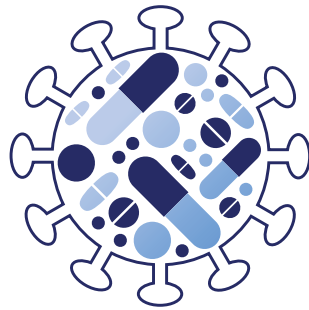# INTERNATIONAL WORKSHOP ON CLINICAL PHARMACOLOGY 2023

OF HIV, HEPATITIS AND OTHER ANTIVIRAL DRUGS

HYBRID WORKSHOP
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ABSTRACT BOOK

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International Workshop on Clinical Pharmacology of HIV, Hepatitis, and Other Antiviral Drugs 2023

11-13 September 2023
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Abstracts Oral Presentations

1

Antiretroviral Drug Exposure and Response in Obese and Morbidly Obese People with HIV

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Background: Obesity is increasingly prevalent among people with HIV (PWH) and can result in suboptimal antiretroviral drug (ARVs) exposure and response. However, this has not been thoroughly evaluated since obese PWH are underrepresented in clinical trials which constitutes an important knowledge gap given that several first-line ARVs have been associated with weight gain. Physiologically based pharmacokinetic (PBPK) modelling can be used to study pharmacokinetics in special populations. The objective of this study was to perform virtual trials using PBPK modelling combined with therapeutic drug monitoring (TDM) data and corresponding viral load from PWH enrolled in the Swiss HIV Cohort Study (SHCS) to determine ARV exposure and response in obese and non-obese PWH and provide dosing guidance.

Methods: The in-house PBPK framework, implemented with our previously verified virtual White obese population, was used with TDM data for 11 contemporary ARVs to verify the predictive performance of the model. The ARVs models were subsequently applied to predict the pharmacokinetics for 6 BMI categories (up to BMI of 60kg/m²). Finally, the clinical relevance of obesity on drug response was evaluated by calculating the proportion of obese and non-obese individuals with trough ARV concentrations below the target threshold and with a viral load above >50 copies/mL.

Results: The PBPK framework correctly predicted the pharmacokinetics of all evaluated ARVs with ~80% of the simulations being within 1.25-fold of observed TDM data. The model predicted an average reduction of ~20% in the exposure (AUC) and ~6% in trough concentrations (Cτ) of ARVs in obese (BMI >30 kg/m²) compared to non-obese (BMI 18.5-25 kg/m²) consistent with the observed clinical data. When considering AUC, the most impacted ARV was etravirine with a 50% reduction for the highest BMI category (50-60 kg/m²). Regarding Cτ, the simulations showed no significant decrease across all BMI categories for darunavir/ritonavir, doravirine and emtricitabine thus resulting in a limited number of obese individuals with Cτ below the efficacy target threshold. The Cτ of the remaining ARVs was predicted to be reduced. For etravirine and rilpivirine, this reduction led to more individuals with Cτ below the efficacy target threshold from ~10% (BMI category: 18.5-25 kg/m²) to ~40% (BMI >40 kg/m²). The SHCS data were mostly available for obese with a BMI of 30-35 kg/m² and showed that obese individuals did not have a higher rate of viral load above 50 copies/mL compared to non-obese individuals which is consistent with the simulated modest changes in ARV pharmacokinetics in this BMI class.

Conclusions: Obesity lowers the exposure of ARVs, nevertheless the minimal concentrations were maintained above the target threshold except for etravirine and rilpivirine in morbidly obese individuals in whom TDM is advised. SHCS data indicated comparable rates of viral load >50 copies/mL in obese compared to non-obese PWH. Thus, dose adjustment of ARVs is a priori not needed in obese PWH. Our data provide reassurance that substantial weight gain in some individuals on treatment with integrase inhibitors and/or tenofovir alafenamide is unlikely to result in suboptimal drug exposure and response.

2

Pharmacokinetic Data of Atazanavir/Ritonavir in Second-line Treatment of Children Living with HIV: Results from the CHAPAS4-trial.

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Background: Atazanavir/ritonavir (ATV/r) is recommended by the WHO for children as a preferred bPI for second-line treatment. Its advantages over lopinavir/ritonavir (LPV/r) are that it can be taken once-daily, has fewer gastrointestinal side-effects and a more favorable lipid profile. ATV/r has been evaluated in African children enrolled in the randomized controlled CHAPAS4 trial (#ISRCTN22964075), where second-line treatment options for children with HIV were investigated. We did a nested PK substudy within CHAPAS4 to evaluate the ATV/r exposure in children with HIV taking once-daily ATV/r as part of their second-line treatment.

Methods: Children living with HIV aged 3 - 15 years failing first-line antiretroviral therapy (ART) were randomized to dolutegravir, atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir in combination with a backbone of emtricitabine/TAF versus standard-of-care nucleoside reverse transcriptase inhibitor combination. Participants in this PK substudy signed additional consent. Children weighing 14 – 24.9 kg received 200/75 mg ATV/r and children ≥25 kg received 300/100 mg ATV/r, as fixed-dose-combination formulations. At steady-state, ATV/r plasma PK samples were taken at t=0 (pre-dose), 1, 2, 4, 6, 8, 12, and 24 hours after observed ATV/r intake with food. ATV/r concentrations were measured using a validated high performance liquid chromatography bioanalytical quantification method. The primary pharmacokinetic parameters were the area under the concentration-time curve over the dosing interval (AUC0-24h), maximum concentration (Cmax), and the trough concentration 24 h after intake (Ctrough) and were calculated by means of non-compartmental analysis. Reference adult PK data were used for comparison. The individual target trough concentration (Ctrough) was defined as 0.15 mg/L (EC90). Statistical analysis was performed using ANOVA on log-transformed values with Tukey post hoc analysis to check for differences in ATV/r AUC0-24 and Ctrough in the different weight-bands and NRTI backbones.

Results: In total 61 children were included in this substudy. Seven children were excluded due to non-adherence, a high RTV dose due to shortage of RTV 25 mg or due to the dose taken at the wrong time, leaving 54 eligible pharmacokinetic profiles to evaluate. There were 7 children in the 14 – 19.9 kg weight band; 16 in 20 – 24.9 kg; 18 in 25 – 34.9 kg and 13 in >35 kg. In the whole study population, the Geometric Mean (GM), (CV%) AUC0-24h was 44.3 mg*h/L (47%) and GM (CV%) Cmax was 4.6 mg/L (47%), which is comparable to the adult reference AUC0-24h and Cmax. The AUC0-24h was significantly higher in children weighing 25 – 34.9 kg (61.1 h*mg/L) compared to children in the 14 – 19.9 kg and 20 – 24.9 kg weight-bands (34.1 and 33.2 h*mg/L, respectively).; p-values < 0.05. There was no difference in AUC0-24h when comparing the different backbones. The GM (CV%) Ctrough was 0.48 mg/L (70%), which is below the adult reference Cmin (0.64 mg/L), but the Ctrough target (0.15 mg/L) was achieved in all subjects.

Conclusions: This nested PK substudy shows that the exposure of ATV/r taken with food in children 3 – 15 years of age weighing ≥ 14 kg on second-line treatment is comparable to adult reference data.

3

Preliminary Results of Therapeutic Drug Monitoring of Long-Acting Cabotegravir and Rilpivirine in Large National Cohort of HIV-1 Infected-Patients (ANRS-MIE-CARLA Study)

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Background: The combination of intramuscular (IM) Rilpivirine (RPV 900mg) and Cabotegravir (CAB 600mg) is the first approved long-acting (LA) regimen for the maintenance treatment of HIV-1 infection. Low plasma concentrations (Cpl) of CAB and RPV 4 weeks after the first injection (M1) were associated with virological failure in clinical trials as well as a high BMI or A6/A1 HIV-1 subtypes (Cutrell AG et al, AIDS 2021). Since, pharmacokinetics real-life data are still limited.

Here we describe RPV and CAB Cpl determined from routine therapeutic drug monitoring (TDM).

Patients and Methods: We conducted a multicenter (n=12) and observational study in patients treated with LA CAB-RPV regimen, for whom RPV and/or CAB Cpl were determined as routine TDM from January 2022 to December 2022. Prior to initiation, an undetectable plasma HIV-1-RNA, sensitive genotype to CAB/RPV according to www.hivfrenchresistance.org (October 2022, V33), HBV co-infection and drug-drug interaction were verified during multidisciplinary meetings. The needle length was adjusted according to the patient's BMI (obesity >30 kg/m2). Immuno-virological, therapeutic (last ART treatment/comedications) and clinical data were collected at baseline and during the follow-up. RPV and CAB Cpl were reported at M1 (4 weeks after the loading doses) and M3 (8 weeks after the maintenance doses) using median values [IQR, CV%]. Suboptimal CAB and RPV Cpl were determined using threshold values of 1,120 ng/mL and 32 ng/mL, respectively, corresponding to the 1st quartile of Cpl at M1 of the pooled phase 3 multivariate data analysis. Description and statistical analyses were performed using R software v 4.2.2 with non-parametric tests.

Results: We included 616 patients: median age of 46 years, 80% of male, 11% obese and 31% overweighed. HIV-1 subtype was available for 69% of patients (60% B; 1.2% A1/A6). Overall, 54% received an oral lead-in (OLI). Median treatment follow-up was 12.4 months. A total of 1,550 RPV and 1,544 CAB Cpl were collected. M1 and M3 median CAB Cpl were 1,838 ng/mL (1,211-2,646 ng/mL, 66%, n=521), and 1,625 ng/mL (1,094-2,201 ng/mL, 57%, n=429), with respectively 23% and 26% of patients below the 1,120 ng/mL threshold. M1 and M3 median RPV Cpl were 49 ng/mL (34-71, 62%, n=523), and 48 ng/mL (34-68, 64%, n=429), with respectively 22% and 20% of patients below the 32 ng/mL threshold. No difference both in CAB/RPV median Cpl and in the proportion of patients with suboptimal exposure was observed between patients treated or not with OLI. During the follow-up, 20% of the patients presented recurrent suboptimal RPV and/or CAB Cpl.

Conclusions: Our study is the first to describe RPV and CAB Cpl following IM regimen in a large cohort of patients. We have observed a significant inter-patient variability, with a moderate proportion of suboptimal Cpl in accordance with FLAIR and ATLAS studies. However, recurrent suboptimal Cpl

were observed during the follow-up for about 1/5 of patients. For a better understanding, we plan to develop mathematical models to quantify and explain the pharmacokinetic variability as well as to describe the virological failures.

4

Abstract number 4 has been withdrawn.

5

Intracellular Tenofovir-Diphosphate Concentrations with Tenofovir Alafenamide During Pregnancy and Postpartum in People with HIV: Results from IMPAACT 2026

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Background: Intracellular NRTI concentrations are strongly correlated with efficacy, adherence, and other clinical outcomes; however, these data are limited in pregnancy. Here we report TFV-DP concentrations in PBMCs (TFV-DP(PBMC)) and dried blood spots (DBS) (TFV-DP(DBS)) in pregnant and postpartum people with HIV receiving TAF.

Methods: IMPAACT 2026 is a phase IV prospective, open-label, non-randomized, opportunistic study. Pregnant women receiving unboosted TAF 25 mg as part of clinical care were eligible. PK assessments occurred in the second (2T) and third trimesters (3T), and 6-12 weeks postpartum (PP). Blood samples for intracellular PK were collected pre-dose, 3-, and 24-hours post-dose. DBS was spotted pre-dose, and PBMCs were isolated at all time points. Maternal and cord blood samples were collected at delivery. Infant washout DBS samples were collected starting 2-10 hours through 5-9 days after birth. TFV-DP was quantified using LC-MS/MS. TFV-DP(DBS) was quantified from 2x7mm punches. TFV-DP(PBMC) was normalized to 10^6 cells and reported as a pooled average in 2T, 3T, and PP. Within-participant comparisons between 2T or 3T and PP used geometric mean ratios (GMR) with 90% confidence intervals (CI).

Results: Twenty-eight participants were enrolled (14 2T and 14 3T). Median (interquartile range; IQR) age was 29 (25, 34) years; 50% Black, 14% white, 11% Asian; 39% Hispanic/Latina; and 89% US and 11% Thailand. 13/14 (93%) and 26/28 (93%) participants were virally suppressed (<200 copies/mL) in 2T and 3T, respectively, 25/28 (93%) at delivery, and 25/28 (89%) in PP. No infant HIV infections were observed (2 unevaluable). Median (IQR) of the pooled TFV-DP(PBMC) were 407 (312, 547), 435 (324, 577), and 412 (255, 506) fmol/106 cells for 2T, 3T, and PP, respectively, and did not significantly differ between 2T or 3T vs. PP (n=9 and 20 paired, respectively). Median (IQR) TFV-DP(DBS) were 580 (511, 925), 869 (589, 1128), and 1253 (392, 1798) fmol/punches for 2T, 3T, and PP, respectively. TFV-DP(DBS) for 2T vs. PP did not significantly differ (-1.0% (-33%, 48%); n=9 paired) but were 26% lower in 3T vs. PP (-37%, -12%; n=19 paired). 9/13 TFV-DP(PBMC) and 15/15 TFV-DP(DBS) cord blood samples were quantifiable. Median (IQR) cord/maternal blood ratio of TFV-DP(PBMC) and TFV-DP(DBS) were 0.047 (0.011, 0.066) and 0.26 (0.24, 0.36), respectively. Median (IQR) TFV-DP(DBS) in infants were 341 (263, 420) at 2-10 hours, 302 (152, 406) at 18-28 hours, 285 (171, 429) at 36-72 hours, and 207 (111, 271) at 5-9 days post-birth. No maternal AEs and one infant AE (Grade 1 tooth development disorder) were related to TAF.

Conclusion: TFV-DP(DBS) was lower in 3T compared to PP, whereas TFV-DP(PBMC) did not significantly differ between 2T or 3T and PP. In comparison to historical data in non-pregnant adults on TAF 25 mg daily, TFV-DP(DBS) and TFV-DP(PBMC) concentrations were lower during 2T, 3T, and postpartum. However, TFV-DP(PBMC) with TAF during pregnancy and postpartum were ~5-fold above concentrations in non-pregnant adults on TDF 300 mg daily, suggesting differences are likely not of clinical concern. Further investigation of factors affecting intracellular TFV-DP in pregnancy and postpartum is warranted.

