suppressed viral loads. All individuals in the national HIVDR database with complete data on key variables were included in the analysis. Logistic regression was used to identify factors associated with resistance, and Mann-Kendall test was used to test significance in the HIVDR trends.

Results: Among 6,311 participants, 5.6% had HIVDR. An increase from 3% in July-September 2021 to 9% in July-September 2023 (p value=0.012). Resistance to INSTIs increased from 0% in April-June 2021 to 23% in Jan-March 2024 (p value=0.013). For NNRTIs and NRTIs, the resistance reduced (p value=0.015 and 0.0330 respectively). Participants aged 20-24 years (aOR=1.6; 95%CI: 1.2-2.2) and those aged ≥50 years (aOR=1.9; 95% CI: 1.3-2.8) had higher odds of HIVDR compared to those aged 1-19 years. Males (aOR=1.5; 95%CI: 1.2-2.0) and those on ART for ≥11 years compared to those on ART for ≤5 years (aOR=1.8; 95% CI 1.3-2.6) also had higher odds of HIVDR. Participants fron HC IVs (aOR=0.54; 95%CI; 0.36-0.81) and HIV specialized clinics (aOR=0.47; 95%CI: 0.3-0.74) had lower odds of HIVDR compared to those from HC IIIs. Higher odds of HIVDR were observed in the northern (aOR=2.5; 95%CI: 1.7-3.5), western (aOR=1.8; 95%CI: 1.8-2.9), and eastern (aOR=1.8; 95%CI: 1.2-2.5) regions compared to the central region. Compared to females, males were 50% more likely to have resistance.

Conclusions: HIVDR, particularly to INSTIs, is rising among individuals with repeat non-suppressed viral loads, with higher likelihood observed in males, individuals aged 20 years and above, and those from HC IIIs and non-central regions. There is need to investigate the underlying factors driving resistance and its variation across demographics and geographic locations.

eP164 | CSF pharmacokinetics and antiviral activity of doravirine: implications in neurocognitive impairment

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Purpose: Doravirine (DOR, MK-1439) containing regimens are recommended in the EACS guideline due to its favorable profiles of efficacy and safety. Limited data are available on DOR pharmacokinetics (PK) in CSF particularly among experienced participants. This study aims to measure DOR concentrations in CSF and compare them to HIV-1 RNA in CSF and neurocognitive (NC) performance.

Method: This was a single-arm, open-label, single-center study. After an initial assessment, 8 participants undergoing treatment with DOR-containing regimens were enrolled and followed for 12 weeks. At week 0 and week 12, blood was collected at 1, 2, and 4 hours post-dose and CSF was collected within 2 hours. Plasma and CSF concentrations were determined by LC/MS-MS. The DOR IC90 against wild-type HIV-1 was 5.1 ng/ml. HIV-1 RNA was measured by RT-PCR. NC performance was estimated by the Montreal Cognitive Assessment (MoCA). Adherence was determined by pill count. Changes in drug concentrations were analyzed using signed rank tests.

Results: DOR concentrations in CSF and the CSF:plasma ratio (CPR) remained stable. At week 12, the median (range) plasma and CSF concentrations was 850 ng/mL (597-915) and 64.8 ng/mL (54.9-72.5) 2 hours post-dose. The proportion of CSF concentrations exceeding IC90 (range) rose from 12-fold (8-23) at baseline to 13-fold (11-14) at week 12. HIV-1 RNA was ≤40 copies/mL in all CSF/plasma specimens and no mutant was noted. Median CD4 T cell count was 601 at the entry and 486 at week 12 (p=0.465). Median MoCA (IQR) was 25 (24-27) at the baseline and 23 (21-28) at week 12 (p=0.281). 4 participants (57%) had NC impairment at baseline and 3 remained impaired at week 12. No concentrations correlated with NC performance.

Conclusions: Stable DOR concentrations in CSF were achieved after 12-week treatment that significantly exceeded the 90% inhibitory concentration for wild-type HIV-1, suggesting therapeutic effectiveness of DOR in the CNS.

eP165 | Pharmacogenetics of dolutegravir and bictegravir plasma and intracellular pharmacokinetics

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Purpose: The aim of this study was to investigate the impact of important polymorphisms in pharmacogenes

Table 1. Description of the study population.

