



26TH INTERNATIONAL
WORKSHOP ON **CLINICAL**
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OTHER ANTIVIRAL DRUGS | 2025

ABSTRACT BOOK

**26th International Workshop on Clinical Pharmacology of HIV,
Hepatitis and other Antiviral Drugs 2025**
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ORAL ABSTRACT PRESENTATIONS

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1

Population Pharmacokinetics of Tecovirimat in Persons with Mpox: Initial Results from ACTG A5418

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Background: The Study of Tecovirimat for Human Mpox Virus (STOMP) (ACTG A5418) assessed the safety, efficacy, and pharmacokinetics (PK) of tecovirimat in clade II mpox infection. We previously showed lower tecovirimat exposures among participants in the open-label arm in comparison to healthy volunteers (HVs), though predicted concentrations at the end of the dosing interval (Ctau) were comparable or above the therapeutic target in non-human primates (NHPs). In clinical trials, tecovirimat did not reduce time to clinical resolution versus placebo, highlighting the need to examine factors affecting tecovirimat PK in persons with mpox and the adequacy of current dosing strategies. Here, we report initial population PK modeling of tecovirimat in persons with mpox and comparisons with historical data in HVs.

Methods: Participants in the randomized and open-label arms received oral tecovirimat 600 mg either twice daily (weight 40-<120 kg) or three times daily (weight ≥120 kg) for 14 days. Intensive PK sampling occurred on treatment day 8 at time 0 (pre-dose), 1, 2, 3, 4, 6, 8, and 10 hours post-dose with sparse sampling on days 3, 8 and/or 15.

Plasma tecovirimat concentrations were quantified by a validated LC-MS/MS assay. The population PK model was developed in Phoenix NLME. One- and two- compartment models with either additive, multiplicative, or combined error models were investigated. Fixed allometric scaling of weight on apparent volume of distribution (V/F) and apparent oral clearance (CL/F), inclusion of an absorption lag time (Tlag), and the effect of meals on relative bioavailability (F) and absorption rate (ka) were assessed in base model development in alignment with prior modeling in HVs. Simulations with 100 replicates per participant were performed with the final base model and predicted AUC0-24h, Cmax, and Ctau estimates were compared to those previously simulated in HVs (US FDA Clinical Pharmacology Review) and the NHP therapeutic target (169 ng/mL).

Results: PK data were available in 75 participants (41 participants with 315 intensive+30 sparse observations; 34 participants with 59 sparse observations; 404 observations total). A one-compartment model with combined error, Tlag, and allometric scaling for weight (centered to 70 kg) fixed at 1 and 0.75 on V/F and CL/F, respectively, best fit the available data. Population estimates (95% CI) for ka, Tlag, V/F, and CL/F were 0.56 1/hr (0.20-0.92), 0.99 hr (0.91-1.07), 367 L (222-510), and 51.6 L/hr (44.7-58.5), respectively. Interindividual variability for ka, Tlag, V/F, and CL/F were 124%, 57.6%, 65.9%, and 42.7%, respectively, and generally indicated more variability than HVs. Median simulated AUC0-24h, Cmax, and Ctau were 38.8%, 38.5%, and 36.4% lower in A5418 participants than HVs. Simulated median Ctau (5th, 95th percentiles) was 599 ng/mL (112, 1523) in A5418 participants, with 8.5% of predicted Ctau values from A5418 falling below the NHP therapeutic target.

Conclusions: Lower tecovirimat exposures and greater PK variability were observed in A5418 participants versus HVs, but simulated Ctau estimates exceeded the NHP therapeutic target in ~91.5% of cases. Investigation into the mechanism of these differences and their relationship to clinical/virologic outcomes is warranted.



2

GS-443902 Concentrations in Peripheral Blood Mononuclear Cells and Dried Blood Spots among Pregnant and Non-Pregnant Women Receiving Remdesivir for COVID-19 Treatment

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Background: Activation of remdesivir (RDV) has typically been assessed by measuring concentrations of GS-443902 (active triphosphate) in peripheral blood mononuclear cells (PBMC). We previously showed concentrations of RDV and its major plasma metabolites were similar between pregnant and non-pregnant women with COVID-19, while those of GS-443902 in PBMC were ~50% lower in pregnancy. Dried blood spots (DBS) provide a simpler alternative to PBMC collection

and may serve as another surrogate measure of cellular drug activation, but pregnancy status and inflammation due to COVID-19 may impact these measures. Here, we evaluated factors that affect GS-443902 in DBS and PBMC and relationships between cell types in pregnant and nonpregnant women with COVID-19.

Methods: IMPAACT 2032 (NCT04582266) was a Phase IV prospective, open label, non-randomized, opportunistic study of hospitalized pregnant and nonpregnant women receiving intravenous RDV as part of clinical care for COVID-19. DBS and PBMC were isolated pre-dose and/or 23 hours post dose on infusion days 3, 4, and 5. GS-443902 concentrations in each cell type were quantified using LC-MS/MS methods from 2x7mm punches (DBS) or cell pellets (PBMCs). Generalized linear mixed effects modeling 1) evaluated the effect of pregnancy and baseline covariates on log-transformed GS-443902 in DBS and PBMC using forward selection ($p < 0.2$) and backwards elimination ($p < 0.1$) after adjusting for infusion number, and 2) assessed relationships between GS-443902 in DBS vs PBMC.

Results: 76 DBS and PBMC observations were available from 51 participants (25 pregnant, 26 nonpregnant). Median (interquartile range) GS-443902 concentrations in DBS were 1807 (1395, 2292) and 1633 (1267, 2412) fmol/punch and in PBMC were 2.96 (0.79, 6.89) and 5.15 (3.22, 8.77) μM for pregnant and nonpregnant participants, respectively. In DBS, GS-443902 concentrations were 19% lower (90% CI -33, -2.5%) during pregnancy; increases in SBP (per 10 mmHg) were associated with an 8.1% decrease (90% CI -11.4%, -4.7%); and increases in ALP (per 10 U/L) and platelet count (per 50×10^9 cells/L) were associated with a 1.4% (90% CI 0.3%, 1.8%) and 5.3% (90% CI 0.8%, 13.4%) increase, respectively. In PBMC, GS-443902 concentrations were 45% lower (90% CI -19.4%, -61.8%) in pregnant vs nonpregnant participants with each additional infusion. Increases in ALP and ALT (per 10 U/L) were associated with a 4.2% decrease (90% CI -7.7%, -0.6%) and 11.4% decrease (90% CI -18.8%, -3.4%) in GS-443902 concentrations in PBMC, respectively. For DBS vs PBMC comparisons, GS-443902 concentrations in PBMCs increased by 7.7% (90% CI 4.0%, 11.6%) for every 100 fmol/punch increase in DBS for nonpregnant women; however, in pregnant women, there was a 4.4% decrease (90% CI -7.9%, -0.8%) for GS-443902 in PBMC for every 100 fmol/punch increase in DBS.



Conclusions: Cellular disposition of GS-443902 between DBS and PBMCs differed by pregnancy status and other clinical factors associated with COVID-19 disease severity. The mechanisms and clinical significance of these differences are unknown. Further investigation into how pregnancy and other disease-specific factors affect cellular concentrations is warranted.



3

Therapeutic Drug Monitoring of Dolutegravir in Children and Adolescents Living with HIV: A Retrospective Study

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Background: Dolutegravir (DTG)-based antiretroviral regimens are recommended as first-line and salvage therapy for HIV in all populations. Achieving therapeutic DTG plasma concentrations in pediatric patients, however, may be challenging due to interindividual variability and adherence challenges. The utility of therapeutic drug monitoring (TDM), particularly in pediatrics, remains understudied. This study aimed to describe the use and usefulness of DTG TDM in pediatric patients.

Materials and methods: TDM data were collected retrospectively from the Québec Antiretroviral Therapeutic Drug Monitoring Program between January 1, 2011 and March 31, 2022. Inclusion criteria were subjects under 18 years old with at least one DTG TDM. We excluded subjects if all their samples' time post-dose were unknown or in the first half of the dosing interval. For samples not drawn exactly at the end of the dosing interval, trough concentrations (C_{tau}) were estimated with mean population half-lives for specific age or weight groups. The efficacy and toxicity C_{tau} thresholds were ≥ 0.32 mg/L and ≥ 1.47 mg/L, respectively. Viral suppression was defined as a viral load < 50 copies/mL. Interindividual and intra-individual coefficients of variation (CV) were calculated. An independent t-test was used to compare mean C_{tau} in subjects with and without viral suppression.

Results: Fifty-three subjects (55% female) contributed 249 DTG samples (mean(SD) 8.6 (4.5) samples per subject). At the time of first DTG TDM, the mean(SD) age and weight were 11.1 (4.2) years

and 43.6 (18.8) kg, respectively, and 86% of subjects had viral suppression. TDM was prescribed for the indication "pediatrics" or "control" in 90.8% of cases. The mean(SD) C_{tau} was 2.07 (1.65) mg/L, with 21% C_{tau} results being therapeutic, 4.8% subtherapeutic, and 55% supratherapeutic (19% were unknown due to missing or absorption-phase time post-dose). Pharmacists recommended DTG intake without food in 17.3% of TDM reports, and recommended a dose decrease if presence of bothersome central nervous system side effects in 45.8% of reports. Following these recommendations, no dose decreases were done. All C_{tau} (n=6) in children weighing 6 to < 14 kg were supratherapeutic. This proportion was also high in patients weighing 30 to < 40 kg (64%) and > 40 kg (56%). Interindividual variability was high (CV 65.4%), while intra-individual variability was lower (median CV 25.6%). No significant difference in mean C_{tau} was found between patients with and without viral suppression ($p > .05$). Proportions of viral suppression increased from 86% to 93% across the first four TDMs, despite relatively stable proportions of C_{tau} above the efficacy threshold. Proportions of C_{tau} within the therapeutic window increased from 18.2% to 36.8%. The proportion of supratherapeutic C_{tau} decreased from 60.4% to 39.3%. Among seven subjects with at least one subtherapeutic C_{tau}, 85.7% reached therapeutic levels by their last TDM.

Conclusions: A large DTG C_{tau} interindividual variability and proportion of supratherapeutic levels were seen in pediatric patients. It remains unclear if these high DTG C_{tau} are clinically relevant in this population. Improved virologic outcomes over successive TDMs suggest some potential benefit. Current DTG weight-band dosing recommendations could be optimized to limit unnecessarily high concentrations.



4

Pharmacokinetic Parameters of Bictegravir in Breastmilk of Healthy, Lactating Volunteers without HIV After a Single Dose of 50mg (Co-Formulated with Emtricitabine 200mg and Tenofovir Alafenamide 25mg)

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Introduction: The risk of transmission of HIV through breastfeeding is very low when sustained viral suppression is reached using antiretroviral therapy. However, to what extent these antiretroviral drugs transfer in to breastmilk is not fully understood. These data are especially lacking for relatively newer drugs – such as bictegravir - that only recently was approved for use in pregnancy. Therefore, the aim of this study was to determine the infant exposure to bictegravir through breastmilk.

Materials and methods: Concentrations of bictegravir were measured in plasma and breastmilk of healthy, lactating women without HIV after a single dose of bictegravir 50mg (co-formulated with tenofovir alafenamide 25 mg and emtricitabine 200mg) at predefined timepoints (pre-dose and 1,2,3,4,5,6,8,10,12,24 hours after ingestion for plasma and pre-dose and 2,4,6,12,24 hours after ingestion for breastmilk). The concentrations were measured using validated LC-MS/MS assays and pharmacokinetic parameters were calculated using non-compartmental analysis (Winnonlin, Phoenix). Breastmilk to maternal plasma ratio, daily infant dosage and relative infant dose were established in order to determine infant exposure to bictegravir through breastmilk.

Results: Twelve volunteers participated in the study. The geometric mean (CV%) of the area under the curve was 1.58 (28.8) mg*h/L in plasma and 0.01 (40.5) mg*h/L in breastmilk, resulting in a geometric mean (CV%) breastmilk to maternal plasma ratio of 0.008 (19.4). The median (IQR) daily infant dose (DID) and relative infant dose (RID) of bictegravir in this cohort was 0.008 (0.003

– 0.012) mg/kg/day and 0.11 (0.05 – 0.30) % respectively. When extrapolated to infants that are exclusively breastfed with 200mL/kg/day, the median (IQR) DID is 0.046 (0.035 – 0.080) mg/kg/day and the RID is .90% (0.71 – 1.33) in infants receiving up to 150 and 200mL/kg/day.

Conclusion: The exposure to bictegravir through breastmilk is very low, with a relative infant dose below 1%. And even though the metabolizing capacity in newborns is not yet fully developed, it is not expected to cause infant toxicity.



5

Plasma Bictegravir/Emtricitabine/Tenofovir Alafenamide Concentrations in Transgender Women with HIV on Estrogen- Based Gender-Affirming Hormone Therapy in Comparison to Cisgender Women Living with HIV

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Background: Estrogen-based gender-affirming hormone therapy (E-GAHT) typically consists of an estrogen +/- an anti-androgen and is essential for many transgender women. However, there is concern regarding drug-drug interactions (DDIs) between antiretroviral therapy (ART) and E-GAHT. This study's objective was to investigate the pharmacokinetics of bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) in transgender women taking E-GAHT compared to pre-menopausal cisgender women.

Methods: We conducted a parallel group study in adult transgender women with HIV taking ART (transgender group) and cisgender women with HIV taking ART (control group). All participants were on suppressive ART for at least 6 months prior to and either taking or switched to BIC/FTC/TAF at entry. All participants in the transgender group were taking at least 2 mg/day of oral estradiol and anti-androgen therapy and could not have any E-GAHT medication changes for at least 3 months prior to entry. At the month 2

visit, blood samples were collected prior to ART and E-GAHT dosing (if applicable) and then at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 24 hours post-dose. BIC, FTC, and TAF plasma concentrations were measured using a validated LC-MC/MS assay. Maximum (C_{max}) and minimum (C_{min}) concentrations were observed, and area under the concentration-time curve (AUC) over 24 hours was calculated by noncompartmental methods. Data are presented as median (IQR) and compared between transgender and control groups by geometric mean ratio (GMR) with 90% confidence intervals (CI).

