The Evolution of Integrase Strand Transfer Inhibitors: VH-184, a 3rd-Generation Inhibitor With an Enhanced Resistance Profile

P043

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Key Takeaways

- **VH-184 is a novel third-generation integrase strand transfer inhibitor with long-acting potential that has demonstrated highly potent antiviral activity similar to DTG**
- **In vitro data demonstrate the enhanced resistance profile of VH-184, showing activity against first- and second-generation INSTI-resistant strains**
- **VH-184 was developed to combine the potency of second-generation INSTIs with an enhanced resistance profile and long-acting potential to support durable treatment over time**

Plain Language Summary

- Integrase strand transfer inhibitors, or INSTIs, are an important type of medicine for the treatment of HIV
- VH-184 is an experimental INSTI being developed by ViiV Healthcare; in laboratory studies, VH-184 was active against HIV that had become resistant to other INSTIs
- In a study where VH-184 was taken by mouth, it reduced the amount of HIV in the blood and was well tolerated
- VH-184 can also stay in the body for a long time, which means it might only need to be given twice a year as an injection

Introduction

- Integrase strand transfer inhibitors (INSTIs) have transformed antiretroviral therapy (ART) by offering durable potency and favorable tolerability
- Although first-generation INSTIs raltegravir (RAL) and elvitegravir (EVG) were an important innovation when first introduced, they have a low-to-moderate barrier to resistance[1]
- In the modern treatment era, second-generation INSTIs, including dolutegravir (DTG), bictegravir (BIC), and cabotegravir (CAB), offer a higher barrier to resistance than RAL or EVG
  - However, the widespread use of second-generation INSTIs increases selective pressure which, together with virus heterogeneity, could impact long-term durability and drive emergent resistance, underscoring the need for next-generation INSTIs with an even higher barrier to resistance
- VH4524184 (VH-184) is a third-generation INSTI with an enhanced resistance profile, showing activity against first- and second-generation INSTI-resistant strains in vitro[2,3]
- In resistance selection studies, no resistance mutations were identified through 112 days of selective pressure with VH-184[3]
- VH-184 monotherapy demonstrated highly potent antiviral activity similar to DTG in a proof-of-concept study, with no treatment-emergent INSTI resistance detected[4]
- VH-184 has long-acting potential, with twice-yearly dosing achievable based on available data[5]
- Here we present the evolution of INSTIs, including findings characterizing the enhanced resistance profile of VH-184

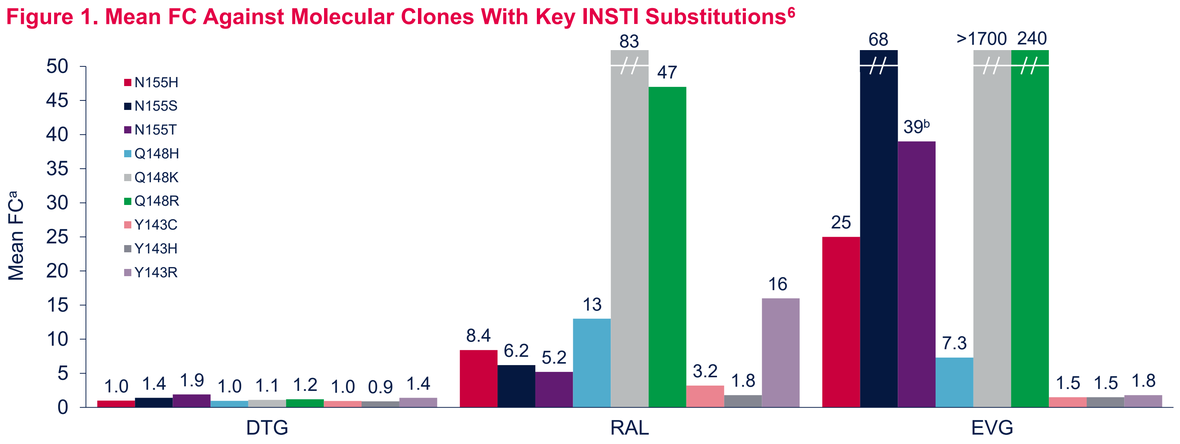
INSTI Evolution: From DTG to VH-184

In Vitro Resistance Profile of DTG

Antiviral Activity of DTG Against Viruses With Signature First-Generation INSTI Mutations

- Resistance selection studies and experiments of the antiviral activity of DTG against first-generation INSTI-resistant molecular clones established the resistance profile of DTG[6]
- No highly resistant mutants were isolated through Day 112 in resistance selection studies with DTG; substitutions that emerged conferred a fold change (FC; maximum, 4.1-fold) in the half-maximal effective concentration[6]
- DTG retained activity against all single INSTI-resistant mutants tested, including those in the Y143, N155, and Q148 pathways (Figure 1)[6]
  - RAL and EVG showed FCs of up to >1700-fold against these same variants

Figure 1. Mean FC Against Molecular Clones With Key INSTI Substitutions[6]



Note that some data extend beyond the maximum mean FC of 50. [a]Each value represents a mean of 3 to 5 independent experiments performed in duplicate. [b]Mean FC value from 1 or 2 experiments.

