Effect of dihydroartemisinin-piperaquine for malaria intermittent preventive treatment on dolutegravir exposure in pregnant women living with HIV

Dr Clifford George Banda (BNDCLI001)

SUPERVISORS

Prof Karen I. Barnes

Prof Gary Maartens

This dissertation is submitted to the University of Cape Town in partial fulfilment of the requirements for the degree of Master of Medicine in Clinical Pharmacology

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Declaration

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Abstract

Background: In sub-Saharan Africa, the disease burden of malaria and HIV infections overlap. In settings with moderate-to-high malaria transmission intensity, pregnant women living with HIV (PWLHIV) require both antiretroviral therapy and malaria intermittent preventive treatment (IPTp). Dihydroartemisinin-piperaquine has been identified as a promising alternative to sulfadoxine-pyrimethamine for malaria prevention in pregnancy. However, another antimalarial drug, artesunate-amodiaquine, similar to dihydroartemisinin-piperaquine, was previously shown to reduce dolutegravir exposure in non-pregnant adults.

Objective: To investigate the effect of dihydroartemisinin-piperaquine for IPTp on dolutegravir plasma exposure in pregnant women on dolutegravir-based antiretroviral therapy.

Methods: We conducted an open-label, non-randomised, fixed sequence, pharmacokinetic study in PWLHIV in Malawi. Dolutegravir concentrations were measured over a 24-hour period, before and after the recommended three-day treatment dose of dihydroartemisinin-piperaquine in 12 pregnant women in their 2nd or 3rd trimester. Non-compartmental analysis was performed, and geometric mean ratios (GMRs) and 90% confidence intervals (CIs) were generated to compare dolutegravir pharmacokinetic parameters between the two treatment periods.

Results: Co-administration of dihydroartemisinin-piperaquine and dolutegravir increased dolutegravir's overall exposure ($AUC_{0\text{-}24hr}$) and maximum concentration (C_{max}) by 30% (GMR,1.30; 90% CI, 1.11-1.52) and 31% (GMR, 1.31; 90% CI,1.13-1.51), respectively. Furthermore, dolutegravir's trough (C_{24}) concentration increased by 42% (GMR,1.42; 90% CI,1.09-1.85). The combined treatments were well tolerated with no serious adverse events observed.

Conclusion: Dihydroartemisinin-piperaquine may be administered as IPTp with dolutegravir-based antiretroviral therapy in pregnant women as the modest increase in dolutegravir exposure, similar to pharmacokinetic parameter values published previously, assures its efficacy without any clinically significant adverse events observed in this small study

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Several people contributed to the research project as detailed below:

- Dr Clifford G. Banda, Prof Karen Barnes, and Prof Gary Maartens designed the study, developed the study protocol, and led in data analysis and interpretation of the study findings.
- Dr Dumisile Nkosi, Ms Marumbo Chirwa, Ms Mayamiko Kapulula, Mr Steven Munharo and Ms Sharon Muyaya assisted with sample and data collection and daily implementation of the study, led by Dr Clifford G Banda
- Ms Lesley Workman coordinated data management for the study
- Dr Elizabeth Allen supported training of the study team and internal quality assurance of the study
- Prof Feiko ter Kuile, Prof Victor Mwapasa. Prof Kamija Phiri and Dr Mwayi Madanitsa supported the study's administrative activities and the infrastructure under which the study was conducted
- Associate Professor Lubbe Wiesner assisted with assaying of blood samples at the University of Cape Town
- All co-authors read and approved the final manuscript

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List of abbreviations

ACT- Artemisinin-based combination therapy

ART- Antiretroviral therapy

AUC- Area under the concentration time curve

BMI- Body mass index

DP- Dihydroartemisinin-piperaquine

DTG- Dolutegravir

IPTp- Intermittent preventive treatment of malaria in pregnancy

PWLHIV- Pregnant women living with human immunodeficiency virus

Publication-ready manuscript

Effect of dihydroartemisinin-piperaquine for malaria intermittent preventive treatment on dolutegravir exposure in pregnant women living with HIV

Authors:

Clifford G. Banda[1,2,3], Dumisile Nkosi[1], Elizabeth Allen[2,4], Lesley Workman[2,4], Mwayiwawo Madanitsa[5,6], Marumbo Chirwa[1], Mayamiko Kapulula[5], Sharon Muyaya[5], Steven Munharo[5], Lubbe Wiesner[2], Kamija S. Phiri[3,5], Victor Mwapasa[3], Feiko O. ter Kuile[7], Gary Maartens[2], Karen I. Barnes*[2,4]

Affiliation:

1. Malawi-Liverpool-Wellcome Trust Clinical Research Programme, Blantyre, Malawi
2. Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa
3. Kamuzu University of Health Sciences, Blantyre, Malawi (formerly College of Medicine and Kamuzu College of Nursing, University of Malawi)
4. WorldWide Antimalarial Resistance Network (WWARN), Pharmacology Scientific Group, University of Cape Town, Cape Town, South Africa
5. Training and Research Unit of Excellence, Blantyre, Malawi
6. Department of Clinical Sciences, Malawi University of Science and Technology, Limbe, Malawi
7. Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, United Kingdom

***Corresponding author**: Karen I. Barnes, Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, K47 Old Main Building, Groote Schuur Hospital, Observatory, 7925, Cape Town, South Africa, karen.barnes@uct.ac.za

Alternative corresponding author: Clifford G. Banda, Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, K47 Old Main Building, Groote Schuur Hospital, Observatory, 7925, Cape Town, South Africa Cape Town, South Africa, cgbanda@mlw.mw

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Running title: DP-Dolutegravir-based ART drug-drug interactions in pregnancy

SYNOPSIS

Background: In sub-Saharan Africa, the disease burden of malaria and HIV infections overlap. In settings with moderate-to-high malaria transmission intensity, pregnant women living with HIV (PWLHIV) require both antiretroviral therapy and malaria intermittent preventive treatment (IPTp). Dihydroartemisinin-piperaquine has been identified as a promising alternative to sulfadoxine-pyrimethamine for malaria prevention in pregnancy. However, another antimalarial drug, artesunate-amodiaquine, similar to dihydroartemisinin-piperaquine, was previously shown to reduce dolutegravir exposure in non-pregnant adults.