	DTG (n=100)	BIC (n=51)	*P* value
Female sex, n (%)	37 (37)	20 (39)	0.79
Age, mean (SD), y	51 (12)	45 (12)	**0.003**
BMI, median (IQR), kg/m²	27 (24-30)	28 (24-31)	0.64
Weight, mean (SD), kg	82 (15)	82 (17)	0.83
Tobacco use, n (%)	21 (21)	21 (21)	0.72
CD4+ T-cell count, median (IQR)	696 (530-863)	562 (439-692)	**0.0003**
Lowest CD4+ T-cell count, median (IQR)	234 (118-342)	199 (113-346)	0.62
Past AIDS	48 (48)	29 (57)	0.33
Ethnicity			0.35
- *Sub-Saharan African*	35 (35)	25 (49)	
- *White*	59 (59)	23 (45)	
- *Hispanic*	4 (4)	2 (4)	
- *Asian*	2 (2)	1 (2)	
Number of participants with 1/2/3/4 plasma sampling occasions	7/9/73/11	3/13/31/4	

Table 2. Parameter estimates for the final dolutegravir plasma pharmacokinetics model with genotypes.

Parameter	Estimate (RSE%)	IIV (RSE%)	IOV (RSE%)
Tlag (hr)	0.263 (-)		
ka (hr-1)	2.24 (-)		
V/F (L)	15.0 (13)	0.16 (84)	0.12 (61)
b_weight, V/F (-)	0.70 (47)		
CL/F (L/h)	0.73 (6)	0.24 (16)	0.12 (25)
b_weight, CL/F (-)	0.46 (38)		
b_cobicistat use, CL/F (-)	0.21 (91)		
b_smoking, CL/F (-)	0.12 (59)		
b_UGT1A1 poor metabolizers, CL/F (-)	-0.34 (27)		
s (-)	0.28 (10)		

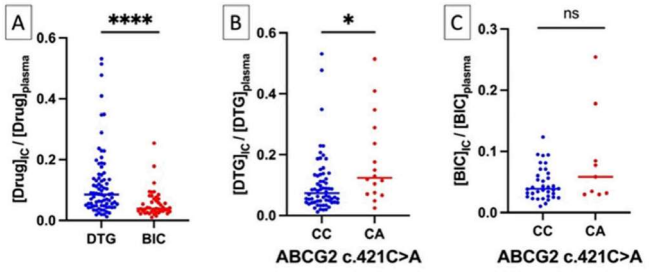

Figure 1. Drug intracellular/plasma ratios for dolutegravir and bictegravir.

on plasma and intracellular pharmacokinetics of dolutegravir and bictegravir.

Method: In this single-center study, persons living with HIV (PLWH) treated with either dolutegravir or bictegravir were recruited. Participants were genotyped using pharmacogenetic panel testing, and pharmacokinetics were studied during routine follow-up visits. Sparse sampling for plasma drug concentrations measurements was performed at several occasions, with intracellular drug quantification in peripheral blood mononuclear cells (PBMCs) measured at one of those occasion. Intracellular/plasma drug concentration ratios were calculated.

For dolutegravir plasma pharmacokinetics, the relationships between CL/F and selected genetic covariates (UGT1A1 metabolizing status, *CYP3A4*22*, CYP3A5 expression status, *ACBC1* c.3435C>T, *ABCB1* c.1199G>1, *ABCG2* c.421C>A, *NR1I2* c.-22-7659C>T, *POR*28)* was studied, building on a previously published popPK model (Parant et al. Ther Drug Monit 2019). For intracellular drug accumulation, the impact of *ABCG2* c.421C>A on dolutegravir and bictegravir intracellular/plasma ratios was specifically assessed, as this important drug transporter polymorphism (SNP) has previously been shown to impact on integrase strand transfer inhibitors (INSTIs) pharmacokinetics.