Results: A total of 25 participants were enrolled, 10 transgender women and 15 cisgender women. E-GAHT consisted of a median estradiol dose of 4 mg (4, 4). Anti-androgen therapy included spironolactone (n=6), cyproterone (n=2), hypopituitarism (n=1), and orchidectomy (n=1). Median BIC C_{max}, C_{min}, and AUC for the transgender group was 9.1 mcg/mL (8.1, 9.6), 2.6 mcg/mL (1.1, 3.1), and 119.5 h*mcg/mL (86.6, 141.2), respectively, compared to 7.2 mcg/mL (6.4, 9), 1.9 mcg/mL (1.4, 3.4), and 123.9 h*mcg/mL (79.7, 133.2), respectively, for the Control group. BIC PK parameters were similar between groups (GMR [90% CI]: 1.1 [0.9, 1.4], 1 [0.6, 1.7], and 1 [0.8, 1.3], respectively). Median FTC C_{max}, C_{min}, and AUC for the transgender group was 2 mcg/mL (1.3, 2.5), 0.1 mcg/mL (0.1, 0.1), and 10.7 h*mcg/mL (8.7, 14), respectively, compared to 2 mcg/mL (1.6, 2.3), 0.1 mcg/mL (0.1, 0.1), and 11 h*mcg/mL (9.8, 15.6), respectively, for the Control group. FTC PK parameters were similar between groups (GMR [90% CI]: 0.9 [0.8, 1.2], 1.1 [0.8, 1.5], and 1 [0.8, 1.2], respectively). Median TAF C_{max}, C_{min}, and AUC for the transgender group was 164 ng/mL (90, 335), 0.5 ng/mL (0.5, 0.5), and 143 h*ng/mL (116, 320), respectively, compared to 250 ng/mL (132, 396), 0.5 ng/mL (0.5, 0.5), and 230 h*ng/mL (189, 394), respectively, for the Control group. TAF PK parameters were similar between groups (GMR [90% CI]: 0.7 [0.4, 1.2], 1 [1, 1], and 0.7 [0.5, 1], respectively). All participants remained virally suppressed (HIV RNA < 200 copies/mL) throughout the study.

Conclusion: BIC/FTC/TAF plasma pharmacokinetics were similar between groups, indicating no clinically significant effect of oral E-GAHT on BIC/FTC/TAF.



6

Target Attainment of Valganciclovir Prophylaxis against Cytomegalovirus

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Background: Cytomegalovirus (CMV) is a human Herpesvirus that causes significant mortality and morbidity in immunocompromised patients. Previous studies show that standard dosing of valganciclovir, the first-line drug, might not sufficiently reduce viral load, indicating the need for treatment optimisation. Factors such as a high interpatient variability in pharmacokinetics, comedications and frequently impaired kidney function, may lead to suboptimal drug concentrations with standard dosing regimens, leading to increased treatment failure, toxicity and resistance. Therefore, therapeutic drug monitoring (TDM) is occasionally considered. To perform TDM and optimise drug regimens, defining a pharmacokinetic (PK) / pharmacodynamic (PD) target is essential. For valganciclovir prophylaxis a PK target of AUC 40 – 50 $\mu\text{g}\cdot\text{h}/\text{ml}$ is often used. The aim of this study was to investigate the target attainment of current standard valganciclovir dosing in solid organ transplant patients.

Materials and methods: In this study a dataset of 157 adult kidney, liver or heart transplant recipients were used to develop a population PK model using Monolix (Lixoft). The dataset included information on drug dosing, age, weight, serum creatinine, type of solid organ transplant (kidney, liver, heart) and sex. eGFR was calculated using CKD-EPI. The population PK model was used to simulate (N=1000) PK profiles for varying dosing regimens, defined by the manufacturer and stratified on eGFR (900 mg q24h for eGFR >60 mL/min/1.73 m², 450 mg q24h for eGFR 40-60 mL/min/1.73 m², 450 mg q48h for eGFR 25-40 mL/min/1.73 m², 450 mg twice weekly for eGFR <25 mL/min/1.73 m²) in Simulx (Lixoft). Simulations were conducted for over a week period, with AUC(0 – 24h) values calculated. Target attainment of AUC ≥ 40 and ≥ 50 $\mu\text{g}\cdot\text{h}/\text{ml}$ over 24 hours was calculated.

Results: The final population PK model was a two compartmental model with first order absorption. Random effects were included for clearance (Cl) and volume of the central compartment (V1). The covariates weight and eGFR were added to Cl and weight and sex to V1.

AUC ≥ 40 $\mu\text{g}\cdot\text{h}/\text{ml}$ (24hr) attainment was 47%; 81%; 25%; 2.9%; 0% for eGFR >90; 60-90; 40-60; 25-40; <25 mL/min/1.73 m² respectively. AUC ≥ 50 $\mu\text{g}\cdot\text{h}/\text{ml}$ (24hr) attainment was 17%; 52%; 6.1%; 0%; 0% for eGFR >90; 60-90; 40-60; 25-40; <25 mL/min/1.73 m² respectively.

Conclusions: Current valganciclovir dosing recommendations show poor target attainment particularly at eGFRs <60 and >90 mL/min/1.73 m². The results of this study indicate that current dosing adjustment based on eGFR might lead to low AUC_{24hr} of valganciclovir which may increase the risk of treatment failure due to subtherapeutic exposure. Furthermore, other studies defining a PK/PD target for valganciclovir are scarce and it remains unclear if the AUC(24hr) $\geq 40 - 50$ $\mu\text{g}\cdot\text{h}/\text{ml}$ target has been well defined. Therefore, there is a clear need for a large, multi-centre study combining both clinical and in vitro data to define a new PK/PD target and to optimise current dosing strategies, considering both exposure-response and exposure-toxicity relationships.



7

An Enzymatic Assay for Rapid and Minimally Instrumented Ganciclovir Triphosphate Monitoring in Infants With Congenital Cytomegalovirus

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One in 200 infants is born with cytomegalovirus (CMV), and 25% experience lifelong consequences such as hearing loss or developmental delay. Intravenous ganciclovir (GCV) and its oral prodrug valganciclovir are the first-line treatments for congenital CMV (cCMV) and have been found to improve hearing and developmental outcomes. However, GCV drug levels vary widely among infants, making optimal dosing difficult without therapeutic drug monitoring (TDM). With standard dosing, underexposure and inadequate treatment occur in 30% of infants, while overexposure and significant toxicity occur in 25% of infants. Intracellular levels of the active form of the drug, GCV triphosphate (GCV-TP), are associated with dose-dependent neutropenia toxicity. However, TDM of GCV-TP is currently performed using liquid chromatography mass spectrometry (LC-MS), which is costly, labor-intensive, and requires specialized equipment, making it impractical for routine clinical use.

To address this gap, we have developed an enzymatic assay for GCV-TP measurement that does not rely on complex instruments or highly trained users. This test is adapted from the rapid, user-friendly, and minimally instrumented REverse transcriptase ACTivity crispR (REACTR) assay that we recently developed for measuring human immunodeficiency virus (HIV) medications. REACTR measures intracellular levels of nucleotide analog drugs based on inhibition of DNA synthesis by HIV reverse transcriptase (RT) enzyme. GCV-TP inhibits HIV RT, allowing us to adapt REACTR to measure GCV-TP. REACTR assays were performed by combining CRISPR-Cas12a, CRISPR RNA,

cytidine-rich DNA template, DNA primer, fluorescent DNA reporter, HIV RT, and GCV-TP concentrations spiked into aqueous buffer or dried blood spots (DBS). Spiked GCV-TP concentrations ($1.45\text{e-}9\text{M}$ to $4.63\text{e-}8\text{M}$) corresponded to the clinical range (100-3200 fmol/6 mm punch) of GCV-TP in DBS of infants with cCMV in a recently completed clinical trial (NCT03107871). GCV-TP-spiked DBS samples were processed with a simple workflow that included dilution to a final volume of 25% in water, protease digestion with thermostable proteinase K at 23°C for 15 minutes, and heat denaturation at 95°C for 10 minutes. The assay was incubated at 37°C in a microplate reader for 60 minutes and fluorescent measurements were taken every minute.

We normalized results using “no drug” and “no enzyme” controls to indicate maximum and minimum signal, respectively, and fit dose response curves to sigmoidal 4-parameter logistic regression curves in GraphPad Prism. Statistically significant differentiation between spiked concentrations was confirmed using repeated measures one-way ANOVA. REACTR selectively measured clinically relevant GCV-TP concentrations in both aqueous buffer and dried blood spots within 30 minutes of incubation. The 50% inhibitory concentration (IC₅₀) of GCV-TP in REACTR was $2.01\text{e-}8\text{M}$, well within the target clinical range. In aqueous buffer samples, REACTR was able to distinguish between 5 clinically relevant concentrations of GCV-TP corresponding to 100, 400, 800, 1600, and 3200 fmol/6mm punch ($p = 0.001$).

This study demonstrates the potential of the REACTR assay as a rapid, accessible, and cost-effective alternative to LC-MS for GCV-TP monitoring in infants with cCMV, paving the way for personalized antiviral dosing and improved clinical outcomes.



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Pharmacogenetic and Pharmacokinetic Profiling of Bulevirtide in Patients with Chronic Hepatitis D: A Preliminary Study

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Background: Bulevirtide is the first approved entry inhibitor for the treatment of chronic hepatitis D, exerting its antiviral effect through the inhibition of the sodium taurocholate co-transporting polypeptide (NTCP). Despite encouraging clinical efficacy, significant inter-individual variability in drug exposure and therapeutic response has been observed. To date, a few data addressed the extent of bulevirtide plasma level variability with the possible contribution of genetic polymorphisms. This study aimed to assess bulevirtide plasma concentrations, biochemical and virological parameters at multiple time points and the potential influence of NTCP gene variants on the clinical outcome, considering virological and biochemical response at week (W) 48.

Materials and methods: A cohort of patients with chronic HDV infection receiving bulevirtide in monotherapy was enrolled. Bulevirtide plasma concentrations and biochemical and virological parameters were quantified at baseline, W4, W12, W24, W36, and W48 using liquid chromatography-mass spectrometry. Pharmacogenetic analysis focused on NTCP single nucleotide polymorphisms (rs8011311 and rs2296651) through PCR-based genotyping.

Results: 13 patients were enrolled: 76.9% were men, the median age was 50 years, the median BMI was 24.4 Kg/m² and 46.2% had cirrhosis. Median baseline ALT were 75 UI/L and HDV RNA Log 5.53. Stiffness resulted decreased at W48 compared to baseline and W24. The lipid profile resulted not influenced by the treatment and a not statistically significant increase in bile acid was

observed. No side effects were reported. Virological outcome was obtained in 3 (23.1%) patients, biochemical outcome in 2 (15.4%) patients and combined response in 1 (7.7%) patient. Median bulevirtide concentrations were 0.4 (IQR 0.3; 2.1) ng/mL at W4, 0.9 (IQR 0.4; 1.9) at W12, 0.6 (IQR 0.3; 1.6) ng/mL at W24, 1.1 (IQR 0.7; 2.6) ng/mL at W36 and 1.2 (IQR 0.7; 7.1) ng/mL at W48. While no co-administered drugs seemed to affect bulevirtide levels, cirrhosis did. Patients with biochemical outcome had slightly higher bulevirtide plasma levels at W36 (1.25 vs. 0.85 ng/mL, $p=0.046$). A not significant trend was found for NTCP rs8011311 G>C genetic variant and bulevirtide plasma exposure at W4 ($p=0.069$) and at W48 ($p=0.062$): particularly, GC/CC genotype patients had reduced concentrations compared to GG genotype patients.

Conclusions: This preliminary study reported for the first time bulevirtide concentrations in patients treated for 48 months and the potential impact of genetic determinants, although a small number of patients was considered. Further studies in larger cohorts are required to achieve personalized dosing strategies enhancing treatment efficacy and safety in HDV-infected patients.



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Physiologically Based Pharmacokinetic Modeling to Inform Lenacapavir Dose Regimen When Co-Administered with Rifamycins in Participants with Tuberculosis

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Introduction: There is a global need to provide rifamycin-based tuberculosis treatments in people who may be receiving lenacapavir (LEN), a potent capsid inhibitor approved for the treatment of multidrug-resistant HIV-1 and with high efficacy as HIV-1 pre-exposure prophylaxis (PrEP). LEN is eliminated by CYP3A, UGT1A1, and P-glycoprotein (P-gp) efflux, which are induced by rifamycins. We developed a physiologically based pharmacokinetic (PBPK) model to propose dosing recommendations for LEN when rifampin (or strong CYP3A inducer) or rifabutin (or moderate CYP3A inducer) are co-administered with subcutaneous (SC) LEN.

Methods: A full-body LEN PBPK model was developed in GastroPlus® (version 9.8.3). Systemic distribution was captured with a perfusion-limited model for all tissues. Pathways for LEN elimination include efflux via direct intestinal secretion and liver uptake leading to biliary secretion and potential recirculation via P-gp, in addition to hepatic and intestinal metabolism by CYP3A4, UGT1A1, and minor contribution from non-specific clearance in liver. Kinetic parameters for LEN interactions with enzymes and P-gp were fitted against in vivo human data. The contribution of different pathways to LEN elimination were validated by comparing simulations to observed data from Phase 1 study participants receiving oral LEN in combination with voriconazole (strong CYP3A inhibitor), cobicistat (strong CYP3A and P-gp inhibitor), efavirenz (moderate CYP3A and P-gp inducer), and rifampin (strong CYP3A4, UGT1A1 and P-gp inducer, and P-gp inhibitor). We

simulated different scenarios of a LEN dosing regimen (oral LEN 600 mg on Days 1 and 2 plus SC LEN administered on Day 1 and every six months thereafter) that could maintain plasma concentrations above the inhibitory quotient-4 (4-fold greater than the in vitro protein-adjusted 95% effective concentrations derived from MT-4 cells; 15.5 ng/mL) throughout the every-six-months interval, regardless of when rifampin/rifabutin (moderate CYP3A/P-gp inducer) treatment was initiated.