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CI,1.09-1.85). The combined treatments were well tolerated with no serious adverse events observed.

Conclusion: Dihydroartemisinin-piperaquine may be administered as IPTp with dolutegravir-based antiretroviral therapy in pregnant women as the modest increase in dolutegravir exposure, similar to pharmacokinetic parameter values published previously, assures its efficacy without any clinically significant adverse events observed in this small study.

INTRODUCTION

In sub-Saharan Africa, there is an overlap of disease burden between malaria and HIV infections. Annually, nearly 30 million pregnancies are at risk of malaria in the region [1]. Pregnant women who are infected with malaria are at increased risk of adverse outcomes including maternal anaemia and severe malaria, as well as low birth weight and stillbirth deliveries. Furthermore, the risk of these malaria adverse outcomes is higher in pregnant women who are living with HIV (PWLHIV) [2–6]. Preventing malaria in pregnancy is, therefore, a key priority of most malaria national control programmes in sub-Saharan Africa.

One of the tools for malaria prevention is to use intermittent preventive therapy during the second and third trimesters of pregnancy (IPTp) in moderate-to-high intensity malaria transmission settings. This strategy involves administration of standard treatment doses of antimalarial drugs regularly during pregnancy. In pregnant women who are not living with HIV, the antimalarial drug currently recommended by WHO is a sulfonamide-based therapy, sulfadoxine-pyrimethamine (SP). However, the efficacy of SP is being undermined by increasing resistance of malaria parasites [7–9]. PWLHIV cannot receive SP for IPTp if they are already on another sulfonamide-based combination, trimethoprim-sulfamethoxazole (cotrimoxazole) to prevent opportunistic infections. As a result, intermittent administration of dihydroartemisinin-piperaquine has been suggested as an effective alternative to SP in pregnant women not living with HIV [7,8,10], and is being explored as add-on therapy to cotrimoxazole in PWLHIV and on antiretroviral therapy [11,12].

Dihydroartemisinin-piperaquine is an artemisinin-based combination therapy (ACT) that contains a short-acting artemisinin derivative, dihydroartemisinin, and a longer acting partner drug, piperaquine. During IPTp, dihydroartemisinin rapidly suppresses any parasite load while piperaquine clears any remaining parasites and confers protection against any new infections due to its long half-life [13]. In non-pregnant adults in Uganda the ACT, artesunate-

amodiaquine, reduced the overall exposure of dolutegravir by 24% and the trough concentrations of dolutegravir were reduced by 42%[14], although these remained above the purported minimum efficacious dolutegravir concentrations of 300 ng/mL [15]; the mechanism of this interaction is unknown. Piperaquine, like amodiaquine, is a 4-aminoquinoline [16], and may thus also reduce dolutegravir exposure. As part of a pharmacokinetic clinical trial aimed at profiling drug-drug interactions between dihydroartemisinin-piperaquine and antiretroviral therapy, we assessed whether a three-day IPTp course of dihydroartemisinin-piperaquine altered plasma dolutegravir exposure in PWLHIV in Malawi.

MATERIALS AND METHODS

Study design and patient selection

An open-label, non-randomised, fixed sequence, pharmacokinetic study was conducted between December 2019 and July 2020 in PWLHIV at Zomba Central Hospital, in the southern region of Malawi. The study protocol was approved by the College of Medicine Research Ethics Committee (P.07/19/2746), the University of Cape Town's Human Research Ethics Committee (266/2019), and the Liverpool School of Tropical Medicine's Research Ethics Committee (19-039). The study was registered on PACTR.samrc.ac.za (PACTR201910580840196) and was conducted in compliance with International Council for Harmonization Good Clinical Practice guidelines, the current ethical principles in the Declaration of Helsinki, and applicable local regulatory requirements.

The inclusion criteria were: i) adult pregnant women (≥18 years of age) with no symptoms of malaria, presenting at the hospital for antenatal care from 16-24 weeks of gestation (confirmed by ultrasound scan); ii) virologically suppressed (viral load <50 copies/mL) on an efavirenz-based antiretroviral regimen; iii) CD4 cell count > 100 cells/mm^3; iv) resident within Zomba hospital catchment area; and v) willing to adhere to follow up procedures including intensive pharmacokinetic sampling. Exclusion criteria were: i) multiple pregnancies; ii)

severe malformations or non-viable pregnancy by ultrasound scan; iii) known allergy or contraindication to any study drug; iv) use of medications known or suspected to interact with dolutegravir or piperaquine and v) medical history of comorbidities likely to influence pharmacokinetic parameters of study drugs, such as renal, liver or cardiac disease.

A sample size of 14 participants was calculated to have at least 80% power to detect a change in AUC outside U.S. Food and Drug Administration (FDA) limits for bioequivalence (i.e. 90% CI for AUC falling within 80 to 125%) for dolutegravir. After accounting for a 10% loss-to-follow-up, 16 participants were planned for recruitment.

