INTERNATIONAL WORKSHOP ON CLINICAL PHARMACOLOGY OF HIV, HEPATITIS AND OTHER ANTIVIRAL DRUGS

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ABSTRACT BOOK

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Oral Presentations

International Workshop on Clinical Pharmacology of HIV, Hepatitis, and Other Antiviral Drugs 2024

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ORAL ABSTRACTS

POSTER ABSTRACTS

1

1 - PRECLINICAL PHARMACOKINETICS OF NOVEL LONG-ACTING TENOFOVIR ALAFENAMIDE/BICTEGRAVIR SOLID INJECTABLE IN RATS

Arshad U.[1,3], *Barlow E.*[2,3], *Cox H.*[1,3], *Sharp J.*[1,3], *Pertinez H.*[1,3], *Herriott J.*[1,3], *Kijak E.*[1,3], *Gallardo-Toledo E.*[1,3], *Hobson J.*[2,3], *Dwyer A.*[2,3], *Massam J.*[2,3], *Curley P.*[1,3], *Rannard S.*[2,3], *Owen A.*[1,3]

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Background: Tenofovir alafenamide (TAF), is a nucleoside reverse transcriptase inhibitor approved for the treatment of HIV in combination with Bictegravir (BIC), an integrase strand transfer inhibitor, and emtricitabine. Daily oral treatment and pre-exposure prophylaxis are highly effective when taken as prescribed. However, inadequate adherence to oral products reduces effectiveness. Another integrase inhibitor, cabotegravir, has been demonstrated to be effective in pre-exposure prophylaxis and is available clinically as a long-acting (LA) injectable. This work describes preclinical pharmacology of a novel TAF/BIC LA solid injectable.

Material and Methods: TAF and BIC formulations were manufactured using emulsion-templated freeze-drying and processed into a compressed solid using vacuum compression moulding (VCM). Male Sprague Dawley rats (n = 4, 250-300g) were administered a single TAF and single BIC subcutaneous implant (2 x 8 mm) in the scapular region using a 12-gauge needle. The implant formulations consisted of 70 wt% BIC or TAF and 30 wt% PVA (24mg of each drug). Plasma samples were collected from the lateral tail vein throughout a 13-week period. Tenofovir (TFV) and BIC concentrations were quantified in plasma using liquid chromatography-tandem mass spectrometry (LC-MS/MS).

Results: Dispersion of formulations in water yielded TAF or BIC particles with 100 – 250 nm and 700 – 850 nm z-average diameters respectively, as measured by dynamic light scattering. TFV plasma concentrations remained above the human Ctrough for 7 days and calculated parameters were as follows; a Cmax of 2681 ng/mL, Tmax of 6 hours, and AUC0-tlast of 59.6 µg.h/mL and T1/2 of 2.1 days. Plasma BIC concentrations exceeded the human oral steady-state Ctrough within 3 hours of administration and remained above this for 84 days (Cmax of 33777 ng/mL, Tmax = 1 day, AUC0-tlast = 17669 µg.h/mL, T1/2 of 31 days). No behavioural issues were encountered, animals gained weight throughout and no overt implant-site reactions were observed.

Conclusions: Preclinical data for a novel TAF and BIC solid injectable demonstrated sustained concentrations in rats over a period of 7 and 84 days, respectively. Assessment of TAF pharmacokinetics in rats is complicated by species-specific metabolisms preventing assessment of TAF itself. Since benefits of TAF over TFV are derived from augmented intracellular permeation, further investigation of TAF PK is needed in a species more representative of human metabolism. Further work is required to optimise the implant pharmacokinetics, and formally assess injection site safety which has been an issue for other LA approaches for TFV prodrugs.

2

2 - DOSE LINEARITY STUDIES OF A GLECAPREVIR AND PIBRENTASVIR LONG-ACTING INJECTABLE FORMULATION IN SPRAGUE DAWLEY RATS

Gallardo-Toledo E.[1,2], *Arshad U.*[1,2], *Pertinez H.*[1,2], *Sharp J.*[1,2], *Herriott J.*[1,2], *Kijak E.*[1,2], *Cox H.*[1,2], *Savage A.*[2,3], *Unsworth C.*[2,3], *Dwyer A.*[2,3], *Hobson J.*[2,3], *Tatham L.*[1,2], *Thomas D.*[4], *Curley P.*[1,2], *Rannard S.*[2,3], *Owen A.*[1,2]

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Background: Glecaprevir (G) and pibrentasvir (P) is a fixed-dose combination (FDC) approved to treat all six types of hepatitis C. However, patient adherence to oral treatment regimens remains a major challenge with considerably lower efficacy in clinical use than reported in RCTs. Long-acting injectables (LAI) could address poor adherence through long-term exposure of both G and P after a single administration.

Materials and methods: Male Sprague Dawley rats (n = 4 per group) were intramuscularly dosed into both thighs with LAI suspensions of G and P alone, and both drugs in a FDC (GP-FDC, 1:1 ratio) as follows: GP-FDC group (75 mg G + 75 mg P, 150 µL/thigh), G group (150 mg G, 150 µL/thigh), P group (150 mg P, 150 µL/thigh), and GP group (75 mg G, 150 µL/left thigh + 75 mg P, 150 µL/right thigh). A second set of experiments evaluated the effects of different GP-FDC active doses (18.75, 37.5, and 75 mg) on the pharmacokinetics (PK) by changing the dosing volume (0.075, 0.15 and 0.3 mL of GP-FDC at 500 mg/mL) or GP-FDC suspension strength (0.3 mL of GP-FDC at 125, 250, and 500 mg/mL). For all studies, blood samples were collected from the lateral tail vein up to 90 days post dose. G and P concentrations were quantified in plasma using a validated method by LC MS/MS.

Results: GP-FDC showed plasma concentration-time profiles above the reported median human Ctrough for both G and P over the 90 days. However, for single drug-LAI suspensions, plasma concentrations of P were above the human Ctrough over 70 days for both P alone and GP groups, whereas a more rapid drop in plasma concentrations were observed for G in both G and GP groups, after 35 and 28 days, respectively. In the second set of experiments, a linear dose dependent PK was observed with increasing volume, with a proportional increase in the AUC0-tlast for both G and P (G: 106, 220, and 390 µg·h/ml and P: 157, 346, and 513 µg·h/ml for 0.075, 0.15, and 0.3 mL, respectively). Conversely, when dose was titred by GP-FDC suspension strength, a non-dose linear increase in the AUC0-tlast for both G and P was observed (G: 156, 325, 390 µg·h/ml and P: 200, 400, 513 µg·h/ml for 125, 250, and 500 mg/mL). Notwithstanding, both experimental conditions provided appropriate plasma exposures; while the 18.75 mg dose maintained G and P exposure above the human Ctrough for 5 and 11 weeks, respectively, the 37.5 and 75 mg doses maintained plasma exposures above the human Ctrough for both G and P throughout the 90 days.

Conclusions: Plasma exposure of both G and P between GP-FDC and single drug-LAI suspensions suggested that P helps to maintain a longer terminal half-life for G. Moreover, PK data demonstrate a sustained exposure over a period of 90 days for both G and P in rats when novel GP-FDC is administered. Optimisation of drug ratios, as well as GLP toxicology assessments, is required to progress to human clinical trials.

3

3 - ONCE DAILY DOSING OF DOLUTEGRAVIR IN COMBINATION WITH RIFAMPICIN IN INFANTS AND CHILDREN LIVING WITH HIV: A POPULATION PHARMACOKINETIC APPROACH

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Background: Dolutegravir clearance is increased in presence of rifampicin, due to induction of UGT1A1 and CYP3A4. This drug-drug interaction between rifampicin and dolutegravir can be overcome by twice-daily dolutegravir dosing with daily dose doubled. However, twice-daily dosing complicates treatment adherence, once-daily being preferred for children. Griesel et al. (2023) showed comparable virological suppression rates of once-daily dosing of dolutegravir versus twice-daily dosing in combination with rifampicin in adults. We therefore aimed to establish a potential once-daily dosing regimen for dolutegravir co-administered with rifampicin for use in the paediatric population.

Methods: We developed a paediatric population pharmacokinetic model of dolutegravir in NONMEM based on intensive pharmacokinetic data from three large paediatric clinical trials i.e. ODYSSEY (NCT02259127), CHAPAS-4 (ISRCTN22964075) and EMPIRICAL (NCT03915366). The model was developed with 2522 dolutegravir plasma concentrations from 235 infants and children aged 3 months to 17 years, with concomitant rifampicin use in 36 subjects. To account for changes in pharmacokinetics as result of body size, all volume and flow parameters were allometrically scaled to a total body weight of 70 kg. Maturation of UGT1A1-mediated dolutegravir clearance in our population was also assessed. Physiologically plausible covariates were tested based on difference in the objective function value (dOFV) and the visual predictive checks (VPCs). A representative virtual population with 7000 children (3-<40 kg), equally distributed among different weight bands and formulations, was developed to perform the once-daily dosing simulations. Dosing of dolutegravir was based on the current World Health Organization (WHO) weight-band dosing recommendations. Our main outcome focused on the percentage of children reaching dolutegravir trough levels above the PA-IC90 of 0.064 mg/L.

Results: A one compartment model with first-order elimination and Erlang type absorption (two transit compartments) best described dolutegravir's pharmacokinetics. In our population, we estimated clearance, absorption rate constant and distribution volume with relative standard error of estimate (RSE) of 2.37 L/h (4.8%), 2.19 h-1 (4%) and 27.5 L (4.4%), respectively. Rifampicin coadministration increased dolutegravir clearance by factor 1.45 (RSE 11.6%). Dispersible tablets had 74% (RSE 8%) higher bioavailability versus film-coated tablets, whereas administration with food increased the bioavailability of film-coated tablets by 35% (RSE 8%) and decreased the bioavailability of dispersible tablets by 39.8% (RSE 9%). Simulations with our final model showed that 92.7% of the children in our virtual population reached dolutegravir trough levels above the PA-IC90 with once-daily dolutegravir (without food) co-administered with rifampicin compared to 81% in adults reported at week 24 in the study of Griesel et al.

Conclusions: Simulations based on our model suggest that once-daily dolutegravir co-administered with rifampicin has potential for children living with HIV. Therapeutic target attainment (above the PA-IC90) in the pediatric population is higher than what was observed in adult clinical data showing similar efficacy compared to twice-daily dolutegravir in co-administered with rifampicin. Further analysis of individual weight bands and other dosage scenarios are currently in process.

4

4 - PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELLING OF THE CO-ADMINISTRATION OF RITONAVIR-BOOSTED ATAZANAVIR AND RIFAMPICIN IN CHILDREN CO-TREATED FOR HIV AND TB

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Background: Children living with HIV are disproportionately affected by tuberculosis. Limited options are available for adequate treatment of both diseases because rifampicin, a mainstay of several anti-TB regimens, reduces the exposure of multiple antiretrovirals like ritonavir-boosted atazanavir (ATV/r). Recent modelling and clinical studies (DERIVE [NCT04121195]) suggest doubling the dose of ATV/r 300/100 mg from once to twice daily would overcome the drug-drug interaction (DDI) effect with rifampicin in adults. In this study, physiologically-based pharmacokinetic (PBPK) modelling was used to investigate if twice daily dosing of ATV/r could overcome the DDI effect of standard doses of rifampicin in children.

Material and Methods: The published PBPK model used for studying DDI between ATV/r and rifampicin in adults was modified into its paediatric version. Equations describing key anatomical and physiological parameters (e.g. organ weights and blood flow) were modified to paediatric versions between ages 7 to 18 years. Adult levels of enzyme activity were maintained in the paediatric model. Rifampicin's drug absorption rate, apparent clearance and volume of distribution were also modified to paediatric values within the simple compartment used to model rifampicin PK. Model predictions were validated using observed clinical PK data of ATV/r alone and rifampicin alone in children with acceptability criteria maintained as absolute average fold error less than 2 between simulated and observed values. ATV/r 300/100 mg once daily and twice daily were each simulated with co-administered 300 mg, 450 mg and 600 mg rifampicin in children distributed in 3 weight-bands: 25-30 kg (7-11 years), 30-39 kg (8-14 years), and 50-70 kg (12-18 years), respectively. Simulated ATV Ctrough was compared against a clinical cut-off, ATV protein binding-adjusted 90% inhibitory concentration (PAIC90, 14 ng/mL).

Results: The paediatric PBPK model was adequately validated with simulated PK of atazanavir and rifampicin having AAFEs <2 compared to their corresponding observed values. With ATV/r 300/100 mg once daily, standard doses of rifampicin reduced ATV Ctrough and AUC by 99 and 67%, 99 and 72%, and 99.8 and 78% in children weighing 25-35 kg, 30-49 kg, and 50-70 kg, respectively. In the same weight-bands, 42, 65 and 94% of the simulated population were predicted to have ATV Ctrough <PAIC90, respectively. When increasing ATV/r to 300/100 mg twice daily with standard doses of rifampicin, 9, 4, and 9% of the simulated population of children were predicted to have ATV Ctrough less than the PAIC90, respectively.

Conclusion: Modelling suggests that coadministration of once daily standard doses of rifampicin with ATV/r 300/100 mg given twice daily would maintain efficacious ATV concentrations in children weighing 25-70 kg (7-18 years). Clinical studies in children are needed to confirm the safety and efficacy of these dosing combinations in children.

5

5 - BICTEGRAVIR EXPOSURES IN ADULTS WITH HIV AND TUBERCULOSIS ON A RIFAMPICIN-BASED TUBERCULOSIS TREATMENT REGIMEN

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Background: Bictegravir (BIC) has not been evaluated in people with HIV (PWH) and tuberculosis (TB) taking rifampicin-based TB treatment. Healthy volunteer data showed that rifampicin reduced BIC exposure by about 80%, however, trough concentrations remained 3-fold above the inhibitory quotient (IQ1) of 0.162 mg/L. Potential exposures below IQ1 in few individuals or breakthrough viremia, may be mitigated by a long dissociation half-life of BIC from the HIV-1 integrase enzyme.