6

Temporal Changes in Dolutegravir and Raltegravir Glucuronide Metabolite to Parent Ratios during Pregnancy and Postpartum

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Introduction: Dolutegravir (DTG) and raltegravir (RAL) based-antiretroviral treatment (ART) are preferred options for pregnant women living with HIV. DTG and RAL are primarily metabolized via uridine diphosphate-glucuronosyltransferase (UGT)-1A to glucuronide metabolites (i.e., DTG-Glu and RAL-Glu), with DTG having a minor metabolic pathway via CYP3A4. Temporal changes in metabolic enzyme activities during pregnancy can impact drug clearance. Indeed, lower DTG and RAL exposures were observed during pregnancy vs. postpartum but these changes did not warrant dose adjustments. Limited data are available supporting the hypothesis that induction of metabolic enzymes during pregnancy is a driver of reduced DTG and RAL exposures. To provide further insight into the relative impact of UGT1A1 induction on drug metabolism during pregnancy, our aim was to quantify the glucuronide metabolite-to-parent ratios of DTG and RAL during the second (2T) and third trimesters (3T) of pregnancy and postpartum (PP).

Material and Methods: Stored plasma samples were analyzed from the International Maternal Pediatric Adolescent AIDS Clinical Trial (IMPAACT) P1026s study (NCT00042289), a phase IV trial investigating the safety and pharmacokinetics (PK) of ARVs and related drugs during pregnancy and postpartum. Intensive PK samples from women receiving DTG 50 mg once daily or RAL 400 mg twice daily as part of their clinical care during 2T, 3T and PP were included. Quantification of RAL-Glu and DTG-Glu metabolites was performed using validated LC-MS/MS assays. Parent drug concentrations were utilized from the original primary analysis of the data. Within-subject metabolite-to-parent (DTG-Glu/DTG) area under the curve (AUC) ratios during the 2T vs. PP and 3T vs. PP were compared using Wilcoxon signed-rank test.

Results: A total of 49 women were included, 21 receiving DTG and 28 RAL. Median (range) age was 31 (19-42) years. PK sampling at 2T, 3T and PP was available in 11, 21 and 21 women for DTG and 10, 28 and 28 women for RAL. PK sampling was performed at a median (range) gestational age of 24 (20-26) weeks during 2T and 33 (30-39) weeks during 3T; and PP PK sampling was 9 (3-14) weeks after delivery.
Median (range) molar DTG-Glu/DTG AUC_{0-24} ratios during 2T, 3T and PP were 0.038 (0.016-0.094), 0.042 (0.023-0.125) and 0.032 (0.016-0.099), respectively. Within-subject ratios were not significantly higher 2T vs. PP (p=0.83, n=11) but trended towards higher 3T ratios vs. PP (p=0.06, n=21). Median (range) molar RAL-Glu/RAL AUC_{0-12} ratios during 2T, 3T and PP were 0.496 (0.344-0.822), 0.676 (0.303-1.633) and 0.410 (0.107-1.194), respectively. Within-subject ratios were numerically but not significantly higher at 2T vs. PP (p=0.13, n=10) and significantly higher at 3T vs. PP (p<0.001, n=28).

Conclusion: Pregnancy-associated induction of UGT1A1 activity in late pregnancy impacted the metabolism of RAL, and to a lesser extent DTG. Information on the induction of metabolic enzymes during pregnancy can help support extrapolation of pregnancy-specific PK models for novel ARVs as well as and other drugs metabolized via similar enzyme pathways.

7

Lower Exposure to Bictegravir in Third Trimester in Pregnant Women Living with HIV

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Background: Antiretroviral treatment in pregnant women living with HIV serves to reduce the risk of mother to child transmission of the virus, but also to guarantee maternal health. Due to physiological changes during pregnancy, drug concentrations may be altered, whereby drug efficacy might be hampered. The aim of this study was to compare the pharmacokinetic profile of bictegravir – an integrase inhibitor which is increasingly being used in the treatment of HIV - during the third trimester of pregnancy and in a non-pregnant state.

Methods: In this multicentre, open-label, non-randomized trial pregnant women living with HIV and using a bictegravir containing regimen were included. Pharmacokinetic sampling (t = 0, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours) was performed in the third trimester and 4-6 weeks postpartum. If possible, cord blood and maternal plasma at the delivery date were also collected. Plasma concentrations were determined with the use of LC-MSMS. Pharmacokinetic parameters were determined with noncompartmental analysis. To evaluate the influence of pregnancy on the pharmacokinetics of bictegravir, a linear mixed-model (with pregnancy as fixed-effect and random effect for participant) was used on the log transformed pharmacokinetic parameters to calculate the geometric mean ratios and 90% confidence interval (CI). Bictegravir trough levels were compared to the protein-adjusted IC95 (PA-IC95) value of 0.162 mg/L. In addition, clinical efficacy and safety outcomes were collected.

Results: 6 women were included, from whom 6 third trimester and 5 postpartum curves were obtained. The median (IQR) age was 35.00 (32.8 - 35.0) years. The geometric mean (CV%) in third trimester for AUC0-24, Cmax, Ctrough, and T1/2 was 51.0 (21) h*mg/l, 4.3 (21) mg/l, 1.0 (34) mg/L and 11.0 (22) (h) respectively. The geometric mean ratio third trimester versus postpartum (90% CI) of AUC0-24, Cmax, Ctrough,,and T1/2 were 0.56 (0.41-0.77), 0.68 (0.50-0.92), 0.38 (0.29-0.49) and 0.56 (0.45-0.71) respectively. None of the bictegravir trough levels were below the PA-IC95. The median (IQR) gestational age in weeks at delivery was 41.1 (41.0-41.7). No virologic failure or mother to child transmission occurred in this cohort. Three cord blood concentrations were obtained, the cord blood:maternal plasma ratios were: 0.65, 1.42 and 1.49 respectively. No congenital abnormalities were reported.

Discussion/Conclusion: The lower exposure to bictegravir in third trimester compared to postpartum might be attributed to increased hepatic clearance trough CYP3A4 and UGT1A1. Despite the decrease, bictegravir trough levels remained above the PA-IC95 and no virological failure or mother-to-child transmission occurred. More data are needed to confirm our findings.

8

Prediction of Maternal Pharmacokinetic of Bictegravir in Pregnancy Using Physiologically-Based Pharmacokinetic Modeling

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Background: Bictegravir (BIC) is used as part of a three-drug combination regimen for the treatment of HIV in adults and pediatric patients who have no previous antiretroviral (ARV) treatment history or to replace the current ARV regimen in those who are virologically suppressed on a stable ARV regimen (1). BIC is primarily metabolized by Cytochrome P450 3A4 (CYP3A4) and UDP Glucuronosyltransferase 1A1 (UGT1A1) and is highly protein-bound (>99%) (2,3). Increased UGT1A1 and CYP3A4 mediated metabolism, and reduced protein binding during pregnancy may impact the pharmacokinetics (PK) and appropriate therapeutic dosing of BIC in pregnant patients (4,5).

Purpose: To characterize the PK of BIC in pregnancy using physiologically-based pharmacokinetic (PBPK) modeling approach.

Method: The whole-body BIC PBPK model in non-pregnant virtual subjects was constructed in Simcyp by incorporating physiochemical and drug-specific parameters. The model was calibrated and validated with clinically observed PK data from phase 1 studies. The optimized model parameters were applied to pregnancy PBPK model to evaluate the PK in 2nd and 3rd trimester (2T, 3T) population. Albumin, Alpha-1 acid glycoprotein, and hematocrit levels of people living with HIV (PLWH) during pregnancy were adapted from IMPAACT p1026s and incorporated as system parameters. Predictions in pregnancy were compared with clinical PK data in pregnant participants with HIV from International Maternal Pediatric Adolescent Aids Clinical Trials (IMPAACT) 2026 study (6).

Results: Predicted exposures (Cmax and AUCinf) of BIC in non-pregnant and pregnant subjects are comparable to the clinical observations from IMPAACT 2026 study. The BIC model predicted Cmax and AUC reduction of 27% and 41% in 2T and 34% and 49% in 3T, respectively, compared to nonpregnant participants. In comparison, Cmax and AUC reduction of 51% and 58% in 2T and 55% and 50% in 3T, respectively, were observed in IMPAACT 2026 study (6).

Conclusion: The mechanistic PBPK model predicted that BIC exposure will be reduced during 2T and 3T of pregnancy, although it underpredicted the magnitude of the reduction observed in the IMPAACT study. The result suggests that PBPK modeling can be an effective tool to predict drug exposure during pregnancy; in this example, to predict potentially low drug exposure during pregnancy that may lead to lack or loss of virologic response. Further assessments are required to determine the relevance of reduced BIC exposure during pregnancy.

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Physiologically Based Pharmacokinetic Modeling of Lenacapavir Pharmacokinetics and Model Validation with Drug-Drug Interactions Between Lenacapavir with Voriconazole or Rifampicin

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Introduction: Lenacapavir (LEN) is a first-in-class capsid inhibitor approved for treating adults with multidrug resistant HIV-1, in combination with other antiretrovirals. Key LEN properties include low solubility, low membrane permeability, high protein binding, majorly excreted unchanged in feces and a substrate of P-glycoprotein (P-gp), CYP3A, UGT1A1. A physiologically based pharmacokinetic (PBPK) model was developed to describe LEN pharmacokinetics (PK) and drug-drug interactions (DDIs) with voriconazole and rifampicin.

Methods: A LEN PBPK model was developed using GastroPlus® v9.8.3. LEN physicochemical and biopharmaceutical properties were defined using in silico and in vitro data. Key assumptions included intestinal absorption (passive diffusion) and carrier-mediated efflux (P-gp-mediated intestinal secretion), tissue distribution limited by blood flow, and elimination via CYP3A- and UGT1A1-mediated metabolism. Kinetic parameters for LEN interactions with enzymes and P-gp were fitted against in vivo human data. Simulating LEN PK data from human studies involved matching (age, weight, BMI, sex, food status). LEN tissue distribution and total systemic clearance PBPK model settings were calibrated using in vivo data (healthy volunteer [HV] study; LEN single intravenous dose, 10 and 20 mg). Dissolution and absorption settings were calibrated using data from another HV study (LEN tablets single oral dose 50–900 mg). DDIs were simulated using standard voriconazole and rifampicin models to replicate human studies. Model simulations were compared with observed LEN data.

Results: In the final model, average prediction errors across simulated LEN single dose Cmax and AUCinf were 26% and 13% (intravenous), and 22.4% and 14% (oral), respectively. The model adequately captured LEN PK parameters, dose dependency and food effect; predicted Cmax and AUCinf, respectively, were within 0.74–1.03-fold and 1.12–1.13-fold of observed data for intravenous LEN, and within 1.09–1.39-fold and 0.82–1.15-fold of observed data for oral LEN in fasted and fed states. Model validation involved simulating LEN exposure (single oral 300 mg dose) with/without voriconazole or rifampicin and comparison with observed data from a HV study. Simulated-to-observed ratios for LEN alone were 1.82 (Cmax) and 1.24 (AUCinf). Higher prediction errors could be due to interstudy variability in observed data. The resulting PBPK model was able to predict voriconazole and rifampicin impact on LEN PK. For voriconazole-LEN interaction, LEN AUCinf DDI ratios were 1.51 (simulated) and 1.41 (observed), and Cmax ratios were 1.10 (simulated and observed), consistent with CYP3A inhibition. For rifampicin-LEN interaction, LEN DDI ratios (simulated/observed) for AUCinf were 0.14/0.15, and Cmax were 0.45/0.18, respectively, consistent with CYP3A and P-gp induction along with P-gp inhibition effects.

Conclusions: The developed PBPK model captured LEN PK data and was consistent with observed data in HV following intravenous or oral LEN doses. The final model was able to predict DDIs between LEN and voriconazole suggesting that LEN elimination pathways were captured well. The prediction of Cmax with rifampicin may require further refinement as the simultaneous contribution of CYP3A and P-gp induction along with P-gp inhibition is a very complex process. This PBPK model can be utilized to predict potential DDIs between LEN and other drugs of clinical relevance.

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Dolutegravir but not Bictegravir Exposure Increases in Vitro Platelet Aggregation

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In the modern era of effective antiretroviral therapy (ART), people living with HIV (PLWH) have near-normal life-expectancies but two-times higher occurrence of cardiovascular disease (CVD). Although CVD is associated with some antiretrovirals, little is known about off-target effects of integrase inhibitors (INSTIs) on platelets, key players in CVD risk and progression. Here, we compared how two common INSTIs, bictegravir (BIC) and dolutegravir (DTG), alone or in their ART drug regimens, affect platelet activation, in an effort to better understand CVD risk in PLWH.

Platelets were isolated from whole blood obtained by informed consent from HIV-negative donors (60% male, aged 25 ±3 yrs). Platelets were exposed in vitro to clinical plasma Cmax concentrations of antiretrovirals and vehicle (Veh) control for 30min. Platelet activation was assessed in response to collagen [1-30μg/ml], ADP or thrombin receptor activator peptide (TRAP)-6 [1-30μM] by light transmission aggregometry and flow cytometry. Platelet adhesion on collagen under physiological flow was also measured upon INSTI exposure in vitro. Results were analysed using 1- or 2-way ANOVA with a Tukey's multiple comparison test.

DTG treatment induced significantly higher ADP-evoked platelet aggregation compared to BIC (+1.49-fold, $p=0.0231$) and Veh (+3.6-fold, $p=0.0062$) at low ADP concentrations. Collagen-activated platelets [3μg/ml] exposed to DTG had +1.94-fold higher percentage aggregation compared to Veh group ($p=0.0042$). Significant differences were conserved upon combinaton ART regimen treatments.

Our results suggest DTG, alone or in clinical ART combinations, may sensitize platelets to low-level ADP and collagen stimulation. This may indicate DTG, but not BIC, has the potential to increase CVD risk. Further evaluation of platelet activation in vivo and in clinical settings is required to validate our findings. Ultimately, this work may lead to identifying drug regimens with a lower CVD risk, allowing personalised options when treating PLWH.

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Genetic Variants Influencing Neuroinflammation Biomarkers in Different Clinical Groups of People Affected by HIV

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Background: Human immunodeficiency virus penetrates the central nervous system (CNS), leading to neuroinflammation, even though antiretroviral treatment efficiently suppresses virus replication. Neurocognitive decline is associated with several inflammatory-related markers, such as total tau (t-tau), its phosphorylated form (p-tau), β-amyloid-1,42 (Aβ-1,42), S100 calcium-binding proteinβ (S100β) and neopterin (neo).
ABC transporters are localized in the blood brain barrier (BBB), regulating the movement of endogenous and exogenous compounds. Genetic-based alterations in the activity of these transporters could probably impact on neuroinflammation and neurocognitive impairment.
No data are available in the literature concerning variants of genes encoding transporters on neurocognitive impairment features in people living with HIV (PLWH).
For these reasons, the aim of this study is to investigate the role of genetic variants in affecting neuroinflammation biomarkers.

Materials and methods: Adult PLWH who underwent a lumbar puncture for clinical reasons were enrolled. T-tau, p-tau, β-1,42, S100β and neo were quantified in cerebrospinal fluid (CSF) with immunoenzimatic tests, whereas genetic variants through real-time PCR.CSF/serum albumin ratio (CSAR) was considered as an indirect marker of the BBB integrity.