Study procedures and pharmacokinetic blood sampling

Figure 1 summarises the study sequences, dosing schedule, and dolutegravir pharmacokinetic blood sampling time points. Participants who provided written informed consent received an IPTp course comprising 3 tablets of dihydroartemisinin-piperaquine given once a day for 3 consecutive days in sequence 1 while on daily efavirenz-based ART (a fixed-dose combination of tenofovir/lamivudine/efavirenz; SYMFI^{TM}, Mylan, USA). Each dihydroartemisinin-piperaquine tablet (D'Artepp®, Guilin, China) contained a fixed-dose combination of 40 mg dihydroartemisinin and 320 mg piperaquine. In this first sequence, plasma sampling to assay efavirenz concentration was not conducted. However, plasma piperaquine sampling was carried out and the findings of the piperaquine concentration profile in this sequence and following a switch of ART from efavirenz to a dolutegravir-based regimen, have been reported separately. Two weeks later, the participants were switched to daily dolutegravir-based ART, according to the current national HIV treatment guidelines. Each fixed-dose dolutegravir-based ART tablet (REYDIN film-coated tablets, Cipla, India) contained 50 mg of dolutegravir, 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate. Since ART was usually administered in the morning, participants were instructed to take permitted concomitant medications (e.g. isoniazid, cotrimoxazole as well as a fixed-

dose combination of ferrous sulfate and folic acid) in the evening. To standardise timing between food and dolutegravir or dihydroartemisinin-piperaquine intake, participants were instructed to take medications at least 2 hours before or after meals.

The first intensive pharmacokinetic blood sampling occasion was when participants had been on dolutegravir-based ART for four weeks to allow for the waning of efavirenz induction. During this four-week lead in period, an electronic device (Wisepill RT 2000, Wisepill Technologies, Somerset West, South Africa) was used to monitor daily drug intake and participants were reminded, through short-text-messages, if a dose was missed. In Sequence 2, intensive blood sampling for dolutegravir plasma concentrations was done pre-dose (0 h) and at 1, 2, 3, 4, 6, 8 and 24 hours after an observed dolutegravir-based ART dose. Thereafter, participants again received a three-day IPTp course of dihydroartemisinin-piperaquine, with the first dose being observed. On the last (3^{rd}) day of dihydroartemisinin-piperaquine treatment, both doses of dolutegravir-based ART and dihydroartemisinin-piperaquine were observed, and participants contributed blood samples for dolutegravir concentrations (sequence 3) at the same time points as those in sequence 2 (Figure 1). Routine antenatal care continued in parallel to all the described study procedures.

Safety assessments

At screening, a detailed medical history, physical examination and ultrasound were performed. Thereafter, participants were followed up until delivery. At each follow-up visit, a symptom-directed history and physical examination were conducted. Adverse events and details on prescription medicines, herbal supplements, over-the-counter medications or dietary supplements (vitamins included) or vaccines since the last visit were elicited using open questions. All adverse events detected at scheduled or unscheduled visits were recorded, graded, and independently assessed by two physician investigators to classify any possible, probable or definite relationships to dihydroartemisinin-piperaquine and

dolutegravir-based ART coadministration. Prior to dihydroartemisinin-piperaquine dosing, HIV viral load was measured, and this was repeated 28 days after dihydroartemisinin-piperaquine coadministration to check whether participants were still virologically suppressed.

Pharmacokinetic analysis

Dolutegravir blood samples were collected in EDTA-coated tubes. Within 5 minutes of collection, samples were centrifuged and separated into cryovials containing 200 μL of plasma. The plasma samples were temporarily stored at -20°C before being transferred, within a week of collection, for storage at -80°C until shipment to the University of Cape Town's Pharmacokinetic Laboratory for quantification of dolutegravir. This laboratory participates in the Clinical Pharmacology Quality Assurance (CPQA) external quality control program under the Division of AIDS of the National Institute of Allergy and Infectious Diseases. Dolutegravir was quantified using liquid chromatography-tandem mass spectrometry (LC-MS/MS). The precision (total assay coefficients of variation) during sample analysis was less than 7.2% at all quality control levels and at the lower limit of quantification (LLOQ) which was 30 ng/mL The full details of the assay, which was CPQA approved, are in supplementary text 1.

Statistical analysis

Data from sequences 2 (steady state dolutegravir concentrations when dolutegravir-based ART was administered alone) and 3 (dolutegravir concentrations when dolutegravir-based ART was coadministered with dihydroartemisinin-piperaquine) were analysed. Using noncompartmental analysis, employing the trapezoidal rule with cubic splines, the following pharmacokinetic parameters were estimated for the two time periods; the area under the concentration-time curve to the last measurable time point at 24 hours post dosing (AUC_{0-24h}), terminal elimination half-life ($t_{1/2}$), maximum concentration (C_{max}) and time to C_{max} (T_{max}).

The apparent clearance (CL/F) of dolutegravir was calculated using the equation dose/AUC_{0-24h}, while the trough concentrations (C_{24}) were estimated from the sample collected just before the next dolutegravir dose. Trough dolutegravir concentrations that exceeded the previous predose concentration and were more than half of the concentration of dolutegravir at the prior sampling point (8 h) were deemed implausible unless intake of dolutegravir occurred before the C_{24} sample collection; in such cases, the C_{24} concentration was imputed from the previous predose concentration[17,18]. Pharmacokinetic data were log-transformed to calculate the geometric mean ratio (GMR) of sequence 3 to sequence 2 pharmacokinetic parameters with 90% confidence intervals (CI) evaluated using paired t-tests and back-transformed to absolute ng/mL concentrations. Changes in pharmacokinetic parameters between the two sequences were considered statistically significant when the 90% CI of the GMR did not cross the value of one[19]. These analyses were further stratified by concomitant isoniazid use to explore the impact of isoniazid prophylaxis, with and without coadministration with dihydroartemisinin-piperaquine, on the plasma exposure of dolutegravir. Pharmacokinetic parameters of piperaquine and birth outcomes will be reported separately. All analyses were performed using Stata version 15.1.