Methods: INSIGHT (NCT04734652) is an open-label, non-comparative phase-2b randomised controlled trial in ART-naïve or non-naïve adults with HIV and TB, initiated on a rifampicin-based TB regimen (< 8 weeks). Participants were randomised in a 2:1 ratio to either the BIC arm (bictegravir/emtricitabine/tenofovir-alafenamide) or a standard of care dolutegravir arm (TLD), dosed twice-daily until 2 weeks post-TB treatment and once-daily thereafter, until 48 weeks. Forty-three participants in the BIC arm were enrolled in a semi-intensive pharmacokinetic (PK) sub-study. Semi-intensive PK sampling was done at pre-dose, 1, 2, 4, 6, and 8-12-hours post-dose during TB treatment and pre-dose, 1, 2, 4, 6-8, 24-25 hours post-dose after TB treatment. BIC concentrations were assayed using a validated LC-MS/MS method. Non-compartmental PK analyses for BIC were conducted in R using the PKNCA package (version 10.2). Participants underwent regular clinical and safety visits, including HIV viral load measurements at baseline, weeks 4, 8, 12, 24, 40 and 48. We report the preliminary PK data and primary endpoint results for the proportion of participants with plasma HIV-1-RNA <50 copies/mL at the end of TB treatment (week 24).

Results: We enrolled 122 participants: 80 in the BIC and 42 in the DTG arm. Forty-three (35%) were female, with median (IQR) baseline viral load (copies/mL) and CD4+ (cells/µL) of 75649 (22784-391299) and 172 (108-352) (BIC arm) and 73735 (21242-544830) and 139 (97-237) (DTG arm). In participants in the semi-intensive PK sub-study, 75 PK profiles were evaluated during TB treatment and 22 PK profiles post-TB treatment. Geometric mean (GM), (CV%) of area under the concentration-time curve from 0 to 24 hours (AUC0-24) and the trough concentration (Ctau) for twice-daily BIC during TB treatment were 30.9 mg*h/L (42.2%) and 0.397 mg/L (73.4%) and for once-daily BIC post-TB treatment were 94.9 mg*h/L (35.9%) and 2.29 mg/L (45.1%), respectively. BIC Ctau during TB treatment were reduced but remained above IQ1 in > 98% of participants. HIV-1-RNA at week 24 was < 50 copies/mL in 71/73 (97%) and 36/37 (97%) of participants in the BIC and DTG arms, respectively, in the per-protocol analysis, [71/75 (95%) in BIC (two early withdrawals) and 36/38 (95%) in DTG arm (one death) in FDA snapshot analysis]. None of the 15 reported serious adverse events were related to study treatment.

Conclusions: INSIGHT interim results suggest that twice-daily bictegravir/emtricitabine/tenofovir-alafenamide with rifampicin-based TB treatment achieves target concentrations for viral efficacy. In the <2% of participants with Ctau below IQ1, viral suppression was maintained, likely due to the long dissociation half-life of BIC from HIV-1 integrase enzyme (163hrs). PK, efficacy and safety data support the use of this regimen in PWH and TB

6

6 - EXPERIENCE OF A NIRMATRELVIR/RITONAVIR DRUG-DRUG INTERACTION EXPERT ADVICE SERVICE

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Background: Nirmatrelvir/ritonavir is a protease inhibitor antiviral drug indicated in the treatment of severe acute respiratory syndrome coronavirus-2 infections in high-risk patients for a severe disease. Unfortunately, ritonavir, used to boost nirmatrelvir pharmacokinetics, can also inhibit or induce the metabolism of other co-administered drugs substrates. This may lead to a subsequent drug-drug interaction (DDI) risk and thus, to adverse drug reaction. To secure the drug's prescription and help clinicians with drug indication, we developed a DDI expert advice service dedicated to nirmatrelvir/ritonavir. The aim of this study was to described this service provided by the clinical pharmacology department of the Rennes University Hospital, Rennes, France.

Material and methods: We collected all DDI advices provided by the five senior clinical pharmacologists of the department regarding nirmatrelvir/ritonavir in 2022 and 2023. These advices were given by phone, email or through a tele-expertise system. The following data were gathered: patient's age and sex, renal function, date of nirmatrelvir/ritonavir initiation, clinical department requiring the expert advice, patient's treatments, and advice provided. Data were presented as medians and interquartile and percentages.

Results: In 2022 and 2023, the expert advice services provided advices for 123 and 224 patients, respectively. These 347 advices relate on 2858 prescription lines. In 2022, advices were provided for 881 prescription lines for patients of median age of 69 years [57-76] and estimated glomerular filtration rate (eGFR) of 77 mL/min [59-91]. The main pharmacological classes were: cardiology drugs (26.8%), endocrinology drugs (16.9%) and immunosuppressive agents (13.6%). The advice was distributed as follows: treatment continuation, treatment discontinuation during the antiviral course, dosage adjustment, and treatment switch in 71%, 19%, 7%, 3% of the cases, respectively. Only 3 patients (2.4%) were denied the drug due to contra-indications. Drug monitoring was proposed in 5% of prescription lines. The top drug request was tacrolimus in 2022. In 2023, advices were provided for 1977 prescription lines for patients of median age of 77 years [67-85] and estimated glomerular filtration rate (eGFR) of 77 mL/min [55-90]. The most common requests were for endocrinology drugs (22%), cardiac drugs (21%), and neurology drugs (18%). The advice was distributed as follows: treatment continuation, treatment discontinuation during the antiviral course, dosage adjustment, and treatment switch in 77%, 14%, 6%, 3% of the cases, respectively. Treatment was denied for 18 patients (8%). Drug monitoring was proposed in only 0.6% of prescription lines. The top drug request was acetaminophen in 2023.
Some serious risks were prevented by the services notably DDI with calcineurin inhibitors (n=44), statins (122), lercanidipine (n=14) or colchicin (n=7).

Conclusions: This DDI expert service advice provided by clinical pharmacologists allows securing the combination of nirmatrelvir/ritonavir with other concomitant drugs. Most of eligible patients to the antiviral drug can benefit from it despite the risk of drug-drug interaction. The typology of advices shifted with time with initially more specialized advices, notably for transplant recipients, to more general practitioner requests probably due to the dissemination of the information beyond the tertiary center and the increase experience gained by hospital practitioners in our center.

7

7 - CELLULAR PHARMACOLOGY OF NRTI ANABOLITES IN PBMCS AND PLATELETS AMONG PERSONS WITH HIV RECEIVING ABC/3TC- OR TAF/FTC-BASED ART

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Background: Nucleos(t)ide reverse transcriptase inhibitors (NRTIs) undergo phosphorylation within a variety of cell types due to structural similarities with endogenous nucleotides. Characterizing the intracellular pharmacology of NRTI anabolites in less commonly studied cell types, such as platelets, may provide insight into associations with cardiometabolic side effects. The objectives of these analyses were to compare (1) relative cellular concentrations of NRTIs in peripheral blood mononuclear cells (PBMCs) and platelets and (2) profiles of platelet metabolomics among persons with HIV (PWH) taking either tenofovir (TFV) alafenamide (TAF)/emtricitabine (FTC) or abacavir (ABC; converted to carbovir [CBV])/lamivudine (3TC).

Materials and Methods: PWH receiving ABC/3TC 600/300mg or TAF/FTC 25/200mg as part of their antiretroviral therapy (ART) with HIV VL <200 copies/mL for ≥6 months, were enrolled (NCT04301661). Adherence was confirmed using video directly observed therapy (vDOT) for 28±3 days prior to pharmacokinetic sample collection (2±1 hours post-dose). Whole blood was processed into PBMCs and platelets. LC-MS/MS methods were used to quantify anabolites (TFV-DP, CBV-TP, FTC-TP, 3TC-TP) in both cell types, in addition to the monophosphate (MP) and diphosphate (DP) fractions in platelets. Drug concentrations (per 106 cells) were normalized to cell volume to determine relative intracellular concentrations in PBMCs and platelets, reported as geometric mean (GM) and GM ratio (GMR). Extracts of resting platelets were analyzed using a previously established targeted metabolomics MS assay. Differences between arms were screened using fold-changes and Wilcoxon rank-sum tests between median metabolite peak intensities.

Results: Data were available in 25 PWH receiving ART containing either ABC/3TC (n=12) or TAF/FTC (n=13); 88% were male, 52% white, 20% Black, and 24% Hispanic/Latino. Median (IQR) age was 46 (38, 54) years and BMI 26.0 (22.1, 31.3). Baseline demographics were comparable between treatment arms. Participants on ABC/3TC were on dolutegravir (n=12); darunavir/cobicistat (n=1) or darunavir/ritonavir (n=1). Participants on TAF/FTC were on bictegravir (n=12) or both raltegravir and rilpivirine (n=1). Overall median (IQR) adherence was 96% (90%, 100%). The GM concentrations of active drug (per 106 cells) in PBMC were 619 fmol for TFV-DP, 78.2 fmol for CBV-TP, 6.72 pmol for FTC-TP and 8.66 pmol for 3TC-TP; and platelets: 10.0 fmol for TFV-DP, 3.25 fmol for CBV-TP, 0.15 pmol for FTC-TP and 0.14 pmol for 3TC-TP. GMRs of NRTI anabolite concentrations in platelets versus PBMC, normalized to cell volume, were: 0.42 (TFV-DP), 1.08 (CBV-TP), 0.56 (FTC-TP) and 0.41 (3TC-TP). Cellular anabolite fractions within platelets were: TFV-DP>TFV>TFV-MP, CBV/3TC-TP>CBV/3TC-MP>CBV/3TC-DP and FTC-TP>FTC-DP>FTC-MP. Metabolomics analysis showed no significant differences in platelet metabolites between arms.

Conclusions: NRTIs exhibited preferential cell loading into PBMCs compared to platelets except for CBV, which has similar concentrations in both PBMC and platelets. The TP fraction was highest across all NRTIs in platelets, and the MP fraction was higher than DP for CBV, 3TC, and TFV. These results suggest that the NRTI type and cell-specific process dictate differential patterns in drug accumulation. Metabolomic profiles in resting platelets did not reveal differences between PWH on either TAF/FTC or ABC/3TC. Further investigation is needed to determine the clinical significance of these findings.

8

8 - FAVIPIRAVIR PHARMACOKINETICS IN SALIVA, TEARS AND NASAL SECRETIONS OF HOSPITALISED COVID-19 PATIENTS FOLLOWING INTRAVENOUS FAVIPIRAVIR ADMINISTRATION.

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Background: SARS-CoV-2 is transmitted between individuals when virions trapped in aerosols or large droplets are expelled through conversation, coughing or sneezing. Due to consistent emergence of new variants, evaluation of therapeutics for SARS-CoV-2 is crucial to maximise treatment options should more virulent or treatment resistant strains arise. Establishing the concentration of potential therapeutics in sites of SARS-CoV-2 transmission is essential to assess compartmentalisation and prophylactic potential. Here we report favipiravir (FVP) concentrations in saliva, tears and nasal secretions in hospitalised COVID-19 patients enrolled on the AGILE CST-6 clinical trial.

Materials and Methods: AGILE CST-6 is a randomised, multicentre, seamless, adaptive, phase I/II platform study to evaluate safety and efficacy of intravenous (IV) FVP for the treatment of COVID-19. Patients with laboratory confirmed COVID-19 were enrolled 2:1 to receive IV FVP or standard of care (SoC); four cohorts of six patients (n=4 FVP, n=2 SoC) were enrolled, with escalating doses per cohort (600 mg, 1200 mg, 1800 mg, 2400 mg). Patients received IV FVP twice daily over 7 days, with paired plasma and non-plasma samples (saliva, nasal swabs, tear strips) collected between 6-12 hours post completion of IV infusion, on Day 1 and 3. FVP was quantified using validated LC-MS methods and FVP concentrations expressed as ng/mL. Descriptive statistics were computed (Pheonix 64, WinNonlin, v8.3) and FVP non-plasma: plasma ratios (NP:P) determined. Relationships between paired quantifiable non-plasma and plasma concentrations were evaluated by linear regression.

Results: Sixteen individuals [7 female at birth; median (range) age, weight, number of days with COVID-19 symptoms were 76.5 years (52-93), 78.6 kg (52.1-125), 5 days (2-11), respectively] received at least 6 doses of IV FVP. Analysis included 32 plasma/nasal, 31 saliva and 30 tear samples. FVP was quantifiable in 100%|91%|97% of saliva|nasal|tear samples collected 6.1-7.2 hours post IV infusion. FVP concentrations increased with dose [600|1200|1800|2400 mg bd] although significant intra- and inter-subject variability was noted within the dosing cohorts. On Day 3, median FVP concentrations were 1336|38730|47000|125468 ng/mL in plasma, 69|1042|4218|9742 ng/mL in saliva, 2455|2247|7968|13420ng/mL in nasal secretions and 693|5762|3620|34985 ng/mL in tears, respectively. Accumulation of FVP was observed in all matrices from Day 1 to Day 3. Median (range) NP:P ratios were saliva 0.06 (0.01-0.28), nasal 0.42 (0.03-21.28) and tears 0.30 (0.00-6.54). Non-plasma and plasma concentrations were significantly correlated on Day 3 ($r > 0.724$; $p < 0.003$). On Day 1, 13% of plasma samples (all 2400 mg dose) were above the FVP SARS-CoV-2 in vitro EC90 (24.9 µg/mL); all non-plasma levels were below this threshold. At Day 3, 56% of plasma samples (≥1200 mg dose), 12% of nasal and 6% of tear samples (2400mg dose) exceeded this threshold.

Conclusions: This is the first report of FVP measured at sites of SARS-CoV-2 transmission. These data suggest that achieving concentrations equivalent to the EC90 may be difficult to achieve in saliva, nasal and ocular compartments, even when administering higher dose IV FVP (2400 mg bd). FVP predominantly penetrates into nasal secretions, followed by tears and saliva, with substantial interindividual variability. PK/PD relationships for IV FVP are under evaluation.

9

9 - OPTIMAL DOSE AND SAFETY OF INTRAVENOUS FAVIPIRAVIR IN HOSPITALISED PATIENTS WITH SARS-COV-2: A PHASE I, OPEN-LABEL, DOSE-ESCALATING, RANDOMISED CONTROLLED STUDY.