Linear regression analyses were performed according to Bonferroni correction ($p < 0.005$) in order to evaluate which demographic, clinical, viral and genetic factors correlated with the different neuroinflammation biomarkers. Only statistical significant values in univariate model were considered in the multivariate one.

Results: 161 patients (73% males) with median age of 48.5 years were enrolled. Patients were stratified in 5 groups as follows: asymptomatic (34.8%), neurological symptoms with unknown etiology (12.4%), HIV-associated neurocognitive disorders (HAND, 18%), HIV-related CNS disorders (17.4%) and other disorders (e.g. cancer, 17.4%). By linear regression analyses, CSAR ($p < 0.001$, OR 0.720, IC95% 0.486; 0.953) and ABCG21194+928CC ($p = 0.001$, OR 6.700, IC95% 2.752; 10.647) were associated with neo in the univariate model, whereas CSAR ($p < 0.001$, OR 0.679, IC95% 0.451; 0.908) and ABCG21194+928CC ($p = 0.003$, OR 5.454, IC95% 1.853; 9.056) were the only factors retained in the multivariate one. Viral load for t-tau ($p < 0.001$, OR 7.84×10^{-5}, IC95% 4.2×10^{-5}; 11.5×10^{-5}) and S100β ($p < 0.001$, OR 11.1×10^{-5}, IC95% 6.1×10^{-5}; 16.1×10^{-5}) and HAND clinical group for β-1,42 ($p = 0.003$, OR 157.164, IC95% 52.720; 261.607) remained in the different univariate models, respectively. No factors were retained for p-tau levels.

Conclusions: to the best of our knowledge, we have for the first time showed transporter genetic variants association with inflammation markers: genetics chronically influences drug penetration, but the role in affecting neuroinflammation has to be clarified in further studies.

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Nirmatrelvir/Ritonavir Real World Drug-Drug Interaction Management Experience.

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Introduction: Paxlovid – a combination of nirmatrelvir/ritonavir (NMV/r) is a treatment of early mild-moderate SARS-CoV2 infection, not requiring hospitalisation for those at high-risk of progression. Ritonavir potentiates the risk of drug-drug interactions (DDIs) due to inhibition of a number of cytochrome P450 (CYP) enzymes, in particular CYP3A4. This necessitates the need for a medication review when prescribing Paxlovid. Infectious diseases and general practice physicians are resultantly building systems to record and assess patients' co-medications as well as implement strategies in mitigating potential DDIs. Agreed national audit standards for Paxlovid administration and risk assessment are lacking.

Methods: A service evaluation was conducted at the Chelsea and Westminster Hospital in London, UK between September 19th and December 14th, 2022. Patient data were obtained from pharmacy databases and electronic patient records. The aim was to assess identified potential DDIs and their management in adult patients with non-severe COVID-19 at high risk of hospitalization, excluding pregnant and breastfeeding women. Potential interaction identification and risk stratification was carried out based on "covid19-druginteractions.org" guidance and/or SmPC review. This included identifying and determining the severity of DDIs through a traffic light system; significant DDIs were defined as red (avoid co-administration) and amber (potential interaction that may require management), whilst minor DDIs were coded as yellow (potential weak interaction). Documented advice regarding the above interactions was also reviewed, such as advice to continue, hold, or to review medication risks.

Results: This analysis included 410 COVID-positive patients. Amongst the 208 who received Paxlovid, 128/208 (62%) of patients had potential interactions identified. 14/128 (11%) of patients with any documented interaction had a red-classified interaction i.e., interactions which precluded co-administration (the most common three drugs were simvastatin at 50%, salmeterol at 21% and eplerenone at 7%), 66/128 (52%) of patients had amber i.e., having a potential for interaction (the most common three drugs were atorvastatin at 20%, rosuvastatin at 15% and amlodipine at 12%), and 65/128 (52%) had yellow i.e., weak interaction potential recorded (the most common three drugs were hydroxychloroquine at 16%, amitriptyline at 13% and codeine at 8%). Notably, 8/14 (57%) of red co-medication interactions and 47/84 (56%) of amber co-medication interactions lacked documented advice to hold therapy, while 6/14 (43%) patients with documented red interactions and 28/84 (33%) of the amber interactions received advice to hold the interacting co-medication, most notably simvastatin, atorvastatin and rosuvastatin. Additionally, 5/84 (6%) of amber interactions had documented discussion on the risks of taking the co-medication/the potential risk of interaction with Paxlovid.

Discussion: This analysis highlights the need for development of standards for the assessment and management of potential DDIs involving Paxlovid. This is especially crucial as Paxlovid becomes increasingly used within both primary and secondary care settings, requiring a robust implementation and DDI mitigation strategy. Documentation practices regarding DDI management showed room for improvement, emphasizing the importance of developing guidelines and audit standards to optimize DDI assessment and management in high-risk COVID-19 patients.

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A Retrospective Descriptive Study of the Management and Consequences of Drug-Drug Interactions between Nirmatrelvir/Ritonavir and Systemic Treatment for Cancer

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Background: Nirmatrelvir/ritonavir (NMV/r) is a combination oral anti-viral agent, used for treatment of Covid-19 in patients at high risk for progression to severe disease. Ritonavir strongly inhibits CYP3A, increasing toxicity of drugs metabolized by this enzyme. Safe administration of NMV/r in patients on systemic treatment for cancer is challenging due to the narrow therapeutic window of cancer therapies. A 2022 analysis of queries in the Liverpool COVID-19 Interaction Checker indicated more than 50% of queried interactions between NMV/r and cancer therapies were clinically significant.[1] Despite the high burden of significant interactions, information regarding the real-world management of interactions between NMV/r and systemic cancer therapies is limited.
We aimed to describe incidence, management, and consequences of clinically significant drug-drug interactions (csDDIs) between NMV/r and systemic cancer therapies in the real world.

Methods: This was a single-centre, retrospective study at the Cancer Centre of South Eastern Ontario between April 14, 2022 and February 28, 2023. Drug interactions were considered clinically significant if either the Liverpool COVID-19 Interaction Checker[2] or the University Health Network/Kingston Health Sciences Centre management recommendations[3] recommended not to co-administer, or for dose adjustment or increased monitoring. These were compared to pharmacist recommendations to determine appropriateness. Where increased toxicity was expected, clinic notes and nursing assessments were screened for new or worsening toxicities.

Results: Forty csDDIs were identified in 66 patients. Patients were older adults (71% over 60 years) with 77% receiving palliative therapy. Hematological and solid tumors were evenly represented. Over half (51.5%) of patients had at least one csDDI. In all cases the expected outcome was increased toxicity from cancer therapy. Most csDDIs were managed by holding or delaying systemic treatment (82.5%). All csDDIs except one, were managed appropriately. The top three interacting drugs were high-dose dexamethasone (22.5%), ibrutinib (17.5%) and bortezomib (10%). Thirty-three patients were included in the toxicity analysis with 27.3% experiencing a new or worsening toxicity potentially related to csDDIs. The majority (88.9%) of which were considered non-severe with one severe (grade three) toxicity identified. In this case NMV/r was administered shortly after the last dose of bortezomib, which may not have been fully cleared due to its long half-life.

Conclusions: csDDIs occurred at a high frequency, emphasizing the importance of clear drug interaction guidance and pharmacist involvement. Pharmacist-led management strategies were appropriate in almost all cases. Most toxicities related to csDDIs were non-severe and should not prevent the administration of NMV/r when indicated. Toxicities that occurred were often related to administration of NMV/r after cancer therapies with long half-lives; when drug interaction guidance recommends holding offending agents, consideration of the time to clearance of the offending agent may help to prevent these toxicities.

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Management of Drug-Drug Interaction and Safety of Oral Anticoagulants with Nirmatrelvir-Ritonavir

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Background: Oral anticoagulants (OA) are commonly prescribed medications implicated in drug-drug-interactions (DDIs) with nirmatrelvir-ritonavir. Limited information exists to guide concomitant use. The manufacturer's monograph cites inhibition of CYP3A4/P-gp and CYP2C9 induction by ritonavir may modulate the anticoagulation effect of warfarin and direct oral anticoagulants. The Ottawa Hospital Covid Clinical Assessment Centre (CAC) consisted of a multidisciplinary team serving ambulatory Covid 19 positive patients. CAC pharmacists provided recommendations on DDI management for patients on OA who were being assessed for nirmatrelvir-ritonavir treatment. Medication management recommendations were guided by The Ontario Science Table clinical decision-making framework. The CAC did not have formalized patient follow-up after initial referral leaving questions regarding how OA were ultimately managed and the safety of co-prescribing OA with nirmatrelvir-ritonavir. This quality improvement initiative aims 1) to summarize OA management for patients being considered for nirmatrelvir-ritonavir and 2) to describe safety experience with co-prescribing OA and nirmatrelvir-ritonavir.

Methods: Information on medication management was collected by CAC pharmacists through surveys. 1130 CAC pharmacist consults were screened to identify patients on baseline OA being assessed for nirmatrelvir-ritonavir eligibility between October 2022 and May 2023. Patients were contacted by telephone to answer questions related to management of DDI and safety outcomes including patient reported bleeding events, thromboembolic events and hospitalizations relating to both.

Results: Sixty-eight patients were identified, of which 55 (81%) were successfully reached via telephone. The mean age of interviewed patients was 74 years and 65% were male. Baseline OA therapy for these 55 patients was 29 (53%) apixaban, 2 (4%) dabigatran, 13 (24%) rivaroxaban, 3 (6%) edoxaban and 8 (15%) warfarin.

Twenty-eight of 55 (51%) patients on baseline OA completed a course of nirmatrelvir-ritonavir. Reasons for not using nirmatrelvir-ritonavir varied with the most common reason being DDIs with other contraindicated medications. Other reasons included pursuing alternative Covid treatments, patient/physician preference, hospitalization and procurement challenges.

For those completing nirmatrelvir-ritonavir, 21 of 28 (75%) reported changes were made to their medications before starting nirmatrelvir-ritonavir and 26 patients (93%) reported at least 2 DDI were identified. Nineteen of 28 patients (68%) continued OA therapy while completing nirmatrelvir-ritonavir but 8 of these 19 (42%) patients required either an OA dose decrease or switch to an alternative OA. Two patients had their OA therapy stopped prior to starting nirmatrelvir-ritonavir while seven patients could not recall how OA was managed. Thirteen of 28 (46%) endorsed restarting their baseline OA therapy 2 days post nirmatrelvir-ritonavir completion, 14/28 (50%) could not recall and 1 patient's OA was held due to a hospitalization unrelated to bleeding or thromboembolic events. There were no reported adverse outcomes related to bleeding, thromboembolic events or hospitalizations.

Conclusion: Approximately half of eligible patients on OA failed to receive nirmatrelvir-ritonavir therapy for the management of Covid 19. However, coadministration of OA with nirmatrelvir-ritonavir appeared safe with no reported bleeding or thromboembolic related complications in this small cohort of patients. Studies with a larger sample size are warranted to confirm the best management strategy.

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Adherence Blood Sampling Devices Are Not All Created Equal: A Comparative Investigation

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The active metabolites of Truvada® and Descovy®, tenofovir-diphosphate (TFVdp) and emtricitabine-triphosphate (FTCtp), are measured in dried blood spots (DBS) to assess long- and short-term adherence. Volumetric absorptive microsampling (VAMS) devices offer advantages over traditional DBS cards and several devices are commercially available. We evaluated three VAMS (TassoM20, TassoM50, and Mitra®) to compare resulting TFVdp and FTCtp concentrations against DBS.

Five males and 3 females living with HIV and taking emtricitabine/tenofovir alafenamide (F/TAF) as part of routine care were enrolled (IRB 08-0047). At a single visit, whole blood was collected into a 3ml EDTA tube by phlebotomy to fill a 20uL Mitra® sponge and a 50uL spot on a Whatman 903 protein-saver DBS card. These were dried for 2-5 hours at ambient temperature then stored at -80°C. At the same visit, TassoM20 (fills 4 sponges with 17.5uL each) and TassoM50 (fills 4 sponges with 43.4uL each) devices were placed on opposite arms for 3-5 minutes or until filled then stored at -80°C according to manufacturer instructions. One Mitra® sponge, 1 3mm DBS punch and 4 replicate TassoM20 and TassoM50 sponges were extracted for each participant by protein precipitation with the internal standard 13C5-TFVdp, followed by liquid-liquid extraction. Chromatographic separation was achieved using anion exchange chromatography and detected by positive TurboIonSpray on an AB Sciex API 5000 triple quadrupole mass spectrometer. The pearson correlation coefficient (ρ) was estimated using SigmaPlotv13. Tasso and Mitra® concentrations were converted to fmol/DBS punch units assuming 3uL of blood per punch and compared against published Descovy® adherence dose per week benchmarks.

While 88% of TassoM20 devices filled all 4 sponges, only 50% of TassoM50 devices filled all 4 sponges. Given this high device failure rate, TassoM50 sponge concentrations are not reported. TassoM20 intra-device %CV of the sponges ranged from 13-62% for TFVdp concentrations and 7.0-42% for FTCtp. For TFVdp, percent change (%Δ) of the individual M-20 sponges vs DBS ranged from -21-277% and results were correlated (ρ= 0.90, $p<0.001$); for FTCtp, %Δ ranged from -51-93% and were modestly correlated (ρ=0.62, $p<0.001$). For TFVdp, %Δ of the median M-20 concentration vs DBS was -15-70% and for FTCtp, %Δ was -54-49% with improved correlations (ρ =0.99, $p<0.001$ and ρ=0.73, $p<0.001$, respectively). For Mitra® concentrations vs DBS, TFVdp %Δ ranged from 9.7-23.6% with strong correlation (ρ=0.99, $p<0.001$) and FTCtp was -6.8-6.4% with strong correlation (ρ=0.94, $p<0.001$). Compared to DBS, misclassification of adherence based on TFVdp and FTCtp cut-offs was observed for 8 of 28 and 4 of 24 TassoM20 sponge values vs 1 of 8 and 0 of 8 Mitra® tip values, respectively.

This is the first comparison of three novel VAMS devices for adherence classification against DBS. TassoM50 devices were found to be unreliable at filling. TassoM20 had high intra-device variability that led to significant deviation from DBS concentrations which could lead to higher adherence misclassification. Mitra® tips provided the most consistent results with the least variability when compared to DBS. Our approach demonstrates the importance of comparative validation as new adherence monitoring devices are considered in clinical research.

