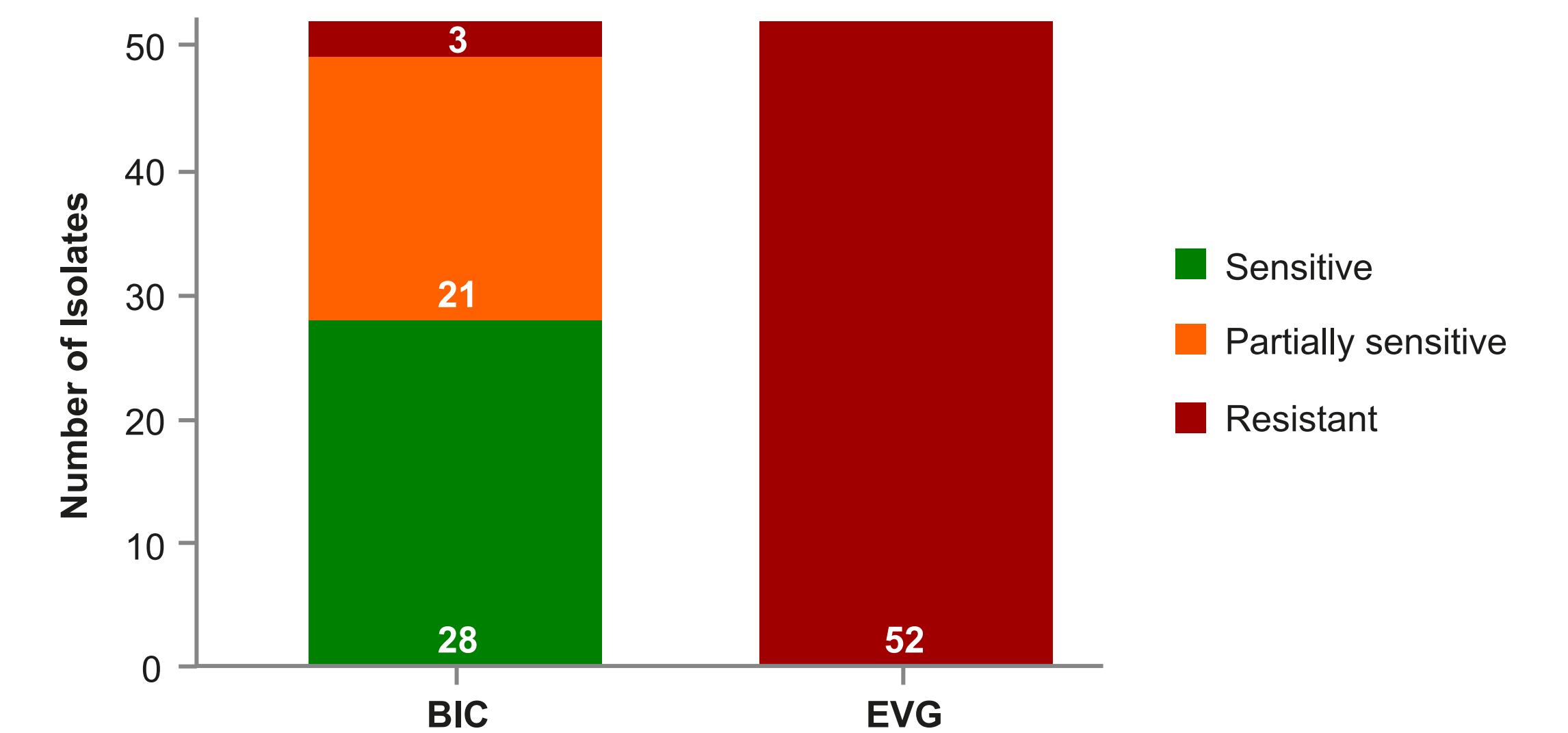
Vertical black bars represent mean fold changes; red dashed lines indicate IQ values. *Substitution patterns from isolates: Q148K/H/R + E138A/K + G140A/C/S (n = 16); Q148R + E138K (n = 3); Q148H/R + G140A/S (n = 24); N155H (n = 6); Q148R (n = 3).

- ◆ For all three drugs, mean IC₅₀ fold changes were the highest for isolates with three RAMs:

	Mean IC ₅₀ fold changes		
	CAB	BIC	EVG
1 RAM	3.3	1.4	< 65
2 RAMs	9.5	2.5	> 144
3 RAMs	47.0	7.6	> 144

- ◆ When considering clinical trough concentrations expressed as inhibitory quotient (IQ_{trough}):
 - 58% of CAB fold changes were > IQ_{trough} = 9
 - 4% of BIC fold changes were > IQ_{trough} = 16
 - 100% of EVG fold changes were > IQ_{trough} = 2

Assessment of Isolate Sensitivity to BIC and EVG



- ◆ When considering clinical and biological assay cutoffs*, isolates varied in levels of sensitivity to BIC and EVG
 - 54% of isolates were sensitive to BIC, 40% were partially sensitive and 6% were resistant
 - 100% of isolates were resistant to EVG
 - Cutoffs for CAB are not currently available

*For BIC, fold changes from 2.5 to 10 signified partial sensitivity and fold changes > 10 signified resistance; for EVG, fold changes > 2.5 indicated resistance.

Abbreviations: B/BIC, bictegravir; C, cobicistat; CAB, cabotegravir; C_{trough}, clinical trough plasma concentration; DHHS, Department of Health and Human Services; EC₉₅, 95% maximal effective concentration; E/EVG, elvitegravir; F, emtricitabine; IC₅₀, half-maximal inhibitory concentration; INSTI, integrase strand transfer inhibitor; IQ, inhibitory quotient; PA, protein-adjusted; PrEP, pre-exposure prophylaxis; PWH, people with HIV; Q8W, every 8 weeks; RAM, resistance-associated mutation; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Disclosures: All authors are employed by Gilead and own stocks/shares in Gilead.