RESULTS

Study profile

Twenty pregnant women were screened for eligibility and 13 were recruited into the study. Among these, 12 participants had quantifiable plasma dolutegravir concentrations at all required time points, as detailed in Supplementary Figure 1. The baseline characteristics of the 12 participants are summarised in Table 1. The median gestational age (range) of pregnant women at the time of intensive sampling was 28 (24-33) weeks. A third of the participants (4/12) were receiving tuberculosis prophylaxis with isoniazid and pyridoxine, initiated when they started antiretroviral treatment in line with the national HIV treatment policy at that time.

Pharmacokinetics of dolutegravir administered alone and with dihydroartemisinin-piperaquine.

The pharmacokinetic parameters of dolutegravir were compared before and after completion of a three-day treatment course of dihydroartemisinin-piperaquine as shown in Table 2 and Figure 2. Dolutegravir exposure was higher when co-administered with dihydroartemisinin-piperaquine, with the $AUC_{0\text{-}24hr}$ and C_{max} increased by 30% (GMR, 1.30; 90% CI, 1.11-1.52) and 31% (GMR, 1.31; 90% CI, 1.13-1.51), respectively. Furthermore, the trough dolutegravir concentration at 24 hours (C_{24}) was 42% higher (GMR 1.42; 90% CI, 1.09-1.85) and apparent clearance was 23% slower (GMR 0.77; 90% CI 0.66-0.90) when co-administered with dihydroartemisinin-piperaquine.

Impact of isoniazid prophylaxis

In a post-hoc analysis, the impact of isoniazid prophylaxis on the plasma exposure of dolutegravir with and without coadministration with dihydroartemisinin-piperaquine was explored. Among the eight participants who were not on isoniazid prophylaxis, the overall dolutegravir exposure was increased by 38% (GMR, 1.38; 90% CI, 1.13-1.70) (Supplementary Table 1) following coadministration with dihydroartemisinin-piperaquine. Four participants were on isoniazid prophylaxis. At baseline, those on isoniazid had higher dolutegravir exposure than those not on isoniazid (Figure 3 and Supplementary Table 1). Following coadministration of dolutegravir, dihydroartemisinin-piperaquine and isoniazid, dolutegravir exposure increased only slightly (GMR, 1.15; 90% CI, 0.93-1.43) (Supplementary Table 1)

Treatment emergent adverse events following coadministration of dihydroartemisinin-piperaquine and dolutegravir-based antiretroviral therapy.

Table 3 summarises the adverse events that occurred within 28 days following coadministration of dihydroartemisinin-piperaquine and dolutegravir-based ART in the 13 recruited participants. There were 16 reported adverse events, 14 of which were not considered as related to the coadministration of dihydroartemisinin-piperaquine and dolutegravir-based ART. Thirteen of these 14 events were assessed as mild, and 1 event (catheter site pain) was assessed to be of moderate severity as paracetamol was given. Two events were suspected to be associated with coadministration of dihydroartemisinin-piperaquine and dolutegravir-based antiretroviral therapy: one was nausea that developed ten minutes after drug administration and resolved within an hour of onset, the other event was a pruritic rash that started two hours after coadministration of the drugs and resolved within a day of onset. Both of these events were of mild severity, required no medical intervention and were not associated with higher dolutegravir exposure.

Viral load changes after coadministration of dihydroartemisinin-piperaquine and dolutegravir-based antiretroviral therapy

In all 13 enrolled participants, viral load suppression was maintained below 50 copies/mL throughout the study.

DISCUSSION

There is limited evidence on drug-drug interactions between dolutegravir and antimalarial therapies in pregnancy. We investigated the impact of the promising antimalarial for IPTp, dihydroartemisinin-piperaquine, on the pharmacokinetic profile of dolutegravir when co-administered in pregnancy. We found that dihydroartemisinin-piperaquine modestly increases the overall exposure of dolutegravir. An unexpected finding was that concomitant administration of isoniazid prophylaxis appeared to result in higher dolutegravir exposure; however, only four participants were on isoniazid. No significant safety concerns were identified in this small study. These findings are reassuring as they suggest that a standard

treatment course of dihydroartemisinin-piperaquine can be administered with dolutegravir-based antiretroviral therapy in pregnancy, regardless of concomitant use of isoniazid prophylaxis, without reducing dolutegravir exposure (as previously reported with the related antimalarial amodiaquine [14]) or increasing the risk of adverse effects.