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PrEP at the Site-of-Action in Transgender Women: A Pharmacology Study of Blood and Rectal CD4+ T Lymphocytes

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Background: HIV disproportionately impacts transgender women (TGW), and feminizing hormone therapy (FHT) may interact with pre-exposure prophylaxis (PrEP). The clinical relevance of this potential interaction is unknown because TGW are underrepresented in clinical trials. Quantifying PrEP's active metabolites within the site-of-action could address this knowledge gap, but safety constraints on tissue collection limit cell yields and make this difficult. Here we explore PrEP pharmacology in CD4+ T lymphocytes from blood (bCD4) and rectal tissue (rCD4) and characterize a novel surrogate of PrEP's active metabolites.

Materials/Methods: We enrolled 26 transgender or nonbinary individuals assigned male at birth in San Diego taking daily TDF or TAF with FTC for PrEP with or without FHT as follows: TDF+FHT n=10, TDF-only n=8, TAF+FHT n=7, and TAF-only n=1. Following 5 directly observed PrEP doses, participants underwent blood and high-resolution anoscopy-assisted tissue biopsy collection at a visit scheduled 17-24 hours post-dose. We isolated blood and tissue CD4+ T lymphocytes by immunomagnetic positive selection, counted (median yields=11.2e[6] bCD4 and 0.28e[6] rCD4), and lysed. Serum estradiol was measured by specific enzyme immunoassay. A portion of cell lysate was treated with sweet potato phosphatase to dephosphorylate all intracellular compounds to TFV. Resulting pooled TFV (pTFV) and TFVdp were extracted from cell lysate by protein precipitation then quantified by HPLC-MS/MS. We collapsed these data with previous rCD4 data from cisgender women (CGW) taking daily TDF+FTC (NCT03917420) to analyze pTFV-TFVdp concordance by fitting linear models (y=mx+b where x=natural log (Ln)-pTFV and y=Ln-TFVdp). Model fits were assessed by Pearson's correlation coefficient (r). Using rank-sum t-test we compared pTFV between TDF groups with or without FHT. Matched analysis was conducted for pooled emtricitabine (pFTC) and emtricitabine-triphosphate (FTCtp). Summarized data are median (min, max).

Results: Age, estimated creatinine-clearance, and body mass index were 35(20-52)years, 106(64-129)mg/dL and 27(19-45)kg/m², respectively. These did not differ by FHT group. Serum estradiol was 133(49-933) and 31(21-139)pg/ml with and without FHT, respectively. TFVdp and pTFV were quantified in 100% of bCD4 and strongly correlated (r=0.98). TFVdp and pTFV were quantified in 0% and 92% of TGW rCD4, respectively and 100% of CGW rCD4. TFVdp and pTFV in rCD4 were correlated (r=0.75). In bCD4, pTFV (fmol/10[6]cells) were: TDF+FHT=77(46-616) versus TDF-only=104(53-187), p=0.19; and TAF+FHT=537(389-1480) versus TAF-only=960. In rCD4, pTFV (fmol/10[6]cells) were: TDF+FHT=154(47-8903) versus TDF-only=416(39-780), p=1.0; and TAF+FHT=51(17-232) versus TAF-only=87. Serum estradiol was not correlated with bCD4 or rCD4 TFVdp or pTFV (r=0.07-0.12). Similarly, FTCtp and pFTC correlated between bCD4 and rCD4 (r=0.85 and 0.97, respectively) and not with serum estradiol (r=0.09-0.14).

Conclusions: This is the first report of PrEP pharmacology within TGW's rectal CD4+ T lymphocytes. While we were unable to quantify TFVdp in TGW's rCD4, we observed no differences in pTFV based on taking FHT vs not. pTFV strongly predicted TFVdp in bCD4 and rCD4 and was easily quantifiable despite smaller specimen extraction volumes. Our study was limited by small sample sizes within each treatment group precluding our ability to make statistical comparisons for TAF+FHT versus TAF-only. Even so, overlapping concentration ranges observed within each group suggest FHT should not impact PrEP efficacy in TGW.

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Saliva, Tear and Nasal PK of Ritonavir-boosted Nimatrelvir (Paxlovid) in Combination with Molnupiravir in Patients with laboratory Confirmed COVID-19

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BACKGROUND: Even with the advent of COVID-19 vaccinations, antivirals play a key role in COVID-19 therapy. It is important that antivirals are administered early during infection to avoid hospitalisation and disease progression. Potentially, combination therapy may increase potency providing robust regimens to prevent resistance emerging. Molnupiravir (MPV) and Paxlovid® (nirmatrelvir/ritonavir; NMV/r) are approved COVID-19 therapies and were studied in combination during the phase I, AGILE-CST8 trial (NCT04746183) in patients with laboratory-confirmed COVID-19. Here we report NMV PK in plasma, saliva, tears and nasal secretions.

MATERIALS & METHODS: Participants with laboratory-confirmed COVID-19 within 5 days of symptom onset were randomised 2:1 to MPV + NMV/r for 5 days (800 + 300/100 mg twice daily; 10 doses, with or without food) or standard of care (SoC) in cohorts of six (n=4 treatment, n=2 SoC). Plasma on Day 1 and plasma and non-plasma samples (saliva, tears, nasal swabs) on Day 5 were collected pre-dose (0h), 0.5, 1, 2 and 4 hours post-dose for quantification of the parent nucleoside of MPV, NHC (plasma) and NMV/r (plasma, non-plasma) by LC/MS. PK parameters were calculated (Phoenix 64, WinNonlin, v. 8.3) and NMV/r non-plasma:plasma ratios determined (RNP:P; based on AUC0-4).

RESULTS: Eight individuals [6 female at birth; median (range) age, weight, number of days with COVID-19 symptoms were 58 years (22-70), 79 kg (62-109), 4 days (3-5), respectively] received all planned doses with 80 plasma, 39 saliva/nasal and 38 tear samples included in the analysis. Day 1 geometric mean (CV%) plasma NHC AUC0-4 and Cmax were 6776 ng.h/mL (34%), 3082 ng/mL (30%) and 8248 ng.h/mL (19%), 3534 ng/mL (18%) on Day 5, which were consistent with a previous study within the AGILE platform (AGILE-CST2). Corresponding Day 1 plasma NMV were 13806 ng.h/mL (50%), 5978 ng/mL (39%) and 22704 ng.h/mL (33%), 6902 ng/mL (37%) on Day 5 with median (range) Tmax of 2.00 hours (0.50-4.00). Day 5 NMV AUC0-4, Cmax, Tmax were 30.7 ng.h/mL (44%), 10.0 ng/mL (54%), 2.00 hours (1.00-4.00) for saliva (n=7), 17036 ng.h/mL (27%), 6660 ng/mL (43%), 1.00 hours (0.50-4.00) for tears (n=6) and 15083 ng.h/mL (70%), 5434 ng/mL (76%), 4.00 hours (2.00-4.00) for nasal secretions (n=7). Associated geometric mean (CV%) NMV RNP:P were 0.18 (45%), 0.86 (20%), 0.70 (33%) for saliva, tears and nasal secretions, respectively. Ritonavir was not measured in swabs (tears/nasal); Day 5 ritonavir saliva RNP:P was 0.008 (20%). Of quantifiable NMV concentrations (Day 1 pre-dose excluded), 93% plasma and 87% saliva were above the in-vitro protein-adjusted EC90 of 292 ng/mL; 100% of swabs were above this threshold.

CONCLUSIONS: This is the first report of NMV PK in combination with MPV and at sites of SARS-CoV-2 transmission. These data suggest therapeutic concentrations were obtained in saliva and within nasal and ocular compartments, although confirmation is required in larger cohorts. Higher plasma concentrations were achieved than those reported for healthy volunteers administered single dose NMV/r (300/100 mg), however are within the range of those observed in the phase II/III EPIC-HR study. Evaluation of PK/PD relationships of this novel COVID-19 regimen are awaited.

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A Novel Approach to Identify PK Determinants of Efficacy: Implications for HIV-1 Latency Reversal by Romidepsin

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Background: Romidepsin (RMD), a histone deacetylase inhibitor, potently reverses HIV-1 latency and is being explored in kick-and-kill HIV cure strategies. The BCN02 and REDUC trials demonstrated mixed results in latency reversal with 3 weekly 4-hour 5mg/m² RMD infusions. Dose fractionation can identify pharmacokinetic (PK) determinants of pharmacodynamics (PD) to optimize clinical dosing strategies. We employed in vitro models to perform dose fractionation and identify PK determinants of HIV-1 latency reversal for RMD.

Methods: Dose fractionation was performed by culturing $0.75\text{-}1\times10^6$ cells/mL of latently infected, Jurkat-derived T-cells integrated with luciferase-expressing HIV-1 NL4-3 (N6 cells) in complete RPMI media with 500nM efavirenz. In experiment one, N6 cells were incubated in 20, 60, or 120ng/ml RMD for 1-24hours to achieve AUC0-24 of 120, 240, and 480ng*hr/ml within each concentration category. Cells from each group were collected in duplicate, washed, incubated in untreated media until 24-hours, then lysed in Glo-lysis. Relative light units (RLU) were obtained by Promega assay system and normalized to time-matched untreated controls to measure HIV-1 transcription. In experiment two, N6 cells were incubated in 1-240ng/ml RMD for 2, 8, and 20-hours to achieve AUC0-24 of 120, 240, and 480ng*hr/ml within each time category using identical procedures. In experiment three, N6 cells were cultured in PVDF Hollow Fiber Bioreactors (HFBs) and the RMD clinical PK profile of a 4-hour infusion was simulated for the following doses: one 5mg/m² 4-hour infusion, two 2.5mg/m² 4-hour infusions administered every 9-hours; three 2.5mg/m² 4-hour infusions administered every 6-hours; two 1.6mg/m² 4-hour infusions administered every 9-hours. HFB media was collected intensively for 5mg/m² and at 2, 4, 6, and 8-hours for the other scenarios to quantify RMD by HPLC-MS/MS. N6 cells were collected and RLU measured at 18-hours, when maximal HIV-1 transcription occurs in HFB-cultured N6 cells. Pearson correlation coefficients (r) were estimated for RLU-vs-exposure time, -concentration, and -AUC0-24 for dose fractionation. Emax models were fit for RLU-vs-time>25ng/ml (RMD's EC$_{90}$ in N6 cells), -Cmax, and -AUC0-18 for clinical simulations.

Results: In experiment one, RLU positively correlated with time (r=0.81, p=0.001) and AUC0-24 (r=0.77, p=0.003) but not concentration (r=-0.12, p=0.54). In experiment two, RLU positively correlated with time (r=0.76, p<0.001), but not AUC0-24 (r=-0.27, p=0.28), and negatively correlated with concentration (r=-0.49, p=0.038). For clinical PK simulations, mean (%CV) Cmax and AUCall of 5mg/m² were 101 (2%)ng/ml and 631 (2.5%)ng*hr/ml, respectively, which were ≤15% of the clinical medians from published PK models. A significant relationship existed for RLU vs time>EC$_{90}$ (r^2=0.85, p=0.001), but not AUC0-18 (r^2=0.31, p=0.27) or Cmax (r^2=0.27, p=0.35).

Conclusions: We conducted dose fractionation in an in vitro model of HIV-1 latency and found RMD exposure time governs HIV-1 transcription. We confirmed this finding in an HFB model simulating RMD's clinical PK profile for different dosing scenarios. The significant relationship observed between transcription and AUC when time was fluctuated to control AUC (experiment one) but not when concentration was fluctuated (experiment two) demonstrates the importance of unlinking these covariates for rigorous PK/PD characterization. Lower doses of RMD administered over longer periods could maximize latency reversal, warranting consideration for long-acting formulations.

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The Role of Copper IUD and Inflammation in Antiretroviral Genital Concentrations in Ugandan Women

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Background: The microenvironment in the female genital tract, including inflammation and drug metabolizing enzymes and transporters (DMET), may alter drug exposure in tissues. We previously found that women using copper IUD (cu-IUD) had lower exposure of tenofovir metabolite in cervical tissue compared to women using depot-medroxyprogesterone acetate (DMPA) or condoms, but the mechanism is unknown. Here we analyzed cervicovaginal cytokines and DMET in Ugandan women living with HIV on different contraception methods to elucidate the role of these factors on female genital tract drug disposition.

Methods: A single visit pharmacokinetic study examining tenofovir and lamivudine disposition in cervical tissues following oral administration was performed. Cervicovaginal swabs, cervical biopsies and plasma were collected from Ugandan women living with HIV, treated with tenofovir/lamivudine regimens and using one of three contraception methods: DMPA injection, cu-IUD, or condoms. Cytokines were measured in cervicovaginal fluid using the Bio-Rad 27-plex Human Cytokine Assay. Lamivudine and tenofovir were measured in plasma and their metabolites (3TCtp and TFVdp) in cervical tissue using LC-MS/MS. Gene expression of CD4, CCR5, MRP4, and AK2 were measured using q-PCR and normalized to GAPDH. Correlations between measured genes and TFVdp was determined using Pearson correlations. Kruskal Wallis tests were used to compare gene expression and cytokine concentrations between contraception methods. To identify significant predictors of drug concentrations, multivariable linear regression was performed on log-transformed data using stepwise regression. Models were evaluated by r2 value and model diagnostics.

Results: 50 virologically-suppressed women were enrolled with a median age of 26 years (range 24-30). CCR5 mRNA expression was significantly higher in women with cu-IUD compared to women using condoms (p = 0.009). The same trend was seen with CD4 and AK2, although not significant (CD4, p = 0.056; AK2, p = 0.09). There were no significant differences for MRP4. TFVdp, dATP, 3TCtp, and dCTP were not correlated with any genes measured. There were no significant differences in any of 27 cytokine concentrations between contraception methods. Following stepwise regression, IL-17, dATP cervical concentrations, estradiol plasma concentrations, and tenofovir plasma concentrations were all significant predictors of TFVdp cervical concentrations. For lamivudine cervical concentrations, dCTP cervical concentrations and plasma lamivudine concentrations were significant predictors. Age was included in final stepwise models for both TFVdp and 3TCtp, but was not significant (TFVdp, p = 0.09; 3TCtp, p = 0.056).

Conclusions: Cu-IUD users having higher CD4 and CCR5 mRNA expression compared to condom users suggests a higher number of inflammation cells present. In addition, IL-17 was a significant predictor of TFVdp cervical concentrations, which further supports the role of immune cells, specifically CD4+ T cells in TFVdp tissue distribution. In contrast, lamivudine drug exposure in the female genital tract may not be affected by genital inflammation and DMET. There was a trend for higher AK2 in cu-IUD users compared to condoms users, which is inconsistent with our previous finding that cu-IUD users have lower TFVdp cervical concentrations and requires elucidation. However, mRNA expression does not represent protein concentrations, and could explain the differences in our findings.