Results: With the LEN PBPK model, the simulated maximum concentration (C_{max}) and area under the plasma concentration versus time curve extrapolated to infinity (AUC_{0-inf}) values for LEN alone administered SC and orally were within 1.5-fold of the observed data. The prediction errors on C_{max} and AUC_{inf} for oral LEN with perpetrators were mostly within the Guest criteria framework proposed for evaluation of quality of drug-drug interaction predictions. Based on model simulations of LEN co-administered with rifampin (or strong CYP3A inducer) or rifabutin (or moderate CYP3A inducer), the following dose adjustments of LEN are recommended to maintain adequate LEN concentrations throughout the duration of treatment:

- On day of initiation of a strong CYP3A inducer (>2 days after LEN is first initiated), administer supplemental dosage of 927 mg LEN SC (2 x 1.5 mL injections) and 600 mg of LEN orally (2 x 300 mg tablets); on day following initiation, administer 600 mg of LEN orally (2 x 300 mg tablets).
- On day of initiation of a moderate CYP3A inducer, administer supplemental dosage of 463.5 mg LEN SC (1 x 1.5 mL injection).

Conclusions: With supplemental dosage, LEN can be co-administered with strong or moderate CYP3A inducers including rifampin and rifabutin for tuberculosis treatment.



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Drug Interactions Between Probe Drugs Dolutegravir (DTG), Midazolam (MDZ) and Digoxin (DIG) with Escalating Doses of Rifampicin (RIF): DORIS Study

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Background: Evidence suggests higher RIF doses (>10mg/kg) maybe more effective for TB treatment. It is unclear if incremental RIF doses will increase risk of drug interactions through more potent induction of metabolic enzymes and transporters. Some data suggest maximum induction is already achieved with standard dose (10mg/kg). We characterised the impact of incremental RIF (10, 20, 35mg/kg) on the pharmacokinetics (PK) of DTG, MDZ and DIG as probe drugs for UGT1A1, CYP3A4 and the transporter P-gp, respectively.

Materials & Methods: DoRIS was an open-label, fixed-sequence, 4-phase study in TB-infected adults living without HIV, nearing the end of the continuation phase of standard anti-TB therapy (ATT). DTG (50mg BID for 1 week) exposure from intensive sampling was compared when dosed with RIF at 10mg/kg (D14), 20mg/kg (D28) and 35mg/kg (D42), and ≥4 weeks post-ATT (at 50mg OD). Single dose MDZ (0.025mg/kg) and DIG (0.25mg) were given on PK sampling days; RIF was administered 1 hour prior to other study medications under fasting conditions. PK parameters were calculated (WinNonlin Phoenix, v.8.5) using drug concentrations and actual time-post dose. Changes in parameters were evaluated

by linear mixed effects determining geometric mean ratio (GMR) and associated 90% CI; changes were considered statistically significant if the CI did not include 1.0.

Results: Of 36 participants enrolled from South Africa and Uganda [11% female at birth, median (range) age 35years (18-62), weight 61kg (50-93)], drug PK were available from a maximum of 33 individuals. Geometric mean DTG C_{tau} were 602, 610, 561ng/mL on D14, D28, D42 vs. 643ng/mL post-ATT and not significantly impacted by incremental RIF (GMR, 90% CI: 0.93 [0.73-1.17]; 1.00 [0.79-1.25]; 0.93 [0.73-1.17], respectively). DTG AUC₀₋₁₂ and C_{max} were significantly lower with RIF on D14: 0.55 [0.49-0.63] and 0.70 [0.63-0.78], D28: 0.59 [0.52-0.67] and 0.71 [0.64-0.80], D42: 0.57 [0.51-0.65] and 0.72 [0.64-0.80]. Twice daily DTG exposures were not significantly reduced further beyond that observed with standard RIF (D28/D14: 1.08 [0.94-1.23], D42/D14: 1.04 [0.91-1.19]). Proportion of C_{tau} above DTG EC₉₀ (342ng/mL) was 76, 85, 92 and 86% on D14, D28, D42 and post-ATT, respectively. Single dose MDZ PK parameters exhibited marked variability (CV% >100%) and were significantly reduced in the presence of RIF (35-65%), but not incrementally with higher RIF doses (D28, D42/D14 AUC₀₋₁₂: 1.39 [0.96-2.01], 0.84 [0.58-1.21]). Conversely, statistically significant increases in single dose DIG AUC₀₋₁₂ were observed in the presence of RIF (7-21%) and for C_{max} with higher RIF doses (20mg/kg: 1.21 [1.09-1.34]; 35mg/kg: 1.17 [1.06-1.30]). DIG AUC₀₋₁₂ was significantly increased to a similar extent with increasing RIF doses beyond 10mg/kg (D28/D14: 1.12 [1.06-1.18], D42/D14: 1.13 [1.07-1.19]). RIF increased supraproportionally with dose [D28, D42/D14 AUC_{0-last}: 3.70 [2.97-4.62] (20mg/kg), 5.88 [4.68-7.40] (35mg/kg)].

Conclusions: DTG exposure was reduced to a similar extent following higher RIF doses, with little impact on C_{tau}. MDZ exposures were not reduced further with incremental RIF whereas small but statistically significant increases in DIG were observed, potentially associated with net inhibition of P-gp upon simultaneous drug administration. These data suggest maximum impact of RIF on UGT1A1/CYP3A4/P-gp at the standard 10mg/kg dose.



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A Preliminary Analysis of the Impact of Pharmacogenetic Variation on Bictegravir and Dolutegravir Concentrations in Individuals with HIV and Tuberculosis

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Background: Bictegravir and dolutegravir are potent antiretrovirals recommended for first-line treatment of HIV. We evaluated the effect of pharmacogenetic variation in drug metabolising and transporter enzymes using the Axiom Precision Medicine Diversity Research Array (>850,000 single-nucleotide polymorphisms [SNP] across the human genome) on drug concentrations of bictegravir and dolutegravir in individuals with HIV and tuberculosis.

Methods: We conducted a pharmacogenetic analysis African participants (black race, mainly isiZulu speaking) randomized to receive bictegravir, emtricitabine, tenofovir alafenamide (BIC arm) or dolutegravir, lamivudine, tenofovir (DTG arm) in the INSIGHT trial (NCT04734652) conducted in Durban, South Africa. The bictegravir regimen or dolutegravir were dosed twice daily during rifampicin-based first-line tuberculosis treatment and once daily thereafter. Trough concentrations of bictegravir and dolutegravir were measured both during and after tuberculosis treatment using validated assays at the Division of Clinical Pharmacology, University of Cape Town. DNA was extracted from buffy coat samples and quality was assessed using the QIAxcel Connect System. Samples were processed on the Applied Biosystems GeneTitan Multi-Channel (MC) Fast Scan Instrument. We performed genome-wide association studies (GWAS) using a pharmacogenomics-focused genotyping panel, which includes variants in genes associated with

drug metabolism and transport. In this preliminary analysis, we focused on identifying associations between genetic variants in key enzymes and drug transporters known to be involved in bictegravir and dolutegravir metabolism and transport. All statistical analyses were conducted using R Studio (Version 2025.05.0+496). An R script was developed for analysis, data cleaning, extraction, and matching polymorphisms with genes, linking genetic variations to drug concentrations. T-tests were performed to compare average changes in drug concentrations (trough concentrations) among different genotypes. Significance was assessed using p-values with a threshold of 0.05.

Results: We enrolled 80 participants in the BIC arm and 42 in the DTG arm. Pharmacokinetic (PK) data for 77 participants in the BIC and 42 and participants in the DTG arm during and after TB treatment was included in the analysis. Bictegravir is primarily metabolized by CYP3A4 and UGT1A1. Since CYP3A5 and CYP3A4 share some substrate overlap (and both are part of the CYP3A subfamily), there has been some interest in whether CYP3A5 expressor status could affect bictegravir clearance. Our results show a specific SNP (rs4646457) within the CYP3A5 gene was associated with higher bictegravir concentrations (p=0.02, effect=4.8 for the CC Genotype vs AA/CC) during and after TB treatment. In addition, we identified rs887829 (located with the UGT1A1 gene), a known genetic marker linked with metabolism of bictegravir, which in the CC genotype (vs CT/TT) was associated with lower bictegravir levels (p=0.008, effect=0.64) during and after TB treatment. This UGT1A1 mutation (rs887829) CC genotype vs CT/TT was also linked with lower dolutegravir levels in our study (p=0.01, effect=0.9) during TB treatment.

Conclusion: We observed significant associations between SNPs in the CYP3A5 and UGT1A1 genes and bictegravir and dolutegravir plasma concentrations. The clinical relevance of these findings requires further evaluation and should also be explored in population PK models to account for other sources of variability in drug concentrations.



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Pharmacokinetics of Abacavir and Lamivudine in Infants with and without Rifampicin Co-Treatment

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Introduction: Fixed-dose combination (FDC) paediatric formulation of lamivudine/dolutegravir/abacavir was recently licensed by the FDA for the treatment of HIV in children, and is expected to be used frequently in low- and middle-income countries. In children living with HIV diagnosed with drug-sensitive tuberculosis, rifampicin is added, which induces UDP-glucuronosyltransferases and renal transporters. These proteins are also involved in the metabolism of lamivudine and abacavir. However, limited pharmacokinetic data are available to quantify this effect.

Objective: This study, evaluated the impact of rifampicin on the pharmacokinetics of abacavir and lamivudine in infants aged between 28 and 365 days, and weighing more than 3 kg.

Methods: This was a pharmacokinetic study nested within the EMPIRICAL trial, a multicenter study. Eighteen infants living with HIV were recruited at clinical sites in Mozambique, Uganda, Zambia and Zimbabwe. They were receiving a once-daily fixed-dose combinations (FDC) of abacavir/lamivudine, 20 mg/60 mg if weighing between 3 and <6 kg, and 120 mg/60 mg if weighing between 6 and <10 kg, in combination

with dolutegravir dispersible tablets, following WHO dosing guidelines. The participants were divided into two groups: a control group (n = 5) receiving only ART, and an experimental group (n = 13) receiving ART with added rifampicin for tuberculosis treatment. Residual blood samples from a previous pharmacokinetic sub-study collected at pre-dose and at 2, 4, 6, 8, and 12/24 hours post-dose were used. Pharmacokinetic parameters (AUC_{0-24h} , $t_{1/2}$, V_d/F , and CL/F) were analyzed using WinNonlin version 8.3. Results were reported as geometric means and coefficients of variation (%CV). The study adhered to ethical and legal standards as outlined in the main EMPIRICAL study protocol.

Results: A total of 18 infants were enrolled. The overall median age was 6.6 months (range: 3.2–11.9), and the median weight was 6.0 kg (range: 3.8–8.2). In the control arm, the median age was 7.1 months (range: 6.2–11.1), whereas in the rifampin arm it was 6.3 months (range: 3.2–11.9). The median weight in the control arm was 6.0 kg (range: 5.7–8.2), while in the rifampicin arm it was 5.9 kg (range: 3.8–8.0). Regarding pharmacokinetic parameters, abacavir GM(%CV) AUC_{0-24h} was 21.0 (19) h×mg/L in infants without rifampicin and 21.9 (74) h×mg/L in infants co-treated with rifampicin. Abacavir GM(%CV) C_{max} was comparable for children without and with rifampicin (6.3 (55) vs. 6.2 (10) mg/L, respectively) as well as the apparent clearance (6.7 vs. 6.0 mL/min, resp.) half-life (2.47 vs. 1.91 h, resp.). For lamivudine, the GM(%CV) AUC_{0-24h} was comparable in both study arms with 12.4 (37) h×mg/L for children without rifampicin and 12.6 (49) h×mg/L for those using rifampicin as well as the apparent clearance (5.7 vs 5.2 mL/min, respectively). Lamivudine GM was 22% higher in children taking rifampicin (2.4 (52) vs. 1.9 (21) mg/L) and GM half-life was 48% shorter (2.50 vs. 4.79 h).

Conclusion: Rifampicin co-treatment had minimal impact on the pharmacokinetics of lamivudine and abacavir. These findings suggest that dosage adjustments are not necessary for lamivudine/abacavir during concomitant rifampicin-containing TB treatment in children.



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Intracellular Carbovir- and Lamivudine-Triphosphate Concentrations in PBMC and DBS among Children with HIV-1 Receiving ABC/DTG/3TC: Results from IMPAACT 2019

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Background: Abacavir (ABC) and lamivudine (3TC) are recommended components of antiretroviral regimens for treatment in infants and children with HIV. ABC and 3TC are converted intracellularly to their active triphosphorylated (TP) forms: carbovir (CBV)-TP and 3TC-TP, respectively. Limited data exists on their cellular pharmacology in pediatric populations, notably red blood cells as measured in dried blood spots (DBS). Intracellular concentrations in DBS and peripheral blood mononuclear cells (PBMC) may provide insight into exposure-response relationships at the site of action and drug adherence, respectively. We describe CBV-TP and 3TC-TP concentrations in DBS and PBMC among children enrolled in the IMPAACT 2019 trial.