We observed an increased overall exposure of dolutegravir (30% and 31% in $AUC_{0\text{-}24h}$ and $C_{max,}$ respectively) when dolutegravir-based antiretroviral therapy was co-administered with dihydroartemisinin-piperaquine. The mechanism behind this increased drug exposure is unclear but could be driven by improved bioavailability or reduction in plasma clearance (CL/F) of dolutegravir when coadministered with dihydroartemisinin-piperaquine. Both piperaquine and dolutegravir are substrates of Cytochrome P450 3A4 (CYP3A4) enzymes, as major and minor[20,21] metabolic pathways, respectively. However, inhibition of CYP3A4 is an unlikely mechanism for the observed increased exposure of dolutegravir as piperaquine is not known to inhibit CYP3A4 and strong inhibitors of CYP3A4, e.g. cobicistat, do not significantly increase dolutegravir exposure [22]. We hypothesise that the increased dolutegravir exposure we observed could be due to dihydroartemisinin-piperaquine inhibiting the efflux transporters that are involved in clearance of dolutegravir. Dolutegravir is a substrate of P-glycoprotein and breast cancer resistance protein (BCRP) transporters [23]. Mefloquine, an aminoquinoline similar to piperaquine, inhibits P-glycoprotein [24], therefore, it is possible that piperaquine could increase dolutegravir exposure by this mechanism. *In vitro* mechanistic studies are warranted to determine if piperaquine (or dihydroartemisinin) are inhibitors of P-glycoprotein or BCRP.

The exposure of dolutegravir when administered with dihydroartemisinin-piperaquine falls within a range of concentrations that have been previously described in pharmacokinetic studies of dolutegravir during pregnancy and in the postpartum period (Table 4) [15,25,26]. In these studies, the observed exposure of dolutegravir was well tolerated, suggesting that the

311 modest increase in exposure in the present study is unlikely to be associated with safety
312 concerns. Furthermore, this modest increase in dolutegravir exposure could help ensure its
313 efficacy; dolutegravir trough concentrations (C_{24}) during coadministration with
314 dihydroartemisinin-piperaquine were above the purported minimum effective concentration
315 of 300 ng/mL in all study participants [15].
316
317 The four participants who were on isoniazid prophylaxis had a higher exposure of
318 dolutegravir at baseline, which increased only slightly following administration of
319 dihydroartemisinin-piperaquine. The mechanism of a possible drug-drug interaction between
320 isoniazid and dolutegravir is unclear. Isoniazid is an inhibitor of CYP3A4, which is a minor
321 metabolic pathway for dolutegravir; however, as pointed out above, strong inhibitors of
322 CYP3A4 do not increase dolutegravir exposure. Isoniazid and dolutegravir are both
323 substrates of BCRP transporter [23,27] while dolutegravir is a substrate of P-glycoprotein [23]; it is
324 possible that isoniazid inhibits BCRP and/or P-glycoprotein. There is a need for adequately
325 powered pharmacokinetic studies to determine if there is a drug-drug interaction between
326 dolutegravir and isoniazid, as these antimicrobials will be frequently used together.
327
328 Although participants were in the second and third trimesters of pregnancy at the time of the
329 study (Table 1), there were no observed differences in dolutegravir pharmacokinetic profiles
330 when stratified by trimester (data not shown). Similarly, dolutegravir concentrations were not
331 associated with weight or body mass index in our cohort. However, these exploratory
332 findings need to be interpreted with caution as there were small numbers in each trimester
333 stratum. The impact of these covariates on dolutegravir exposure in pregnancy should be
334 investigated in future larger studies.
335
336 Our study has limitations. First, as noted above, we included only a small number of women
337 on isoniazid prophylaxis given the changes in national policy. We were, therefore, unable to

accurately assess the impact of isoniazid on dolutegravir exposure when co-administered with dihydroartemisinin-piperaquine. Second, our participants had received an IPTp treatment course of dihydroartemisinin-piperaquine 6-weeks prior to coadministration with dolutegravir. However, a significant carry-over effect from this initial treatment course was unlikely because participants were on an efavirenz-based antiretroviral therapy which enhances the metabolism of piperaquine by induction of CYP3A4[28], and has been shown to reduce piperaquine's elimination half-life in pregnant women to a mean of 6 days [29]. A 6-week washout period between the two treatment courses provided adequate time to eliminate the longer-acting partner drug, piperaquine. Third, due to safety restrictions put in place to mitigate the spread of the SARS-CoV-2 virus, we were unable to recruit the planned 16 participants. However, the recruited 12 participants in our cohort provided adequate power (80%) to detect a change in AUC outside the FDA limits for bioequivalence for dolutegravir [19]

The combination of dolutegravir-based antiretroviral therapy and dihydroartemisinin-piperaquine was tolerated in this small study and did not result in any serious adverse events. These safety profiles are consistent with previously approved drug labels for both treatments[30,31]. There were no changes in viral load following this drug treatment combination.

In conclusion, a standard treatment course of dihydroartemisinin-piperaquine can be administered with dolutegravir-based antiretroviral therapy in pregnant women living with HIV as the modest increase in dolutegravir exposure, similar to pharmacokinetic parameter values published previously, assures its efficacy without any clinically significant adverse events observed in this small study