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The Accuracy of Physiologically Based Pharmacokinetic Modelling: Model Predictions Versus Clinical Data of Increased Dose Boosted Atazanavir to Overcome the Drug-Drug Interaction with Rifampicin

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Background: Tuberculosis incidence remains elevated in HIV even with suppressive ART. Clinically significant drug-drug interactions exist between WHO preferred protease inhibitors such as atazanavir and rifampicin-based TB treatment, complicating treatment of co-infection. Using physiologically-based pharmacokinetic (PBPK) modelling, several dose combinations of ritonavir-boosted atazanavir (ATV/r) were simulated in attempt to overcome the drug-drug interaction with rifampicin (Montanha et al 2022). Thereafter, the most likely simulated dose (300/100 twice daily) was investigated in a dose escalation clinical trial. Here, we compare the earlier predicted ATV/r PK parameters with their corresponding values observed in the later clinical study.

Material and Methods: DERIVE (NCT04121195), a dose-escalation trial in virologically suppressed people living with HIV on ATV/r and without tuberculosis was conducted in Uganda. ATV/r dosing was escalated between four pharmacokinetic sampling visits: PK1 – 300/100 mg once daily (OD); PK2 – 300/100 mg with 600 mg rifampicin OD; PK3 – 300/100 mg twice daily (BD) with 600 mg rifampicin; and PK4 – 300/100 mg with 1200 mg rifampicin OD. Dolutegravir BD was also administered during PK2-PK4 due to the risk of subtherapeutic concentrations of atazanavir when co-administered with rifampicin. The noncompartmental analysis parameters are presented here and compared against their corresponding values earlier predicted before the clinical trial.

Results: Regarding ATV/r 300/100 mg BD and rifampicin 600 mg OD, observed geometric mean versus model-predicted geometric mean of ATV were: Cmin, 0.49 vs 0.51 µg/ml; Cmax, 3.85 vs 3.50 µg/ml; and AUC0-24, 43.0 vs 47.8 µg.h/ml. For ATV/r 300/100 mg BD and rifampicin 1200 mg OD, observed geometric means versus model-predicted geometric mean of ATV were: Cmin, 0.48 vs 0.20 µg/ml; Cmax, 3.31 vs 3.00 µg/ml; and AUC0-24, 40.0 vs 34.8 µg.h/ml. In contrast, Cmax and AUC0-24 for ATV/r 300/100 mg OD and rifampicin 600 mg OD were over-predicted. Observed geometric mean versus model-predicted geometric mean of ATV/r 300/100 mg OD combined with rifampicin 600 mg OD were: Cmin, 0.02 vs 0.01 µg/ml; Cmax, 1.19 vs 2.73 µg/ml; and AUC0-24, 5.89 vs 18.9 µg.h/ml. Similar to the earlier model predictions, ATV/r 300/100 mg BD was observed to overcome the drug-drug interaction effect with rifampicin 600 mg OD in the clinical study.

Conclusion: This works confirms the importance of PBPK modelling as a predictive tool, particularly for complex and 'difficult to study' populations.

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Tenofovir Plasma and Intracellular Pharmacokinetics in Insti-Based Regimens

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Background: Tenofovir (TFV) as tenofovir alafenamide (TAF), associated with Emtricitabine (FTC), is the backbone of most 3 drugs regimens. Scarce data on TFV intracellular (IC, intra-PBMC)

accumulation are reported in literature. Therefore, our aim was to evaluate TFV plasma and IC pharmacokinetics (PK) when dosed with bictegravir (BIC) or dolutegravir (DTG) as third drug in the clinical setting, exploring the potential role of adherence on PK parameters and virological efficacy.

Methods: Patients (pts) administered with TAF/FTC/BIC as single tablet regimen (STR) and TAF/FTC plus DTG were included, after informed consent given. Plasma and IC TFV-DP concentration as Ctrough were measured by means of UHPLC-MSMS validated method at the end of dosing interval (24+/-4 hours after intake). Non-compartmental PK parameters were expressed as geometric mean (CI95%). Pharmacy refills were used to calculate the proportion of days covered (PDC) in the immediate period before the PK analysis. Pts characteristics were compared by Mann-Whitney and Spearman's test, as appropriate.

Results: 86 pts were included in the study: 61 on BIC/TAF/FTC and 25 DTG+TAF/FTC. 83% of them were male, age and BMI were 51 years (48-53) and 26.3 Kg/m2 (22.8-29.8). Geometric mean TFV plasma Ctrough plus BIC and DTG resulted to be respectively 14.9 (13.3-16.6) and 10.7 (7.8-13.6) ng/mL (p=0.001). TFV IC Ctrough resulted to be 327.5 (283.0-372.0) and 144.6 (76.1-213.1) ng/mL (p<0.001), and TFV IC/plasma ratio 23.1 (19.9-26.3) and 13.9 (7.4-20.4) (p<0.001). Plasma PK of other ARVs (BIC, DTG, FTC) were in line with those reported in literature.
In total population linear and significative correlation was reported between TFV plasma and IC Ctrough (0.557, p<0.001) and between TFV plasma Ctrough and age (0.432, p<0.001), creatinine (0.380, p=0.001) and inverse with eGFR (-0.453, p<0.001). No correlation with BMI was observed.
We did not find any difference in cumulative adherence between the two groups, while a difference of rate of virosuppression, higher in BIC group, was observed (p=0.001). Analyzing the virosuppressed population, we found a higher TFV IC Ctrough in BIC vs DTG (p=0.010), without difference in adherence (p=0.343).

Conclusions: TFV plasma exposure was found to be higher when dosed with BIC as compared to DTG and concomitantly TFV-DP accumulation in PBMCs was different in two groups, 2-fold higher with BIC despite the same adherence rate. In our population, role of adherence to ART has no impact on virosuppression or correlation with PK

parameters. Further studies are warranted.

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Development of a Universal Taggant for Adherence to Any Medication or Placebo

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Background: Medication adherence is a significant driver of pharmacokinetic and clinical outcomes. Currently available adherence monitoring tools exhibit significant limitations including: inaccuracy (e.g. self-report), technical challenges (e.g. electronic monitors), need for patient engagement (e.g. digital pills), or limited interpretability (e.g. short half-life drug concentrations representing recent dosing only). However, building on work that has established the utility of long half-life (~17d) intraerythrocytic tenofovir-diphosphate as a cumulative adherence marker for tenofovir-based therapies, we sought to identify long half-life taggants that could be added to any medication or placebo to universally assess adherence. The aim of this human pilot study was to determine whether an inert, stable-labeled isotope, adenine 5+ ($^{15}N_5$-labeled adenine), could fulfill the role of a long half-life taggant to assess gradients of adherence.

Methods: Two milligrams of adenine 5+ per capsule was compounded with microcrystalline cellulose. Participants were randomized to one of two directly observed dosing regimens separated by washout: 1 then 4 doses per week, or 3 then 7 doses per week. Each dosing and washout period lasted 12 weeks except during COVID, when 8 weeks of dosing was allowed. This analysis evaluates data through 8 weeks. Dried blood spots (DBS) were collected weekly via convenience sampling (to mimic real-world adherence assessment), and stored at -80°C until analysis. Biologically, adenine 5+ is taken up by red blood cells (RBC) and converted to ATP5+. Given the abundance of ATP in RBC, the taggant measurement (ATP5+) was compared with the

endogenous ATP2+. A 7mm DBS punch was extracted with 70:30 methanol-water and the ATP5+ to ATP2+ ratio was quantified via LC-MS/MS. The percent difference between baseline and study timepoints was calculated for ATP5+:ATP2+ ratios and the primary outcome was steady-state state concentration (Css), i.e., (AUC0-8wk/time8wk).

Results: N=13 individuals (10 white; 7 female) contributed 193 measurements. The median (range) age and weight at baseline was 30 (23-38) years and 81.3 (55.3-93.7) kg. Seven participants completed 1 dose/week, and six completed 3, 4, and 7 doses/week, respectively. The percent difference in ATP5+:ATP2+ from baseline plateaued after approximately 4 weeks, suggesting a ~10-day operational half-life. The median (IQR) Css percent increases from baseline for the 1, 3, 4, and 7 weekly dose regimens, were 29.8% (16.6-60.1), 116% (83.5-153), 129% (108-152), and 315% (113-507), respectively. The within person Css increase (IQR) from 1 to 4 doses was 4.04-fold (2.59-4.77), and 2.31-fold (1.36-3.31) from 3 to 7 doses (dose proportional increases would be 4 and 2.33, respectively).

Discussion: Within this pilot study, the percent change in taggant concentration from baseline appeared to increase in proportion to dose level (adherence). These findings will guide future investigations with this promising adherence biomarker. A universal taggant could be added to any medication or placebo and conveniently collected in blood via DBS to assess adherence, which could better inform the accuracy of drug efficacy and clinical decision making in clinical trials and real-world settings.

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Exposure-Response Relationship for Immune-modulatory Agent Vesatolimod in People with HIV

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Background: Vesatolimod (VES) is an orally administered, highly selective toll-like receptor 7 (TLR7) agonist in clinical development for HIV cure in combination with other agents. VES selectively targets TLR7 on early endosomes and induces interferon (IFN)-α and IFN-stimulated genes (ISGs) to enhance innate and adaptive immune response against viral infection. The fold increase of 2 ISGs (ISG15 and OAS1) post first dose was found to be associated with delayed HIV rebound after stopping antiretroviral treatment in a study of 25 HIV controllers. Increased VES dose was associated with an increased rate of flu-like adverse events, leading to the maximum allowable clinical dose of 8 mg. The objective of this analysis was to evaluate the relationship between VES exposure and its immune-modulatory effect to support the VES dose selection rationale for future HIV cure studies.

Material and Methods: Eighteen biomarkers from 9 studies with VES dose ranging from 0.3 to 12mg were grouped into 3 tiers based on their proximity to IFN-α of the VES-induced type I IFN-dependent pathway and biological impact. Tier 1 included cytokines that were directly induced by VES, such as IFN-α, chemokines CXCL10 and CXCL11, and interleukin (IL)-1 receptor antagonist, or ISGs: ISG15, OAS1, and MX1. Tier 2 included immune cell activation biomarkers (CD69+ NK cell, HLA-DR+CD4+ CD38+ T cell, HLA-DR+CD8+ CD38+ T cell) induced by type I IFNs. Tier 3 included proinflammatory biomarkers that are less specific to VES induction, but that may be related to flu-like adverse events (CCL2, CCL4, IL-6, IL-8, C-reactive protein, tumor necrosis factor-α, IFN-γ, eotaxin).

Changes from baseline of all biomarkers at 24 hours after first dose were analyzed for their relationship to VES exposure, using data from 9 clinical studies. Changes were first tested by Spearman rank correlation; biomarkers significantly correlated with exposure at a significance level of alpha=0.05 were further evaluated with the maximum exposure-response model (Emax).

Results: Among the biomarkers significantly correlated with VES exposure, most were tier 1 biomarkers. There was no significant correlation between most tier 3 proinflammatory cytokines and VES exposure, consistent with the selectivity of VES of IFN-dependent pathways over proinflammatory pathways.

Based on subsequent exposure-response modeling, the highest Emax values were estimated for tier 1 biomarkers, suggesting that these are the most responsive to VES treatment. The estimated half-maximal effective concentrations (EC50) of all biomarkers were close to or higher than the median observed VES AUC or Cmax at 6 or 8 mg, suggesting increased immune-modulatory effects of VES up to this dose range and beyond.

Conclusions: The strong relationship between VES exposure and tier 1 biomarkers related to type I IFN activation, and the lack of correlation between VES exposure/low magnitude of effect with tier 3 proinflammatory biomarkers, supports the role of VES in selective immune modulation related to antiviral activity. This exposure-response analysis also supports the selection of VES dosing of 6-8 mg to maximize efficacy via the immune-modulatory effect, while balancing safety in future combination trials for HIV cure.

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Relative Bioavailability of Dolutegravir (DTG) and Emtricitabine/Tenofovir Alafenamide (F/TAF) Administered as Paediatric Tablet Formulations in Healthy Volunteers

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Background: In the EDCTP2-funded UNIVERSAL project (RIA2019PD-2882) a paediatric fixed dose combination (FDC) product containing dolutegravir/emtricitabine/tenofovir alafenamide (DTG/F/TAF) will be developed. While drug-drug interaction studies were performed with adult formulations of DTG and F/TAF, data on paediatric

tablets for oral suspension (TOS) are currently lacking. Therefore, we undertook a relative bioavailability (RBA) study in healthy volunteers to investigate a potential pharmacokinetic effect when paediatric DTG (30 mg dose) and F/TAF (180/22.5 mg dose) TOS are taken together. These data will support the UNIVERSAL project in selecting doses for the paediatric DTG/F/TAF FDC.

Methods: This single dose, open-label, 3-period, randomised, cross-over RBA study in healthy adult volunteers was conducted from November 2022 to March 2023 at the Radboud university medical center, Nijmegen, the Netherlands. Participants received the following treatments with a washout period of 7 days in between: single dose of 3 X 60/7.5 mg (180/22.5 mg) F/TAF TOS (Reference treatment A); single dose of 6 X 5 mg (30 mg) DTG TOS (Reference treatment B); single dose of 180/22.5 mg F/TAF TOS plus 30 mg DTG TOS (Test treatment C). Treatment sequences were equally randomized. Blood samples were collected at time = 0 (pre-dose) and at time = 0.17, 0.33, 0.5, 0.75, 1.0, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24 and 48 hours post-dose. Plasma concentrations of DTG, emtricitabine (FTC), TAF and tenofovir (TFV) were measured using a validated LC-MS/MS method. Two treatments are considered bio-equivalent if the 90% CI of the geometric least square mean (GLSM) ratio of AUC and Cmax determined by noncompartmental analysis of all compounds is within 0.70 and 1.43.

Results: 16 healthy volunteers were enrolled. One dropped out prior to dosing and two participants only received reference treatment B (DTG). Test treatment (C) was bio-equivalent to the reference treatments (A or B) for DTG, TFV and FTC. GLSM ratios (90% CI) were DTG 1.02 (0.94-1.10) for AUC0-∞ and 1.16 (1.10-1.23) for Cmax; TFV 0.84 (0.70-1.01) for AUC0-last and 1.06 (0.92-1.23) for Cmax; FTC 0.97 (0.92-1.02) for AUC0-∞ and 1.05 (0.94-1.17) for Cmax. Test treatment (C) was not bio-equivalent to the reference treatment (A) for TAF because the lower boundary of the 90% CI of the GLSM ratio was below 0.70 for AUC0-∞ (0.62) and Cmax (0.65). As half of the participants had a test versus reference ratio above 1 and TFV was bio-equivalent, no trend in TAF exposures was identified.

Conclusions: DTG, TFV and FTC met the predefined bioequivalence criteria in our study when co-administered compared with products administered separately, whereas this was not the case with TAF. No consistent effect on TAF PK was observed, likely due to high inter-subject

variability. These data will inform the dose ratio of the FDC as well as dose selection for a paediatric DTG/F/TAF FDC to be developed in the UNIVERSAL project.

