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

Michelle L. D'Antoni, Brie Falkard, Kristen Andreatta, Stephanie Cox, Cal Cohen, Christian Callebaut

Gilead Sciences, Inc., Foster City, CA, U.S.A.

Poster eP.B1.021

Scan or click for more information

https://presentations.gilead.com/item/020cd91051

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 (IC_{50}) 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 failure[1]
- 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 seroconversions[4–12]

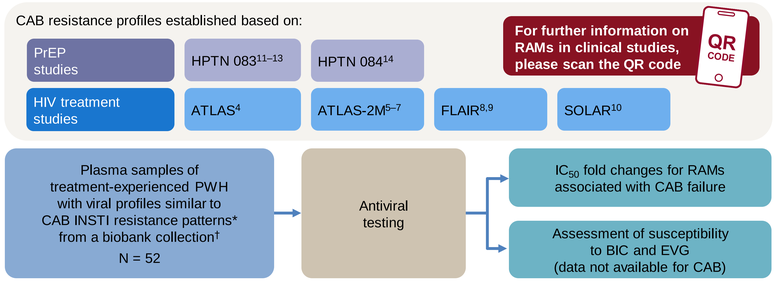
Objective

- 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

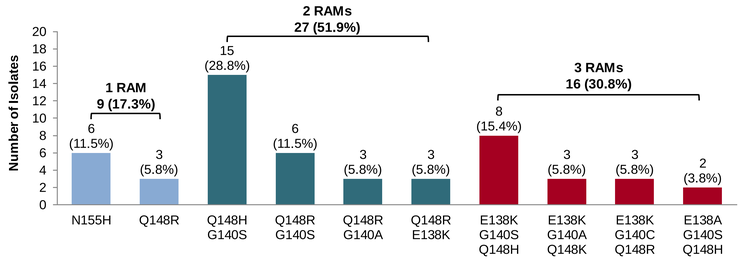
Study Design Schema

- Antiviral resistance testing was performed using person-derived clinical isolates (N = 52) with viral profiles similar to CAB INSTI resistance patterns[4–14]



*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)

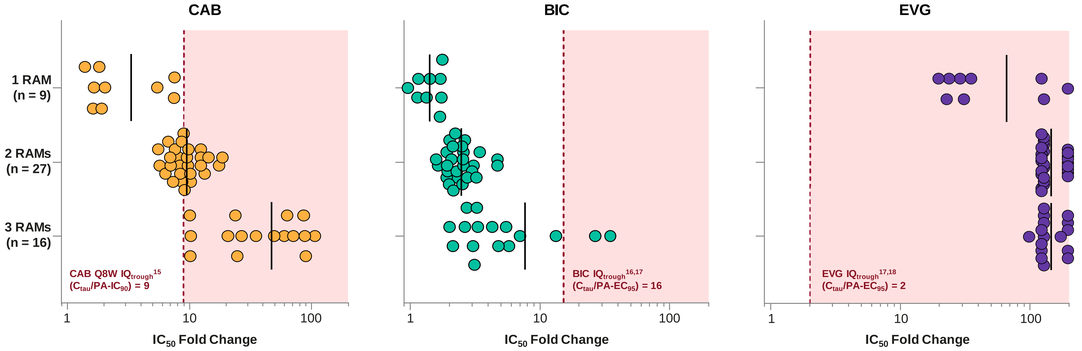


*Information about the samples from the biobank is limited and clinical data are not available.

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

Results

IC_{50} 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 further information on fold change values, please scan the QR code

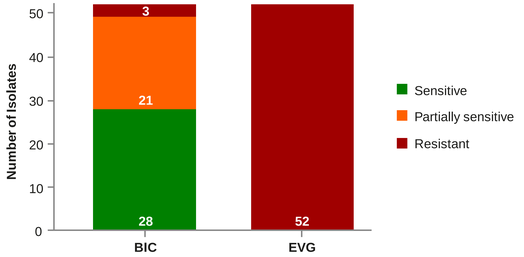
QR CODE

- For all three drugs, mean IC_{50} 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.

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.

Acknowledgments: Medical writing support was provided by Joanna Nikitorowicz-Buniak, PhD (Aspire Scientific Ltd, U.K.), and was funded by Gilead.

Abbreviations: B/BIC, bictegravir; C, cobicistat; CAB, cabotegravir; C_{tau}, clinical trough plasma concentration; DHHS, Department of Health and Human Services; EC_{95}, 95% maximal effective concentration; E/EVG, elvitegravir; F, emtricitabine; IC_{50}, 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.