- Only 2 double mutants (E138K/Q148K and Q148R/N155H) reduced DTG susceptibility ≥10-fold; notably, the single mutations driving these pathways were not selected during DTG passage[6]
- These findings demonstrated that DTG retained potent activity against HIV-1 variants harboring first-generation INSTI-resistant mutations, with a resistance profile markedly distinct from that of RAL and EVG[6]

Findings from in vitro studies established DTG as a second-generation INSTI with potent activity against signature first-generation INSTI-resistant mutants

Phase 3 Trials of DTG: VIKING-3 and VIKING-4

Results From VIKING-3 and VIKING-4 Confirmed Clinical Activity of DTG in Adults Who Were Heavily Treatment Experienced With INSTI-Resistant HIV-1

- The phase 3 VIKING-3 (single-arm, open-label) and VIKING-4 (randomized, double-blind, placebo-controlled) studies evaluated DTG 50 mg twice daily in adults with multi-class drug resistance, including resistance to RAL and/or EVG, on a failing regimen[7,8]
- In VIKING-3, 63% of participants achieved HIV-1 RNA <50 c/mL at Week 48 when receiving DTG twice daily with optimized background regimen despite extensive resistance[9]
- VIKING-4 confirmed the antiviral activity of DTG, with DTG functional monotherapy demonstrating a significant reduction in HIV-1 RNA vs placebo at Day 8 (treatment difference, −1.16 log_{10} c/mL; $P<0.001$)[8]
- Virologic response in both VIKING-3 and VIKING-4 was associated with baseline integrase genotype and was most attenuated in participants harboring Q148 mutations with accumulating secondary substitutions (Figure 2)[8,9]

Figure 2. Proportions of Participants in VIKING-3 and VIKING-4 Achieving Virologic Suppression (Snapshot HIV-1 RNA <50 c/mL) on DTG 50 mg Twice Daily + OBR at Week 48[8,9]

OBR, optimized background regimen; RAM, resistance-associated mutation. [a]Among other baseline virus mutation subgroups, HIV-1 RNA <50 c/mL at Week 48 was 100% (1/1) in the T66 subgroup, 79% (22/28) in the Y143 subgroup, 82% (27/33) in the N155 subgroup, and 50% (4/8) in the subgroup with ≥2 primary mutations. [b]Including L74I, E138A/K/T, and G140A/C/S.

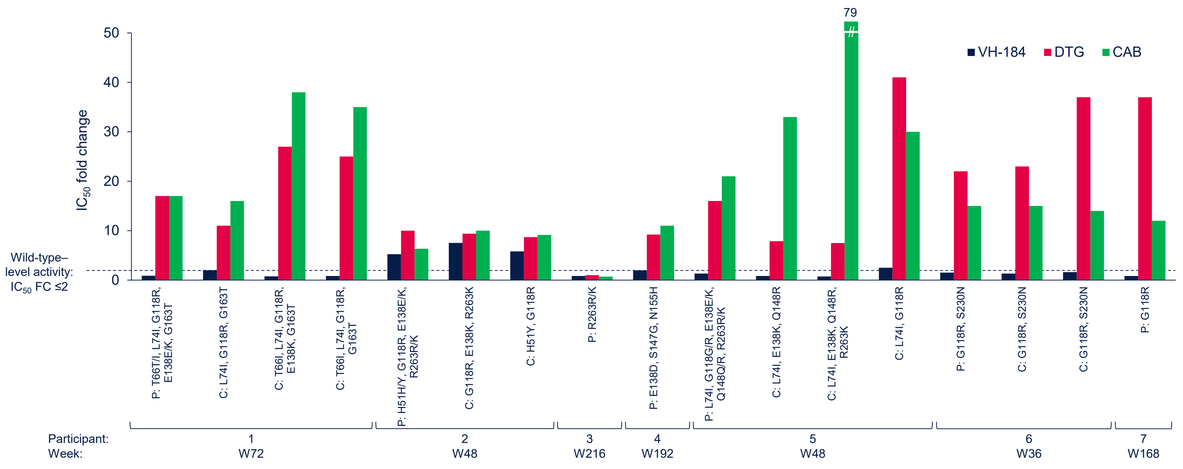
VIKING-3 and VIKING-4 established the high barrier to resistance of DTG, demonstrating efficacy in participants with first-generation INSTI resistance