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Thigh Injections of Cabotegravir + Rilpivirine in Virally Suppressed Adults With HIV-1

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Background: Cabotegravir (CAB) + rilpivirine (RPV) long-acting (LA) administered via gluteal intramuscular (IM) injections is recommended by treatment guidelines for maintaining HIV-1 virologic suppression. Previous data in healthy participants receiving single CAB+RPV LA IM injections to the vastus lateralis (thigh muscle) were supportive of further evaluation. Here we present the results of a substudy evaluating the pharmacokinetics (PK), safety, tolerability, and efficacy of CAB+RPV LA following short-term repeat IM thigh administration in adults with HIV-1 who had received ≥3 years of gluteal injections while participating in the ongoing Phase 3b ATLAS 2M study.

Material and Methods: ATLAS-2M participants volunteered and reconsented for the substudy, which included a screening phase, thigh injection phase [Day 1–Week (W) 16], and return to gluteal injection phase (W16–24). The substudy injection schedule was unchanged from the main study [every 8 week arm (Q8W) arm, CAB 600 mg + RPV 900 mg; every 4 week (Q4W) arm, CAB 400 mg + RPV 600 mg]. CAB and RPV PK parameters following the last gluteal injections and first and last thigh injections were determined by noncompartmental analysis and compared by mixed-effects modeling. Statistical significance was determined when the 90% confidence interval (CI) of the geometric least squares mean ratio (GMR) fell outside of the 0.8–1.25 range. Safety, tolerability, participant-reported outcomes, and efficacy were assessed.

Results: 118 participants (Q8W, n=54; Q4W, n=64) enrolled; median (range) age was 48 years (24–71), 38% were female sex at birth, 82% were White. In the Q8W arm, statistically higher parameters were observed with thigh vs. gluteal injections for the first CAB thigh injection $AUC_{(0-\tau)}$ and Cmax (GMR [90% CI], 1.21 [1.13-1.30] and 1.35 [1.22-1.49], respectively), first RPV thigh injection Cmax (1.26 [1.12-1.40]), and last RPV thigh injection $AUC_{(0-\tau)}$, Cmax, and $C\tau$ (1.29 [1.20-1.38], 1.18 [1.09-1.28], and 1.18 [1.07-1.29], respectively). No statistically significant differences occurred in the Q4W arm. No participants had HIV-1 RNA ≥50 c/mL during the substudy; 3 per arm withdrew for non-virologic reasons. Across 210 Q8W and 494 Q4W thigh injections, 132 and 195 injection site reactions (ISRs) occurred, respectively; most were Grade 1 (55–76%) or 2 (19–38%), with 4–7% Grade 3. The median duration of ISRs was 3–3.5 days. One Grade 2 ISR led to withdrawal. Overall, 28–33% preferred thigh injections, largely due to ease of access.

Conclusions: CAB and RPV parameters following 16 weeks of thigh injections were similar to gluteal administration, with no clinically significant differences observed. These results support rotational/short-term CAB+RPV LA IM lateral thigh administration within an established gluteal regimen. Additional analyses will assess the potential for early or chronic thigh administration.

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Population PK Modeling of Teropavimab and Zinlirvimab and Evaluation of Flat Dosing in Combination with Lenacapavir for Long-Acting HIV Treatment

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Background: Teropavimab (TAB) and zinlirvimab (ZAB) are recombinant, fully human monoclonal antibodies against HIV envelope glycoproteins, with mutations in the Fc domain to prolong their half lives in vivo. Lenacapavir (LEN) is the first-in-class HIV-1 capsid inhibitor recently approved for treatment of HIV-1 infection in heavily treatment-experienced adults, in combination with other antiretrovirals. The triple combination regimen of TAB, ZAB and LEN is under investigation as a potential long-acting HIV treatment with dosing every 6 months. In a Phase 1b study (NCT04811040), a single dose of TAB and ZAB utilizing weight-based dosing with LEN was well tolerated and effective in maintaining viral suppression for 26 weeks in people with HIV (PWH) who switched from their standard-of-care therapy. The purpose of this modeling study was to develop population pharmacokinetic (PopPK) models of TAB and ZAB and to use these models to assess flat-dosing regimens of TAB and ZAB to use in combination with LEN in adult PWH.

Methods: TAB and ZAB pharmacokinetic (PK) data were obtained from four clinical studies in viremic or virally suppressed PWH (TAB: n=34; ZAB: n=36) who received single intravenous doses of TAB (30 mg/kg) and/or ZAB (10 or 30 mg/kg) alone or in combination, with or without LEN. TAB and ZAB serum concentrations were measured using validated Mesa Scale Discovery-electrochemiluminescence immunoassays. PopPK models of TAB and ZAB were developed using nonlinear mixed-effect modeling. Covariate analyses were performed to evaluate the effects of demographics, baseline characteristics, combination regimen, and disease status on the PK of TAB and ZAB. Model simulations were performed to predict the concentrations of TAB and ZAB following flat vs weight-based dosing.

Results: TAB and ZAB PK data in PWH were adequately described by two-compartment PopPK models. Increased body weight was associated with increased volume of distribution and clearance of both TAB and ZAB. PWH who were viremic had a significant increase in the clearance of TAB and ZAB compared with those who were suppressed at baseline. Model simulations suggest that a flat dose of 2550 mg would result in similar exposures as 30 mg/kg for both TAB and ZAB, based on the body weight distribution in recent Phase 3 HIV studies of adult PWH, with an average body weight of ~85 kg.

Conclusions: The PopPK analyses predicted comparable exposure between a flat dose of 2550 mg and a weight-based dose of 30 mg/kg for both TAB and ZAB. Considering the safety and efficacy results with 30 mg/kg TAB and 30 mg/kg ZAB in the Phase 1b study, 2550 mg TAB and 2550 mg ZAB in combination with LEN every 6 months is expected to be a well-tolerated and effective dose regimen for evaluation in future clinical trials in adult PWH for long-acting HIV treatment.

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Rapid Activation of AT-752, a Novel Nucleotide Prodrug with Pan-Serotype Activity Against Dengue Virus, to the Triphosphate Metabolite AT-9010 in Human Peripheral Blood Mononuclear Cells After Oral Administration in Healthy Participants

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Background: AT-752 is a novel guanosine nucleotide prodrug inhibitor with sub-micromolar, pan-serotype activity against dengue (EC90 = 0.64 µM against DENV-2). AT-752 undergoes multi-step activation to the intracellular triphosphate (TP) metabolite AT-9010 (TP of AT-273, the guanosine nucleoside). Here, we report intracellular pharmacokinetics (PK) of AT-9010 in human peripheral blood mononuclear cells (PBMCs), a major target for dengue infection, following oral administration in healthy participants in a first-in-human (FIM), double-blind, randomized, placebo-controlled study examining safety, tolerability and PK of escalating single (Part A) and multiple (Part B) oral doses of AT-752.

Participants and Methods: Eligible participants were randomized to receive oral AT-752 as: Part A) single ascending doses (250, 500, 1000 and 1500 mg; n=31) or placebo (pooled n=10); or Part B) once daily dose (1000 mg QD x 7 days, n=6), twice daily dose (750 mg BID x 4.5 days, n = 6), thrice daily dose (750 mg TID x 4.3 days, n=6), or placebo (pooled n=6). PBMC samples were obtained up to 24 h after single doses and up to 72 h for multiple doses. AT-9010 was extracted from isolated PBMCs using strong anion exchange solid-phase extraction and converted to AT-273, which was quantified using a validated HPLC/MS-MS methodology. Lower limit of quantification was 3.34 fmol/sample.

Results: Following single ascending doses, PBMC AT-9010 levels increased from 0.66-9.0 µM at 6 h and from 0.18-6.9 µM at 24 h when AT-752 doses escalated from 250-1500 mg. These TP levels exceeded the corresponding plasma AT-273 by 2.5 and 9.5-fold at 6 h, and 3.5 and 35-fold at 24 h, for the 250 and 1500 mg doses, respectively. With multiple ascending doses, AT-9010 levels increased rapidly to peak 4 h after the first dose with maximum TP levels of 6.0, 6.1 and 4.1 µM for AT-752 1000 mg QD, 750 mg BID and 750 mg TID, respectively. Following repeat dosing, mean trough TP levels were comparable between the 1000 mg QD (8.8 µM) and the 750 BID (9.3 µM) doses and were higher for the 750 mg TID (22.5 uM), exceeding plasma trough levels of AT-273 by up to 45-fold. AT-9010 levels declined slowly after reaching peak with an observed mean half-life of 30.5, 35.6 and 47.3 h for the QD, BID and TID regimens, respectively, which was consistent with the corresponding plasma half-life of AT-273 of 28.2, 31.8 and 28.4 h, respectively. Additionally, PBMC AT-9010 and plasma AT-273 levels were significantly correlated ($r2 = 0.515$).

Conclusion: AT-752 was rapidly activated to achieve high and sustained levels of AT-9010 in PBMCs upon oral dosing in healthy subjects. Formation of AT-9010 increased as doses escalated and exceeded plasma levels of AT-273. PBMC AT-9010 and plasma AT-273 levels were significantly correlated, supporting use of plasma AT-273 as a surrogate of AT-9010. AT-752 750 mg BID x 5 days, which achieved highest and most sustained TP levels, led to faster resolution of fever, a key clinical symptom in patients with dengue in a recently completed proof-of-concept study.

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Quantification of Nucleoside Reverse Transcriptase Inhibitors and Their Metabolites in Dried Blood and Plasma Spots after 14 days Intake Cessation

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Background: Patient adherence to their antiretroviral regimen is vital for achieving successful treatment. The benefits of dried blood spots (DBS) as an alternative sampling strategy for adherence monitoring include simplified collection, processing and storage requirements. A novel DBS card (HemaSep; HS) separates plasma from whole blood upon contact, eradicating the need for centrifugation. HS can be used to simultaneously quantify NRTI in plasma (outer ring; HS-PL) and their phosphorylated metabolites in the cellular fraction (inner spot; HS-C). Here we describe the pharmacokinetics (PK) of tenofovir (TFV), emtricitabine (FTC) and lamivudine (3TC); and their active di/triphosphate metabolites (TFV-DP, FTC-TP, 3TC-TP) in HIV-negative subjects

receiving tenofovir disoproxil fumarate (TDF)/3TC or tenofovir alafenamide (TAF)/FTC over 15 days, followed by 14-day washout period.

Materials and Methods: Thirty participants were randomised (1:1) to receive e once daily dolutegravir (DTG)/FTC/TAF (Arm 1) or DTG/3TC/TDF (Arm 2) for 15 days. On day 15, blood was collected at pre-dose and over 14 days (0, 1, 4, 24, 48, 72, 96, 168, 336 hr) post intake cessation. HS were spotted (100μL per spot). For HS-C, the whole inner spot (~12mm) was extracted with 70:30 MeOH:20% formic acid, followed by WAX SPE. The calibration range was 0.25-250 pmol/sample and concentrations were expressed as pmol/punch. NRTI were quantified from HS-PL by extracting the entire outer ring with 80:20 acetonitrile:0.1% formic acid. The calibration range was 0.025-250 ng/sample, and measured concentrations were normalised to ng/mL. Quantification was performed using LC-MS and PK parameters calculated using non-compartmental methods.

Results: A total of 29 subjects were evaluable – one subject discontinued (Arm 2). TFV-DP [concentrations] were detectable in HS-C for 14 days in 100% subjects receiving TDF ($t1/2$= 23 days) and 87% on TAF ($t1/2$= 18 days). TFV-DP exposures were ~17-fold lower in those receiving TAF. [TFV-DP] in subjects receiving TDF|TAF were, on average, 17.2 |1.4 pmol/punch (Cmax) and 12.3|0.9 pmol/punch (at 7 days intake cessation; 7d ic). 3TC-TP and FTC-TP exhibited a more rapid decay phase in HS-C ($t1/2$ ~3 days). [FTC-TP|3TC-TP] were 7.5|14.4 pmol/punch (Cmax) and 0.3|1.4 pmol/punch (7d ic). For NRTI, [TFV] were detectable in HS-PL for 14 days in 79% subjects receiving TDF ($t1/2$ = 3.2 days) and 80% on TAF ($t1/2$ = 2.8 days). TFV exposures were ~4.7-fold lower with TAF. [TFV] in subjects receiving TDF|TAF were 389.1|43.4 ng/mL (Cmax) and 2.4|1.8 ng/mL (7d ic). 3TC ($t1/2$= 2.7 days) and FTC ($t1/2$= 2.1 days) were detectable for up to 14 days in 71% and 60% patients. [FTC|3TC] were 2888|2478 ng/mL (Cmax) and 2.9|6.2 ng/mL (7d ic).

Conclusions: TFV-DP concentrations in the cellular fraction (HS-C) were greater in subjects receiving TDF, compared with those receiving TAF. This is likely due to lack of Cathepsin A in erythrocytes and warrants further investigation into the partitioning of TAF within whole blood. These data support the utility of HS for simultaneous measurement of NRTI and their phosphorylated metabolites, as markers of both recent (NRTI and

FTC-TP/3TC-TP) and cumulative (TFV-DP) dosing, for the purpose of adherence monitoring.

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Comparison of F/TAF Adherence Assessment in Sample Matrixes Facilitating Remote Collection: Hair and Tasso

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Background: Remote adherence monitoring may provide support and motivation to engage patients in their HIV care between clinic visits. Hair and blood (collected by Tasso volumetric absorptive microsampling devices) are sample matrixes with simple, minimally invasive approaches for self-collection. In individuals taking emtricitabine/tenofovir alafenamide (F/TAF) as part of routine care for HIV, we compared adherence classifications assessed by hair strands through longitudinal FTC analysis by a novel mass spectrometry imaging (MSI) technique or by blood through quantification of FTCtp (a short-term adherence measure) and TFVdp (a long-term adherence measure).

Materials and Methods: Five males and 2 females living with HIV and taking F/TAF were enrolled (IRB 08-0047) and provided 5 hair strands plucked from occipital scalp and blood collected in 4 sample sponges of a TassoM20 device at a single visit. FTC and another component of a volunteer's antiretroviral regimen (bictegravir, rilpivirine, or cobicistat) were measured in the proximal 2 cm of hair strands, reflecting 2 months of dosing, by infrared matrix-assisted laser desorption electrospray ionization (IR-MALDESI) MSI. Metabolite concentrations from extracted Tasso sample sponges were measured by LC-MS/MS on an AB Sciex API5000 triple quadrupole mass spectrometer. Mean FTC response in hair over the proximal 2 weeks and over 2 months was

compared to median Tasso concentrations of FTCtp and TFVdp, respectively. Daily FTC incorporation over this period was compared to a benchmarked adherence threshold differentiating 3 or fewer doses/week from more frequent dosing. Median Tasso concentrations were compared to published F/TAF adherence benchmarks in dried blood spots (DBS) by converting to fmol/DBS punch, assuming 3uL of blood per punch. Pearson correlation coefficients (ρ) were estimated using Matlab.