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Background: AGILE is a Phase Ib/IIa platform for rapidly evaluating candidate therapeutics for the treatment of COVID-19. In this trial (NCT04746183), we evaluated the safety and optimal dose of a novel intravenous (IV) formulation of favipiravir (FVP) in hospitalised participants with SARS-CoV-2.

Materials and Methods: CST-6 was a dose-escalating, open-label, randomised, controlled Bayesian adaptive Phase Ib trial carried out at the NIHR Liverpool Clinical Research Facility. Participants (hospitalised adults with PCR-confirmed SARS-CoV-2 infection within 14 days of onset of symptomatic COVID-19) were randomised 2:1 in groups of 6 participants (n = 4 FVP, n = 2 SoC) to 600mg, 1200mg, 1800mg and 2400mg doses of IV FVP twice daily for 7 days or standard of care (SoC). Throughout the study period, clinical data, safety evaluations, virology and pharmacokinetics were collected at predefined timepoints. FVP was quantified using validated LC-MS methods with FVP concentrations expressed as ng/mL. The primary outcome was safety, with toxicity considered to be unacceptable if the probability of 30% or greater dose-limiting toxicity related to FVP over controls was 25% or greater, as calculated by the Bayesian model. Secondary outcomes included clinical progression scores, pharmacokinetic parameters and virological endpoints.

Results: Of 30 participants screened, 24 were enrolled between 10/Sep/2022 and 01/Nov/2023 [10/24 female; median age was 74 years (range 52-93)]. FVP was well tolerated at all doses, despite a high background rate of adverse events reflecting the frailty and co-morbidity of participants. As in previous studies of FVP, transient hyperuricaemia was observed in patients in the treatment cohorts. This was asymptomatic in all cases and resolved on completion of treatment. There were no serious adverse events or severe (≥ grade 3) adverse events that were deemed possibly or probably related to FVP by an independent, blinded assessor. The probability of greater than 30% excess toxicity over controls at 2400mg, as estimated by the Bayesian model was 2.7%. PK exposures increased proportionally to dose, although there was notable variability between participants within each cohort. Significant FVP accumulation in plasma occurred; for cohorts 1-4 respectively (600|1200|1800|2400mg BD), median day 1 Clast (6-12 hours post-infusion) was 500 (below LLQ)|4242|5109|23573 ng/mL, median day 3 Clast was 1335|38730|47000|125468 ng/mL.

Conclusions: In this phase Ib multiple ascending dose study of a novel IV formulation of FVP we administered higher sustained doses than previously used, up to 2400mg twice daily. Despite the frail and co-morbid nature of the population admitted to hospital with COVID-19, IV FVP was safe and well tolerated at this dose. Plasma PK studies demonstrated accumulation at days 3 and 5, in contrast to previous studies which employed loading doses. Significant PK variability was noted between individuals. Although well tolerated, based on PK data we report and recent FVP EC90 data, we do not recommend FVP for later stage clinical trial evaluation as a treatment for COVID-19. FVP remains a potentially important candidate as a treatment for emerging viral threats including pandemic influenza.

10

10 - 2024 UPDATES TO THE QUÉBEC ANTIRETROVIRAL THERAPEUTIC DRUG MONITORING GUIDELINES – KEY CHANGES OVER 10 YEARS

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Background: Therapeutic drug monitoring (TDM) of antiretrovirals has the potential to improve virologic response and tolerability. In 2013, TDM guidelines in Québec (Canada) were published to assist clinicians. In 2016, an addendum was developed for newer antiretrovirals (dolutegravir, elvitegravir, rilpivirine). From 2018 to 2023 we underwent an update to the guidelines.

Methods: An externsive literature review of published articles and grey literature was conducted using predefined terms. Three waves of literature review were completed (2018, 2020/2021 and 2022). After August 1st 2022, additional articles or conference proceedings were added if judged important. Indications for TDM for each antiretroviral were categorized based on strength of the recommendation (A – strongly recommended; B – moderately recommended; C – optional; D – not recommended) and quality of the evidence (I – prospective TDM trial; II – retrospective or prospective observational data; III – expert opinion or small number of cases ≤ 10). The rating was determined by two pharmacists by consensus. If consensus was not met, a decision was taken by the working group. Target concentrations were also reviewed. We present key changes, including the percent of recommendations in the current guidelines that were modified compared to the previous recommendations.

Results: Older antiretrovirals (n=5) were removed and newer agents (n=6) added to the 2024 guidelines. Overall, 374 references were retained. When comparing indications for antiretroviral TDM in 2013 (including the 2016 addendum) with the 2024 guidelines, for antiretrovirals and indication categories that were present in both guides, there was a total of 288 indication category-antiretroviral pairs. Overall, the quality of the evidence improved for 16.6% (n=48) and decreased for 4.5% (n=13) of the recommendations. For the integrase inhibitors, the strength of the recommendations increased in 5.5% (4/72) of cases and decreased in 19.4% (14/72) of cases. For the non nucleoside reverse transcriptase inhibitors, these values were 14.6% (14/96) and 10.4% (10/96), and for the protease inhibitors 11.5% (11/96) and 12.5% (12/96). For integrase inhibitors, the majority (70.6%) of the cases where the strength of the recommendation dropped was associated with no longer recommending TDM; 50% of these changes were based on new studies with improved quality. Specifically for integrase inhibitors, the 2024 guidelines strongly or moderately recommend TDM for 11.2% and 20.6% of the indication category-antiretroviral pairs, respectively; most commonly for drug interactions, low-level viremia or virologic failure, people with significant viral resistance mutations, pregnancy, severe hepatic impairment, suspected malabsorption, and pediatrics. For intramuscular cabotegravir/rilpivirine, we do not recommend routine TDM (D-III). We moderately recommend TDM for this regimen for obese persons who have at least one additional risk factor for virologic failure (B-II). Our target concentrations for virologic efficacy were changed for darunavir, etravirine, nevirapine, rilpivirine; and for toxicity for atazanavir, lopinavir, nevirapine and dolutegravir.

Conclusions: Over the last 10 years, the quality of the evidence to support or not antiretroviral TDM has improved. For integrase inhibitors, the strength of the recommendations have decreased for about 20% of the recommendations. Antiretroviral TDM is still moderately to strongly recommended in some situations.

11

11 - ESTIMATION OF GANCICLOVIR EXPOSURE BY MACHINE LEARNING

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Background: Valganciclovir, an oral prodrug of ganciclovir (GCV), is prescribed to prevent cytomegalovirus infection following transplantation. Dosing adjustments are often based solely on creatinine clearance to achieve a target GCV AUC0-24 h of 40-50 mg.h/L. However, this approach can result in significant overexposure or underexposure to the drug, potentially compromising efficacy or increasing toxicity. This study aimed to develop and validate machine learning (ML) algorithms capable of accurately estimating GCV AUC, thereby improving dosing precision.

Methods: We simulated 5000 patients for each dosing regimen using two published population pharmacokinetic models (Lalagkas et al., Veniza et al.). These simulated patients were split into training (75%) and testing (25%) datasets. To further evaluate generalizability, an additional validation dataset of 200 patients per regimen was created using two distinct models (Caldés et al., Chen et al.). We developed three ML algorithm configurations using creatinine clearance in combination with either 2 or 3 drug concentrations sampled between T0 and T12h, and 3 concentrations restricted between T0 and T6h. The performance of these ML configurations was assessed in both the testing and validation datasets and compared to Maximum a Posteriori Bayesian estimation (MAP-BE) applied to the Lalagkas et al. and Veniza et al. models within the validation datasets.

Results: Among the ML algorithms evaluated, XGBoost consistently demonstrated the lowest root mean square error (RMSE) during a 10-fold cross-validation, indicating superior predictive accuracy. Models incorporating 3 blood samples yielded the most precise GCV AUC predictions. In the testing dataset, these models exhibited a relative bias ranging from -0.02% to 1.5% and a relative RMSE between 2.6% and 8.5%. In the validation dataset, the models achieved a relative bias of 1.5% to 5.8% and 8.9% to 16.5%, with a relative RMSE of 8.5% to 9.6% and 10.7% to 19.7% for the Caldés et al. and Chen et al. models, respectively. Notably, the ML algorithm predictions of AUC were significantly more accurate compared to those obtained through the MAP-BE method.

Conclusions: The XGBoost machine learning models provided highly accurate estimates of GCV AUC from as few as 2 or 3 blood samples in combination with creatinine clearance. This approach represents a robust limited sampling strategy that can optimize therapeutic drug monitoring, potentially enhancing the clinical management of patients undergoing valganciclovir therapy by reducing the risks associated with drug overexposure and underexposure.

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12 - ADHERENCE INSIGHTS FROM TAF/FTC-BASED ART CO-ENCAPSULATED WITH AN INGESTIBLE SENSOR AMONG VIROLOGICALLY SUPPRESSED PERSONS WITH HIV

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Background: QUANTI-TAF (NCT04065347) measured adherence for approximately 16 weeks using digital pills with ingestible sensors (ID-Cap System, etectRx) paired with tenofovir-diphosphate/emtricitabine-triphosphate (TFV-DP/FTC-TP) concentrations in dried blood spots (DBS) among 84 persons with HIV (PWH) receiving daily oral tenofovir alafenamide/emtricitabine (TAF/FTC)-based antiretroviral therapy (ART) for ≥6 months. This analysis focused on digital pill adherence patterns.

Material and Methods: We categorized each recorded dose by interval length (>36 hours [late/missed]; 36-18 hours [on-time]; <18 hours [early/stacked]). Chi-squared tests compared the proportion of observed dosing intervals and detected versus manually entered doses. Kaplan-Meier analysis evaluated digital pill system use from enrollment to end-of-study, censored at week 16. We used generalized estimating equations with a logit link to calculate the odds ratio (OR [95% CI]) of a missed dose according to day of the week, or between Sunday-Thursday and Friday-Saturday. We summarized HIV-1 RNA, adherence, and TFV-DP/FTC-TP in DBS at visits with suppressed HIV-1 RNA (<200 copies/mL) and low (<85%) cumulative (enrollment to visit) digital pill adherence as proportion (%) or median (IQR).

Results: Overall, adherence was 93% (8650 recorded doses/9280 expected). Dosing intervals were mostly on-time (7991 [92%]), with smaller numbers of late/missed doses (356 [4%]) or early/stacked doses (303 [4%]), P<0.0001. Significantly more doses were detected (7948 [92%]) than manually entered (702 [8%]), P<0.0001. The proportion of participants on-study was 84/84 (100%) at week 4, 81/84 (96%) at week 8, 77/84 (92%) at week 12, and 73/84 (87%) at week 16. Median (IQR) cumulative adherence was 100% (100%-100%) at week 4 and 99% (96%-100%) at week 12 and at week 16. The OR (95% CI) for a missed dose was higher on Friday compared with Monday (1.35 [1.02, 1.79]; P=0.04) or Tuesday (1.34 [1.04, 1.73]; P=0.03), and on Saturday compared with Sunday (1.39 [1.08, 1.79]; P=0.01), Monday (1.58 [1.14, 2.19]; P=0.006), Tuesday (1.57 [1.23, 2.02]; P=0.0004), Wednesday (1.38 [1.01, 1.88] P=0.04), or Thursday (1.47 [1.11, 1.96]; P=0.008). Accordingly, the OR (95% CI) for a missed dose was higher on Friday-Saturday compared with Sunday-Thursday (1.37 [1.15, 1.63]; P=0.0005). 335/404 total visits (83%) assessed HIV-1 RNA (all <200 copies/mL) and 247/335 (74%) of these visits also had cumulative adherence results (not measured before enrollment). 19/247 (8%) of these visits showed virologic suppression with low cumulative adherence: HIV-1 RNA was 0, <20, or between 26-86 copies/mL at 9/19 (47%), 4/19 (21%), and 6/19 (32%) visits, respectively. Median (IQR) cumulative adherence, TFV-DP in DBS, and FTC-TP in DBS at these 19 visits was 79% (70%-82%), 2418 (2039-3444) fmol/punches, and 2.79 (2.20-3.94) pmol/punches, respectively.

Conclusions: Digital pill system use remained high for 16 weeks and provided detailed adherence insights among virologically suppressed PWH receiving TAF/FTC-based ART. PWH receiving daily oral ART may stack doses to compensate for late/missed doses; missed doses were more likely to be on Friday-Saturday compared with Sunday-Thursday. Modern ART's potency is highlighted by virologic suppression even with intermittent non-adherence. Future research could leverage digital pill systems for adherence monitoring in clinical trials of novel oral dosing regimens such as long-acting weekly oral ART.

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13 - LONG-ACTING CABOTEGRAVIR AND RILPIVIRINE PLASMA EXPOSURES IN THE CLINICAL SETTING: THE ROLE OF PHARMACOGENETICS

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Background: Wide inter-individual variability in the pharmacokinetics of rilpivirine (RPV) and cabotegravir (CABO) has been reported in the first weeks after starting long acting injectable drugs (LAI) treatment. Furthermore, reduced RPV and/or CABO plasma trough concentrations combined with other risk factors (i.e. resistance-associated mutations, BMI ≥ 30 kg/m2) have been related with increased risk of virologic failure. However, data on the potential role of pharmacogenetics in affecting LAI pharmacokinetics and, possibly, the clinical outcome are lacking. Consequently, we aimed at evaluating the impact of genetic polymorphisms in affecting LAI drug exposure in PWH.

Material and Methods: RPV and CABO concentrations were quantified by chromatography, both in plasma and in peripheral blood mononuclear cells (PBMCs), before starting therapy (oral administration, baseline, only for RPV) and at 1, 3, 5, 7, 9 and 11 months (M) of therapy with LAI administration. The 4×PA-IC90 were considered as the efficacy cut-off values, set at 50 and 664 ng/mL for RPV and CABO, respectively. Regression analysis was performed in order to evaluate which factors are able to predict the efficacy-related values of 50 ng/mL for RPV and 664 ng/mL for CABO respectively at 3 months of therapy.
Polymorphisms in genes encoding enzymes and transporters involved in drug metabolism and elimination (CYP2C19, CYP3A4, CYP3A5, UGT1A1, ABCB1, ABCG2) were analyzed through real-time PCR.