Materials and Methods: IMPAACT 2019 was a Phase I/II study evaluating the pharmacokinetics, safety, tolerability, and efficacy of fixed dose combination (FDC) ABC/dolutegravir (DTG)/3TC in children <12 years of age and weighing 6-<40kg with HIV-1 (NCT03760458). Participants were enrolled across five weight bands (WB, 6-<10 kg, 10-<14 kg, 14-<20 kg, 20-<25 kg, and ≥25-<40 kg). Those weighing 6-<25 kg received 60/5/30 mg dispersible tablets (3–6 tablets based on weight), while those 25-<40 kg received a 600/50/300 mg immediate-release tablet once daily. Participants were ART-naïve or virologically suppressed on stable ART for ≥6 months prior to entry. DBS and PBMC samples were collected at weeks 1, 4, 12, 24, 36, and 48 in all participants; and weeks 8, 16 and 20 among those with the documented M184V mutation. CBV-TP and 3TC-TP were quantified using a validated LC-MS/MS assay. Results are reported as either fmol (CBV-TP) or pmol (3TC-TP) per 2x7mm punches (DBS) or 106 cells (PBMC); values below the limit of quantification (BLQ) were imputed as half the lower limit of quantification (LLOQ). Linear mixed effects models were performed with log-transformed CBV-TP and 3TC-TP in each cell type to account for repeated measures across study visits and compare concentrations by WB. Geometric means (GM) with 95% confidence intervals (CIs) were calculated and compared to historical data in adults (n=12) with HIV-1 on ABC/3TC (NCT04301661).

Results: A total of 314 DBS and 304 PBMC results were available in 55 participants (44% female; 67% Black, 31% Asian; 7% with M184V). CBV-TP and 3TC-TP were quantifiable in all DBS samples; in PBMC, 10 (3.3%) CBV-TP and 6 (2.0%) 3TC-TP were BLQ. The GM (95% CI) for CBV-TP and 3TC-TP in DBS were 583 (526-646) fmol/punches and 8.99 (8.17-9.88) pmol/punches, respectively. The GM (95% CI) for CBV-TP and 3TC-TP in PBMC were 146 (95.6-153) fmol/106 cells and 7.97 (6.88-9.24) pmol/106 cells, respectively. No differences were identified by WB for CBV-TP or 3TC-TP in DBS or PBMC. Compared to historical data in adults, GM CBV-TP was approximately 52% and 86% higher in DBS and PBMC, respectively; 3TC-TP concentrations were comparable (-11% in DBS and +8% in PBMC).

Conclusions: CBV-TP and 3TC-TP concentrations were quantifiable and generally consistent across study visits and WBs in both DBS and PBMC in children receiving FDC ABC/DTG/3TC. These results support evaluating DBS utility in pediatric studies and further exploring factors that may influence



intracellular concentrations and relationships with adherence.



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Pharmacokinetics of Long-Acting Cabotegravir and Rilpivirine in Seminal Plasma throughout the Dosing Interval

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Despite the suppression of HIV RNA in blood, HIV persistence in anatomical compartments is a major barrier to a cure. The male genital tract (MGT) is an important immune-privileged site. HIV curative strategies rely on the ability of antiretrovirals (ARVs) to adequately penetrate the MGT, which contains anatomical (e.g. blood-testis barrier) and physiological (e.g. drug efflux transporters) barriers that protect spermatozoa from potentially harmful xenobiotics. Adequate and suppressive ARV concentrations are necessary to decrease HIV replication in genital secretions; these have important implications for transmission. However, the extent to which long-acting ARVs penetrate the MGT across the extended dosing interval is unknown. This study aims to characterize the pharmacokinetics of long-acting cabotegravir (CAB) and rilpivirine (RPV) in blood plasma (BP) and seminal plasma (SP) throughout the dosing interval.

Adult cisgender males continuing CAB±RPV intramuscular injection bimonthly were included. Participants provided time-matched blood and semen samples prior to injection, at predetermined timepoints throughout the dosing interval, and immediately before the next injection. Quantification of total CAB±RPV concentrations in BP and SP were completed using validated ultra-performance liquid chromatography-tandem mass spectrometry methods (lower limit of quantification: 0.1 ng/mL). The protein-unbound fractions in both matrices were determined using rapid equilibrium dialysis and multiplied by total concentrations to estimate protein-unbound concentrations. Protein-unbound

concentrations were compared to half-maximal effective concentrations (EC₅₀). Total and protein-unbound SP-to-BP ratios (SP:BP) were calculated across the dosing interval. Pooled non-compartmental analysis was performed using Phoenix WinNonlin to obtain pharmacokinetic parameters to calculate AUC_{tau} SP:BP. Data are reported as median (range). Actual times were used in pharmacokinetic analyses.

Five participants provided 16 time-matched BP and SP samples. Three participants received CAB alone and 2 participants received CAB/RPV. Total CAB SP concentrations were 21.0 ng/mL (3.7-89.8) and total RPV SP concentrations were 5.6 ng/mL (4.0-13.5). Total SP:BP were 0.01 (0.002-0.01) and 0.07 (0.06-0.1) for CAB and RPV, respectively. This remained consistent throughout the dosing interval. CAB protein-unbound fractions were 0.1% (0.07-0.5%) in BP and 43.9% (31.2-56.1%) in SP. RPV protein-unbound fractions were 0.4% (0.2-1.4%) in BP and 20.7% (7.5-27.4%) in SP. Protein-unbound CAB concentrations were 2.5 ng/mL (1.4-8.2) in BP and 9.3 ng/mL (1.6-36.2) in SP, yielding a protein-unbound SP:BP of 4.1 (0.2-11.5), which remained consistent throughout the dosing interval. Protein-unbound RPV concentrations were 1.0 ng/mL (0.6-2.2) in BP and 6.5 ng/mL (2.8-33.5) in SP, yielding a protein-unbound SP:BP of 2.7 (1.1-7.3). CAB and RPV protein-unbound SP concentrations were 43.4-fold (12.2-361) and 2.9-fold (1.0-36.2) above their respective EC₅₀ values across the dosing interval. Total AUC_{tau} SP:BP was 0.01 (0.01-0.02) and 0.07 (0.06-0.08) for CAB and RPV, respectively. Protein-unbound AUC_{tau} SP:BP was 3.8 (2.3-10.6) for CAB and 3.0 (2.4-3.6) for RPV.

Although total SP concentrations were <10% of concentrations in BP for both ARVs, protein-unbound concentrations were >2.5-fold in SP. These patterns remained consistent throughout the dosing interval. Total and protein-unbound AUC_{tau} SP:BP followed similar trends, suggesting adequate exposure. Importantly, protein-unbound CAB and RPV concentrations exceeded EC₅₀ values throughout the dosing interval in SP. Additional longitudinal studies are warranted to confirm these findings.



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Pharmacokinetics of Long-Acting Cabotegravir and Rilpivirine in Virologically Suppressed Adolescents Living with HIV-1 in Sub-Saharan Africa: Data from the LATA trial

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Introduction: Adolescents living with HIV face unique challenges in maintaining virological suppression, with adherence to daily oral antiretroviral therapy (ART) being a major barrier. Long-acting injectable (LA) ART with cabotegravir (CAB) and rilpivirine (RPV), administered once every 8 weeks (Q8W), has shown promising efficacy and acceptability in adults and adolescents, but limited data are available for adolescents in African settings. The LATA trial (NCT05154747) is evaluating Q8W LA CAB/RPV (600/900mg) versus once daily oral lamivudine/tenofovir disoproxil fumarate/dolutegravir in virologically suppressed (HIV-1 RNA < 50c/mL) adolescents aged 12 to <20 years in Sub-Saharan Africa. Here, we present pharmacokinetic (PK) data from a nested sub-study in the CAB/RPV trial arm to assess drug exposure at the end of year 1 of LA CAB/RPV in adolescents living with HIV-1 in Africa.

Methods: We aimed for ≥20 evaluable PK curves, with a male/female ratio of ~1:1. Participants received loading doses of LA CAB/RPV (600/900 mg) at Weeks 4 and 8 post randomisation, followed by maintenance dosing Q8W. An optional

4-week Oral Lead-In (OLI) with CAB/RPV was available between randomisation and Week 4. Participants who did not opt for the OLI continued their current oral ART during that period. Five blood samples, protected from light and processed and frozen at -80°C within recommended 3 hours of blood draw (achieved for 138/140 (99%) samples), were taken around the second maintenance dose (week 24) at t=0 (pre-injection), 3 days (+/-1 day), 7 days (+/-2 days), 28 days (+/-7 days) and 56 days (+/-7 days, pre-week 32 injection). CAB and RPV concentrations were measured using a validated UPLC-MS/MS method. PK parameters (AUC_{0-56d}, C_{max} and C_{trough}) for CAB and RPV were calculated using non-compartmental PK analysis. The numbers of adolescents with CAB and RPV C_{trough} below 4x PA-IC₉₀ and Q1 (the lower quartile of drug concentrations observed in adult patients) are summarized. AUC_{0-56d} and C_{trough} levels are compared to adult phase III data from the LATTE-2 and ATLAS-2M trials and to data from the MOCHA trial in adolescents (cohort 2).

Results: Twenty-eight adolescents from Uganda, Zimbabwe, and South Africa were included (13/15 female/male). 16 (57%) had received a 4-week CAB/RPV OLI. At week 24 visit, median(range) age was 17.4 (12.7-20.4) years, BMI 21.0 (14.0-28.9) kg/m². For CAB, the AUC_{0-56d}, C_{max} and C_{trough} geometric mean (GM) (%CV) were 4887 (30) h*mg/L, 5.35 (42) mg/L and 2.19 (47) mg/L respectively. For RPV, AUC_{0-56d}, C_{max} and C_{trough}, GM (%CV) were 150.12 (29) h*mg/L, 0.194 (33) mg/L and 0.078 (28) mg/L respectively. Three adolescents (11%) had a CAB C_{trough} below 1.12 mg/L (Q1 threshold), and one (4%) below 0.66 mg/L (4x PA-IC₉₀), at 0.63 mg/L. All adolescents had RPV C_{trough} values above both 0.032 mg/L (Q1 threshold) and 0.048 mg/L (4x PA-IC₉₀). CAB and RPV exposures were comparable to values reported previously in adults and adolescents.

Conclusion: LA CAB/RPV therapy in this African adolescent cohort resulted in drug exposures consistent with earlier adult and adolescent populations. The 96-week primary analysis will provide data on the efficacy of CAB/RPV LA injectables in African adolescents.



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Inter- and Intraindividual Variability of Long-Acting Cabotegravir/Rilpivirine Pharmacokinetics after 1 Year of Continuous Use

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Background: Low plasma concentrations of long-acting cabotegravir/rilpivirine (LA CAB/RPV) are associated with increased risk of virologic failure. However, real world data from the Swiss cohort found that trough LA CAB/RPV concentrations demonstrate high interindividual variability (coefficient of variation [CV]: CAB 31%, RPV 35%), and intraindividual variability (CV: CAB 52%, RPV 29%) during the first 12 months of use. We sought to characterize the variability in trough plasma concentrations of CAB and RPV in people with HIV (PWH) receiving LA CAB/RPV after 1 year of continuous use.

Methods: We conducted a prospective pharmacokinetic study in virologically suppressed PWH who had received >12 months of continuous LA CAB/RPV (600mg/900mg) given intramuscularly every 2 months. All doses were administered by the same 4 nurses. Plasma samples were collected pre-injection at 3 consecutive visits and CAB/RPV concentrations were quantified via LC-MS/MS. The primary outcomes were inter- and intraindividual CAB and RPV trough concentration variability reported as percentage CV, Fleiss Kappa, and intraclass correlation coefficient (ICC). The secondary outcome was proportion of participants with CAB or RPV concentrations below 4x PA-IC90 (CAB=664 ng/mL; RPV=48 ng/mL). We performed descriptive statistics (median; interquartile range [IQR] or range) for participant demographics and outcomes.

Results: Overall, 141 trough samples were obtained from 47 participants receiving LA CAB/RPV for 65 weeks (IQR 56, 82) at entry. Most participants were male (83%) and White (74%) with a median age of 45 years (IQR 33, 59) and

body mass index of 28.2 kg/m² (IQR 26, 33). Geometric mean CAB and RPV concentrations were 1447.7 ng/mL (range 104.4-4191 ng/mL) and 76.8 ng/mL (range 22.16-232.2 ng/mL), respectively. Interindividual CV for CAB was 47.3% (IQR 46.2, 48.9) and 47.2% (IQR 45.5, 48.7) for RPV. CAB and RPV Fleiss Kappa was -0.008 and -0.007, respectively, indicating poor interindividual agreement. Intraindividual CV for CAB was 24.6% (IQR 15.4, 38.5%) and 27.5% (IQR 19, 41.8%) for RPV. ICC was 0.81 and 0.72 for CAB and RPV, respectively, indicating good intraindividual agreement for CAB and moderate intraindividual agreement for RPV. There were 20 (14%) RPV and 10 (7%) CAB concentrations below 4x PA-IC90. Thirty-nine (83%) participants remained virologically suppressed throughout the follow-up period. Of the 8 (17%) participants with detectable viremia, 10 HIV RNA measurements were >20 copies/mL (range 23-75 copies/mL). Only 1 participant had CAB <4x PA-IC90 but none had RPV <4x PA-IC90. All 8 participants subsequently re-suppressed (HIV-RNA <20 copies/mL) while remaining on LA CAB/RPV.

Conclusions: After 1 year of continuous use, inter- and intraindividual variability persists for CAB and RPV. In our cohort, interindividual variability for CAB and RPV was higher compared to previously reported data during the initial 12 months of use. Additionally, intraindividual variability for CAB was lower, while RPV variability was similar to prior data during the first 12 months of use. There were more RPV concentrations below 4x PA-IC90 than CAB; however, all participants remained virologically controlled on LA CAB/RPV.