Results: Patterns of FTC accumulation matched those of the concomitant antiretrovirals measured simultaneously by IR-MALDESI MSI in hair strands from each volunteer. Based on these FTC patterns, daily dosing behavior was classified as adherent for a median 91% (range: 51-100%) of days in the prior 2 months. Longitudinal FTC profiles characterized a long period of missed dosing extending up to sample collection in only one hair sample, with corresponding classification of FTCtp and TFVdp measurements in matched Tasso samples consistent with 3 or fewer doses/week. Three other FTC profiles indicated brief periods of consecutive days with missed dosing more than a month in the past. Two-month mean hair FTC was not well-correlated with Tasso TFVdp concentrations compared to 2-week hair FTC vs Tasso FTCtp ($\rho= 0.02$ and $\rho= 0.52$, respectively). However, binary adherence classifications differentiating fewer than or greater than 3 doses/week were concordant between hair and both metabolites. Estimates of average dosing frequency classified by hair over 2-week and 2-month periods were highly correlated with dosing frequency classified by FTCtp ($\rho= 0.80$) and TFVdp ($\rho= 0.69$), respectively.

Conclusions: Tasso blood sampling and hair collection provided consistent information about short- and long-term patient adherence among study participants. The ease of sample collection by these methods may offer an advantage to their implementation for at-home adherence monitoring to promote continued adherence and potentially identify individuals in need of support.

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Frailty and the Effects of Polypharmacy in Older People Living with HIV

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Background: Older people living with HIV (OPLWH) face an increasing burden of ageing associated complications, with frailty and polypharmacy being significant challenges compared to their younger counterparts and older people without HIV and are associated to poorer health outcomes.

At Chelsea and Westminster Hospital (CWH), we implemented the HIV/geriatric clinic involving multidisciplinary-team consultations with geriatricians, HIV consultants and HIV specialist pharmacists. This clinic aimed to evaluate the prevalence and outcomes associated with frailty and polypharmacy among OPLWH. A modified Comprehensive Geriatric Assessment (CGA) was performed alongside pharmacist-led medication reviews.

Materials and methods: All patients reviewed between December 2022 and June 2023 in the HIV/geriatric clinic at CWH, London, UK, were included. Data on physiological, psychological and functional wellbeing calculated using the Rockwood clinical frailty score from the modified CGA and the medication review recommendations were collected. Drug-drug interactions (DDI) between antiretrovirals (ARVs) and non-ARVs were classified and DDIs between non-ARVs were also considered. DDIs were defined as red (avoid co-administration), amber (potential interaction requiring management) and yellow (potential weak interaction). Anticholinergic Cognitive Burden (ACB) was calculated for each patient. Descriptive statistics, risk ratios and differences were calculated using STATA version 15.1.

Results: We reviewed 50 OPLWH; 38 (76%) by telephone, 6 (12%) in-person and 6 (12%) virtually. The median age of the OPLWH was 83 years (IQR

81-86), 86% were male, 86% had VL<50 copies/mL and the median year of HIV diagnosis was 2001 (IQR 1991-2006).

The mean frailty score was 3, 8 patients (17%) had a frailty score of >6 with 14 patients (31%) reporting >1 fall within 12 months.

Polypharmacy was seen in 44 (90%), with 20 (41%) on >10 medications daily. Nine patients (18%) with polypharmacy had DDIs with ARVs of which 22 were rated as "amber", 6 as "yellow". Non-ARV DDIs included cumulative antihypertensive effects and CNS depression.

ACB >2 was present in 17 (35%), score of 1 in 10 (20%) and none in 22 (45%). Patients prescribed anticholinergic medication (ACM) had 1.9 times the risk of a fall compared to patients not taking ACM (95%CI:0.7-5.13). A 35% greater risk of falls in patients on polypharmacy (95%CI:0.20-0.50) was measured.

18 patients or relatives (44%) reported concerns regarding memory. Those taking ACM had 1.23 times the risk of concerns regarding memory (95%CI:0.60- 2.53).

Pharmacist-led medicine review, has led to ARVs changes in ten patients (20%) with switches to either dolutegravir/lamivuidine or bictegravir/emtricitabine/tenofovir alafenamide. Co-medication changes, including de-prescribing, were recommended in 30 OPLWH (60%) and dossette-pill boxes were initiated for six patients (12%) to support medication adherence.

Conclusion: Our findings, focusing mainly on PLWH over the age of 80 years, demonstrate that this population has significant comorbidities and is at risk of polypharmacy and DDIs. Modernization of ARVs (e.g., booster removal, pill burden reduction) and pharmacist interventions may help reduce adverse events, improve adherence, and modify ACB. Integrating geriatric care into HIV clinical practice presents an ideal opportunity to optimize resources to address the needs of OPLWH.

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Novel Adherence Measures to Improve HIV Treatment Monitoring in Resource Limited Settings

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Background: HIV drug resistance is a major global challenge, and adherence, particularly problematic in children and adolescents living with HIV (CALWH), contributes to this challenge. Despite innovations in assessing antiretroviral adherence like TFVdp in dried blood spots (DBS), which can predict incomplete adherence-induced virologic failure, challenges exist. TDF is not uniformly prescribed in resource limited settings (RLS) and DBS metabolites like TFVdp require frozen conditions to prevent degradation which can be costly to store, handle and ship, making large-scale adherence monitoring difficult. We explored alternative approaches for adherence monitoring tailored to RLS.

Materials and Methods: Samples were obtained from two cohorts within a parent study of treatment failure and drug resistance in longitudinally followed Kenyan CALWH in the AMPATH program, to develop two adherence measures. First, in a cross-sectional assessment of 30 participants with undetectable viral load (VL), we collected DBS and 50μl whole blood aliquots (WBAs), then quantified TFVdp and 3TCtp by previously reported LC-MS/MS methods. We analyzed WBA-DBS drug concentration concordance using linear models, fit for $y=mx+b$ (y=DBS; x=WBA concentrations). Second, we used the 90th percentile of 3TCtp DBS concentration in 5 participants from this subset that ultimately exhibited VL>200copies/ml, and the established

TFVdp DBS adherence threshold for 4 doses/week, to conduct a sensitivity analysis of DBS to predict VL>200 copies/ml in an independent dataset. For this analysis, we collected DBS and quantified TFVdp and 3TCtp as above from a convenience sample of 73 participants, 48 with VL≥1,000 copies/mL and 25 with VL<1,000 copies/mL (WHO failure cutoff), based on sample availability. Participants were dichotomized by VL>200 copies/mL in the 180 days post collection.

Results: Among the two cohorts, 100% were on a regimen containing 3TC and 36% were on TDF. In the WBA vs DBS comparison, for 3TCtp we fit 30 paired observations (r2=0.84) with an estimated (%CV) intercept of 107 (75%) and slope of 0.63 (12%). For TFVdp, we fit 11 paired observations (r2=0.92) with an estimated (%CV) intercept of 294 (147%) and slope of 0.91 (14%). Median (IQR) percent change for WBA 3TCtp and TFVdp relative to DBS was 25% (7, 60) and -2.4% (-19, 33), respectively. In the sensitivity analysis, of the 68 participants with VL measurements within 180 days post-DBS collection, 48 (71%) exhibited VL>200 copies/mL. Sensitivity and specificity of 750 fmol/sample 3TCtp to predict VL>200 copies/ml were 71% and 80%, with 74% accuracy. Sensitivity and specificity of 1000 fmol/sample TFVdp to predict VL>200 copies/ml were 68% and 86%, with 73% accuracy.

Conclusions: This is the first report of two new approaches for adherence assessment tailored for RLS, including the use of WBA instead of DBS to measure 3TCtp, and the use of 3TCtp in DBS to prospectively predict detectable VL with equal accuracy as DBS TFVdp. We observed between-assay bias for WBA and DBS 3TCtp, and characterized their relationship to account for this bias. Upon further validation, such approaches may optimize HIV care in RLS, particularly in this unique and vulnerable population of Kenyan CALWH.

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Lack of Acute Impact on Blood Pressure Following Supratherapeutic Oral Doses of Dolutegravir and Cabotegravir Among Healthy Adults

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Background: Conflicting data exist regarding the association between integrase strand transfer inhibitor (INSTI)-based antiretroviral therapy and blood pressure (BP) changes among people living with HIV (PLWH). Dolutegravir (DTG) and cabotegravir (CAB) are guideline-recommended INSTIs and structural analogs which separately demonstrated no significant effect on arterial blood pressure, heart rate, or electrocardiogram parameters following supratherapeutic dosing in nonclinical toxicology studies. Neither DTG nor CAB have demonstrated impact on the QTc interval in healthy adults. The primary objective was to evaluate acute changes in mean blood pressure following supratherapeutic oral dosing of DTG and CAB in healthy adults.

Material and Methods: BP measurements were evaluated from healthy adults randomized to a single oral dose of DTG 250mg or to repeat oral doses of CAB 150mg every 12 hours x 3 doses over 2 days in separate phase 1 thorough QTc (TQTc) studies. Participants were included if screening systolic BP (SBP) and diastolic BP (DBP) were within the range of 90-140 and 45-90 mmHg, respectively. BP was assessed to align with pharmacokinetic timepoints pre-dose and at 3 hrs post-dose (maximum plasma concentration (Cmax)) and 24 hrs post-dose (plasma trough concentration). Since CAB was dosed every 12 hours, additional BP assessments were taken 12 hrs post-dose (corresponding to trough concentration following dose#1 and 15 hrs post-dose (corresponding to Cmax following dose#2).

Summary statistics were calculated and DTG and CAB concentrations and changes in BPs were graphically explored.

Results: Overall, BP data were available from 81 healthy adults randomized to DTG (n=41) and CAB (n=40). Baseline characteristics were similar between the studies with mean (range) age of 35 (18-55) years and BMI (range) of 26 (19-31) kg/m². In the DTG study, 60% of participants were female sex at birth and 79% were African-American; these were 23% and 40%, respectively, in the CAB study. In the DTG study, mean SBP at baseline vs. 3-hr post-dose vs. 24-hr post-dose measurement on Day 1 was 110 vs. 115 vs. 114 mmHg and mean DBP was 67 vs. 70 vs. 70 mmHg, respectively. In the CAB study, mean SBP at baseline vs. 3-hr vs. 24-hr post-dose#3 measurement on Day 2 was 110 vs. 109 vs. 112 mmHg and mean DBP was 68 vs. 69 vs. 70 mmHg, respectively. No participant in either DTG or CAB studies had any adverse event (AE) or drug-related AEs attributed to BP changes. Dolutegravir maximum plasma concentrations were 3-fold greater than therapeutic concentrations following both once and twice daily dosing with weak to no correlation with changes in BP. Similarly, weak to no correlation with BP changes was observed with maximum plasma CAB concentrations 2.8 to 14-fold greater than therapeutic concentrations following oral daily, monthly, and every 2 monthly long-acting dosing.

Conclusions: Supratherapeutic exposures following single oral DTG and repeat oral CAB dosing demonstrated no clinically relevant changes in acute blood pressure in healthy adults. No strong exposure-response relationship was identified for either DTG or CAB with changes in BP.

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Lenacapavir Pharmacokinetics in Asian Versus Non-Asian People with HIV-1 Infection

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Background: Lenacapavir (LEN) is a potent, first-in-class capsid inhibitor approved for the treatment of adults with multidrug resistant HIV-1 infection, in combination with other antiretrovirals. In the ongoing global Phase 2/3 CAPELLA study (NCT04150068) people with HIV (PWH) received oral LEN loading doses (Days [D] 1 and 2: 600 mg; D8: 300 mg) then subcutaneous (SC) LEN maintenance dosing (927 mg every 6 months) starting on D15. Current data indicate maximal antiviral activity of LEN is achieved when mean Ctrough is at or above 15.5 ng/mL (the inhibitory quotient-4 [IQ4]; ≥4-fold higher than the in-vitro protein-adjusted 95% effective concentration in MT-4 cells). Ethnic differences could affect pharmacokinetics (PK) of a drug. The aim of this analysis was to compare exposure metrics of LEN in Asian versus non-Asian PWH in CAPELLA to evaluate the impact of ethnic differences on LEN exposure.

Methods: In the CAPELLA study, sparse LEN plasma concentrations were collected prior to oral and SC doses. Therefore, for observed data, statistical comparison between Asian and non-Asian PWH was conducted for Ctrough values at Week (W) 26 and W52 only. In addition, a previously developed 2-compartment LEN population PK (PopPK) model with allometric fixed exponents for body weight on CL and Vs was used to derive post hoc values for several LEN exposure metrics: AUCtau, Cmax, and Ctrough. LEN exposures in Asian versus non-Asian PWH were compared statistically using analysis of covariance with bodyweight as a covariate. Geometric mean ratios (GMRs) were calculated for all parameters.

Results: Overall, 15 participants in the CAPELLA study were Asian and 56 were non-Asian. Median (range) BMI and bodyweight were lower in Asian (21.4 kg/m² [14.9–29.6] and 60.0 kg [41.4–68.4]) than non-Asian PWH (26.9 kg/m² [18.7–42.6] and 80.3 kg [46.5–126.0]). Analysis of observed data indicated that bodyweight-adjusted GMR (90% confidence interval [CI]) for Ctrough was slightly higher for Asian than non-Asian PWH i.e. W26: 113.7% (80.9–160.0); W52: 123.1% (91.0–166.5). Similarly, for PopPK-derived exposure metrics, body weight-adjusted GMRs (90% CI) for AUCtau, Cmax and Ctrough were slightly higher in Asian than non-Asian PWH. Adjusted GMR (90% CI) for AUCtau D1–W26 was 132.1% (109.4–159.5). For Cmax, adjusted GMR (90% CI) D1–W26 was 143.8% (109.4–189.1). Adjusted GMR (90% CI) for Ctrough W26 was 87.2% (62.1–122.6). Mean LEN plasma Ctrough values were above 15.5 ng/mL in all PWH at all time points.

Conclusions: No clinically relevant differences in LEN exposures were observed between Asian and non-Asian heavily treatment-experienced PWH. Mean LEN concentrations were maintained above the efficacious target (IQ4) in Asian and non-Asian PWH. No dose adjustment of LEN for Asian PWH is required.