Results: 177 PWH were enrolled: 85.3% males with median age of 50.7 years (IQR 43.3; 59.1). Median plasma and PBMC antiretroviral drug levels at different timings are reported in table 1. Following associations were found: baseline plasma RPV and ABCB1 3435 CT/TT (p=0.039) and UGT1A1 023 TT (p=0.028), 1M CABO intracellular levels and ABCB1 1236 CT/TT (p=0.047), M3 ratio CABO and CYP2C19 AA (p=0.025) and UGT1A1 023 CT/TT (p=0.009), M3 RPV plasma and CYP3A4*22 (p=0.035), M5 ratio CABO and ABCG2 421 CA/AA (p=0.020), M5 plasma CABO and UGT1A1 023 TT (p=0.010), M9 plasma RPV and CYP3A4*22 (p=0.046), M11 plasma RPV and ABCB1 1236 CT/TT (p=0.042), M11 intracellular RPV and ABCG2 421 CA/AA (p=0.012) and finally, 11M CABO plasma concentrations and CYP2C19 GA/AA (p=0.006).
Regression analysis reported age and CYP3A4*22 as predictors of the RPV efficacy cut-off value of 50 ng/mL (34.5% of patients were below this level), whereas gender, CYP2C19*2 AA and ABCG2 421 AA predictors of the CABO cut-off value of 664 ng/mL (7.9% of patients were below this level) at 3 months of therapy.

Conclusions: This is the first study reporting a potential impact of genetic variants in affecting LAI concentrations and the risk of suboptimal drug exposure. Further research is needed to elucidate the complex interactions between genetics, drug metabolism, and treatment outcomes, ultimately paving the way for personalized and precision medicine approaches in HIV care.

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14 - MINIMAL IMPACT OF PREGNANCY ON RILPIVIRINE PHARMACOKINETICS: A POPPK APPROACH

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Background: Rilpivirine is the most popular non-nucleoside transcriptase inhibitor (NNRTI) recommended to prevent the risk of mother-to-child transmission of HIV. However, a decrease of rilpivirine plasma exposure in the second trimester could be expected due to an increased metabolism and/or elimination in pregnant women. The latter could compromise the efficacy of the ARV strategy. The objectives were to assess maternal rilpivirine plasma concentrations during pregnancy and postpartum.

Material and methods: A multicenter, cross-sectional, cohort was conducted from 2020 to 2023. Pregnant women living with HIV receiving rilpivirine 25mg once-daily containing regimen were enrolled. Plasma concentrations of rilpivirine were determined by UPLC-MS/MS (Waters Acquity) during the three trimesters (Tn) of pregnancy and postpartum. The gestational age was recorded for each sample., A population pharmacokinetic approach was performed, using Monolix 2023R1 suite, to analyze the plasma concentrations. Rilpivirine trough plasma concentrations (C24h) were estimated using individual parameters. Rilpivirine C24h were interpreted using an efficacy threshold of 50 ng/mL. The results are presented as median (IQR).

Results: 72 (97% sub-Saharan African) pregnant women were enrolled: age 34 years old (28-38). All were receiving FTC/TFV (as TDF or TAF) associated NRTIs with no boosted PI/r or reported CYP3A4 inhibitor. For these women, 222 plasma concentrations were determined corresponding to 20 at T1, 85 at T2, 92 at T3 and 25 postpartum. Population pharmacokinetic parameters (RSE%) were: ka 1 h-1 (fixed), V/F 727 L (10.7%), CL/F 6.4 L/h (9.1%). Inter-individual variabilities were: 39% (22.7%) and 53% (14.5%) for V/F and CL/F, respectively. Between-occasion variabilities were 73% (8.2%) and 24% (14.1%) for V/F and CL/F, respectively. Additive and proportional errors were 3.7 ng/mL (46.5%) and 0.08 (36.1%), respectively. There was no effect of gestational age or trimester on ka, V/F or CL/F parameters to improve the between-occasion variabilities. Rilpivirine estimated C24h were 90 ng/mL (50-103). Among the 72 patients, 14% of patients presented C24h below the 50 ng/mL. All women presented undetectable viral load during their pregnancy.

Conclusions: In this population of mostly sub-Saharan African pregnant women living with HIV, no significant effect of pregnancy (trimester or gestational age) on rilpivirine pharmacokinetic parameters was reported. Surprisingly, no decrease in rilpivirine plasma exposure was reported during pregnancy and all patients maintained an undetectable viral load during pregnancy. These results suggest that no systematic dose adjustment should be recommended in this setting. Nevertheless, a close therapeutic drug monitoring should still be performed considering the low genetic barrier to resistance of rilpivirine.

Poster Presentations

International Workshop on Clinical Pharmacology of HIV, Hepatitis, and Other Antiviral Drugs 2024

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15 - PHARMACOKINETIC DATA OF LOPINAVIR/RITONAVIR IN SECOND-LINE TREATMENT OF AFRICAN CHILDREN LIVING WITH HIV

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Background: Children living with HIV require specific strengths and formulations of antiretrovirals. Lopinavir/ritonavir (LPV/r) is recommended by the WHO for children as preferred bPI for second-line. As pediatric 100/25mg tablets have inconsistent availability in some countries, using adult 200/50mg tablets for children could simplify procurement. For children weighing 25-34.9kg, the daily recommended dose of 600/150mg could be achieved by dosing two 200/50mg tablets in the morning and one in the evening, instead of three 100/25mg tablets twice daily (current WHO-recommendation). In CHAPAS-4 (#ISRCTN22964075) second-line treatment options for children with HIV were investigated. We performed a nested PK substudy to evaluate LPV/r exposure in children with different NRTI backbones.

Methods: Children with HIV aged 3-15 years failing NNRTI-based first-line treatment were randomized to 4 anchor drugs with emtricitabine/tenofovir alafenamide or standard-of-care NRTIs (abacavir or zidovudine with lamivudine). Children weighing 14–24.9kg received 200/50mg LPV/r twice daily; children weighing 25–34.9kg received 400/100mg LPV/r in the morning and 200/50mg in the evening; children weighing ≥35kg received 400/100mg LPV/r twice daily. At steady-state, PK blood-samples were taken at pre-dose, 1, 2, 4, 6, 8, and 12h after LPV/r intake with food. LPV concentrations were measured using a validated HPLC method. Lopinavir AUC0-12h, Cmax, and Ctrough were calculated using non-compartmental analysis. PK data of children receiving similar dosages were used for comparison. The individual target Ctrough was defined as 1.0mg/L. Statistical analysis was performed using ANOVA on log-transformed values with Tukey post-hoc analysis to detect differences in LPV PK parameters between weight-bands and NRTI backbones.
Results: 51 children were included in this substudy. Eleven children were excluded for varied reasons. There were 9 children in the 14–19.9kg weight band, 10 in 20–24.9kg, 9 in 25–34.9kg and 12 in ≥35kg. The overall Geometric Mean (GM), (CV%) AUC0-12h was 116.15h*mg/L (37%) and the GM (CV%) Cmax was 12.52mg/L (32%), which is comparable to the reference AUC0-12h and Cmax. The GM (CV%) Ctrough of 7.71mg/L (52%) in this sub-study is ∼57% higher than the reference value, and near to the Ctrough associated with dyslipidemia in adults (8mg/L), possibly explaining why CHAPAS-4 children on LPV/r showed the least favorable lipid profiles. The Ctrough and the Cmax were significantly higher in children weighing 25–34.9kg (11.7 and 15.38mg/L) compared to children in the 14–19.9kg and ≥35kg weight-bands (6.19 and 12.52mg/L; 6.96 and 12.10mg/L, respectively); p-values ranging from 0.021 to 0.048. These children received a higher milligram per kilogram body weight dose in the morning compared to children in the other weight-bands. There was no difference in PK parameters when comparing according to backbone.

Conclusions: This PK sub-study shows that the AUC0-12h and Cmax of LPV after administration of LPV/r with food in children 3–15 years of age weighing ≥14kg on second-line treatment is comparable to reference data of children. In addition, it shows that the use of the adult LPV/r 200/50mg tablet could potentially be extended from the currently WHO-recommended 35kg down to 25kg. Relatively high Ctrough concentrations may be associated with dyslipidemia.

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16 - PHARMACOKINETICS OF MOLNUPIRAVIR AND FAVIPIRAVIR IN PLASMA SEPARATION CARDS FROM PATIENTS WITH COVID-19: AGILE CST-2 AND CST-6

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Background: Molnupiravir (MPV) and favipiravir (FVP) are broadly active antiviral ribonucleoside analogs. Both have demonstrated efficacy in treatment of COVID-19 and have been investigated for use against other high-consequence infections. Collection of liquid plasma (L-PL) in remote settings, where diseases like haemorrhagic fevers are endemic, can be challenging. HemaSep dried blood spots (HS-DBS) offer a useful alternative to L-PL, separating plasma upon contact as a distinct outer ring (HS-PL) and shipped at ambient temperatures. HS-DBS were collected alongside L-PL in the AGILE CST-2/CST-6 clinical trials to evaluate the pharmacokinetics of single and repeat doses of these agents in patients with confirmed COVID-19 disease.

Materials and Methods: AGILE-CST-2 and CST-6 were open-label 2:1 randomised controlled phase I trials comparing MPV and FVP, respectively, with standard of care, designed to determine the optimal dose for treatment of symptomatic COVID-19 patients (CST-2; n=12, CST-6; n=16). MPV was orally delivered twice daily (BD) for 10 doses, with dose escalations (300|600|800mg BD) across 3 cohorts, whereas FVP was intravenously administered BD for 14 doses, with dose escalations across 4 cohorts (600|1200|1800|2400mg). Paired L-PL and HS-DBS were collected over 0-4hr post-dose (CST-2) and 0-12hr post-dose (CST-6) following administration of single (day 1) and multiple doses (day 5–CST-2; day 3–CST-6). HS-PL were excised and extracted with 50:50 acetonitrile:1mM ammonium acetate (CST-2) and acetonitrile (CST-6). Concentrations of MPV active metabolite ß-d-N4-hydroxycytidine (NHC) and FVP were quantified using LC-MS (NHC- HS-PL: 2.5–250ng/sample, L-PL:2.5-5000ng/mL; FVP- HS-PL: 50-5000ng/sample, L-PL:1000-100000ng/mL). HS-PL values were normalised to ng/mL and pharmacokinetic parameters (Cmax, AUClast) derived using non-compartmental analysis. Linear regression and Bland Altman plots were used to compare methods.

Results: NHC L-PL geometric mean Cmax increased with each dosing cohort (n=4/cohort) 300|600|800 mg [Day 1 - 1197ng/mL|2440ng/mL|3447ng/mL; Day 5 - 1065ng/mL|1865ng/mL|3546ng/mL]. The mean difference between all HS-PL and L-PL NHC was 27% (-69%-143%). HS-PL Cmax were; Day 1 – 1749ng/mL|2441ng/mL|4986ng/mL; Day 5 – 1559ng/mL|1992ng/mL|4618 ng/mL. Intersubject variability within each dosing cohort was <61% (L-PL) and <90% (HS-PL). L-PL and HS-PL concentrations (r=0.967; p=<0.001; n=81) and AUClast (r=0.958; p=<0.001; n=23) were highly correlated with a mean difference of 1.32ng/mL between the two methods.
FVP L-PL geometric mean Cmax increased between days and with increasing doses 600|1200|1800|2400 mg [Day 1 – 16481 ng/mL| 28006 ng/mL| 52044 ng/mL| 88486 ng/mL; Day 3 – 11713 ng/mL| 61907 ng/mL| 85362.4 ng/mL| 195066.5 ng/mL]. The mean difference between all HS-PL and L-PL FVP was -6% (-115%-72%). HS-PL concentrations were [Day 1–14307ng/mL| 38107ng/mL|57448ng/mL|90607ng/mL; Day 3– 15216ng/mL| 62019ng/mL| 78527ng/mL|145964ng/mL]. Intersubject variability within each dosing cohort was <60% (L-PL) and <48% (HS-PL). FVP L-PL and HS-PL concentrations were highly correlated (r =0.965; p=<0.001; n=124)(AUClast; r=0.942; p=<0.001; n=32). The mean difference between the two methods was 1.08 ng/mL.

Conclusion: HemaSep DBS are a useful alternative to L-PL for collection and transport of clinical samples for studies of high-risk infections in field settings, as NHC and FVP concentrations were correlated with respective L-PL values, with a minimal mean difference between methods. HS-PL concentrations were generally higher than respective L-PL, likely due to variable plasma ring volumes.

17

17 - MODEL BASED COMPARISON OF CABOTEGRAVIR PHARMACOKINETICS FOLLOWING THIGH AND GLUTEAL INJECTIONS

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Background: Cabotegravir (CAB) long-acting (LA) intramuscular (IM) gluteal injections are approved for HIV-1 pre-exposure prophylaxis (PrEP) and combination treatment with rilpivirine. The [i]vastus lateralis[/i] (lateral) thigh muscle is a potential alternative site of administration in cases of gluteal injection fatigue or physical obstruction. We aimed to characterize CAB pharmacokinetics (PK) and its association with demographics following thigh administration in comparison to gluteal administration using population PK (PPK) analysis.

Material and Methods: Fourteen participants (pts) who were HIV-negative and received a 600mg single thigh injection in Phase 1 Study 208832 and 118 pts who were HIV-positive and received thigh injections [400mg monthly (QM) x 4 or 600mg every-2-months (Q2M) x 2] after >3 years of gluteal injections in Phase 3b Study 207966 (ATLAS-2M) provided CAB concentrations for the analysis. An established gluteal PPK model was fit to PK data following both gluteal and thigh injections, enabling within-person comparison in ATLAS-2M pts. Gluteal parameters were fixed. Thigh parameters including absorption rate constant (KA-thigh) and bioavailability (F-thigh) were estimated. CAB PK profiles following chronic or intermittent thigh injections administered QM and Q2M were simulated and compared to gluteal injections. PK target was that 95% of pts maintain concentrations >0.45 µg/mL, the 5th percentile of observed CAB trough concentration following the gluteal initiation injection in Phase 3 Studies.

