Characterization of the Clinical Drug–Drug Interaction Profile of VH4524184 (VH-184), a Third-Generation Integrase Strand Transfer Inhibitor

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Key Takeaways

- VH4524184 (VH-184) is a novel third-generation integrase strand transfer inhibitor (INSTI) with long-acting potential and highly potent antiviral activity similar to dolutegravir
- We evaluated the drug–drug interaction profile of oral VH-184 using cytochrome P450 3A4 (CYP3A4) modulators and the transporter probe substrates metformin (organic cation transporter 1 [OCT1]/multidrug and toxin extrusion protein 1/2-kidney [MATE1/2K]) and digoxin (P-glycoprotein [P-gp])
- VH-184 exposure was affected by CYP3A4 modulators, consistent with the second-generation INSTIs dolutegravir and bictegravir, but had no meaningful impact on OCT1/MATE1/2K or P-gp substrates, demonstrating a favorable precipitant profile that may broaden compatibility with co-administered medications
- Future work will assess the clinical significance of CYP3A4 modulators on long-acting injectable VH-184 exposure

Plain Language Summary

- VH-184 is an experimental medicine being studied for the treatment of HIV. It may only need to be given twice a year, as an injection either into the muscle or under the skin
- Treatment of HIV is lifelong, and as people with HIV grow older, they typically take medicines for other health conditions too. Because drugs can interact with one another, it's important to understand how an HIV medicine reacts when taken alongside other medications
- In this study, we found that certain other medicines could change how much VH-184 is in the body. However, VH-184 itself did not affect specific pathways the body uses to process and eliminate some common medicines, suggesting it may be able to be taken safely alongside them

Introduction

- People with HIV-1 are living longer,[1] and as this population ages, increasing cardiometabolic risk and polypharmacy make the drug–drug interaction (DDI) profile of antiretroviral therapy an important consideration[2]
- VH4524184 (VH-184) is a third-generation integrase strand transfer inhibitor (INSTI) with an enhanced resistance profile, potent antiviral activity, and long-acting potential[3-5]
- In previous studies, oral VH-184 has shown a promising DDI profile
  - VH-184 had no meaningful impact on cytochrome P450 3A (CYP3A) substrates[4]
  - VH-184 could be co-administered with common oral contraceptives[6]
- We assessed the DDI profile of VH-184 using CYP3A4 inhibitors/inducers and the transporter probe substrates metformin (organic cation transporter 1 [OCT1]/multidrug and toxin extrusion protein 1/2-kidney [MATE1/2K]) and digoxin (P-glycoprotein [P-gp])

Methods

- We conducted a phase 1, open-label study in adults without HIV (ClinicalTrials.gov identifier, NCT07066722)
- To assess VH-184 as an object, a single dose of oral VH-184 100 mg was administered before and after steady-state dosing with each precipitant: once-daily itraconazole 200 mg (a strong CYP3A4 inhibitor), once-daily rifabutin 300 mg (a moderate CYP3A4 inducer), or 3-times–daily phenytoin 100 mg (a strong CYP3A4 inducer)
- To assess VH-184 as a precipitant, single doses of transporter probe substrates metformin 500 mg (OCT1, MATE1/2K) and digoxin 0.25 mg (P-gp) were administered alone and with steady-state oral VH-184 200 mg once daily
- Plasma concentration–time data were analyzed using non-compartmental methods
- Geometric mean ratios (GMRs; 90% CIs) of maximum plasma concentration (C_{max}), area under the concentration–time curve (AUC) from time 0 to end of dosing interval (AUC_{0-t}), and AUC from time 0 to infinity (AUC_{0-inf}; CYP3A4 only) were calculated for VH-184 with vs without CYP3A4 modulators and for transporter substrates with vs without VH-184
- The primary endpoints were C_{max} and AUC_{0-t} for VH-184 with vs without CYP3A4 modulators and C_{max} and AUC_{0-t} for metformin and digoxin with vs without VH-184; safety was a secondary endpoint

Results

Baseline Demographics and Characteristics

- We enrolled 61 participants from the United States
- Across cohorts, most participants were male sex (90%), median age was 33 years, and 39% identified as Hispanic or Latine (Table 1)