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Development, Validation and Application of a Novel LC-MS Method for Quantification of Favipiravir Ribofuranosyl-5'-Triphosphate (F-RTP) in Human Peripheral Blood Mononuclear Cells (PBMCs)

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Background: Favipiravir (FVP) is a prodrug that is metabolised intracellularly to the active moiety, favipiravir ribofuranosyl-5'-triphosphate (F-RTP). Due to its broad antiviral activity against a range of RNA virus families, FVP is being evaluated as a potential treatment for coronavirus disease-19 (COVID-19), but to date, clinical trials have proven inconclusive. Physiologically based pharmacokinetic (PBPK) modelling has indicated that a higher dose of FVP may be required to generate levels of F-RTP needed to sufficiently inhibit viral replication. The described LC-MS method was validated to measure F-RTP concentrations in PBMCs as part of the AGILE CST-6 clinical trial (NCT04746183) investigating the safety and pharmacokinetics of escalating doses of intravenous (IV) FVP in hospitalised patients with COVID-19.

Materials and Methods: PBMC were isolated from whole blood obtained from healthy donors and subsequently lysed using methanol-water (70:30, v/v) to obtain a final cell count of 2×10^6 cells/mL. Aqueous solutions of calibrators and quality control (QC) samples were spiked into 1 mL of lysed cells to produce a calibration range between 24–2280 pmol/sample. Cellular components were precipitated in acidified acetonitrile. Internal standard (tenofovir-d6 diphosphate; 20 µL) was added to all samples which were vortex mixed, followed by weak anion exchange solid phase extraction. Eluents were dried under nitrogen then reconstituted in methanol-water (70:30, v/v). F-RTP was separated on a Biobasic AX column coupled to an AB Sciex 5500 triple quadrupole mass spectrometer. The method was validated in accordance with FDA bioanalytical method guidelines.

F-RTP was quantified in a sub-set of AGILE CST-6 patients (n=4; 10 samples) receiving IV FVP 600mg twice daily for 7 days. Whole blood was collected in cell preparation tubes (CPT) 6-12 hr after the first dose (1 hr infusion) on day 1, 3, 5 of treatment. The CPT were centrifuged at room temperature and PBMCs washed, counted and lysed in exactly 1 mL of methanol-water (70:30, v/v). The stability of F-RTP in whole blood was evaluated in paired blood samples collected from patients receiving IV FVP (n = 4) - CPT tubes were processed immediately (control) and after 1 hour of storage at ambient temperature.

Results: F-RTP (m/z 527.8→272.0) eluted from the column at 1.51 minutes. Extraction recovery for F-RTP was 39% and matrix effect was 83%. Accuracy (% bias) was ≤10% and %CV was < 10% for all QC levels. F-RTP was quantifiable in all PBMC samples analysed (n=10), and concentrations were, on average (range), 122.7 (54.5-215.7) pmol/10^6 cells in patients receiving IV FVP 600 mg twice daily. Significant degradation (17-85%) of F-RTP was noted in blood samples (n=4) that had been left at ambient temperature (~1 hr) compared with immediately processed samples (within 10 minutes).

Conclusion: The developed method is both accurate and precise and has been successfully employed to analyse patient samples from AGILE CST-6. The rapid degradation of F-RTP in whole blood, within 1 hr of collection, emphasises the importance of immediate processing of PBMC samples in to ensure valid and robust quantitative data for this metabolite in future clinical trials.

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The Effect of Molnupiravir on COVID-19 Symptoms: A Retrospective Analysis of the AGILE CST-2 Trial

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Background: Molnupiravir is an antiviral used to treat COVID-19 in patients at risk of severe disease. Functioning as a nucleoside analogue, molnupiravir leads to fatal genomic errors once metabolised and incorporated into viral RNA. Overall, molnupiravir appears to have little to no effect on hospitalisation or mortality. However, in the PANORAMIC trial, the largest to date, molnupiravir did hasten symptomatic recovery.

In the Phase II AGILE Candidate-Specific Trial-2 (CST-2), molnupiravir led to reduced viral load compared with placebo, but without symptomatic benefit at day 15 or 29.

This study aims to present unpublished data from the AGILE CST-2 trial. It is hypothesised that clinical data before day 15 will demonstrate faster symptom resolution with molnupiravir, consistent with the a priori aim to determine virological efficacy, and could additionally reveal factors associated with molnupiravir response.

Methods: Prospective data from the AGILE CST-2 trial were accessed for analysis. In this double-blind trial, volunteers with PCR-confirmed SARS-CoV-2 infection were randomised 1:1 to molnupiravir or placebo within 5 days of symptom onset, using a permuted block method. Eligible participants were aged at least 18 years, outpatients, in generally good health, and ambulant with peripheral oxygen saturations >94% on room air.

Symptom severity was defined by the validated, 32-item Influenza Patient-Reported Outcome ("FLU-PRO") score and its 9-item supplementary questionnaire, collected on days 1 through 15, 22, and 29 from enrolment. Mean scores from individual FLU-PRO questions were aggregated into symptom domains for statistical analysis.

Mean FLU-PRO scores between the two arms were compared at day 5 and day 8 using independent, two-tailed t-tests.

Further statistical analysis will include:
- comparison of mean FLU-PRO scores stratified by age (≥50, <50) and vaccination status (any vaccination, no vaccination),
- Kaplan-Meier plots for time to symptom resolution.

Results: FLU-PRO responses were converted to numerical values, where "1" represented symptom absence and "5" represented severe symptoms.

At day 5, participants taking molnupiravir reported lower mean FLU-PRO scores compared to placebo (1.51 versus 1.59, $p = 0.036$). FLU-PRO scores were significantly lower when considering upper respiratory tract symptoms (1.45 versus 1.58, $p = 0.048$), but not lower respiratory, constitutional, or gastrointestinal symptoms.

No difference in mean FLU-PRO scores was observed at day 8 (1.37 versus 1.37, $p = 0.846$).

When asked: "have you returned to your usual health today?", the molnupiravir arm trended towards earlier recovery (67% versus 53% at day 15, 75% versus 66% at day 22, and 81% versus 74% at day 29).

Preliminary, unadjusted results are presented for this abstract. Final statistical analysis and verification are pending.

Conclusions: Initial statistical analysis suggests that molnupiravir led to reduced severity of COVID-19 symptoms at day 5 in the AGILE CST-2 cohort, consistent with the findings of the PANORAMIC trial.

Final analysis should permit commentary on factors associated with molnupiravir response and the suitability of the different methods used to determine symptom severity.

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Nyctanthes Phyto-compounds as Novel RNA Tunnel Inhibitors against Dengue Virus NS5 Polymerase: DFT, Molecular Docking and MD Simulation Study

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Background: Over the last few decades, dengue hemorrhagic fever has increased dramatically because of dengue virus. Dengue virus (DENV) NS5 RNA-dependent RNA polymerase (RdRp), an important drug target, synthesizes viral RNA and is essential for viral replication. Despite the clear medical importance of dengue virus infection, the mechanism of viral replication, commonly targeted by antiviral therapy, is poorly understood. In this study, we are investigating the identification of a novel drug against dengue virus infection using nyctanthes compounds.

Methods: A library of 60 nyctanthes compounds was prepared, and their drug-like properties were evaluated by SwissADME and ProTox servers. Stabilizing geometric optimization was achieved through DFT calculations. The ligands were docked with GLIDE (Schrodinger suite) at the DENV NS5 polymerase (5JJS), and their binding energies were evaluated using MMGBSA. We chose the best pose for each molecule and then assessed its interaction with the receptor using Maestro. A Linux cluster computer running MD was used to simulate molecular dynamics MD simulations for 100ns.

Results: All nyctanthes compounds have negative binding energies, however, four compounds interact more strongly with active site residues than reference drugs. MD analysis of these four compounds suggested that all complexes were inhibitory action due to similar conformational stability and flexibility patterns. The hydrogen-bonding interactions and the binding energy of active-site residues for these compounds-protein complex revealed strong inhibitory activity than the reference complex.

Conclusions: Overall, this study suggests that Nyctanthes phytoconstituents have better binding affinities toward RdRp protein. Thus, compounds might act as a potential inhibitor against the Dengue virus.

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Population Pharmacokinetic Evaluation of Long-Acting Cabotegravir Injection in HIV-positive and HIV-negative Participants Enrolled in Asia

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Background: Long-acting cabotegravir is approved for HIV treatment (with rilpivirine) and pre-exposure prophylaxis (PrEP). Cabotegravir pharmacokinetic parameters have shown correlation with certain intrinsic/extrinsic factors that may differ between Asian and non-Asian populations, e.g., UGT1A1 (primary elimination pathway of cabotegravir) polymorphisms, body weight (BWT; clearances and volumes of distribution [Vd] increase with BWT) and body mass index (BMI; long-acting terminal half-life [T1/2] increases with BMI). We compared cabotegravir pharmacokinetics and exposure between Asian and non-Asian populations using population pharmacokinetic (PPK) approaches.

Methods: Asian participants/population were defined as ethnically Asian participants enrolled in Asia. Previously a robust cabotegravir PPK model has been developed based on 23,926 concentrations from 16 studies in 1647 adults that included only 1.2% Asian participants (Japan n=8;

Korea n=12). Current analysis compared plasma concentrations from additional 144 Asian participants from North-East Asia (NEA) and South-East Asia (SEA) from subsequent treatment studies (201584 and 207966) and PrEP studies (206898 and 201738) against the model-predicted concentrations in the same population. Cabotegravir post-hoc pharmacokinetic parameters and exposure following monthly and once-every-2-months (Q2M) regimens were estimated in all Asian participants (n=164) using the PPK model, and compared against non-Asian participants (n=2744) and across Asian countries. CAB safety threshold was 13.1 µg/mL, median maximum plasma concentration (Cmax) following daily oral cabotegravir 60 mg observed in Study LAI116482, which was the highest Cmax observed in long-term studies but not associated with any toxicity.

Results: In total, 2069 concentrations were collected from 164 Asian participants (female-at-birth n=2) enrolled in China (n=47), Japan (n=17), Korea (n=27), Thailand (n=53), and Vietnam (n=20). Median BWT and BMI (Asian/non-Asian) were 66.4/76.3 kg and 23/25.4 kg/m², respectively. The PPK model adequately predicted cabotegravir concentrations in Asian participants who were not included in the model-building dataset (n=144) as a whole population and as subgroups stratified by country, BWT, BMI and smoking status, demonstrating that the PPK model built based on predominantly non-Asian data is adequate to describe and predict cabotegravir pharmacokinetics in Asian population. T1/2 and BWT-normalized clearances and Vd were similar in Asian and non-Asian participants and similar across Asian countries. Cabotegravir exposure was similar across Asian countries, but higher in Asian than non-Asian participants. Median Cmax (Asian/non-Asian) was 3.46/2.19 µg/mL following the initial injection, 5.76/4.27 µg/mL at steady state following monthly regimen, and 5.56/3.88 µg/mL at steady state following Q2M regimen, all below the safety threshold of 13.1 µg/mL.

Conclusions: Cabotegravir exposure in Asian and non-Asian populations can be adequately described and predicted by the same PPK model. Cabotegravir pharmacokinetics and exposure are similar across countries in NEA and SEA, suggesting that pharmacokinetic data from any NEA/SEA population may be used to guide cabotegravir pharmacokinetic evaluation and regulatory considerations in the NEA/SEA region, thereby potentially avoiding unnecessary pharmacokinetic studies in these populations for future

cabotegravir programs. Cabotegravir exposure is higher in Asian than non-Asian population, likely due to lower BWT in Asian population, but Cmax remains below the safety threshold. Therefore, the benefit-risk profile of cabotegravir is not affected and no dose adjustment is recommended in Asian population.

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Population Pharmacokinetic Analysis of DOVATO (DTG/3TC) as a Fixed-Dose Combination (FDC) In Antiretroviral Therapy (ART)-Naive HIV-1-Infected Adolescents

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Background: Dolutegravir (DTG) and lamivudine (3TC) fixed dose combination (FDC, 50/300 mg) is marketed as DOVATO which provides a novel, well-tolerated, 2-drug, first-line regimen for human immunodeficiency virus (HIV)-infected, treatment-naïve and -experienced virologically suppressed adults. This analysis was to characterize the population pharmacokinetics (PopPK) of DOVATO in antiretroviral (ARV)-naive HIV-infected adolescents with screening plasma HIV-1 RNA between 1,000 and ≤500,000 c/mL. Additionally, covariates of interest were explored to understand their impact on PK of DTG and 3TC in adolescents.

Methodology: Intensive and sparse concentration-dosing data from TANGO (adults) and DANCE (adolescents) studies were used to refine previously developed PopPK models for DTG and 3TC. The refined models were used to simulate plasma PK profiles for DTG and 3TC in HIV -1 infected adult and adolescent subjects. Individual secondary PK parameters were derived and

compared with PK parameters calculated using noncompartmental analysis.

Results: Consistent with previous analyses, DTG PK in HIV-1-infected, treatment-naïve adolescents enrolled in DANCE (adolescents) were well described by a linear 1 compartment model with first-order absorption and elimination. The estimated typical (95% confidence interval [CI]) parameter values were: apparent clearance (CL/F) = 0.876 (0.841 – 0.911) L/h, apparent central volume of distribution (Vc/F) = 16.5 (15.7 – 17.2) L, and first-order absorption rate constant (Ka) = 2.13 (1.7 – 2.56) 1/h. IIV for CL/F and proportional error was relatively low (%CV = 26% and 26.9%, respectively). Weight, bilirubin, ethnicity, and race were significant determinants of CL/F, and weight was a determinant of Vc/F.
For 3TC, a 2-compartment model with linear first-order elimination and first-order absorption could adequately described the PK profile of 3TC in adult (TANGO) and adolescent (DANCE) subjects. The typical values (95% CI) of the CL/F, Vc/F [Vp/F] apparent intercompartmental clearance (Q/F), and Ka were 21.1 (20.3, 21.8) L/h, 119 (110, 128) L, 3.33 (3.02, 3.64) L, and 2.22 (1.57, 2.86) 1/h, respectively. IIV was included for CL/F, Vc/F, and proportional residual error in the model and were estimated with %CV values of 27.6%, 43.7%, and 53.1%, respectively. Only eGFR [CL/F] and weight [apparent clearances and volumes] were included as covariates in the 3TC model, and their effect was not found to be clinically relevant in exposure analysis, with borderline significance for the Q1 and Q4 of eGFR distribution in the analysis dataset. Because clinical dosing of 3TC (50 to 300 mg) is critically attributed to a patient's renal function according to current guidelines, the identification of eGFR as a significant covariate in this analysis poses no requirement for additional changes to the current dosing schemes.

Conclusion: The findings are consistent with the conclusion of the previous analyses in HIV-infected, treatment-naïve, and virologically suppressed treatment-experienced adult subjects; the effects of identified covariates are small and not clinically relevant. The exposure of DOVATO FDC (DTG/3TC, 50/300 mg) following repeat oral administration are similar between adult and adolescent subjects. No further dose adjustment is therefore recommended for adolescent subjects as compared to the current labels for both DTG and 3TC.

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