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FIGURES

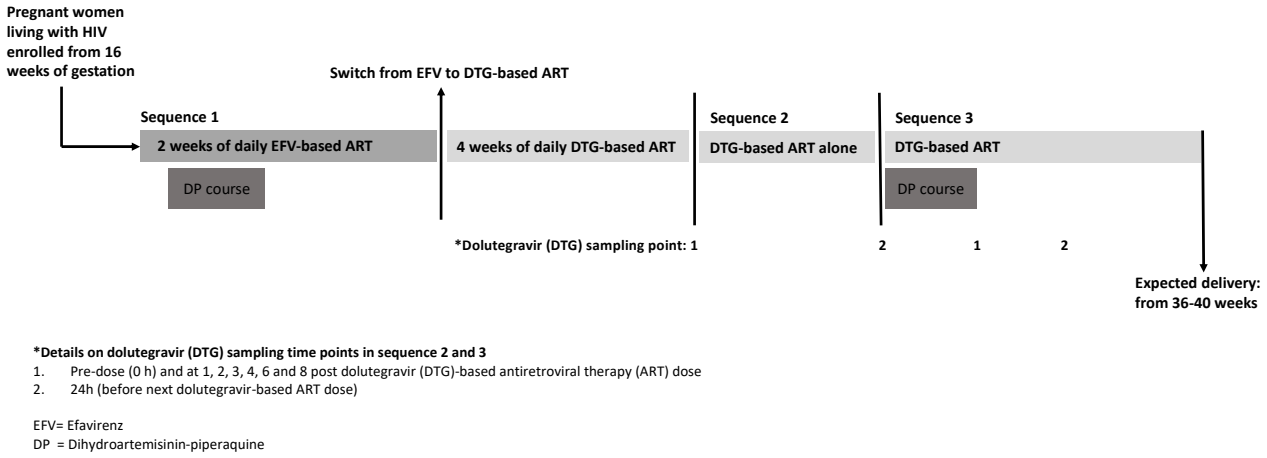


Figure 1. Study design. Fixed sequence study switching from efavirenz- to dolutegravir-based antiretroviral therapy. Intense plasma pharmacokinetic sampling of dolutegravir was done at 4 weeks post-initiation of daily dose of 50 mg of dolutegravir-based antiretroviral therapy and conducted in two sequences: when dolutegravir-based ART was administered alone (sequence 2) and following coadministration with a three-day treatment course of dihydroartemisinin-piperaquine [DP] (sequence 3).

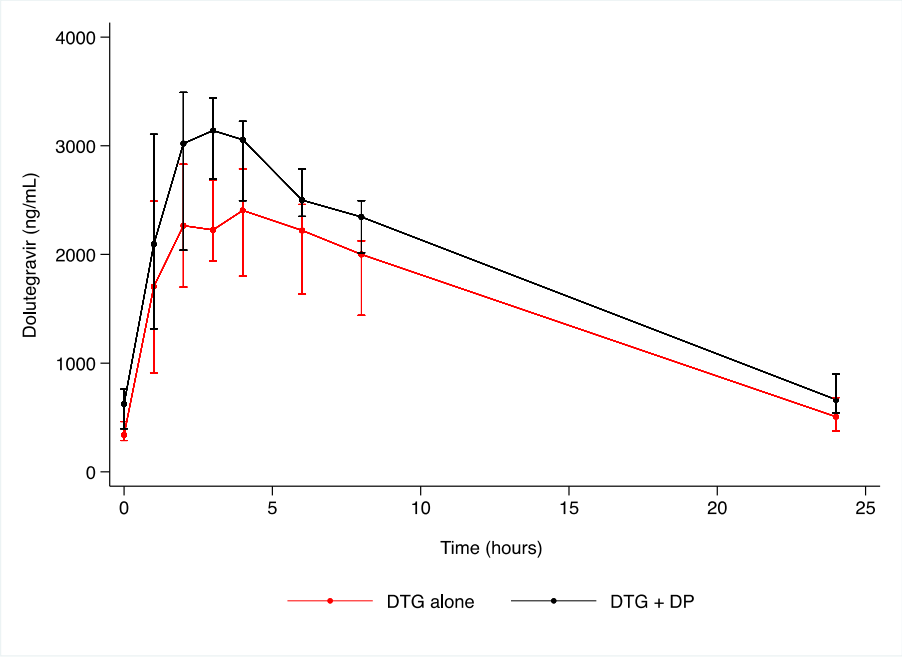


Figure 2. Plasma dolutegravir concentration-time profile following administration of dolutegravir (DTG) -based antiretroviral therapy alone (red line) and with a treatment course of dihydroartemisinin-piperaquine [DP] (black line) in 12 pregnant women. Data are presented as medians (interquartile ranges [IQR])