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Lack of Clinically Significant Drug–Drug Interactions Between the Third-Generation Integrase Strand Transfer Inhibitor VH4524184 (VH-184) and Combined Oral Contraceptives

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Background: Long-acting antiretroviral therapy offers people with HIV-1 more convenient and sustainable treatment options, improving quality of life and adherence. VH4524184 (VH-184) is a third-generation integrase strand transfer inhibitor (INSTI) that has potent antiviral activity, long-acting potential, and an enhanced in vitro resistance profile compared with second-generation INSTIs. Since VH-184 may be administered concomitantly with combined oral contraceptives (COCs), it is important to understand any clinically relevant drug–drug interactions. In this study, we assessed the impact of VH-184 on the pharmacokinetics (PK) of a common COC containing ethinyl estradiol (EE) and norethindrone acetate (NEA).

Material and Methods: We conducted a phase 1, open-label, single-sequence, 1-way study in female participants without HIV aged 18 to 45 years. Participants received once-daily oral EE 30 µg/NEA 1.5 mg alone (treatment period 1; Days 1–10) or with once-daily oral VH-184 200 mg (treatment period 2; Days 11–20) after a 21-day run-in period of EE/NEA followed by a 7-day washout period. The primary endpoint was maximum plasma concentration (C_{max}) and area under the concentration–time curve from time 0 to the end of the dosing interval (AUC_{0–τ}) for EE and NEA. Secondary endpoints included VH-184 PK parameters, safety, and tolerability.

Results: Of 26 participants enrolled, 20 completed the study. Five participants discontinued before treatment period 1, and 1 participant withdrew

after completing treatment period 2 but before the follow-up visit. Geometric least squares mean ratios (90% CI) with vs without VH-184 of C_{max} and AUC_{0–τ} were 1.041 (0.974–1.112) and 1.107 (1.062–1.153) for EE, respectively, and 1.210 (1.133–1.293) and 1.234 (1.194–1.274) for NEA, respectively. Steady-state VH-184 concentrations were achieved in ~10 days, consistent with prior studies. Overall, 12 (46%) participants reported 16 treatment-emergent adverse events (TEAEs). The only TEAEs reported by >1 participant were headache (n=3), abdominal pain (n=2), fatigue (n=2), and positive SARS-CoV-2 test (n=2). All TEAEs had a maximum intensity of grade 1. Five (19%) participants reported 6 drug-related TEAEs, none of which were reported by >1 participant. The 4 drug-related TEAEs reported during treatment period 2 were labeled events for EE/NEA and/or INSTIs. No TEAEs led to discontinuation during either treatment period. No serious AEs or deaths were reported. Five participants experienced asymptomatic grade 1 or 2 transaminase elevations after treatment period 2 (Day 21). There were no clinically relevant changes in other laboratory parameters, electrocardiograms, or vital signs.

Conclusions: VH-184 had no effect on the steady-state PK of EE after repeat oral administration with a common COC containing EE/NEA. A slight increase in NEA exposure was observed with VH-184 coadministration, which was not considered clinically significant. EE/NEA did not meaningfully affect the steady-state PK of VH-184. VH-184 combined with EE/NEA was well tolerated in female participants without HIV. These results indicate that VH-184 can be administered with COCs containing EE/NEA without impacting the efficacy of COCs or the PK of VH-184.



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Antiviral Activity, Safety, and PK/PD of ACC017 in Antiretroviral Naïve HIV-Infected Adults: A Randomized, Double-Blind, Placebo/Dose-Parallel-Controlled Short-Term Monotherapy Study

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Background: ACC017 is a novel HIV-1 integrase strand transfer inhibitor (INSTI) with potent anti-HIV activity, an in vitro resistance profile different from those of other INSTIs, and favorable preclinical safety and pharmacokinetic properties. To evaluate the antiviral activity, safety, pharmacokinetics, and pharmacokinetics/pharmacodynamics of ACC017 as short-term monotherapy.

Materials and Methods: A two-phase design was in this study. In the first phase, antiretroviral-naïve HIV-infected adults were randomized to receive ACC017 (5 mg, 40 mg, or 80 mg) or placebo once daily for 10 days. The randomization ratio was 10:2 (ACC017:placebo) for each dose. The second phase consisted of an open-label combination therapy stage where all subjects continued receiving their originally assigned dose of ACC017 (5mg, 40mg, or 80 mg, with no placebo) in combination with FTC/TAF (200 mg/25 mg) for 18 days. Plasma samples were collected to measure HIV-1 RNA levels and evaluate ACC017 pharmacokinetic parameters. The primary outcomes were the log₁₀ reduction in HIV-RNA from baseline on Day 11, and the proportion of participants with plasma HIV-RNA concentrations of less than 50 copies/mL at Day 29. Secondary outcomes included the assessment of ACC017 pharmacokinetics, immunologic changes, safety, and tolerability. This trial is registered with ClinicalTrials.gov, number NCT06719310.

Results: Thirty-six participants were enrolled (n = 12/group). Significant reductions in plasma HIV-RNA from baseline to Day 11 (24 h after the day 10 dose) were observed for all ACC017 dose groups compared with placebo (P<0.001), with a mean decrease of 1.44-2.34 log₁₀ copies/mL. A well characterized dose-response relationship was observed for viral load decrease. In addition, none of the participants had viral breakthrough. At Day 29, 86.11% (31/36) of the participants had HIV-RNA <50 copies/mL. Increases in mean AUC_{0-24h}, C_{max}, and C_{24h} were slightly less than dose-proportional, with median T_{max} of 2.53-3.50 h. Steady state was achieved after 3-4 days of once-daily dosing. At steady state, accumulation ratios (Day 10/Day 1) for AUC_{0-24h}, C_{max}, and C_{24h} were 1.13-1.26. Plasma HIV-RNA reduction was best predicted by C_{τ,ss} using an E_{max} model. ACC017 showed an adverse event profile similar to placebo, and there were no study drug discontinuations due to adverse events.

Conclusion: ACC017 demonstrated potent antiviral activity and good short-term tolerability in HIV-1 infected adults. Its pharmacokinetics in HIV-infected individuals were similar to those in uninfected individuals receiving similar doses in prior studies, and showed a predictable pharmacokinetics/pharmacodynamics relationship, which supports once-daily dosing in initial treatment patients in future studies.



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Assessing ChatGPT's Capability in Understanding and Reporting Antiretroviral Therapy Drug-Drug Interaction Effects: Quantitative and Qualitative Results from the ACCURATE-DDI Study

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Background: Artificial intelligence platforms such as ChatGPT are transforming access to medication information. However, their ability to accurately identify, describe, and provide clinically relevant management guidance for antiretroviral (ARV) drug-drug interactions (DDIs) remains unclear. This study evaluates the accuracy of ChatGPT's analysis of ARV-related DDIs compared to established HIV-specific DDI checkers.

Materials and Methods: Using ChatGPT4o-mini in November 2024, we tested 94 ARV DDI pairs. Pairs included prescription and non-prescription medications, oral and non-oral routes of administration, and pharmacokinetic and pharmacodynamic interactions, with an even distribution of non-interacting, potential, and serious interacting combinations. ChatGPT was queried using the following prompt: "Is there a drug interaction between Drug A and Drug B? a) no interaction, b) potential interaction, c) serious interaction." Using the HIV/HCV Drug Therapy Guide and the University of Liverpool HIV Drug Interactions Checker as references, we calculated accuracy (overall and stratified by DDI severity), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Qualitative analysis was conducted on responses for a subset of 25 pairs tested with the ChatGPT prompt, "Can I take Drug A with Drug B?" Severity, mechanism, clinical effects, and management were scored (0 = incorrect, 1 = mixed, 2 = correct), yielding a composite score (maximum = 8). Responses were independently assessed by HIV pharmacist/pharmacologist reviewers; score discrepancies of ≥ 2 between two reviewers were resolved by consensus involving a third reviewer.

Results: ChatGPT correctly classified 40.4% (38/94) of DDI pairs, with errors primarily due to false negatives (34/56 errors; 60.7%). Among 31 non-interacting pairs, ChatGPT correctly classified 9 (29%) as true negatives; the remaining 22 (71%) were false positives. Among 32 potential DDI pairs, ChatGPT categorized 29 (91%) correctly; 3 (9%) were false negatives. All 31 serious interaction pairs were incorrectly classified (false negatives). Overall sensitivity was 46.0%, specificity 29.0%, PPV 56.9%, and NPV 20.9%. In qualitative analysis, the mean composite score across all pairs was 3.9/8. Among non-interacting pairs (mean composite score 2.7/8), ChatGPT incorrectly warned about non-existent DDIs (mean severity 1/2). Mechanism (0.6/2), clinical effects (0.7/2), and management (0.4/2) were often incorrect. Across potential interaction pairs (mean composite score 4.2/8), ChatGPT was better able to categorize the severity (1.6/2), compared to mechanism (0.7/2), clinical effects (0.9/2), and management (1/2). For serious DDI pairs (mean composite score 4.3/8), ChatGPT showed limited accuracy in identifying severity (0.4/2), despite often correctly identifying mechanism (1.4/2) and clinical effects (1.6/2). Serious DDI management was often incorrect (0.9/2). ChatGPT failed to identify ritonavir-mediated DDIs involving non-CYP3A4 pathways, incorrectly claimed that non-CYP3A4 substrates would be boosted when co-administered with cobicistat, and failed to identify pharmacodynamic interactions.

Conclusion: ChatGPT demonstrated limited accuracy and specificity, often generating responses that combined correct and incorrect information. Notably, ChatGPT demonstrated a tendency to issue unfounded warnings about non-existent or clinically insignificant drug interactions while underreporting the severity of serious DDIs. ChatGPT is not yet a reliable tool for ARV DDI information, but performance may improve with future updates.



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An Enzymatic Assay with Lateral Flow Readout for Measurement of Tenofovir Diphosphate and Long-Term HIV Medication Adherence

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Although drug concentration feedback provides objective information that may help to improve HIV medication adherence and health outcomes, conventional testing with liquid chromatography tandem mass spectrometry (LC-MS/MS) is arduous and expensive. Urine tenofovir lateral flow assays (LFAs) for measuring adherence are rapid and inexpensive but cannot distinguish between recent (<1 week) and long-term (1-3 month) adherence. The REverse transcriptase ACTivity (REACT) assay rapidly measures tenofovir diphosphate (TFV-DP), a metabolite that indicates long-term oral PrEP/ART adherence, based on the drug's inhibition of DNA synthesis by HIV reverse transcriptase (RT) enzyme. Recent clinical validation of REACT showed correlation with LC-MS/MS measurements and excellent accuracy at distinguishing TFV-DP concentrations that indicate sufficient adherence but required an external instrument for fluorescence readout. Here we integrate REACT with CRISPR enzymes and reporters to provide an instrument-free LFA readout.

We combined CRISPR RNA, Cas12a, DNA template, nucleotides, HIV-RT, biotin-FITC reporters, and spiked TFV-DP concentrations corresponding to 2, 4, and 7 doses/week (350, 700, and 1250 fmol/3mm² punch) into rehydrated dried blood spots from three donors not receiving any antiretroviral drugs. The test line of the LFA strip detects the presence of uncleaved CRISPR reporters, so we also included "no drug" and "no enzyme" conditions to determine the minimum and maximum signal achievable. We incubated REACT assays at 37°C for 45 minutes and visualized reaction products on commercially available LFA strips (Abingdon Health PCRD Flex) that were immersed in reaction tubes for 10 minutes. We

scanned the LFAs to quantify the test line intensity, calculated signal-to-background ratios (SBR), and determined a positivity threshold at 3 standard deviations above the mean of the "no drug" condition to allow quantitative analysis of our results. We optimized reagent concentrations (Cas enzyme, nucleotides, and reaction time) to tune the LFA signal to be above the positive threshold.

In the "no drug" condition, LFA strips were unable to capture biotin-FITC reporters, resulting in faint test line intensities ($SBR = 1.33 \pm 0.22$, $N=6$) that set a positivity threshold at $SBR = 1.99$. Meanwhile, in the "no enzyme" condition, LFA strips provided strong test line intensities well above the positivity threshold ($SBR = 4.85 \pm 0.27$). LFA test line intensities correlated with TFV-DP concentrations ($r = 0.995$). At TFV-DP concentrations of 350, 700, and 1250 fmol/punch, the SBR values were 1.57 ± 0.10 , 1.82 ± 0.13 , and 2.60 ± 0.29 , respectively. Additionally, the LFA signal intensity at 1250 fmol/punch (7 doses/week) was significantly different from the "no drug" condition ($p = 0.001$), the 350 fmol/punch condition ($p = 0.0007$), and the 700 fmol/punch condition ($p = 0.003$).

Taken together, our results constitute an important proof of concept of LFA readout of enzymatic assays for measuring TFV-DP concentrations and long-term HIV medication adherence that may be suitable for use in resource-constrained settings. Ongoing work is focused on tuning the LFA readout to TFV-DP thresholds relevant for different use cases among key populations (e.g. adherence monitoring or resistance screening) and validating our results with clinical samples.



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Longitudinal Monitoring of Cabotegravir and Rilpivirine Exposure from Hair Strand Concentrations

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Background: Virological failure among individuals using long-acting injectable (LAI) treatment for HIV has been associated with low trough concentrations of cabotegravir (CAB) + rilpivirine (RPV) despite on-time injection. A non-invasive method for monitoring months of drug exposure from LAI treatment may help identify persons at-risk. We have developed an approach for the long-term characterization of daily CAB and RPV exposure from LAI treatment in hair strands using mass spectrometry imaging (MSI).

Methods: Eighteen participants receiving LAI CAB+RPV for HIV treatment (6 female, 11 male, 1 non-binary) provided five hair strands plucked from the occipital scalp and plasma. CAB and RPV were measured along individual hair strands by infrared matrix assisted laser desorption electrospray ionization (IR-MALDESI) MSI. Profile variability was assessed by relative standard deviation (RSD). Agreement between CAB/ RPV in hair and LC-MS/MS plasma concentrations was evaluated by Pearson correlation coefficient (r), also used for comparison to participant BMI. All values reported as median (range).