Results: 1254 concentrations from 366 thigh injections and 2022 concentrations from 1631 gluteal injections were analyzed. Similar to gluteal administration, KA-thigh was associated with sex and BMI. KA-thigh was correlated with and was generally faster than KA-gluteal, described by the additive linear relationship: KA-thigh = KA-gluteal + 0.000253 h[sup]-1[/sup]. Terminal half-life of thigh administration was 26% (male) and 39% (female) shorter than for gluteal administration. F-thigh was 90% of gluteal injection. PK target was maintained following chronic QM thigh injections or alternating thigh-gluteal injections for either QM or Q2M regimens but not following chronic Q2M thigh injections.

Conclusions: PPK modeling and simulation support chronic thigh administration of CAB LA QM and intermittent thigh injections for both QM and Q2M regimens. However, simulated chronic Q2M thigh administration did not maintain PK target established in pivotal trials and therefore is not recommended.

18

18 - DEVELOPMENT OF A USP-4 IVIVC METHODOLOGY FOR LAI ANTIVIRALS: CASE STUDIES WITH CABOTEGRAVIR AND RILPIVIRINE

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Background: Long-acting injectables (LAI) offer a promising approach to improving adherence and efficacy in the treatment of HIV. Establishing a reliable in vitro-in vivo correlation (IVIVC) is critical for predicting the in vivo performance of these formulations. This study aimed to develop a USP apparatus 4 (USP-4) IVIVC methodology specifically for LAI antivirals, using Cabotegravir (CAB) and Rilpivirine (RPV) as model compounds.

Material and Methods: CAB and RPV formulations were subjected to in vitro release testing using the USP-4 apparatus with dose release from a float-a-lyzer dialysis device. Method optimisation investigated adjustment of parameters such as temperature, dialysis membrane MWCO, and flow rate, Tween 20 excipient concentration and pH of the circulating buffer. Cumulative release profiles were sampled and analysed over a period of 30 days and fitted with a biexponential mathematical model to allow extrapolation to estimate longer release durations. For in vivo analysis, clinical LAI pharmacokinetic (PK) data for CAB and RPV were obtained from literature, and in vivo release profiles derived through deconvolution using intravenous (IV) bolus disposition impulse responses estimated for both drugs via PBPK scaling due to lack of clinical IV data. IVIVC predictions and comparisons were made both by convolution of the in vitro release with IV disposition for direct comparison with the in vivo PK exposure profile, and by Levy-plot correlations of in vitro and in vivo cumulative release.

Results: Results obtained show sustained in vitro cumulative release for CAB and RPV over 30 days in the USP-4 system. However, in vitro cumulative release extrapolated for the duration of in vivo PK profiles was lower than cumulative release derived from in vivo data. Concordantly, convolution of the in vitro release profiles with estimated IV bolus disposition response underpredicted observed LAI PK exposure profiles. However, inclusion of a linear-multiple scaling factor revealed the shape of the in vivo PK exposure profile was predicted by the in vitro release profile. This is illustrated in the Levy correlation plots showing partial correlation between in vitro and in vivo release but with deviation away from the line of unity.
Conclusions: Initial results from developing a USP-4 methodology for application to LAI formulations and IVIVC to clinical LAI PK exposures indicate potential for prediction of in vivo PK exposure, or utility as a means of ranking/comparing formulations by in vitro release. Work is ongoing to further investigate optimisation of experimental parameters, and to expand the library of LAI formulations being investigated to identify trends across a range of LAI products, and confirm generalisability of the methodology.

19

19 - THE EFFECT OF P-GLYCOPROTEIN, BREAST CANCER RESISTANCE PROTEIN, AND CYP3A4 MODULATORS ON THE PHARMACOKINETICS OF THE TLR-7 AGONIST VESATOLIMOD IN PEOPLE LIVING WITH HIV

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Background: Vesatolimod (VES) is a toll-like receptor 7 (TLR-7) agonist being evaluated as an immunomodulator to enhance antiviral responses in the clear-and-control HIV cure strategy. Per nonclinical data, VES is a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and CYP3A. Cobicistat (COBI; a P-gp, BCRP, and strong CYP3A inhibitor), voriconazole (VOR; a strong CYP3A inhibitor), and rifabutin (RFB; a moderate CYP3A inducer) have the potential to alter VES plasma concentrations, and these medications may be administered to people living with HIV (PLWH) as part of antiretroviral therapy (ART) or to treat fungal or bacterial infections.

Materials and Methods: NCT05458102 was an open-label study to evaluate the effect of P-gp/BCRP/CYP3A4 modulators on VES pharmacokinetics (PK) in virologically suppressed PLWH on stable ART. In cohort 1, the following study drugs were administered orally in 3 periods sequentially: period 1, VES 2 mg; period 2, COBI 150 mg once daily for 5 days with VES 2 mg coadministered on day 2; period 3, VOR 400 mg twice daily on day 1 and 200 mg twice daily on days 2-6 with VES 2 mg coadministered on day 3. In cohort 2, the following study drugs were administered orally in 2 periods sequentially: period 1, VES 6 mg; period 2, RFB 300 mg once daily for 9 days with VES 2 mg coadministered on day 6. VES PK samples were collected over 96 hours after each dose of VES. VES PK parameters were estimated using noncompartmental analysis and compared between treatments using an analysis of variance.

Results: In cohort 1 (N=15), when VES was coadministered with COBI, median Tmax occurred 1.5 hours earlier and the geometric least-squares mean (GLSM) VES AUC, Cmax, and t1/2 increased 4.3-, 7.5-, and 1.2-fold, respectively. When VES was coadministered with VOR, there was no change in median Tmax or in GLSM VES AUCinf, Cmax, and t1/2.
In cohort 2 (N=2), when VES was coadministered with RFB, median VES Tmax occurred 3.85 hours earlier and individual increases in VES AUC and Cmax were 26- and 98-fold and 2.6- and 10-fold, respectively. In 1 participant with evaluable VES t1/2 for both periods, t1/2 decreased from 23.9 hours for VES alone to 14.3 hours when VES was coadministered with RFB. Nonclinical investigations identified RFB as a P-gp and BCRP inhibitor and as a potent inhibitor of VES efflux in Caco-2 cells.
Eight participants (47.1%) experienced drug-related treatment-emergent adverse events (TEAEs), which were mainly grade 1. One participant (5.9%) experienced TEAEs greater than grade 1 which were considered related to VES+RFB. There were no serious TEAEs or deaths.

Conclusions: The larger magnitude of PK interaction between VES and COBI compared with VES and VOR suggests that transporters (P-gp and/or BCRP) play a greater role than drug-metabolizing enzymes (CYP3A), and that the interaction is predominantly pre-systemic. The increase in VES PK exposure when coadministered with RFB and the subsequent nonclinical results that identified RFB as a P-gp and BCRP inhibitor suggest that RFB inhibits these efflux transporters involved in VES absorption.

20

20 - DOSE PROPORTIONALITY AND HALF-LIFE OF TENOFOVIR IN HAIR SAMPLES FROM THOSE WITH DIFFERING ADHERENCE TO TDF OR TAF-BASED REGIMENS MONITORED BY DIRECTLY OBSERVED THERAPY

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Background: Objective adherence metrics to antiretroviral therapy have been proven useful in interpreting clinical trial results. Hair tenofovir (TFV) concentrations are indicative of average adherence over approximately one month. The pharmacokinetics of TFV in hair have not been fully elucidated for TDF and TAF therapy following directly observed therapy (DOT) in people without HIV infection. The DOT-DBS and TAF-DBS studies, which used DOT to determine TFV-DP concentration benchmarks associated with variable adherence regimens, collected hair at regular intervals. This analysis aimed to assess concentrations, dose proportionality, comparability, and the apparent half-life of TFV in hair from TDF and TAF.

Methods: Hair samples were collected from adults without HIV in the DOT-DBS and TAF-DBS studies receiving either TDF 300mg/FTC 200mg or TAF 25mg/FTC 200mg, respectively, at 33%, 67%, or 100% of daily doses. Participants were randomized to one adherence group for 12 weeks followed by a 12-week washout and then randomized to a different adherence group and followed for 12 additional weeks (36 weeks total). Approximately 100-200 hair strands were cut from the occipital portion of the scalp every three weeks. TFV concentrations were determined by a previously validated LC-MS/MS assay—reported as ng TFV/mg hair—and week 12 and 36 concentrations were summarized by treatment (TDF or TAF) and adherence group (33%, 67%, or 100%). Dose proportionality was assessed using the power model. Ln TFV concentrations were modeled linearly versus Ln dose. Proportionality was assumed if the slope's 90% Confidence Interval (CI) was within 0.80 and 1.25. The apparent half-lives from TAF and TDF were determined assuming exponential decay during the 12-week washout phase.

Results: Seventy samples were collected from 38 DOT-DBS participants (50% male; 7% black, 55% white, 26% Hispanic) and 68 samples were collected from 35 TAF-DBS participants (51% male; 14% black, 69% white, 17% Hispanic). Mean (%CV) TFV concentrations from TDF treatment were 0.0165 ng/mg (40.9%), 0.0454 (182%), and 0.0395 ng/mg (36.5%), while from TAF treatment they were 0.0142 ng/mg (30.9%), 0.0275 (28.5%), and 0.0409 ng/mg (42.1%) in the 33%, 67% and 100% adherence groups, respectively. Concentrations of TFV from TDF were less than dose proportional (slope 90% CI: 0.62, 0.96) and proportionality was still not achieved after removing one 67% dosing outlier (90% CI: 0.62, 0.94). TFV from TAF was dose proportional (slope 90% CI: 0.8, 1.04). The TFV Half-life (IQR) was estimated to be 30 days (26, 35) from TAF and 25 days (23, 28) from TDF.

Conclusions: Hair TFV concentrations were of similar magnitude between TDF and TAF treatment despite much lower plasma TFV exposures arising from TAF, previously reported in people living with HIV. These findings may suggest unique TAF pharmacology in hair follicles, which may contain cathepsin A or CES1 causing local TFV release. Hair TFV concentrations from TDF were not dose proportional but were dose proportional from TAF. The apparent washout half-lives of TFV depend on hair growth rate. These findings inform using hair TFV to assess adherence to TDF and TAF PrEP regimens.

21

21 - THE HIV PHARMACOLOGY DATA REPOSITORY (PDR): SETTING A NEW STANDARD FOR CLINICAL AND PRECLINICAL PHARMACOKINETIC DATA SHARING

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Background: Rapidly expanding clinical pharmacology modeling tools can be used to derive biological meaning through in silico study of archived pharmacokinetic (PK) data pools. Yet, a rate limiting step to employing these approaches is the ability to access high-quality concentration vs time (CvT) data, aggregated across disparate study designs in a way that is meaningful and usable for PK modeling. This is partly due to a lack of standardization for PK data description. To this end, we defined and applied a minimum information standard (MIS) for PK data description in the development of a web-based database: the HIV Pharmacology Data Repository (HIV PDR) and demonstrate scientific utility through population PK modeling.

Materials/Methods: We defined the MIS with key reportable variables divided into 3 categories: Intervention (drug, route, time, and quantify), System (species dosed and anatomical compartment sampled), and Concentration (chemical entity and concentration units quantified, including pro-drugs, drugs, and metabolites). We identified 610 archived CvT Excel datasets fulfilling this MIS and created data dictionaries to harmonize terminology. The resulting database is stored in an SQL server with the front-end developed using an ASP.NET core with Angular and the back-end on an SQL Server 2017. We extracted CvT values for tenofovir (TFV) and its active metabolite (tenofovir diphosphate; TFVdp) within human plasma and peripheral blood mononuclear cells (PBMC) from study participants dosed with tenofovir disoproxil fumarate (TDF) and fit a population PK model using NONMEMv7.4.

Results: Our data dictionaries collapsed 924 bioanalytical synonyms (analyte name and units) into 145 unique variables with units parsed in a separate column. Additionally, 246 descriptors of species and anatomical compartment were collapsed into 15 and 80 unique variables, respectively with taxonomical and anatomical hierarchies. The final database aggregates 80,043 CvT datapoints of 77 chemically distinct compounds. Our extracted TDF dataset contained 913 plasma and 708 PBMC observations from 88 human study participants across 3 dosing levels (150, 300, and 600mg) under first-dose and steady-state conditions. The final model fit first order absorption (Ka) and elimination (CL) from the central compartment (Vc); a peripheral compartment (Vp and Q); one gut transit compartment (Ktr) to capture absorption delay; and a PBMC compartment to capture TFVdp formation and degradation (K35 and K53, respectively). Parameter estimates (%RSE) were; CL=51.1L/hr (3.2%); Vc=223L (fixed), Vp=687L (4.7%), Q=173L/hr (4.4%), Ka=1hr-1 (fixed), K35=0.0255hr-1 (11.1%) and K53=0.0269hr-1 (11.5%). A 600mg dose was associated with longer absorption delay (Ktr_1=1.36hr-1) compared to the lower doses (Ktr_2=6.1hr-1). Vc, Ka, and Ktr depend on sampling near Cmax and were fixed to estimations from a separate model using a subset of data with rich PK sampling schemes.

Conclusions: We applied this MIS in curating PK CvT data collected from previously siloed studies into a user-friendly database to support data sharing, management, and mining for the community of translational scientists working to optimize HIV therapeutics. Our observation of TFV's dose-dependent absorption delay is a novel finding from the pooled CvT analysis, demonstrating the power to derive new PK knowledge from resources like the HIV PDR.