Table 1. Baseline Demographics and Clinical Characteristics

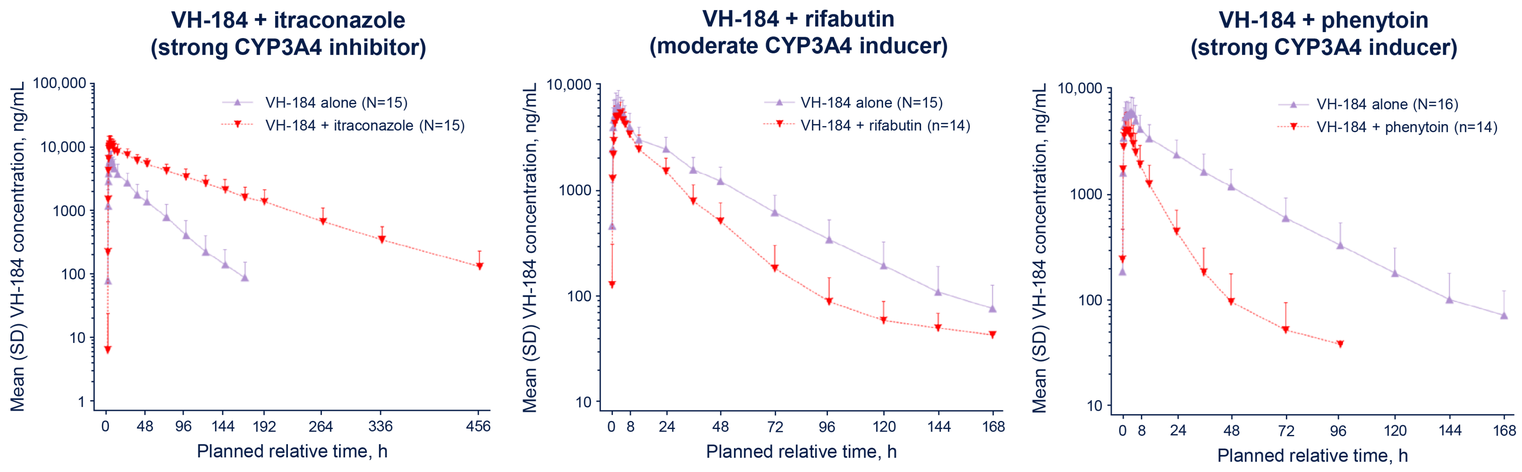
Parameter	Participants receiving VH-184 and CYP3A4 modulators			Participants receiving VH-184 and transporter substrates	
	Itraconazole (N=15)	Rifabutin (N=15)	Phenytoin (N=16)	Metformin and digoxin (N=15)	Overall (N=61)
Male sex, n (%)	14 (93)	13 (87)	15 (94)	13 (87)	55 (90)
Age, median (range), y	41 (29-60)	36 (22-60)	30 (25-53)	30 (27-61)	33 (22-61)
Race, n (%)					
American Indian or Alaska Native	0	0	0	1 (7)	1 (2)
Asian	1 (7)	1 (7)	2 (13)	0	4 (7)
Black or African American	2 (13)	5 (33)	3 (19)	2 (13)	12 (20)
White	10 (67)	8 (53)	10 (63)	10 (67)	38 (62)
Multiple races	2 (13)	1 (7)	1 (6)	2 (13)	6 (10)
Hispanic or Latine ethnicity, n (%)	5 (33)	5 (33)	6 (38)	8 (53)	24 (39)
BMI, median (range), kg/m^2	27 (20-31)	25 (20-31)	25 (21-30)	27 (21-30)	26 (20-31)

BMI, body mass index.

Effect of CYP3A4 Modulators on VH-184

- VH-184 exposure was increased by the strong CYP3A4 inhibitor itraconazole and decreased by the moderate and strong CYP3A4 inducers rifabutin and phenytoin, respectively
  - Concentrations of VH-184 are shown in Figure 1, and GMRs for C_{max} and AUC are summarized in Table 2

Figure 1. Concentrations of VH-184 as an Object With and Without CYP3A4 Inhibitor or Inducers



The lower limit of quantification for VH-184 was 25 ng/mL.

Table 2. GMRs of PK Parameters: Effect of CYP3A4 Modulators on VH-184 as an Object