Results: Participants were sampled during their 3rd (2nd-7th) LAI dosing interval, typically (16/18) when returning to clinic for an injection. Sampling occurred 58 (30-68) days after prior injection, reflecting a mix of individuals receiving Q4W (6/18) and Q8W (12/18) treatment. Longitudinal profiles from MSI sample analysis evaluated 86 (46-101) days of growth, capturing at least the most recent and up to 2 prior LAI dosing intervals. CAB and RPV were detectable in all samples, and patterns of LAI treatment (from initiation to maintenance dosing) could be differentiated in a single sample at Q4W or Q8W frequency (Figure 1). LAI hair profile variability [CAB RSD: 52% (34-

84); RPV RSD: 42% (10-89)] was greater than variability of QC standards [RSD: 32% (22-66)] and adherent oral FTC dosing (ENLIGHTEN study, NCT04232540) [RSD: 29% (13-72)]. Positive correlation was observed between hair and plasma CAB/ RPV ($r_{CAB}=0.31$; $r_{RPV}=0.30$). These measurements were each negatively correlated with BMI (CAB: $r_{Hair}=-0.28$, $r_{Plasma}=-0.33$; RPV: $r_{Hair}=-0.31$, $r_{Plasma}=-0.44$).

Conclusions: Identifying patterns and variability of CAB and RPV exposure has important implications for optimizing care of persons using LAI for treatment. The increased variability for CAB noted in hair uptake may reflect increased variability in plasma concentrations and should be further investigated as a noninvasive measure of systemic pharmacokinetics.



LB-#1

Can Low-Cost Oral Alternatives Be Used in Place of Oral Lenacapavir When Initiating Long-Acting Lenacapavir PrEP in Low- and Middle-Income Countries?

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Background: Lenacapavir (LEN) was approved by FDA June 2025 as 6-monthly subcutaneous (SC) PrEP. Since LEN takes time to reach protective plasma concentrations following injection, two options are available for initiating long-acting LEN PrEP.

Option 1: 600 mg oral LEN on days 1 and 2, with 927 mg SC LEN also given on day 1.

Option 2: (as studied in RCTs) 600 mg oral LEN on days 1 and 2, followed by 300 mg oral LEN on day 8, with 927 mg long-acting LEN on day 15.

The need for oral LEN when initiating long-acting LEN PrEP poses significant challenges to rapid adoption in low- and middle-income countries (LMIC). Generic manufacturers would need to develop and gain approval for two new products rather than one (oral and injectable). Small market size for the oral product constitutes a barrier for manufacturers, and a fiscal challenge for LMIC healthcare providers is also anticipated, particularly when multiple low-cost oral options are already available. The current work analysed publicly available LEN pharmacokinetics with and without oral LEN at initiation to estimate how long oral PrEP with a low-cost alternative would need to be given while long-acting LEN reached protective levels.

Materials and Methods: LEN plasma pharmacokinetic (PK) data were available for both current initiation options (Option 1: n = 31; Option 2: n = 14)¹. PK data following a single SC dose of 927 mg (dosed as 2 x 1.5 mL injections) without oral LEN in healthy volunteers was also available (n = 8)². Plasma concentrations and measures of spread (confidence interval areas, error bars) were digitised using GetData Graph Digitizer³.

Digitisation of confidence intervals was less certain due to issues of data overlap and figure resolution, but deemed sufficient quality for interpretation. Data were replotted to facilitate comparison between dosing schemes. In line with previous evaluations, LEN Inhibitory Quotient 4 (IQ4; 4 x in vitro protein-adjusted EC50) was used as the target.

Results: For both Option 1 and Option 2, median plasma LEN concentrations achieved IQ4 on day 1 and were maintained above IQ4 for 6 months. Conversely, in the absence of oral LEN at initiation, LEN plasma concentrations following SC dosing did not robustly achieve IQ4 until 35 – 42 days post administration. Following day 42, plasma concentrations were similar between different dosing schemes until the end of the 6-month dosing interval, indicating that oral bridging is unlikely to be needed for subsequent doses.

Conclusions: These data support feasibility of low-cost oral PrEP (e.g. TDF/FTC or TAF/FTC) as an alternative to oral LEN when initiating long-acting LEN PrEP but highlight that it would need to be given for 35 – 42 days. Such an approach may mitigate the need for development of a generic LEN oral product, and reduce ongoing PrEP costs to facilitate timely equitable access in LMIC.

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POSTER ABSTRACT PRESENTATIONS

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"Waves of Resistance: The Impact of Malnutrition and Mobility on ART Pharmacokinetics and Resistance Among Key Populations in Kalangala Islands, Uganda"

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Background: Kalangala district is an isolated fishing community on Lake Victoria with 84 islands. The district has only 15 health facilities. However, only 8 are accredited to offer ART services. The district presents unique barriers to ART effectiveness among Key Populations (KPs). According to Uganda AIDS Commission (2024), it was ranked 2nd with the highest HIV prevalence in Uganda (13.1) way above the National average of 5.2. High mobility in search of fish catches and widespread malnutrition are hypothesized to significantly affect ART pharmacokinetics, adherence, and drug resistance. This study examines how malnutrition and mobility impact ART drug levels, treatment outcomes, and resistance patterns among KPs in Kalangala Islands.

Methods: A cross-sectional study was conducted between July 2024 and January 2025, enrolling 250 Key Population living with HIV from four island-based health facilities. Participants were stratified into: Fisherfolk (45.2%), Sex workers (28.4%), People who inject drugs (15.6%), Transgender (10.8%).
Pharmacokinetics Analysis: Blood samples were collected at 0-, 4-, and 8 hours post-dose to assess Tenofovir (TFV), Lamivudine (3TC), and Efavirenz (EFV) levels. Therapeutic drug levels were defined as TFV ≥ 40 ng/mL and EFV $\geq 1,000$ ng/mL.
Nutritional & Mobility Assessment: BMI < 18.5 kg/m² was used to classify malnutrition. 52.8% of participants were food insecure, with 31.6% experiencing moderate malnutrition. Mobility was assessed using client locator log and self-reported travel frequency over 6 months. 67.4% of

fisherfolk travelled across islands weekly, with 12.3% missing ART refills.

Adherence & Resistance: ART adherence was evaluated using appoint register and a Visual Analog Scale (VAS, 0–100%). Viral resistance genotyping was performed for individuals with HIV RNA $> 1,000$ copies/mL after 6 months on ART. Poor adherence was defined as $< 75\%$ ART intake over 6 months.

Results: 41.2% of participants had suboptimal adherence ($< 75\%$), mainly due to mobility (64.7%) and food insecurity (23.5%). 57.6% of fisherfolk and 48.9% of sex workers missed ART doses due to relocations. Individuals traveling ≥ 3 times/month had 2.5 times higher odds (95% CI: 1.7–3.9, $p < 0.001$) of missing doses.

34.9% had sub-therapeutic ART drug levels, significantly correlated with malnutrition ($p < 0.001$).

23.1% developed drug resistance mutations, with M184V (48.6%) for Lamivudine and K103N (35.2%) for Efavirenz.

Malnourished participants had 3.1 times higher odds (95% CI: 2.0–4.8, $p < 0.001$) of sub-therapeutic ART levels and 1.9 times higher odds ($p = 0.002$) of developing resistance.

Overall, 78.3% achieved viral suppression (HIV RNA < 400 copies/mL), significantly below the UNAIDS 95% suppression target.

Conclusions: High mobility and malnutrition significantly impact ART pharmacokinetics, leading to sub-therapeutic drug levels, poor adherence, and increased resistance rates among Key Populations in Kalangala Islands. Mobile fisherfolk are at the highest risk, with over 35% failing to achieve viral suppression.



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The Impact of Dolutegravir on Depressive Side Effects: A Multivariate Analysis of Age, Gender, Anti-Depressant Use and Race in CHARTER Cohort of People with HIV

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Background: Integrase strand transfer inhibitors (InSTIs) are first-line therapy in the U.S. and other countries. One InSTI drug, dolutegravir (DTG), has been linked to neuropsychiatric adverse events but few reports have used standardized assessments of depression or assessed the concomitant influence of age and antidepressant use. The aim of these analyses was to determine the relationships between InSTI use, aging, antidepressant use, and depressive symptoms in people with HIV (PWH).

Methods: All 280 participants were comprehensively assessed in the CHARTER Aging project; were taking ART; and had plasma HIV RNA ≤ 200 copies/mL. The project enrolled participants based on chronological age $< \text{or} \geq 60$ years. The Beck Depression Inventory (BDI)-II and four subscales were compared to demographic characteristics, use of InSTIs and antidepressants, and clinical biomarkers in a cross-sectional design by multivariable linear regression, including backward selection by Akaike Information Criterion.

Results: Participant characteristics included median age 56 years (28.7% > 60), 18.3% female, 38.8% black, 71.7% AIDS, median CD4⁺ T-cells 625/ μL , median duration of the current ART regimen 19.4 months, and 67.8% InSTI use. Overall, InSTI use was not associated with BDI-II but DTG use trended toward association with worse BDI-II scores ($p=0.064$). Multivariable analysis identified that non-black race ($p=0.0033$), DTG use ($p=0.0042$), female sex ($p=0.011$), antidepressant use ($p=0.039$), and age ≥ 60

($p=0.056$) were associated with worse BDI-II scores. The effects of DTG were present in the Apathy ($p=0.0027$), Cognitive ($p=0.019$), and Somatic ($p=0.020$) BDI-II subscales. Interaction analyses identified that DTG was associated with worse BDI-II principally among those older than 60 years (interaction $p=0.026$, see Figure).

Conclusions: DTG may increase depressive symptoms in older PWH and those who use an antidepressant. Additionally, DTG worsened depressive symptoms in females or non-Black individuals. Others have reported neuropsychiatric adverse events associated with DTG, but this is the first study to use a standardized depression assessment and to identify an interaction with antidepressants, which may provide mechanistic and clinical insights to improve the care of PWH.



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Mechanistic Viral Dynamic Modeling of In Vitro Cytomegalovirus Infection Based on Viral DNA and Viral Titer

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Aims: Ganciclovir and its prodrug valganciclovir are the standard treatments for cytomegalovirus (CMV) infection. Despite their efficacy, these antiviral agents have a very narrow therapeutic window due to high myelotoxicity. Although the in vivo viral dynamics of CMV have been studied, previous published models have relied solely on viral DNA profiles, which indicates the amount of both infectious and non-infectious virus instead of infectious virus only. In this study, both viral DNA and viral titer (i.e., infectious virus) were characterized, and their relationship was elucidated through the development of a mechanistic viral dynamic model of in vitro CMV infection.

Methods: The viral dynamic model development was carried out using NONMEM (v.7.5). First, natural cell growth rate of the susceptible cell counts (S) and death rate (δ) of infected cells (I) were derived from the cell counts data of the uninfected and infected group. Next, a target cell-limited (TCL) model [1] was applied to characterize the viral dynamics by fitting both the viral DNA and viral titer data. Key viral kinetic parameters estimated included viral infection rate (β), cell growth rate (λ), production rate of viral DNA (π) and viral clearance (γ). Different functions were tested to describe the relationship between total (V) and infectious virus (V_i).

Results: The fitting results showed that the natural cell growth curve can be best described by an exponential saturated function of which the natural growth rate was 0.77 day⁻¹. When the cells were infected, the proliferation of susceptible cells drastically reduced by 87%, decreasing from 0.77 to 0.1 day⁻¹ with a death rate of infected cells of 0.996

day⁻¹. A TCL model well captured the viral load profile with $\beta = 1.27 \times 10^{-8}$ copy⁻¹/day, $\lambda = 0.1$ day⁻¹, $\pi = 7.48 \times 10^4$ copy/cell/day. The relationship between V and V_i can be best characterized using a power-law model: $V_i = f(V) = B \cdot V^{\text{Hill}}$, where $B = 0.032$ and $\text{Hill} = 0.848$, indicating each new DNA copy came with approximately 0.03 infectious virion.

Conclusions: This is the first known viral kinetic model of in vitro CMV infection that characterizes the dynamics of CMV as well as the relationship between viral DNA and viral titer, providing an ideal basis to study the in vitro PK-PD of CMV and ganciclovir in a dynamic in vitro infection model with the potential to translate to a clinical setting afterwards.

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Antiviral Dose Response against CMV Infection Varies with the Timing of Treatment Initiation

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Background: Cytomegalovirus (CMV) is a herpesvirus that can cause significant mortality in patients who are immunocompromised. Optimizing dosing strategy of antiviral drugs is still crucial due to their narrow therapeutic windows and limited studies in PK/PD targets. While these drugs are all active against CMV activity, the extent to which the initiation time of antiviral administration affects pharmacodynamic outcomes is still unknown. Our study aims to evaluate the antiviral effects of ganciclovir, foscarnet and letermovir under varying treatment initiation times in an in vitro infection model.

Methods: The in vitro infection model consisted of human lung fibroblast cells (MRC5) that were infected with the HCMV Towne strain (MOI = 0.1). Ganciclovir, foscarnet and letermovir concentrations of 0.5 - 10 mg/L, 7.5 - 60 mg/L, and 0.5 - 34 µg/L, respectively, were used to assess antiviral effects as these are relevant to the reported range of the half-effective maximal concentration (EC50) values. Ganciclovir and foscarnet treatment was initiated at 0, 3, 6 and 10 days post-infection. While Letermovir was initiated at 3 days before infection, 0, 3 and 6 days post-infection. Supernatant was collected to measure viral load using qPCR. Log10 genome copies reduction was calculated relative to non-drug treated samples.