22

22 - PHARMACOMETRICS ANALYSES AND MODELING OF CONCENTRATION-CORRECTED QT INTERVAL, AND CONCENTRATION-CREATINE KINASE MB IN HEALTHY ADULTS, AND TREATMENT-NAÏVE PEOPLE WITH HIV-1 ON AINUOVIRINE MONOTHERAPY, AND COMBINED WITH LAMIVUDINE AND TENOFOVIR DF: THE POOLED ANALYSES OF EARLY CLINICAL PHARMACOLOGY STUDIES

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Background: People with HIV-1 (PWH) are susceptible to corrected QT (QTc) interval prolongation, especially when on some specific antiretroviral regimens. Ainuovirine (ANV) is a new-generation NNRTI developed for HIV-1 treatment. The pooled analyses aimed to investigate effects of ainuovirine monotherapy, and combined with lamivudine (3TC) and tenofovir DF (TDF) on electrocardiography, and myocardial biomarker of healthy people, and treatment-naïve PWH.

Methods: Sixty-eight (n=68) healthy adults were enrolled, and exposed to ANV in single ascending dose (SAD), food effect (FE), and drug-drug interaction (DDI) with 3TC/TDF studies; 28 PWH were enrolled into multiple ascending dose (MAD) study, and received ANV monotherapy for 10 successive days. ANV, 75 to 300 mg, was given to all participants under the fasting condition. A basic structure model (c-QTc) was established between observed plasma ANV concerntration and change in corrected QT interval (ΔQTcF) with the linear mixed effect method. All model parameters were estimated using the first-order conditional estimation with interaction (FOCEI), with the linear model prioritized. An additional statistical random effect model was used to depict inter- and intra-individual variations without covariate adjusted. A simple linear regression model was also used to evaluate the correlation between ΔQTcF and plasma concentration, regardless of inter-individual variability. A 95% confidence interval containing 0 for the slope indicates negative QT prolongation. Changes in concentration-creatine kinase MB (c-CKMB) were also analyzed using a similar methodology for evaluation of ANV myocardial safety.

Results: A total of 492 post-dose ECG sampling points from 85 participants were included in the analysis. A linear population c-QTc model was established, which demonstrated the 95% CI of [-0.018, 0.0064] for the slope (containing 0), with favorable goodness-of-fit, precision, and reliability. The simple linear regression model showed a slope of -0.003 [-0.010, 0.004], with no statistically significant difference from 0 (P=0.409). CKMB levels did not change significantly with ACC007 monotherapy, and remained well below the upper limit of normal (ULN, 3.6 ng/mL); CKMB levels were significantly higher and beyond the ULN (25 U/L) in 16/23 participants on ANV plus 3TC/TDF. Elevations in CKMB was not associated with exposure of ANV or 3TC but with that of TDF in PWH on combined therapy.

Conclusions: ANV monotherapy had no significant effect on QTc prolongation, at a dose range of 75 to 300 mg, in both healthy adults and PWH. No significant association was found between change in CKMB and ANV exposure. Exposure to co-administered TDF might contribute to increase in CKMB but required no dose adjustment based on systemic exposure bioequivalence.

23

23 - PREDICTING DRUG–DRUG INTERACTIONS BETWEEN AINUOVIRINE AND RIFAMPICIN PLUS ISONIAZID USING PBPK MODELLING

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Objectives: Ainuovirine (ANV) is a newly developed next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) metabolized by CYP2C19. The primary objective of this study was to simulate and predict drug–drug interaction (DDI) between Ainuovirine and rifampicin (RIF) combined with Isoniazid (INH) using physiologically based pharmacokinetic (PBPK) modelling. Additionally, we aimed to recommend suitable dose adjustments for ANV for the treatment of people living with HIV (PLWH) coinfected with tuberculosis.

Methods: A comprehensive whole-body PBPK model for DDI was developed using PK-SIM® (version 11.2, Open system Pharmacology, USA). This model was validated against Phase 1 DDI Study of ANV with RIF and reported clinical data for all drugs administered alone and ANV-RIF/ANV-INH dual- and triple-drug concomitantly. The model contained the potent induction and concentration-dependent inhibition mechanisms of RIF and INH on CYP2C19. The model was considered verified if the predicted pharmacokinetic values versus observed were within 0.5-2 fold. Alternative dosing regimens for ANV were simulated to ensure that the Ctrough exceeded the clinical reference interval's lower limit of 153.04±59.22 ng/mL, while the Cmax remained below the upper limit of 526.45±143.52 ng/mL.

Results: The PBPK model was successfully verified according to the criteria. Simulation of different dose adjustments predicted that a change in regimen to 225mg ANV (75+150 mg, while 75mg co-administered with RIF plus INH, 150mg after 12 hours) may alleviate the inhibition effect of INH on ANV Cmax and induction effect of RIF on ANV Ctrough at steady state, both were within the clinical reference intervals.

Conclusions: The developed PBPK model characterized the opposite effect-mediated DDI between RIF and INH on ANV, accurately predicting a narrowed therapeutic window when 150mg daily of ANV co-administered with RIF plus INH. A change in the ANV dosing regimen from 150mg to 225mg was predicted to mitigate the effect of the DDI on the Cmax and Ctrough of ANV, maintaining plasma concentration levels above the therapeutic threshold while not too high.

24

24 - IN-VITRO CHARACTERIZATION AND PHYSIOLOGICAL-BASED PHARMACOKINETIC MODELLING FOR MOLNUPIRAVIR AND ITS ACTIVE METABOLITE

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Introduction: Molnupiravir (MOL) is recommended by WHO for treatment of COVID-19 patients with mild to moderate symptoms, but may also have application as a broad spectrum antiviral. MOL is converted to its active metabolite NHC after absorption, which induces error catastrophe, stopping viral replication. This work aimed to develop and validate a physiologically-based pharmacokinetic (PBPK) model for better prediction of MOL drug disposition, requiring assessments of apparent permeability (Papp), intrinsic clearance (Clint), and blood/plasma ratio for MOL and NHC. Validation of an LC-MS/MS method for quantifying MOL and NHC in various matrices was also undertaken.

Methods: An LC-MS/MS method was developed and validated for simultaneous quantification of MOL and NHC in transporter buffer, human plasma, and human liver microsomes. Papp of MOL in Caco-2 cell monolayers was determined at 50 µM. Papp determination for NHC was unnecessary since it is formed subsequent to absorption. Clint of MOL and NHC were investigated in human liver microsomes. Blood-to-plasma ratio of NHC was determined via standard methodology. Clinical data from a published study (Khoo et al.,2021) was utilized to develop and validate a PBPK model, with simulations carried out in Teoreler (www.liverpool.ac.uk/centre-of-excellence-for-long-acting-therapeutics/teoreler), a web-based pharmacokinetic platform. A dose of 800 mg was simulated, utilizing the in vitro generated parameters, and apparent clearance from clinical PK studies.

Results: The LC-MS/MS method had a runtime of 3.5 minutes and an analytical measuring range of 7.81-2000 ng/mL (linear regression 1/X, R^2=0.99) for MOL in all matrices and NHC in human plasma, and human liver microsomes. For MOL and NHC the LOD and LOQ were 1.95 ng/mL and 7.81 ng/mL. Intra- and inter-day precision and accuracy metrics were within acceptable limits and recovery rates of MOL and NHC from matrices were consistently above 70%.
MOL demonstrated a Papp of 1.46 x10-6cm/s. In human microsomes MOL exhibits an elimination, potentially attributable to hepatic carboxylase enzymes, whereas NHC exhibited no intrinsic clearance with a Kel values of 0. Both MOL and NHC showed a blood-to-plasma ratio of ~1.
PBPK model simulations for NHC in plasma incorporating these in vitro parameter values, combined with the necessary observed apparent clearance from an empirical fitting to the clinical data, and Kps predicted using Poulin and Theil method showed acceptable agreement with observed clinical PK exposure, with an AFE of 1.02 ± 0.24. Mean simulated vs. observed PK parameters were within an acceptable two-fold range.

Conclusion: A highly sensitive, precise, and accurate LC MS/MS method for the quantification of Molnupiravir and NHC in diverse matrices is presented. The PBPK model using the generated in vitro data for MOL and NHC showed good performance, and can be applied for forward simulation to meet the needs of future clinical use cases.

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25 - SAFETY, PHARMACOKINETICS, AND ANTIVIRAL ACTIVITY OF AINUOVIRINE AS 10-DAY MONOTHERAPY IN TREATMENT-NAÏVE ADULTS WITH HIV-1

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Background: Ainuovirine (ANV) is a novel non-nucleoside reverse transcriptase inhibitor (NNRTI) for treatment of HIV-1 infection. This study aimed to evaluate the safety, pharmacokinetics, and antiviral activity of short-term ANV monotherapy in antiretroviral treatment-naive adults with HIV-1.

Methods: A single-center, open-label, dose-ranging study was conducted among 28 treatment-naive adults with HIV-1. Participants received ainuovirine monotherapy, at the dosage of 75, 150, or 300 mg, once daily, for 10 days.

Results: Baseline characteristics were similar across dose cohorts (75 mg, n=8; 150 mg, n=10; 300 mg, n=10). Across all dose cohorts, all adverse events were rated as mild to moderate in severity. No serious adverse event was reported. ANV was readily absorbed, with the maximum concentration achieved at a median time of approximately 2-3 h after dosing. The ANV exposure (AUC and Cmax) increased slightly greater than the dose proportionality after single dose (day 1). Plasma ANV concentration reached the steady state at day 10 of dosing. Saturated Cmax,ss, AUCmax,ss, and Cmin,ss were observed at 150 and 300 mg on day 10 after repeated dosing. The inhibitory quotient (IQ) was 69.6 folds (150 mg, Cmin,ss=153.0 ng/mL) for wild type (EC50=2.2 ng/mL), 10.0 folds for K103N mutant (EC50=15.3 ng/mL), and 6.9 folds for Y181C mutant (EC50=22.1 ng/mL), respectively. Mean changes in HIV RNA from baseline (log10 copies/mL [90%CI]) were -1.73 [-1.90, -1.57], -1.72 [-1.87, -1.57], and -1.66 [-1.80, -1.51], respectively, on day 11.

Conclusion: ANV demonstrated favorable safety and pharmacokinetics, and potent antiviral activity in treatment-naive adults with HIV-1. An once-daily dosing regimen of 150 mg was recommended for subsequent confirmatory efficacy trial.

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26 - PHARMACOKINETICS, SAFETY, AND EFFICACY STUDY IN PREGNANCY AND EXISTING CUMULATIVE DATA/EVIDENCE TO SUPPORT CLINICAL USE AND LABELING OF BICTEGRAVIR/EMTRICITABINE /TENOFOVIR ALAFENAMIDE (B/F/TAF) IN PREGNANT WOMEN WITH HIV

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Background: Safe, effective, and convenient treatment options are needed for pregnant women with HIV. Bictegravir is metabolized by uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) and cytochrome P450 3A4 (CYP3A4). Pregnancy is associated with physiological changes, including increased CYP3A4 and UGT1A1 activities; however, limited data exist on the pharmacokinetics, safety, and efficacy of B/F/TAF during pregnancy.

Material and Methods: An open-label study (NCT03960645) was conducted in virologically suppressed pregnant women with HIV-1 (n=33). Steady-state plasma pharmacokinetic samples were collected over 24 hours following once-daily oral B/F/TAF dosing during second/third trimesters of pregnancy, and postpartum. Bictegravir exposure parameters during pregnancy and postpartum were compared and contextualized with prior pooled Phase 3 data in nonpregnant participants. Plasma HIV-1 RNA/DNA was measured in mothers and their neonates. Efficacy response was calculated as the proportion of mothers with HIV-1 RNA <50 copies/mL (missing=excluded) at delivery. Exposure-efficacy response (E-R) relationships were visualized and contextualized using pooled Phase 3 data. Literature evidence from contemporary studies of B/F/TAF in different populations was collated for additional comparisons.

Results: While plasma bictegravir AUCtau was lower (~59%) during pregnancy than postpartum, the difference was less pronounced when compared to nonpregnant adults with HIV (~40%). Bictegravir AUCtau was similar during second and third trimesters. Mean bictegravir Ctrough was >6× inhibitory quotient (IQ)1 during pregnancy. All pregnant women maintained virologic suppression (VS), with HIV-1 RNA <50 copies/mL at delivery (n=32 [100%]) and no observed virologic failure or treatment-emergent resistance. B/F/TAF was well tolerated, with no adverse events (AEs) leading to premature discontinuation; AEs were consistent with those expected in this pregnant population. No cases of perinatal HIV transmission in neonates (n=29) occurred. E-R relationship visualizations for once-daily B/F/TAF showed robustly high and plateaued responses over a large exposure range. Current literature is supportive of these data. In IMPAACT 2026 [1], similar efficacy/safety and bictegravir exposure changes during pregnancy were described in a different demographic population. In the INSIGHT trial [2], coadministration of twice-daily B/F/TAF with a rifampicin-based tuberculosis regimen in adults with HIV and tuberculosis showed continued robust efficacy (~97%) at Week 24 despite much lower mean trough bictegravir exposures (~2.5× IQ1).

Conclusions: Despite lower bictegravir exposures during pregnancy, all mothers maintained VS, and B/F/TAF was generally well tolerated, which suggests appropriateness of B/F/TAF use during pregnancy with no need for dose adjustments. E-R analysis and existing literature evidence further support the likelihood of robust efficacy at the bictegravir exposures observed in pregnancy. Based on our pregnancy study data [3], the US Department of Health and Human Services perinatal guidelines were updated (Jan. 31, 2024) to include bictegravir as an alternative integrase strand transfer inhibitor in certain groups of pregnant people and nonpregnant people who are trying to conceive. Furthermore, these data and the evidence from IMPAACT 2026 and INSIGHT supported the recent (2024) FDA approval and labeling of B/F/TAF for pregnant subpopulation.

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27 - THE CASE OF DOLUTEGRAVIR PLUS DARUNAVIR ANTIRETROVIRAL REGIMENS: IS IT ALWAYS USEFUL TO DOUBLE THE DRUG DOSES?

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Background: It has recently been shown that dolutegravir trough concentrations are differently affected by antiretroviral drug combinations [doi:10.1097/QAD.0000000000003843]. Here, we focused on dolutegravir plus darunavir-based combinations, with the aim to investigate the effect of the booster and/or the timing of administration on drug plasma trough concentrations.