Results: 100 PLWH receiving dolutegravir and 51 PLWH receiving bictegravir were included (Table 1). UGT1A1 poor metabolizers showed a 32% decrease in plasma clearance of dolutegravir (Table 2). Studying intracellular

drug accumulation, dolutegravir was found to accumulate significantly more in PBMCs than bictegravir (P <0.0001). The *ABCG2* c.421C>A single nucleotide polymorphism impacted intracellular drug accumulation, with increased accumulation for A carriers in dolutegravir ($P = 0.01$) and bictegravir ($P = 0.06$) (Figure 1).

Conclusions: Our findings indicate that both UGT1A1 metabolizing status and the *ABCG2* c.421C>A SNP have impacts on pharmacokinetics of second generation INSTIs.

eP166 | Pharmacokinetics and safety of MK-8527 in adults with moderate or severe renal impairment

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Purpose: MK-8527 is an oral nucleoside reverse transcriptase translocation inhibitor being developed for HIV-1 prevention. MK-8527 is phosphorylated intracellularly to its active triphosphate (TP) form, MK-8527-TP. Previous studies indicate that renal excretion plays a prominent role in MK-8527 elimination. This study evaluated MK-8527 pharmacokinetics (PK) and safety in participants with moderate or severe renal impairment (RI).

Method: In this open-label, Phase 1 study (NCT06295796), participants with moderate RI (eGFR 30-59 mL/min, using CKD-EPI 2021) or severe RI (eGFR 15-29 mL/min) received a single dose of MK-8527 6 mg. Participants (matched for age and BMI) with normal renal function were enrolled as controls. PK of plasma MK-8527 and intracellular MK-8527-TP in peripheral blood mononuclear cells (PBMCs) were assessed. Safety was monitored using adverse event (AE) reporting.

Results: Six participants were enrolled in each group (control, moderate RI, severe RI; **Table 1**); all participants completed the study. Participants with moderate or severe RI had a 1.8-fold or 2.2-fold higher plasma MK-8527 $AUC_{0-\infty}$, respectively, compared with controls (-**Table 2**). Plasma MK-8527 C_{max} was generally similar between participants with moderate RI, severe RI, and controls. Participants with moderate or severe RI had prolonged $t_{1/2}$ for plasma MK-8527 and PBMC MK-8527-TP and decreased CL/F and Vz/F for plasma MK-8527 compared with controls. Participants with moderate or severe RI had 2.0-fold or 2.4-fold higher intracellular MK-8527-TP $AUC_{0-\infty}$ compared with controls and 2.2-fold or 1.8-fold higher intracellular MK-8527-TP C_{max} compared with controls, respectively. No AEs were reported in this study.

Conclusions: Plasma MK-8527 exposure was increased in participants with moderate or severe RI, consistent with renal excretion as a major pathway in MK-8527 elimination. Exposure of intracellular MK-8527-TP was also increased in participants with moderate or severe RI. A single 6-mg dose of MK-8527 was well tolerated in participants with moderate or severe RI.

Table 1. Participant Demographics and Baseline Characteristics

Category	Control n = 6	Moderate RI n = 6	Severe RI n = 6
Female, n (%)	3 (50)	2 (33)	3 (50)
Age, median (range), years	60.0 (52-68)	65.0 (52-69)	70.0 (60-73)
Weight, median (range), kg	88.9 (78.8-100.4)	100.3 (86.2-116.3)	85.4 (64.6-105.5)
BMI, median (range), kg/m^2	30.6 (28.7-33.7)	33.7 (30.5-37.5)	27.8 (25.3-34.3)
eGFR,[a] mean (SD), mL/min	100.8 (10.0)	44.3 (8.8)	22.9 (5.1)
Race, n (%)			
Black/African American	3 (50)	4 (67)	5 (83)
White	3 (50)	2 (33)	1 (17)
Ethnicity, n (%)			
Not Hispanic or Latine	5 (83)	6 (100)	6 (100)

BMI, body mass index; BSA, bovine serum albumin; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; RI, renal impairment.

[a] Baseline eGFR (based on the 2021 CKD-EPI equation) was obtained twice (≥72 hours apart) during participant screening, and mean values were used to determine renal function. Values represent de-indexed eGFR using individual BSA for each participant.