Results: Throughout the 15-day experiment (infection period), we observed a dose-response effect on viral suppression when treatment was delayed until 6 days post-infection for ganciclovir, and until 3 days post-infection for foscarnet. For ganciclovir, earlier treatment induces higher viral load reduction proportionally. At 10 mg/L, we have found 3.8, 2.4 and 1.8 log10 reduction when treatment was initiated without delay, at 3, and 6 days post-infection, respectively. While for

foscarnet, a reduction of 2 log10 was observed at the highest concentration when treatment was initiated without delay and at 3 days post-infection. Conversely, a dose-response effect on antiviral activity was only observed in the absence of delayed letermovir treatment where more than 1 log10 viral reduction was observed. Consistent with our findings, we have found that EC50 values increased with delayed treatment of the three drugs. This indicates that anti-CMV potency depends on treatment initiation time as well as the infection age of the cell culture. Overall, we have observed that dosing delays affect pharmacodynamic outcomes differently for different drugs. We have found that ganciclovir has the most potent effect in suppressing viral load burden amongst other drugs when treatment is initiated with delay.

Conclusion: Our in vitro data suggests that the dose-response effect on antiviral activity for anti-CMV drugs depends on treatment initiation time. Delayed treatment is consistently found associated with higher EC50 values. These findings suggest that potency decreases with infection age. Additionally, the impact of dosing delays on pharmacodynamic outcomes varied between different drugs. The PK/PD of these drugs is thus different and will be further investigated in a dynamic hollow fibre infection model. In conclusion, our overall findings suggest that timing of drug administration is crucial for improving clinical outcomes in CMV treatment.



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Evaluation of Potential Changes in Prescribing Patterns Through the Use of an HIV Interactions Checker Database

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Background: People aging with HIV often experience comorbidities and polypharmacy, leading to a higher risk for adverse events and drug-drug interactions (DDIs). On the other hand, contemporary antiretrovirals have a lower potential for DDIs which may, in turn, have an impact on the treatment of common comorbidities (e.g., cardiovascular, mental diseases, opportunistic infections). We aimed to evaluate potential changes in prescribing patterns by analyzing DDI queries over a 5-year period of time.

Material and methods: An extraction of DDI queries was performed on the HIV interaction checker of the University of Liverpool (<https://www.hiv-druginteractions.org>) between January 1, 2020 and December 31, 2024. The antiretroviral drug name, co-medication class, co-medication name, interaction color and the country of origin were collected and sorted by year. Interaction colors were defined as green (no interaction), yellow (potential interaction of weak clinical relevance), amber (potential clinically relevant interaction managed with clinical monitoring or dose adjustment) and red (deleterious interaction).

Results: A total of 7,274,301 queries from 48 countries were recorded on the website with an increase of 441% from 2020 to 2024. The main users of the checker were from UK (46.7%) and USA (34%) followed by Spain (2.7%), Brazil (2.4%) and Australia (1.8%). Overall, the most frequently searched antiretrovirals were dolutegravir (21%), bictegravir (20%), emtricitabine/tenofovir (TDF or TAF) (17.8%), darunavir with ritonavir or cobicistat (11.1%) and raltegravir (3.7%). From 2020 to 2024, an increase in queries for bictegravir (+11.3%

points), dolutegravir (+7% points), cabotegravir (+3% points) and doravirine (+2.3% points) was observed, in contrast with darunavir (-4.2% points), raltegravir (-3% points) and elvitegravir (-2.9% points). The top10 searched therapeutic classes were antibacterials (9.3%), lipid lowering agents (9.4%), herbals/supplements/vitamins (9.1%), gastrointestinal agents (7.9%), analgesics (6.6%), antidepressants (6.2%), anti-coagulant/anti-platelets (4.9%), hypertension/heart failure agents (4.8%), anticonvulsants (4.3%) and steroids (4.1%). Overall, the prevalence of queries with green, yellow, amber and red color coding were 76.6%, 4.6%, 14.9% and 4.0%, respectively. Among amber DDIs, queries involved mainly darunavir (26.0%), dolutegravir (19.6%) bictegravir (15.4%) together with herbals/supplements/vitamins (19.2%), lipid lowering agents (13.9%) or antidiabetics (9.3%). Among red DDIs, queries involved mainly darunavir (31%), bictegravir (19.4%) and elvitegravir/cobicistat (11.1%) together with gastrointestinal agents (15.7%), steroids (14.5%) and antibacterials (14.4%). In 2024, compared to 2023, a decrease in rifampicin queries was reported (-53%), as for rosuvastatine (-25%), omeprazole (-33%), pantoprazole (-33%), apixaban (-25%), warfarine (-33%) and rivaroxaban (-51%). From 2020 to 2024, a transition of amber (-5.9% points) or red (-3.1% points) DDIs to green (+9.1 points) DDIs was observed.

Conclusions: Over the 2020-2024 period, we observed a substantial increase in DDI queries, suggesting that the DDI checker is increasingly integrated in clinical practice. We observed a reduction in the severity of DDIs in the recent years which likely explained by the broader use of contemporary antiretrovirals with a favorable DDI profile (i.e., dolutegravir, bictegravir, cabotegravir or doravirine).



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Pharmacokinetics of Nitazoxanide in Plasma Separation Cards from Patients with SARS-CoV-2: AGILE CST-3a/b

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Background: Nitazoxanide (NTZ) is an anti-parasitic which has demonstrated inhibitory activity against a range of viruses, including in vitro inhibition of severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2). Liquid plasma (L-PL) collection in resource-limited settings (RLS), where high-consequence infections are endemic, can be challenging. HemaSep dried blood spots (HS-DBS) offer a useful alternative to L-PL, separating plasma upon contact as a distinct outer ring (HS-PL) and can be shipped at ambient temperatures. HS-DBS were collected alongside L-PL in the AGILE CST-3a/3b clinical trials to evaluate the pharmacokinetics of single and repeat doses of NTZ in healthy participants (CST-3a), and patients with SARS-CoV-2 (CST-3b).

Materials and Methods: AGILE-CST-3a and 3b were open-label single-arm phase Ia/b trials with the aim of determining the optimal dose for treatment of symptomatic SARS-CoV-2 patients (CST-3a; n = 14, CST-3b; n = 8). Participants in CST-3b, with confirmed SARS-CoV-2 infection, were randomised 2:1 to receive NTZ or standard of care. NTZ was administered twice daily (BD) at 1500mg for 5 days. Paired L-PL and HS-DBS were collected over 0-8hr post-dose (CST-3a) and 0-4hr post-dose (CST-3b) following administration of single (day 1) and multiple doses (day 5). 100uL whole blood was applied to HemaSep cards. HS-PL (entire outer plasma ring) and L-PL samples were extracted with 0.1% formic acid in acetonitrile. Concentrations of

NTZ metabolite tizoxanide (TZN) were quantified using LC-MS (HS-PL: 2.35 – 1960 ng/sample, L-PL: 10 – 10000 ng/mL). HS-PL values were normalised to ng/mL and pharmacokinetic parameters (C_{max}, AUC_{last}) derived using non-compartmental analysis. Linear regression and Bland Altman plots were used to compare methods.

Results: TZN L-PL geometric mean C_{max} increased with repeated dosing (Day 1 | Day 5) - CST-3a: 14860.8 ng/mL | 20342.8 ng/mL; CST-3b: 10946.5 ng/mL | 17678.3 ng/mL). HS-PL C_{max} also displayed similar increases in concentration - CST-3a: 18206 ng/mL | 25479.1 ng/mL; CST-3b: 12073.2 ng/mL | 23434.9 ng/mL. Geometric mean ratios (GMR [95% CI]) indicate differences between days 1 and 5 were significant for both L-PL (CST3a: (1.48 [1.17, 1.86])), CST3b: (1.61 [1.16, 2.25]) and HS-PL (CST3a: (1.47 [1.08, 2.01])), CST3b: (1.95 [1.15, 3.28])). The mean difference between HS-PL and L-PL TZN concentrations was: CST-3a; 20.4% (-48.5% - 83.9%; n = 116) | CST-3b; 2.65% (-185.8% - 71.2%; n = 102). Intersubject variability for C_{max} and AUC_{last} were <60% (CST-3a) and <58% (CST-3b).

L-PL and HS-PL concentrations and AUC_{last} (CST-3a - r = 0.8343; p = <0.001; n = 24, CST-3b - r = 0.8045; p = <0.001; n = 16) were highly correlated with a mean difference of 5.53 ng/mL (CST-3a) and 1.01 ng/mL (CST-3b) between methods. In both CST-3a and CST-3b, all HS-PL and L-PL concentrations remained above the EC90 target (1430 ng/mL) at pre-dose on day 5.

Conclusion: HS-DBS are a viable alternative to L-PL for clinical sample collection and transport for studies of high-consequence infections in RLS, as TZN concentrations were strongly correlated with respective L-PL values, with a minimal mean difference between methods. Generally, HS-PL concentrations were greater than respective L-PL values, likely due to variable plasma ring volumes.



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Pharmacokinetics of the Inactive Favipiravir Metabolite, Favipiravir Hydroxide (M1), as a Proxy for Establishing Metabolic Activity in Patients Receiving Intravenous Favipiravir for Treatment of SARS-CoV-2 Infection

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Background: Favipiravir (FVP) has demonstrated in vitro activity against several RNA viruses, and its use for treatment of high consequence infectious diseases (HCIDs) continues to be evaluated. FVP is primarily metabolised by aldehyde oxidase (AO) to the pharmacologically inactive, favipiravir hydroxide (M1). FVP has complex pharmacokinetics (PK), with auto-inhibition of AO by FVP leading to increased FVP concentrations in plasma over time. Interindividual variability is a hallmark of FVP PK, but the cause of this is undetermined. Here we report M1 concentrations in plasma from patients hospitalised with COVID-19 enrolled on the AGILE CST-6 clinical trial.

Methods: AGILE CST-6 is a phase I randomised, adaptive study to evaluate safety and efficacy of intravenous (IV) FVP for treatment of COVID-19. Patients with laboratory confirmed COVID-19 were randomised 2:1 to received IV FVP or standard of care (SoC). Four cohorts with 6 patients were enrolled, with escalating dose per cohort (600, 1200, 1800, 2400 mg). Patients received IV FVP infusions for 1 hour twice daily (BD) for 7 days. Plasma samples were collected on Day 1, 3 and 5 at 0 – 1 and 6 – 12 hours post-completion of infusion. Extra samples were taken on Day 1 and 3 at predose and 2 – 4 hours post-completion of

infusion. FVP and M1 [concentrations] in plasma were determined using validated LC-MS methods and concentrations expressed as ng/mL. PK parameters for M1 and FVP were derived using WinNonlin (Phoenix 64, v8.5). Fixed effect linear modelling of the data was performed using SPSS (IBM, v29.0.1).

Results: A total of 153 samples were evaluable from 16 patients. M1 increased with dose but decreased from Day 1 to Day 5. Geometric mean (GM) C_{max} [M1] were (600|1200|1800|2400 mg) 5873, 9706, 18576, 25868 ng/mL on Day 1, 4901, 6808, 10311 and 12475 ng/mL on Day 3 and 4275, 7021, 8701 and 15185 ng/mL on Day 5. [FVP] C_{max} were 16481, 38006, 52044, 88486 ng/mL on Day 1, 16526, 61907, 85362 and 195067 ng/mL on Day 3 and 23461, 86743, 115781 and 202676 ng/mL on Day 5. Median (range) M1:FVP ratios were 600mg: 0.41 (0.06–0.75); 1200mg: 0.18 (0.01–0.60); 1800mg: 0.14 (0.05–0.81) and 2400mg: 0.10 (0.04 – 0.46) and decreased from Day 1 to Day 5 – M1:FVP were Day 1: 0.42 (0.06–0.81); Day 3: 0.13 (0.01–0.66) and Day 5: 0.10 (0.02–0.48). Interindividual variability was high with %CV >57%. Dose (94% lower FVP with 600 mg vs. 2400 mg; p<0.001), M1:FVP ratio (33% decrease in FVP with increasing ratio; p<0.001) and treatment day (60% decrease in FVP on Day 1 vs. Day 5) were independent, significant predictors of [FVP].

Conclusion: M1 concentrations decrease as FVP plasma concentration increases – both with escalating dose and over treatment duration, indicating potential saturation of metabolic pathways and increased inhibition of AO (due to accumulation of FVP). High interindividual variability in M1:FVP suggests the presence of fast and slow metabolisers. [FVP] was independently predicted by dose, M1:FVP ratio, and treatment day, highlighting the complex pharmacokinetic profile of FVP.



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TFV-DP and FTC-TP Using Volumetric Absorptive Microsampling Compared with DBS among Persons Receiving TDF/FTC or TAF/FTC

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Background: The phosphorylated moieties tenofovir-diphosphate (TFV-DP) and emtricitabine-triphosphate (FTC-TP) can be quantified in erythrocytes using dried blood spots (DBS) following tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF), with emtricitabine (FTC). There are established adherence:concentration benchmarks for DBS TFV-DP/FTC-TP; however, the comparability of volumetric absorptive microsampling (VAMS) methods (e.g., Mitra) has not been extensively evaluated.

Material and Methods: Paired DBS and VAMS (Mitra 20µL) samples from two studies were analyzed: (A) ATEAM (NCT02968576): subset of 20 participants (35 person-visits) who received single-dose TDF/FTC (300mg/200mg) on two occasions (separated by a 14-day washout), measured at 24 hours post-dose; and (B) TAF-DBS (NCT02962739): subset of 6 participants (26 person-visits) who received TAF/FTC (25mg/200mg) at 33%, 67%, or 100% of daily dosing (2 participants/adherence level), measured at weeks 1-6. DBS TFV-DP/FTC-TP concentrations were quantified from a 3mm punch (TDF/FTC) versus 2*7mm punches (TAF/FTC); VAMS concentrations were quantified from a 20µL tip (units/sample). Mean values of replicate VAMS samples (up to 3 tips) were used for comparison to singlet DBS. Linear mixed-effects models compared log-transformed DBS and VAMS TFV-DP/FTC-TP and results were reported as percentage increases (95% CIs) in DBS for every 10% increase in VAMS. Repeated-measures Bland-Altman analyses calculated DBS:VAMS mean bias ratios/conversion factors (95% CIs), and DBS:VAMS proportional biases (95% CIs) to evaluate if DBS

and VAMS differences changed across the range of concentrations.