Materials and methods: This retrospective, observational study included consecutive PWH receiving dolutegravir plus darunavir antiretroviral regimens for at least 3 months, with at least 1 assessment of dolutegravir plasma concentrations. We considered true trough drug concentrations (i.e. blood samples taken 12 or 24 h after the last drug intake) or trough concentrations back-estimated by pharmacokinetic modeling taking into account the time interval between the last dose intake and the blood sample and the drug terminal half-life. Samples without clear information on the timing of the last drug dose and/or blood draw were excluded from the study. PWH concomitantly treated with strong drug inducers (i.e. rifampicin, carbamazepine, NNRTIs) were not included.

Results: 200 TDMs of dolutegravir from 116 PWH were included in the statistical analyses. Dolutegravir and darunavir trough concentrations ranged, respectively, from 70 to 3648 ng/mL (inter-individual variability 60%) and from 102 to 11876 ng/mL (inter-individual variability 72%). As shown in Table 2, the antiretroviral drug combination associated with the highest dolutegravir trough concentration was dolutegravir plus darunavir/cobicistat, both given once daily (1410±788 ng/mL), whereas dolutegravir once daily plus darunavir/ritonavir twice daily had the lowest trough concentrations (686±481 ng/mL). Doubling the dose of dolutegravir did not result in a significant increase of drug trough concentrations compared to once daily regimens. Among the once daily regimens, the highest darunavir trough concentrations were measured with ritonavir (2850±1456 ng/mL, $p<0.05$ versus cobicistat-based regimens). Doubling the drug dose resulted in a significant increase of darunavir trough concentrations (4445±2926 ng/mL, $p<0.05$).

Conclusions: Dolutegravir trough concentrations were significantly reduced in PWH receiving darunavir/ritonavir twice daily. This is likely related to the inductive effect of ritonavir (but not of cobicistat) on the enzymes (glucuronosyltransferase) and/or drug transporters involved in the regulation of dolutegravir disposition [doi:10.1093/jac/dkx055]. Doubling the dose of dolutegravir did not result in a significant increase in the drug trough concentrations. This evidence should be carefully considered in clinical conditions that require higher dolutegravir exposure, such as in presence of DDIs with medications known to reduce dolutegravir bioavailability or in highly experienced PWH.

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28 - SINGLE-ASCENDING DOSE AND FOOD EFFECT STUDIES TO ASSESS SAFETY AND PHARMACOKINETICS OF AINUOVIRINE, A NOVEL NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR, FOR TREATMENT OF HIV-1 INFECTION

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Background: Ainuovirine is a novel non-nucleoside reverse transcriptase inhibitor (NNRTI) for treatment of HIV-1 infection. This first-in-human study was conducted to characterise the tolerability, pharmacokinetics, and food effect of single-ascending oral doses of ainuovirine in healthy adults.

Methods: In the single-dose escalation study, three cohorts of each 10 participants, aged from 18 to 45 years, were randomly allocated to receive a single-dose ainuovirine 75, 150 or 300 mg, respectively. Inhibitory quotient (IQ) was defined as the ratio of the clinical trough concentration (C24h) to the 50% effective concentration (EC50). In the food effect study, 16 participants were equally assigned to a randomised, open-label, two-period crossover study, and received a single oral dose of ainuovirine 150 mg in the fasting state or after a high-fat meal, with a 14-day washout period between periods.

Results: Ainuovirine was well tolerated. Across all dosage groups, most adverse events were rated as mild in severity. Ainuovirine was readily absorbed, with a median Tmax of approximately 3 hours. Ainuovirine exposure (Cmax and AUC) increased to a lesser extent than the dose proportionality. Median apparent terminal half-life (T1/2z) remained similar across three dose cohorts, slightly longer than 24 hours. The IQs for wild type (EC50=2.2 ng/mL) were 36.4, 51.7, and 61.0 folds, respectively; 5.2, 7.4, and 8.8 folds for K103N mutant (EC50=15.3 ng/mL), respectively; and 3.6, 5.1, and 6.1 folds for Y181C mutant (EC50=22.1 ng/mL), respectively. The geometric mean ratios of Cmax, AUC0-t, and AUC0-∞ in fed/fasting state were 190.07%, 136.73%, and 141.71% respectively, with 90% CI of 169.52-213.12%, 128.32-145.69% and 131.59-152.61%. The food effect of ainuovirine was evaluated clinically not significant.

Conclusion: Ainuovirine was well tolerated and showed a dose-dependent, nonlinear pharmacokinetics, eliciting no dose-limiting toxicity in healthy volunteers. Clinically insignificant food effect required no restriction in dosing without meal.

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29 - VIRAL DYNAMIC MODELLING OF NIRMATRELVIR AGAINST IN VITRO SARS-COV-2 INFECTION WITH DIFFERENT TREATMENT INITIATION TIMES

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Background: The timing of antiviral treatment initiation plays an important role in drug efficacy. In vitro experiments have shown that delayed therapy initiation significantly decreased the antiviral efficacy of nirmatrelvir against SARS-CoV-2 infection. Further investigation is needed to gain understanding of the relationship between viral dynamics and the timing of treatment initiation to achieve better treatment response and to utilize existing SARS-CoV-2 data for emerging viral pathogens.

Aims: The aim of this study is to investigate the SARS-CoV-2 viral dynamics using a systems pharmacology modelling, which incorporates viral load profile and the effect of therapy delay.

Methods: In vitro data were obtained from antiviral experiments with five drug concentrations (0.004, 0.0156, 0.0625, 0.25, and 1 ug/mL) alongside a non-treatment control. The viral dynamic modelling was performed using the R package nlmixr2.
A target cell-limited (TCL) model and TCL model with eclipse phase (TCLE) in combination with different drug effect models were tested. Viral kinetic parameters such as viral infection rate (β), death rate of infected cells (δ), and viral production rate (ρ) were first estimated using control group data. A direct effect model was then incorporated to describe the antiviral effect when there was no treatment delay. An indirect response model was adapted to modify the drug effect when the treatment was delayed. An additive residual error model was applied in all the tested models. The estimation was performed using the first-order conditional estimation with interaction (FOCEi) method. Models were evaluated and selected based on objective function value (OFV) and goodness of fit (GOF).

Results: The in vitro data were well captured by a TCL model with sigmoid Emax drug effect. A direct effect model could best describe the concentration-effect relationship when the treatment started from day 0, while an adapted indirect response model had better performance when the therapy initiated from day 1 onwards, by adding a response controlling factor (k).
The final estimates (RSE%) of viral kinetic parameters (β = 1.52×10^-7 (2.12%) 1/PFU/day, δ = 2.43 (62.1%) 1/day, ρ = 86.9 (4.92%) PFU/cell/day) and drug effect parameters (Emax = 1, hill coefficient = 1.64 (57.7%), EC50 (no therapy delay) = 0.039 (8.36%) ug/mL, EC50 (with therapy delay) = 0.017 (7.64%) ug/mL, k = 2.48 (26.1%)) fit the experimental data well.

Conclusions: A TCL model with sigmoid Emax drug effect model was developed to characterize the concentration-effect relationship of nirmatrelvir against SARS-CoV-2. Following this, the model will be validated with clinical data. This systems pharmacology model is an excellent tool to estimate therapy success and failure in SARS-Cov-2 after. In the future the model can be applied to other emerging viruses to test novel therapeutics.

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30 - POPULATION PHARMACOKINETICS OF AINUOVIRINE AND EXPOSURE-RESPONSE ANALYSIS IN THE HIV-INFECTED INDIVIDUALS

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Objective: Ainuovirine (ANV) is a novel new-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) for treatment of human immunodeficiency virus type 1 (HIV-1) infection. This study aimed to evaluate the population pharmacokinetic profile and exposure-response relationship of ANV among people living with HIV (PLWH).

Methods: Plasma concentration-time data from phase 1 and phase 3 clinical trials of ANV were pooled for developing the population pharmacokinetic (PopPK) model. Exposure estimates obtained from the final model were used in exposure-response analysis for virologic and safety responses.

Results: ANV exhibited a nonlinear pharmacokinetic profile, which was best described by a two-compartment model with first-order elimination. There were no significant covariates correlated to the pharmacokinetic parameters of ANV. The PopPK parameter estimate (RSE%) for CL/F was 6.46 L/h (15.0), and the clearance of ANV increased after multiple doses. The exposure-response model revealed no significant correlation between the virologic response (HIV-RNA <50 copies/mL) at 48 weeks and the exposure, but the incidence of adverse events increased with the increasing exposure.

Conclusions: Our PopPK model supported ANV 150 mg once daily as the recommended dose for PLWH, requiring no dose adjustment for the studied factors. Optimization of ANV dose may be warranted in clinical practice due to an increasing trend in adverse reactions with increasing exposure.

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31 - A SINGLE ONCE DAILY ABC/DTG/3TC TABLET PREDICTS SAFE AND EFFECTIVE EXPOSURES IN CHILDREN 3 TO <6KG

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Background: Abacavir (ABC)/dolutegravir (DTG)/lamivudine (3TC) is a fixed-dose combination (FDC) tablet approved for adults and children with HIV weighing ≥6kg and aged ≥3 months. We evaluated whether ABC/DTG/3TC (60mg/5mg/30mg) dispersible tablet (DT) once daily would achieve therapeutic targets in children weighing 3-<6kg (aged ≥4 weeks).

Materials and Methods: We used a population pharmacokinetic (PopPK) model-based approach leveraging existing data with single entities and FDC formulations from adults, infants, and children with HIV. Drug-specific PopPK models incorporating expected enzyme and renal maturation functions were developed for ABC, DTG and 3TC and used to predict pediatric drug exposures. Simulations were performed with 1000 replicate trials of 200 participants. Exposure metrics (AUC0-24, Cmax, and C24) were calculated for each drug and compared with pre-defined exposure target range (DTG C24 geometric mean [GM] 0.697-2.26 µg/mL, ABC AUC0-24 GM 6.3-50.4 µg*h/mL, and 3TC AUC0-24 GM 6.3-26.5 µg*h/mL). We reviewed safety findings for ABC, DTG and 3TC in the lowest weight bands (WBs) of three pediatric trials (P1093, ODYSSEY and IMPAACT 2019), alongside available literature describing PK and safety of ABC and 3TC in neonates and infants under 3 months (including PETITE Study).

Results: Predicted GM steady-state plasma exposures of ABC, DTG and 3TC in children 3-<6kg receiving a single FDC of ABC/DTG/3TC DT were within the target ranges for each component. AUC0-24, Cmax and C24h of ABC, DTG and 3TC were also comparable to prior pediatric and adult studies. Review of pediatric safety data showed similar safety profiles across WBs and were consistent with the known safety profile of the individual drugs. Most children in these studies were on the higher WHO doses of 3TC 60mg and ABC 120mg for this WB.

Conclusions: Predicted drug exposures support the potential use of a single FDC of ABC/DTG/3TC DT in infants weighing 3-<6kg (aged ≥4 weeks), with efficacy and safety expected to be comparable to prior pediatric studies in children ≥6kg. The once daily single tablet treatment option may be a practical solution for infants with early HIV diagnosis.

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32 - POPULATION PHARMACOKINETICS OF ABC/DTG/3TC FDC TO SUPPORT DOSING IN PEDS WITH HIV-1 (IMPAACT 2019)

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Background: Once-daily fixed-dose combinations (FDC) containing abacavir (ABC), dolutegravir (DTG), and lamivudine (3TC) have been approved in the US for adults and children with HIV weighing ≥6 kg (Dispersible tablet (DT) and Tablets). This analysis assessed the ability of previously developed ABC, DTG, and 3TC pediatric population pharmacokinetic (PopPK) models using multiple formulations to describe and predict PK data in young children using DT and Tablet formulations of ABC/DTG/3TC FDC in the IMPAACT 2019 study.

Methods: IMPAACT 2019 was a Phase I/II, multi-center, open-label study assessing the PK, safety, tolerability, and efficacy of ABC/DTG/3TC FDC (Tablets and DT) in children with HIV-1 aged <12 years and weighing ≥6 to <40 kg. Intensive and sparse PK samples were collected through 48 weeks (N=55 participants with 590 ABC, 598 DTG, and 597 3TC observations). Existing drug specific pediatric PopPK models for ABC (2-compartment), DTG (1-compartment), and 3TC (1-compartment) were applied to the IMPAACT 2019 plasma drug concentrations data without re-estimation (external validation) of PopPK parameters. Exposures were then simulated across weight bands for each drug and compared with pre-defined exposure target ranges.

Results: Goodness-of-fit and visual predictive check plots demonstrated good agreement between observed concentrations for ABC, DTG, and 3TC from IMPAACT 2019 and the respective PopPK models. The post-hoc PK parameter estimates were comparable to the NCA PK parameter estimates from IMPAACT 2019. Thus, new PopPK models to specifically describe the IMPAACT 2019 data were not necessary. Simulated geometric mean (GM) C24h DTG exposures were consistent across the weight bands (0.74 - 0.95 µg/mL) for both formulations. The predicted ABC GM AUC0-24 ranged from 14.89 to 18.50 µg*h/mL for both formulations. Similarly, predicted GM AUC0-24 ranges for 3TC were consistent across the weight bands (10.50 - 13.20 µg*h/mL). The predicted GM exposures were within the pre-defined GM target range set for each drug and comparable to the previously observed PK with adults and pediatric participants with individual drugs.

Conclusions: This model-based approach leveraged existing pediatric data and models to confirm FDC ABC/DTG/3TC dosing for DT and Tablet using PK data collected in IMPAACT 2019. This analysis supports ABC/DTG/3TC FDC dosing in children weighing ≥6 kg.

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33 - PHARMACOKINETIC MODELLING TO ENABLE EARLY ATTRITION OF REPURPOSED ANTIVIRAL DRUG COMBINATION CANDIDATES WITH A HIGH LIKELIHOOD OF FAILURE IN COVID-19

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Introduction: COVID-19 remains a concern in some patient population groups such as those who are immunosuppressed. While antiviral monotherapy is available, development of combination therapy could offer improved efficacy whilst reducing the risk of developing resistance. Repurposing drugs already approved or at late stage development can speed up the time to market, reduce risk of failure and decrease costs relative to more traditional development programs. To avoid unnecessary waste of resources when selecting drugs for potential repurposing, it is essential to rule out compounds that are unlikely to achieve efficacious concentrations at safe doses in patients.