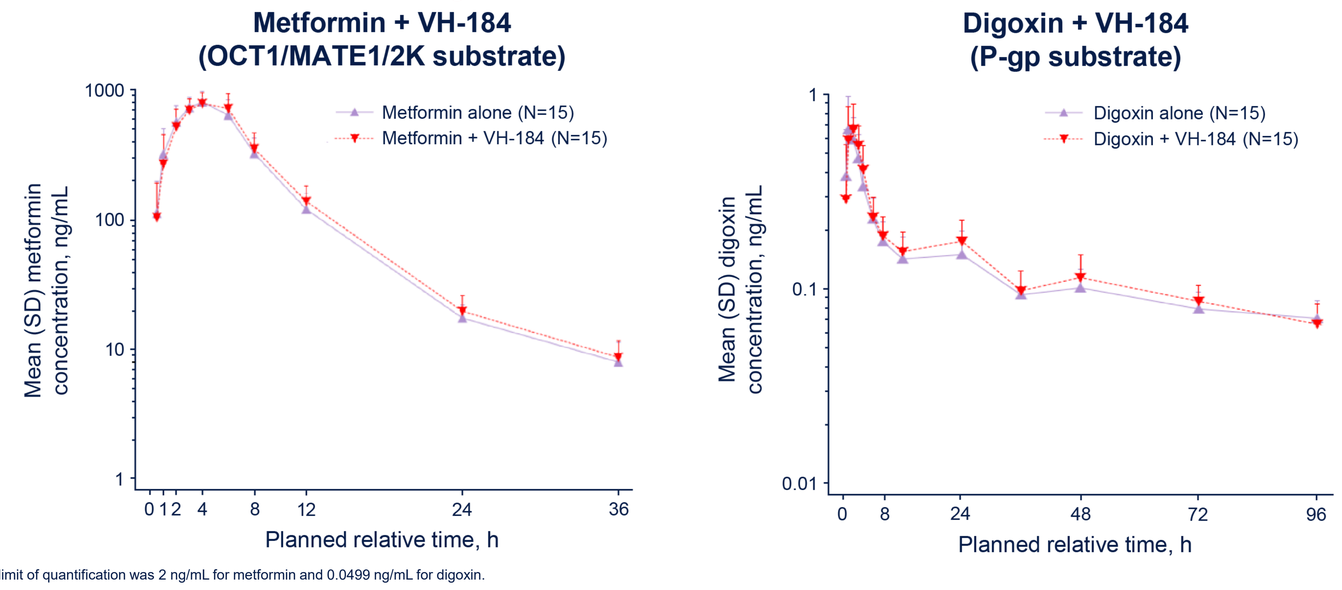
Parameter	GMR (90% CI)[a]		
	Itraconazole (strong CYP3A4 inhibitor; N=15)	Rifabutin (moderate CYP3A4 inducer; N=15)[b,c]	Phenytoin (strong CYP3A4 inducer; N=16)[d]
C_{max}, ng/mL	1.817 (1.447-2.283)	0.886 (0.736-1.067)	0.609 (0.475-0.782)
AUC_{0-t}, h × µg/mL	4.984 (3.857-6.441)	0.574 (0.468-0.704)	0.247 (0.183-0.333)
AUC_{0-inf}, h × µg/mL	4.997 (3.864-6.462)	0.572 (0.466-0.702)	0.248 (0.184-0.335)

PK, pharmacokinetic. [a]GMRs of VH-184 PK parameters with vs without co-administration of CYP3A4 modulators. [b]Fifteen participants received VH-184 alone and 14 received VH-184 + rifabutin. [c]Data from a sensitivity analysis (n=13) excluding outlier data from 1 participant who had anomalously low VH-184 concentration compared with all other participants in the cohort. [d]Sixteen participants received VH-184 alone and 14 received VH-184 + phenytoin.

Effect of VH-184 on Transporter Substrates Metformin and Digoxin

- VH-184 did not meaningfully affect metformin or digoxin exposure
  - Concentrations of metformin and digoxin are shown in Figure 2, and GMRs for C_{max} and AUC_{0-t} are summarized in Table 3

Figure 2. Concentrations of Metformin and Digoxin With and Without VH-184 as a Precipitant



The lower limit of quantification was 2 ng/mL for metformin and 0.0499 ng/mL for digoxin.

Table 3. GMRs of PK Parameters: Effect of VH-184 on Transporter Substrates Metformin and Digoxin

Parameter	GMR (90% CI)[a,b]	
	Metformin (OCT1, MATE1/2K substrate; N=15)	Digoxin (P-gp substrate; N=15)
C_{max}, ng/mL	1.007 (0.885-1.145)	1.022 (0.882-1.184)
AUC_{0-t}, h × µg/mL or h × ng/mL[c]	1.041 (0.916-1.183)	1.126 (0.835-1.518)

PK, pharmacokinetic. [a]GMRs of transporter substrate PK parameters with vs without co-administration of VH-184. [b]Metformin and digoxin AUC_{0-inf} were not protocol-defined endpoints. [c]h × µg/mL for metformin or h × ng/mL for digoxin.

Safety and Tolerability

- There were no VH-184–related grade ≥3 adverse events (AEs), serious AEs, or deaths
- 31 (51%) participants discontinued treatment, mostly due to AEs from CYP3A4 modulators

Conclusions

- In this clinical DDI study, oral VH-184 was generally well tolerated with a favorable safety profile
- VH-184 exposure showed a strong increase with a strong CYP3A4 inhibitor (~5-fold increase in AUC_{0-t}) and a weak-to-moderate decrease with moderate-to-strong CYP3A4 inducers (~43% and ~75% decreases in AUC_{0-t}, respectively), supporting a DDI profile consistent with the second-generation INSTIs dolutegravir and bictegravir[7,8]
- VH-184 did not meaningfully impact the pharmacokinetics of OCT1/MATE1/2K or P-gp substrates, demonstrating a favorable precipitant profile and supporting compatibility with co-administered medications that are substrates of these transporters
- This study assessed oral VH-184; the clinical significance of CYP3A4 inhibitors/inducers on long-acting injectable VH-184 exposure will be evaluated after dose selection
- The phase 2b INNOVATE study (NCT07202546) is evaluating oral VH-184 in people with HIV-1 naive to treatment; part 2 will assess a long-acting injectable formulation

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