Results: (A) ATEAM (TDF/FTC) participants included 13 (65%) females, 17 (85%) whites, and had a median (range) age of 27 (24, 37) years. Following single-dose TDF/FTC, every 10% increase in VAMS TFV-DP was associated with a DBS TFV-DP increase of 8.5% (7.5%, 9.6%; $P<0.0001$); every 10% increase in VAMS FTC-TP was associated with a DBS FTC-TP increase of 6.0% (4.4%, 7.5%; $P<0.0001$). DBS concentrations were lower than VAMS (mean bias ratios: TFV-DP, 0.34 [0.19, 0.63; $P=0.001$]; FTC-TP, 0.14 [0.10, 0.21; $P<0.0001$]). Every unit increase in log-transformed concentrations was associated with a DBS:VAMS proportional bias change of -9.6% (-20.2%, 2.4%; $P=0.11$) for TFV-DP and -29.1% (-43.4%, -11.1%; $P=0.004$) for FTC-TP. (B) TAF-DBS (TAF/FTC) participants included 3 (50%) females, 6 (100%) whites, and had a median (range) age of 30 (28, 33) years. Following repeated TAF/FTC dosing, every 10% increase in VAMS TFV-DP was associated with a DBS TFV-DP increase of 9.9% (9.2%, 10.6%; $P<0.0001$); every 10% increase in VAMS FTC-TP was associated with a DBS FTC-TP increase of 9.3% (8.2%, 10.5%; $P<0.0001$). DBS concentrations were higher than VAMS (mean bias ratios: TFV-DP, 1.43 [0.94, 2.18; $P=0.09$]; FTC-TP, 1.69 [1.54, 1.85; $P<0.0001$]). Every unit increase in log-transformed concentrations was associated with a DBS:VAMS proportional bias change of 0.1% (-6.4%, 7.1%; $P=0.97$) for TFV-DP and -3.4% (-14.5%, 9.2%; $P=0.57$) for FTC-TP.

Conclusions: Following TAF/FTC, VAMS concentrations can be used to estimate DBS concentrations using the equations, $VAMS(TFV-DP)*1.43=DBS(TFV-DP)$ and $VAMS(FTC-TP)*1.69=DBS(FTC-TP)$. TFV-DP/FTC-TP concentrations were low in ATEAM (single-dose TDF/FTC) which led to lower precision; conversion factors following TDF/FTC will require further refinement from repeated dosing studies with paired DBS and VAMS.



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Clinical Outcomes of Switching to Dolutegravir/Lamivudine Dual Therapy in People Living with HIV: A Single-Center Retrospective Study

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Background: Dual therapy with dolutegravir/lamivudine (DTG/3TC) has emerged as a simplified antiretroviral regimen with favorable safety and efficacy profiles. This study aimed to investigate the reasons for switching to DTG/3TC, virologic outcomes, renal function trends, and adverse events in people living with HIV (PLWH).

Methods: A retrospective review was conducted on 38 adult PLWH followed by a single physician who switched to DTG/3TC between 2015 and 2021. Demographic data, treatment history, reasons for switching, laboratory parameters, and clinical outcomes were analyzed.

Results: The most frequent reason for switching was to avoid potential renal toxicity (44.7%, 17/38). The median age was 51.5 years, and the median follow-up duration was 54 months. No virologic failure was observed, including in three patients with NRTI mutations (K65R, M41L, K70T/S). Significant increases in CD4+ T-cell counts were noted. Early improvements in glomerular filtration rate and reductions in proteinuria were recorded. The treatment discontinuation rate due to adverse events was 5.3% (2/38). The overall mortality rate was 18.4% (7/38), with myocardial infarction being the leading cause of death (4/7).

Conclusion: Switching to DTG/3TC dual therapy in well-controlled PLWH demonstrated high virologic suppression rates and favorable safety outcomes. It appears to be an effective and well-tolerated treatment option in selected patients.



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Physicochemical Stability of DELSTRIGO®: A Combination of Three Active Substances [Tenofovir Disoproxil Fumarate (TDF), Lamivudine (3TC) Doravirine (DOR)] in the Management of Occupational in the Management of HIV Post-Exposure Prophylaxis (PEP)

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Introduction: The 1st-line PEP recommended by the French National Authority for Health is the combination of TDF, 3TC or emtricitabine and DOR. DELSTRIGO® combines the advantages of a single tablet, simplifying daily administration, and reduced cost. However, DELSTRIGO® is only available in bottles of 30 tablets (cp) which is not sized for the appropriate management of PEP. In addition, once opened, the stability of the tablets in the bottle remains unknown.

This study aimed to assess the physicochemical stability of DELSTRIGO® film-coated tablets under various storage conditions to support their repackaging for emergency kit use in hospital-based PEP management.

Materials and methods: DELSTRIGO® tablets marketed by MSD Laboratory containing the 3 active ingredients (TDF/3TC/DOR) were used. European Pharmacopoeia-quality reference substances for TDF, 3TC and DOR, and liquid chromatography (LC) solvents were used. Tablets were repackaged in individual PVC blisters. Film-coated tablets were stored under different storage conditions for 6 months: closed bottle 20-25°C (control), repackaged in blisters stored at 25°C with 60% residual humidity (RH) and under

intentionally unfavorable stress conditions (40°C and 75% RH, H₂O₂, HCl and NaOH).

An LC method was developed to track variations in TDF, 3TC and DOR content in tablets. The appearance of compounds resulting from the degradation of these three compounds was also monitored by comparing chromatographic profiles.

Results: The analytical conditions for monitoring the quantities of DOR, TDF and 3TC have been developed and validated in line with current recommendations. When the tablets were stored at 25°C and 60% RH, the levels of each active substance remained between 95.0% and 105.0% of the expected values, and the chromatographic profiles showed no appearance of additional products compared with the control. On the other hand, under certain stress conditions, significant degradation (>0.15%) of TDF and DOR was observed, leading to changes in chromatographic profiles compared with the control.

Conclusion: This study demonstrates that if DELSTRIGO® tablets are stored for 90 days under controlled, degradation-limiting conditions (tinted blister pack, 25°C/60% RH), they present an acceptable content and no substantial degradation appears to occur. These results pave the way for unitary repackaging of DELSTRIGO®, thus improving PEP management. Further analysis is underway to extend these conclusions to a 6-month period.

1 Houssen, M et al, *Pharmaceutics* vol. 16,8 977. 24 Jul. 2024.



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Single-Dose Pharmacokinetics and Safety of ACC017, A Novel HIV Integrase Inhibitor, in Healthy Adult Participants: A First-in-Human Study

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Background: Since 2018, the World Health Organization has recommended integrase strand transfer inhibitors (INSTIs) as first-line and second-line antiretroviral therapies for all people living with human immunodeficiency virus (HIV). ACC017 is a novel INSTI with potent anti-HIV activity, an in vitro resistance profile different from those of other INSTIs, and favorable preclinical safety and pharmacokinetic properties, which is being developed for the treatment of HIV-1 infection.

Methods: This randomized, double-blind, placebo-controlled, single-dose escalation study was conducted from 24 January 2024 to 20 May 2024, at a single center in China. Thirty-six healthy participants, aged 18 to 55 years, were randomly assigned in a 4:1 ratio to receive a single dose of ACC017 (5 mg, 20 mg, 40 mg, 80 mg or 120 mg) or placebo. Safety, tolerability and pharmacokinetics were evaluated through blood sampling, vital sign monitoring, electrocardiograms (ECGs), laboratory testing and pharmacokinetic analysis performed at regular intervals. This trial is registered with ClinicalTrials.gov, number NCT06278389.

Results: Among the participants receiving ACC017 (5 to 120 mg), six subjects (22%, 6/27) reported seven adverse events (AEs) while three subjects (33%, 3/9) in the placebo group experienced four AEs. There was no statistically significant difference in the incidence of AEs between the two groups. All observed AEs were mild (Grade 1) and resolved spontaneously without intervention. Pharmacokinetic analysis showed that the average maximum plasma concentration (C_{max}) of ACC017 was 193.7, 926.0, 900.8, 1671.7 and 2055.5 ng/mL across dose levels. The corresponding average area under the plasma concentration-time curve

from time zero to infinity (AUC_{0-∞}) values were 3191.7, 15252.4, 16918.9, 29286.7 and 31759.4 h*ng/mL. Both C_{max} and AUC_{0-∞} exhibited less than dose-proportional increases were observed. The median time to peak concentration (T_{max}) ranged between 2 and 4 hours with mean terminal half-life of 10.5 to 13.1 hours.

Discussion: ACC017 demonstrated good tolerability and dose-dependent, nonlinear pharmacokinetics. The inhibitory quotient (IQ), defined as the ratio of the clinical trough concentration (C_{24h}) to the protein-binding adjusted 90% effective concentration (pa-EC₉₀), was 3.2 to 29.8 for ACC017 at doses of 5 to 80 mg. These findings suggest that a once-daily oral dosing regimen of ACC017 at low doses may achieve therapeutic concentrations, supporting its potential as a promising antiretroviral therapy for HIV-1 infection.



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Effect of Food on Pharmacokinetics of ACC017, A Novel HIV-1 Integrase Inhibitor, in Healthy Adult Subjects

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Background: ACC017, a novel HIV-1 integrase strand transfer inhibitor (INSTI) with potent anti-HIV activity, an in vitro resistance profile different from those of other INSTIs, and favorable preclinical safety and pharmacokinetic properties, which is being developed for the treatment of HIV-1 infection. The aim of this study was to investigate the effect of food on the single-dose pharmacokinetic properties of ACC017.

Material and Methods: A randomized, open-label, single-center, two-period crossover study was conducted in 12 healthy Chinese adults. Twelve subjects, aged between 18 and 55 years old, were randomized in a 1:1 ratio to either fasting (group A) or fed (group B) conditions. During period 1, after an overnight 10-hour fast, the subjects in group A received a single 40 mg dose of ACC017 under fasting conditions, while the subjects in group B received ACC017 40mg 30 min after a standard high-fat breakfast meal. Following a 7-day washout period, the subjects were crossed over to the opposite condition. Blood sampling, vital signs monitoring, electrocardiograms (ECGs), laboratory testing and pharmacokinetic analysis were performed at regular intervals to evaluate the effect of food on ACC017. This trial is registered with ClinicalTrials.gov, number NCT06278389.

Results: All subjects (N=12) completed the study, and none of them experienced any adverse events (AEs) or serious adverse events (SAEs) under either fasting or fed conditions. The average maximum plasma concentration (C_{max}) of ACC017 was 261.6 ng/mL in the fasting state and 447.9 ng/mL in the fed state. Food intake increased the area under the plasma concentration-time curve from zero to

the time of the last quantifiable concentration (AUC_{0-t}) from 16678.0 h*ng/mL (fasting state) to 27597.9 h*ng/mL (fed state), and the average area under the plasma concentration-time curve from time zero to infinity (AUC_{0-∞}) from 17050.0 h*ng/mL to 28037.5 h*ng/mL. The geometric mean value of C_{max} was increased by 83.90% in the fed state, as were AUC_{0-t} by 70.22% and AUC_{0-∞} by 68.98%. The median time to C_{max} (T_{max}) was 4 hours in both states. The mean terminal half-life was also similar (12.0 vs 11.5 hours).

Conclusions: This study demonstrates that a standard high-fat breakfast modestly increases the exposure to a single oral dose of ACC017 40 mg, but it did not affect the absorption rate. The exposure increases of ACC017 (68.98% to 83.90%) are not anticipated to impact safety. Clinical experience from phase IIa trials further supports this recommendation.



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The Impact of Pretreatment Drug Resistance on AINUOVIRINE-Based Antiviral Therapy in HIV-Infected Patients: A Subgroup Analysis from the RACER Study

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Background: Pre-treatment drug resistance (PDR), particularly to non-nucleoside reverse transcriptase inhibitors (NNRTIs), presents a significant therapeutic challenge in antiretroviral treatment (ART). This study aims to evaluate the virological response to ainuovirine (ANV)-based antiviral therapy in HIV-1-infected patients with NNRTI-PDR.

Materials and Methods: We conducted a PDR analysis in two cohorts of the RACER study, a randomized, double-blind, double-dummy, positive parallel group, phase 3 trial conducted in 9 sites across China. The entire pol and IN genes were amplified and sequenced using HIV genotypic resistance testing. PDR was defined as detection of any mutation (potentially, low, intermediate, or high resistant) by oligonucleotide ligation assay when confirmed by Sanger sequencing. All patients were followed up for 48 weeks to observe the virological outcomes of ART. The virological suppression was defined as plasma HIV-RNA <50 copies/mL at week 48 of ART.

Results: A total of 630 subjects were finally enrolled and randomly assigned (1:1) to either ANV (n = 315) or Efavirenz (EFV, n = 315) groups in the RACER study. Among the 593 included study participants, PDR was detected in 12.5% (n=74). Of these, 69 (11.6%) were resistant to NNRTIs and 5 (0.84%) were resistant to NRTIs. The virological suppression rates of the PDR-negative group and the ANV group with NNRTI-PDR were 88.1% (37 of 42) and 88.8% (239 of 269) respectively, which were significantly higher than those in the EFV group with NNRTI-PDR (74.1%, 20 of 27).

Conclusion: ANV exhibits significantly better antiviral activity compared to EFV, and the prevalence of PDR negatively impacts the outcomes of ANV-based ART. Considering the additional safety advantages of ANV over EFV, ANV is recommended for patients with NNRTI-PDR.