Aim: To conduct pharmacokinetic modelling & simulations to predict drug concentrations in patients for drug combinations identified as having activity against SARS-CoV-2 in vitro.

Methods: Literature searches were performed using PubMed to identify clinical concentration-time profiles for drug combinations determined as having synergistic activity against SARS-CoV-2 in Calu-3 and AAT cells. Published data was digitalised using WebPlotDigitiser and formatted for pharmacokinetic analysis. One-, two- and three- compartment models were fitted to the data as appropriate using R. Selected models were used to simulate plasma concentration-time profiles in a patient population (n=1000) at dose regimens considered to have an acceptable safety profile. Simulated plasma concentrations were compared with the in vitro calculated EC90 values for SARS-CoV-2.

Results: In vitro studies identified 37 drug combinations with synergistic efficacy against SARS-CoV-2. Five drugs could not undergo PK modelling due to unavailability of clinical concentration data in the literature. Two drugs had been withdrawn from the market due to adverse events so did not undergo any further PK evaluation. Three drugs were eliminated from further evaluation due to other reasons (formulation challenges, prior clinical testing, etc). Of the remaining combinations, PK simulations identified 18 combinations where at least one drug would not achieve efficacious systemic concentrations in patients.

Conclusions: Modelling and simulations of pharmacokinetic data used in conjunction with EC90 values obtained from in vitro studies can optimise the selection of lead candidates for drug repurposing by eliminating those with a high certainty of failure. Early attrition enables resources to be dedicated to candidates more likely to succeed.

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34 - TFV-DP ADHERENCE INTERPRETATIONS FROM TDF USING AN UPDATED 50% METHANOL AND 50% WATER EXTRACTION METHOD FOR DBS

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Background: Intraerythrocytic tenofovir-diphosphate (TFV-DP) and emtricitabine-triphosphate (FTC-TP) in dried blood spots (DBS) has been used in many clinical trials to better understand cumulative and recent adherence, respectively. The original validated extraction utilized 70% methanol and 30% water (70:30) which required controlled extraction conditions for reproducible results. We recently validated a 50% methanol and 50% water extraction (50:50) which yields better and more reproducible drug recoveries with fewer limitations on the control of extraction conditions. The aim of this study was to compare the extraction performances (70:30 vs 50:50) and to adjust the original TFV-DP interpretations which was based on 70:30, using the 50:50 extraction process.

Methods: DBS from the Benchmark study were used for this analysis. The Benchmark study included 53 African cisgender women without HIV randomized to 2, 4, or 7 doses per week, directly observed, for 8 weeks. An additional 17 pregnant women received 7 doses/week for 8 weeks. DBS samples were collected weekly; each sample included five 50uL spots. 396 samples were available for this analysis. Both extraction methods were run in parallel to assess the relative efficiency of extracting TFV-DP and FTC-TP: Two 3mm punches were removed from the same 50uL spot from each card, and one punch was extracted with 70:30 and the other with 50:50. TFV-DP and FTC-TP concentrations were quantified using validated LC-MS/MS. A linear regression on the logarithmic scale was used to compare the results from the two extraction methods. The fold difference between extraction methods was applied to the original 70:30 TFV-DP adherence interpretations, which were <350 (< 2 dose/week), 350-699 (2-3 doses/week), 700-1249 (4-6 doses/week), and ≥1250 fmol/punch (7 doses/week). These were generated from the DOT-DBS study conducted in the USA.

Results: Data from the 70:30 extraction were within 10% of the original 70:30 TFV-DP adherence table estimates based on DOT-DBS, validating these interpretations for African cisgender women. The 50:50 extraction resulted in 1.27 (95% CI 1.25, 1.28) higher TFV-DP concentrations compared with the 70:30 extraction. The conversion factor of 1.27 was applied to the previous 70:30 TFV-DP benchmarks to produce the following interpretations for 50:50 extraction: <450 (< 2 dose/week), 450-899 (2-3 doses/week), 900-1599 (4-6 doses/week), and ≥1600 fmol/punch (7 doses/week).

Conclusions: This study used samples from a directly observed dosing study in cisgender African women to demonstrate that 70:30 extraction matched previous TFV-DP adherence interpretations. The new 50:50 extraction resulted in 1.27 fold higher recoveries enabling the establishment of a new interpretation table for 50:50 extraction. Future studies can use either table for adherence assessment based on the extraction used.

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35 - CASE REPORT: DOLUTEGRAVIR DOSING POST ROUX-EN-Y GASTRIC BYPASS SURGERY

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Background: Adequacy of dolutegravir drug exposure when administered after the duodenum (such as Roux-en-Y jejunostomy tube or Roux-en-Y gastric bypass surgery) is largely unknown. In addition, various gastrointestinal modifications including changes in gastric volume, acidity, emptying time, enterohepatic circulation and delayed entry of bile acids may be present post-surgery. Existing data is limited to individual case reports or case series with the timing of collection post-surgery varying. Pharmacokinetics are more likely to be altered in the early stages post-surgery. There is evidence of decreased exposure of dolutegravir following a Roux-en-Y gastric bypass surgery. In some cases, a temporary increase in dolutegravir dose to 50 mg BID may be considered.

Case report: A 53-year-old white male with HIV on antiretroviral therapy with dolutegravir/abacavir/lamivudine FDC and recent non-adherence with 1 month of missed doses is admitted for emergency Roux-en-Y gastric bypass surgery due to a septic shock and perforated gastric viscus with a suspected gastric tumor. He is non-obese and had a low BMI of 18.5. He was not virologically suppressed at the time of the surgery with an HIV VL 560 copies/mL and a CD4 count of 160 cells/mm3. The dolutegravir dose was increased to 50mg BID with food post-surgery to mitigate potential decreased levels. Dolutegravir trough levels were measured at 7 days post dose increase (steady state); which was two weeks post-surgery. A reduction in dolutegravir trough concentrations were observed compared to reference Cmin levels prior to the AM dose but not the supper dose (1137ng/mL and 2167ng/mL versus reference of 2120 ng/mL). A target dolutegravir trough has not yet been established nor has a dose limiting toxicity. His HIV viral load re-suppressed to < 40 copies/mL at 1 month post-surgery and has remained suppressed at 2, 3 and 5 months post-surgery with an increase of CD4 cells to 290 cells/mm3 at 5 months post-surgery.
It was decided to continue dolutegravir BID long-term in this patient due to one level being at reference and one below reference, the challenges with obtaining new steady state levels, tolerability of the regimen, as well as ongoing intermittent non-adherence.

Conclusion: This case study continues to highlight the importance of performing pharmacokinetic assessments in patients with the potential for impaired drug absorption to ensure antiretroviral success. Dolutegravir BID has been shown to be well tolerated for long-term use, however there is the potential to reduce the dose in the future based on adherence and therapeutic drug monitoring.

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36 - ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION OF AINUOVIRINE IN HEALTHY ADULTS: A RADIOLABELED MASS BALANCE AND BIOTRANSFORMATION STUDY

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Background: Ainuovirine (ANV) is a new-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) for treatment of human immunodeficiency virus type 1 (HIV-1) infection. The absorption, distribution, metabolism, and elimination of ANV was evaluated in a human radiolabeled mass balance and biotransformation study.

Methods: A single-center, single-dose, non-randomized, open-label study was conducted, in which six healthy males received a single dose of oral suspension containing [14C]ANV at 150 mg/approximately 100 µCi on the first day in the study under fasting condition. Whole blood, plasma, urine, and fecal samples were collected at the specific time points during the study. The data of pharmacokinetic (PK) parameters of the total radioactivity in plasma, concentration ratio of total radioactivity in whole blood to plasma, and mass balance were obtained by measuring the total radioactivity of [14C]ANV in plasma, whole blood, urine, and feces. The main metabolic elimination pathways and characteristics of ANV in human body were obtained by analyzing the radioactive metabolite profiles in plasma, urine, and feces; and the structure of major metabolites was identified using radioisotope and mass spectrometry.

Results: The time to maximum plasma total radioactivity (Tmax) was 3.42 h; the mean maximum concentration (Cmax) was 327 ng·Eq./g; and the half-life of the total radioactivity terminal elimination phase (t½) was 43.5 h. Within 0 - 240 h, the mean cumulative excretion rate of total radioactivity was 101.64 %. Specifically, the mean total excretion accounted for 28.10% of the administered dose in urine, and 73.54% of the administered dose in feces, suggesting that [14C]ANV was primarily excreted into feces. The primary clearance pathway of [14C]ANV was mono-oxygenated to form M341, which was further glucuronidated, and metabolized by the liver, and excreted into feces and urine. The secondary metabolic pathway was glucuronidation of the unchanged drug to form M501, which was excreted into urine.

Conclusions: Ainuovirine is primarily metabolized by the liver, and excreted into feces and urine, with a low plasma clearance, in the human body.

Keywords: ainuovirine, human immunodeficiency virus 1, non-nucleoside reverse transcriptase inhibitor, pharmacokinetics, mass balance

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37 - EFFECT OF FLUCONAZOLE ON THE PHARMACOKINETICS OF AINUOVIRINE IN HEALTHY ADULT SUBJECTS

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Introduction: Ainuovirine (ANV) is a newly developed next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) for used in combination therapy for people living with HIV (PLWH) in China, which is metabolized by CYP2C19. The aim of this phase 1 study was to assess the drug-drug interaction (DDI) and safety of ainuovirine when coadministered with fluconazole, a strong CYP2C19 inhibitor, by experimentally obtained in healthy adult subjects, and a physiologically-based pharmacokinetics (PBPK) model was developed for dose prediction of ainuovirine.

Methods: This was a single-center, open-label, parallel-group, fixed-sequence, two-period study in healthy subjects (aged 20–45 years). 36 healthy subjects were allocated into two groups. In group A, 18 healthy subjects received oral ainuovirine (150 mg) once daily in Period 1 (Days 1–7), followed by coadministration with oral fluconazole (200 mg) once daily in Period 2 (Days 8–14). In group B, 18 healthy subjects received oral fluconazole (200 mg) once daily in Period 1 (Days 1–7), followed by coadministration with oral ainuovirine (150 mg) once daily in Period 2 (Days 8–14). Blood samples were collected before and after dosing. A PBPK model (PK-SIM® version 11.2, Open system Pharmacology, USA) of ainuovirine and fluconazole was developed and validated to predict their DDIs.

Results: All subjects (N = 36) completed the study. In group A, when coadministered with fluconazole, geometric means of ainuovirine pharmacokinetics parameters Cmin,ss, AUC0-24,ss increased up to 233.0% and 349.6% respectively, versus ainuovirine alone, whereas the median Tmax,ss was unaffected. In group B, there were no apparent effects of ainuovirine on Cmax,ss, AUC0-24,ss and Tmax,ss for fluconazole. Possible treatment-related adverse events (AEs) assessed by investigators were fewer in Group A (83.3%) versus Group B (94.4%), no death or grade ≥3 serious AE was reported. The PBPK modelling supports a dose reduction by half for coadministration of ainuovirine and strong CYP2C19 inhibitors such as fluconazole.

Conclusion: Coadministration of ainuovirine with fluconazole significantly increased ainuovirine systemic exposure, whereas ainuovirine did not appear to affect the exposure of fluconazole. The PBPK modelling supports a dose reduction by half (i.e., 75 mg) for coadministration of ainuovirine and strong CYP2C19 inhibitors such as fluconazole.

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38 - CABOTEGRAVIR POPPK ANALYSIS OF ADULTS & ADOLESCENTS LIVING WITH HIV/AT RISK FOR HIV RECEIVING PREP

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Background: Cabotegravir (CAB) is an integrase strand transfer inhibitor approved in adults and adolescents (12 to <18 years) weighing >35kg as long-acting injectable (LAI) HIV-1 prevention, and for treatment in combination with rilpivirine. An existing CAB population pharmacokinetic (PopPK) model was limited to adult PK (Han 2023). We set out to extend and optimize that existing PopPK model for adolescents (12 to <18 years) by incorporating available adolescent PK data from the IMPAACT 2017/MOCHA (NCT03497676) and HPTN 083/084-01(NCT04824131/ NCT02720094) clinical trials.

Materials and Methods: PK data following oral lead-in (30mg once daily, QD for at least 4 weeks) and LAI treatment (an initial 600mg 4-week loading dose followed by 400mg Q4W or 600mg Q8W) from 147 adolescents with HIV (IMPAACT 2017) and 62 HIV-negative adolescents (HPTN 083/084-01) with weight of 35.2-168 kg, body mass index (BMI) of 15.8-51.6 kg/m2 and 12 to 17 years were added to adult data (n=1647). The PopPK model parameters were re-estimated based on this pooled dataset using NONMEM 7.3. The updated PopPK model was used to simulate PK profiles for CAB for Q4W and Q8W regimens in adolescents and adults. Individual exposure metrics (e.g. Ctau,ss) were derived and compared between adolescents and adults.

Results: A 2-compartment model with 1st-order absorption adequately described CAB PK in adolescents and adults. No new covariates were identified as compared to the adult PopPK model. Weight and smoking status were significant determinants of CL/F, and only weight was a determinant of Vc/F, Vp/F, and Q/F. Needle length, female sex, splitting of the injection, and BMI were significant determinants of KA IM (absorption rate for LAI). Adolescents had CAB LA exposure at steady state (Ctau,ss median, 5th-95th: 2.36, 0.849-4.13 µg/mL for 600mg Q8W) comparable to that of adults (Ctau,ss : 1.91, 0.786-3.33 µg/mL for Q8W), with their exposure levels falling within the same range across all dosing phases, and contained within the established efficacy and safety thresholds of 0.45 and 22.5µg/mL.

Conclusions: The addition of adolescent data to the adult PopPK dataset allowed expansion of the prior PopPK model down to 35 kg and optimization of predictions in adolescents. Given the similarity of CAB PK across adolescents and adults, same dosing regimens apply for adults and adolescents.