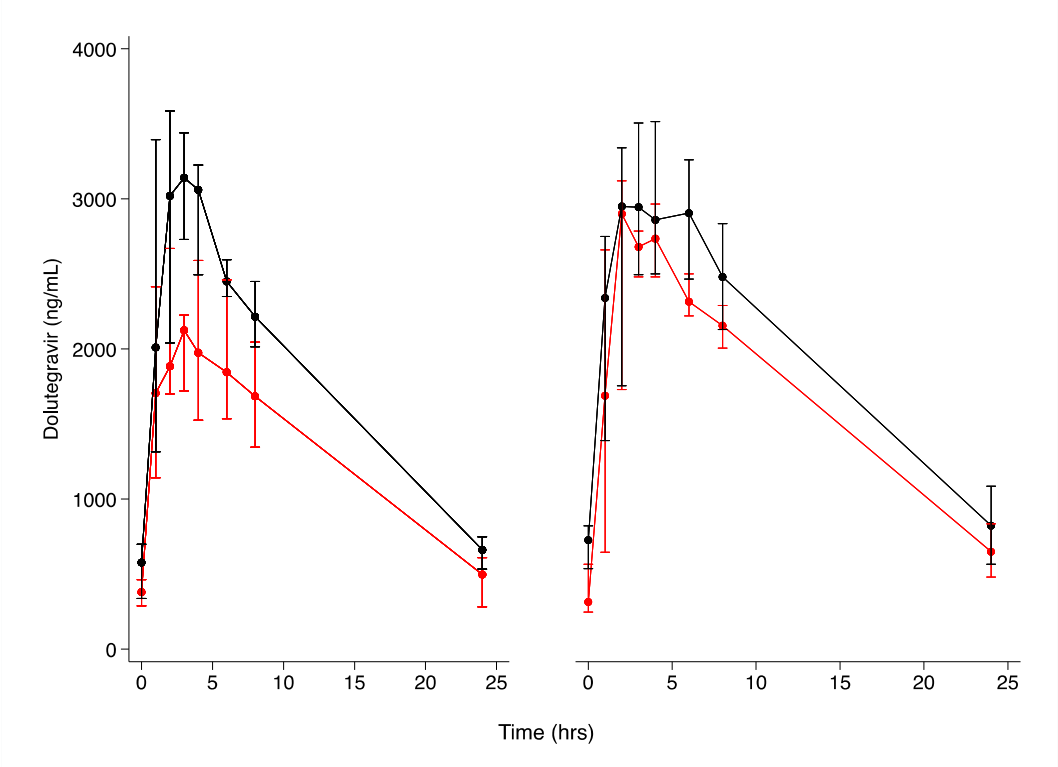


Figure 3. Plasma dolutegravir concentration-time profile following administration of dolutegravir-based antiretroviral therapy alone (red line) and with a treatment course of dihydroartemisinin-piperaquine (black line) in 8 pregnant women who were not on daily isoniazid prophylaxis (graph plots on the left), and in 4 pregnant women who were on isoniazid prophylaxis (graph plots on the right). Data are presented as medians (interquartile ranges [IQR]).

TABLES

Table 1. Baseline characteristics of study participants included in the analysis (N=12)

Age in years (median, [range])	35 [20-42]
Estimated gestational age in weeks (median, [range])	28 [24-33]
Second trimester (n, [%])	5 [41.7%]
Third trimester (n, [%])	7 [58.3%]
Weight (kg, median [range])	62.9 [49.7-82.5]
BMI (kg/m^2, median [range])	24. 3 [20.7-32.0]
CD4 count ($cells/mm^3$, median, [range])	609 [387-1219]
Haemoglobin (g/dL, median [range])	10.8 [8.8-13.7]
Concomitant medication (n, [%])	
Cotrimoxazole prophylaxis	12 [100%]
Isoniazid prophylaxis and pyridoxine	4 [33.3%]
Ferrous sulfate plus folic acid	12 [100%]

Table 2. Dolutegravir exposure when administered alone compared with coadministration with dihydroartemisinin-piperaquine (DP) [N=12]

	Geometric Mean (90% CI)		GM Ratio (90% CI)	
Pharmacokinetic parameter	**DTG-based ART plus DP (Sequence 3)**	**DTG-based ART only (Sequence 2)**	**Sequence 3 / Sequence 2**	**P-value***
$AUC_{0\text{-}24hr}$ (ng.hr/mL)	43,659 (39,939-47,726)	33,555 (29,479-38,196)	**1.30 (1.11-1.52)**	**0.004**
C_{max} (ng/mL)	3,270 (3,030-3,529)	2,504 (2,213-2,832)	**1.31 (1.13-1.51)**	**0.001**
C_{24} (ng/mL)**	701 (593-830)	495 (404-606)	**1.42 (1.09-1.85)**	**0.008**
T_{max} (hr)	2.6 (2.1-3.3)	2.3 (1.8-3.1)	1.13 (0.80-1.61)	0.379
$t_{1/2}$ (hr)	9.9 (8.8-11.1)	9.0 (8.2-9.9)	1.10 (0.95-1.27)	0.063
CL/F (litres/hr)	1.15 (1.05-1.25)	1.49 (1.31-1.70)	**0.77 (0.66-0.90)**	**0.004**

GM: Geometric Mean, DTG: Dolutegravir, ART: Antiretroviral therapy, CI: Confidence interval

Bold represents statistical significance

* Paired t-test

** One participant had an implausible dolutegravir trough concentration due to dosing prior to 24-hour sample. This value was imputed to the previous pre-dose concentration

Table 3. Treatment emergent adverse events by MedDRA system organ class and preferred term (version 24.0), stratified by severity and assessed causality* (N=13)

	Suspected to be due to DP coadministration with DTG			Not suspected to be due to DP coadministration with DTG		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Gastrointestinal disorders						
Nausea	1					
Vomiting				1		
Toothache				1		
Infections and infestations						
Urinary tract infection				2		
Upper respiratory tract infection				2		
Musculoskeletal and connective tissue disorders						
Pain in extremity				1		
General disorders and administration site conditions						
Catheter site pain					1	
Nervous system disorders						
Dizziness				1		
Hypoesthesia				1		
Headache				1		
Skin and subcutaneous tissue disorders						
Night sweats				1		
Rash pruritic	1			2		
TOTAL	2			13	1	

*There was no serious adverse event.

Table 4. Overview of pharmacokinetics (PK) of dolutegravir (DTG) in pregnancy, postpartum period, and non-pregnant adults

Study	Number of participants	Period at time of PK sampling	*Other concomitant treatment	Pharmacokinetic parameter		
				$AUC_{0\text{-}24hr}$ ng.h/mL	C_{max} ng/mL	C_{24hr} ng/mL
[a]Banda CG et al (present study)	12	2nd-3rd trimester	None (Sequence 2)	33,555 (29,479-38,196)	2,504 (2,213-2,832)	495 (404-606)
	12	2nd-3rd trimester	DP (Sequence 3)	43,659 (39,939 – 47,726)	3,270 (3,030 – 3,529)	701 (593 – 830)
[b]Waitt C et al[25]	28	3rd trimester	None	35,322 (19,196 – 67,922)	2,534 (1,462 – 3,986)	642 (188 – 3,088)
	17	Postpartum	None	40,127 (22,795 – 59,633)	2,899 (1,397 – 4,224)	777 (348 – 1,210)
[c]Mulligan N et al[26]	15	2nd trimester	None	47,600 (33,400 – 63,700)	3,620 (2,570 – 4,630)	730 (630 – 1,340)
	28	3rd trimester	None	49,200 (36,400 – 62,000)	3,540 (2,660 – 4,240)	930 (680 – 1,340)
	22	Postpartum	None	65,000 (47,800 – 88,400)	4,850 (3,830 – 5,970)	1,280 (800 – 1,950)
[d]van Lunzen J et al[15]	15	2 weeks post DTG initiation in ART naïve non-pregnant adults	None	48,100 (40%)	3,400 (27%)	1,200 (62%)