In Vitro Resistance Profile of VH-184

Findings Support VH-184 as a Third-Generation INSTI With an Enhanced Resistance Profile

- In an early in vitro experiment, VH-184 retained activity against all single INSTI-resistant mutants tested, including those in the Y143, G118, N155, and Q148 pathways, as well as the R263K mutation[3]
- The resistance profile of VH-184 was evaluated against a panel of second-generation INSTI-resistant HIV-1 pseudotyped virus populations and clonal variants derived from participants meeting confirmed virologic withdrawal criteria in the phase 3 SAILING[10] (n=7; Week 132) and phase 3b DAWNING[11] (n=7; Week 216) studies[2,12]
  - The proportion of virus populations and clonal variants achieving inhibitory quotients for VH-184 and BIC coverage against clonal strains was evaluated by combining exposure, viral potency, and clonal FC
- VH-184 retained wild-type activity across variant genotypes with key second-generation INSTI resistance mutations from DAWNING, with enhanced activity compared with DTG and CAB across most variants (Figure 3)[2]
- VH-184 exposures combined with the enhanced resistance profile have the potential to demonstrate higher inhibitory quotients across the breadth of mutant strains compared with BIC (Figure 4)[12]

Figure 3. Antiviral Activity of VH-184, DTG, and CAB Against INSTI-Resistant Pseudotyped Virus Populations and Clonal Variants From DAWNING[2]



C, clonal variants; IC_{50}, half-maximal inhibitory concentration; P, virus populations; W, week.

Figure 4. Heat Map Depicting the Proportion of Individuals Achieving Each IQ for the Listed Clonal Variants[12]

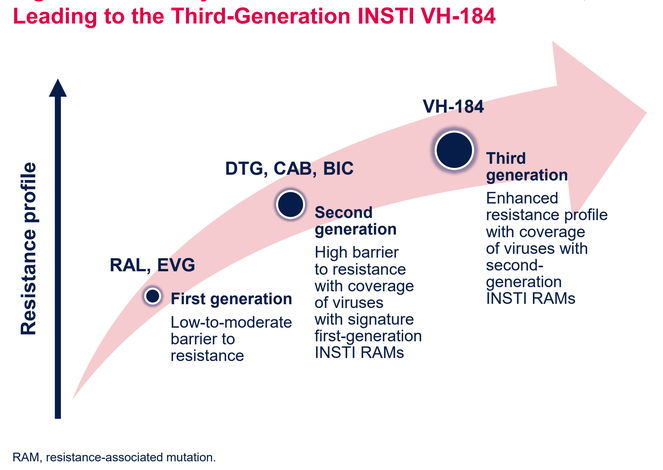
C_{tau}, plasma drug concentration at the end of the dosing interval; IQ, inhibitory quotient; PA-EC_{90}, protein-adjusted 90% effective concentration. [a]The IQ represents the ratio of drug exposure to viral susceptibility; IQ = (plasma drug concentration, C_{tau})/(PA-EC_{90} × ClonalFC). C_{tau} based on oral VH-184 45 mg and BIC 50 mg.

VH-184 showed an enhanced resistance profile, retaining activity against INSTI-resistant pseudotyped viruses

INSTI Evolution and VH-184 Development

- The INSTI class has evolved from the first-generation INSTIs RAL and EVG to the second-generation INSTIs DTG, BIC, and long-acting CAB; VH-184 is the first third-generation INSTI to enter clinical development
- VH-184 retains potent antiviral activity against a broad panel of first- and second-generation INSTI-resistant variants
- Oral VH-184 monotherapy demonstrated highly potent antiviral activity in a proof-of-concept study, with up to a mean reduction in viral load of 2.31 log_{10} c/mL and no resistance to VH-184 detected[4]
- VH-184 represents the next step in the evolution of the INSTI class (Figure 5), showing
  - An enhanced resistance profile[2]
  - Potency similar to DTG with no treatment-emergent INSTI-resistance during monotherapy[4]
  - Potential for extended dosing intervals[5]

Figure 5. Summary of the Evolution of the INSTI Class, Leading to the Third-Generation INSTI VH-184



RAM, resistance-associated mutation.

Conclusions

- Together, these data further support the development of VH-184 as a core agent in a complete long-acting regimen
- VH-184 will be further evaluated among people naive to ART in the phase 2b INNOVATE study (NCT07202546); an upcoming study in people with INSTI resistance is also planned

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