[a] Geometric mean (90% confidence interval)

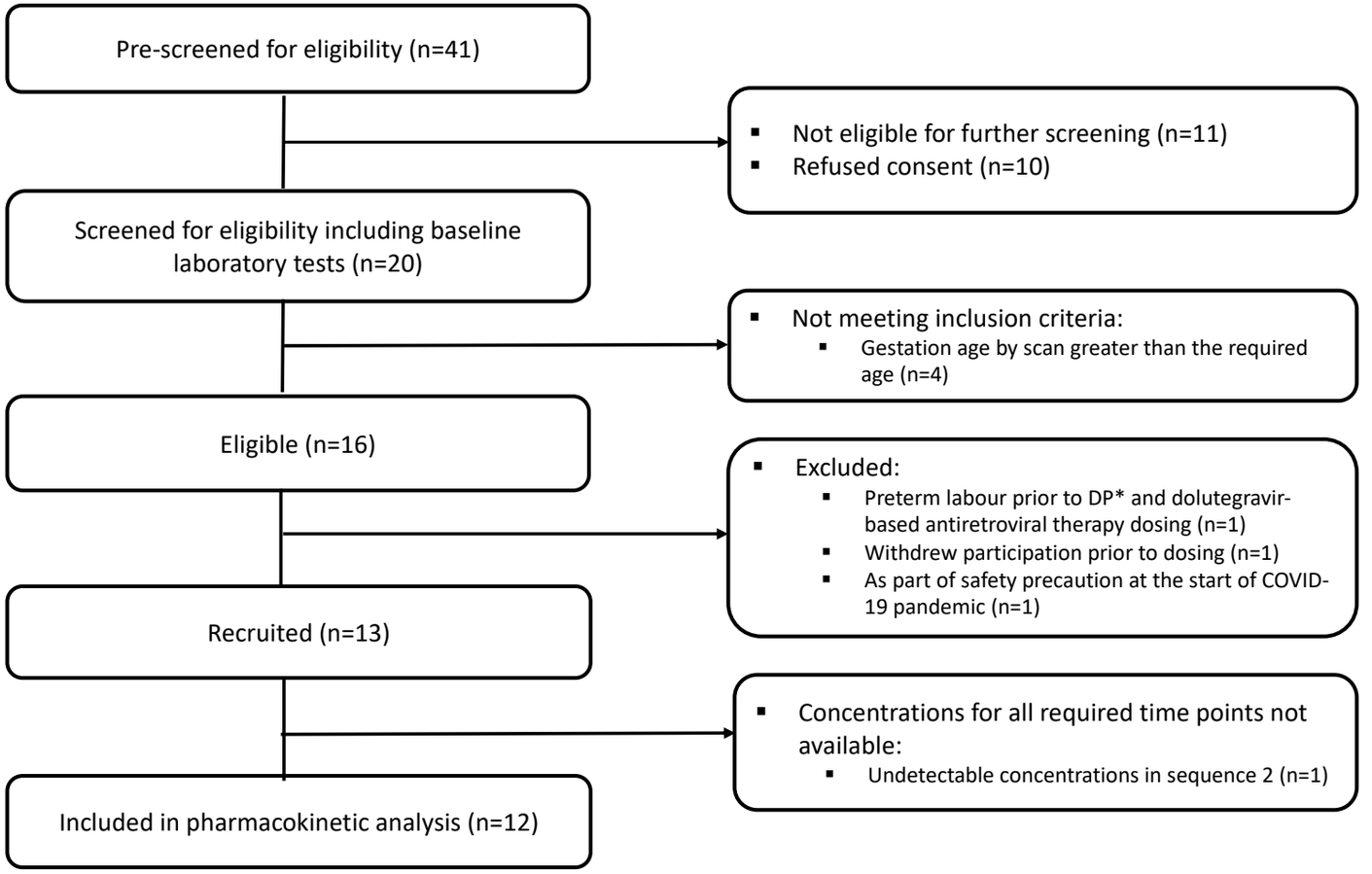
[b] Geometric mean (range)

[c] Median (IQR)

[d] Geometric mean (coefficient of variance, %)

DP = dihydroartemisinin piperaquine

* Other concomitant medication other than standard co-medication in people with HIV which includes cotrimoxazole prophylaxis and, in some, isoniazid prophylaxis



*DP: Dihydroartemisinin-piperaquine

Supplementary figure 1: Study profile

Supplementary Table 1. Dolutegravir exposure when administered alone compared with coadministration with dihydroartemisinin-piperaquine (DP), stratified by concomitant intake of isoniazid prophylaxis (N=12)

	Participants not on isoniazid prophylaxis (n=8)				Participants on isoniazid prophylaxis (n=4)			
	Geometric Mean (90% CI)		GM Ratio (90% CI)		Geometric Mean (90% CI)		GM Ratio (90% CI)	
Pharmacokinetic parameter	**DTG-based ART + DP (Sequence 3)**	**DTG-based ART alone (Sequence 2)**	**(Sequence 3 / Sequence 2)**	**P-value***	**DTG-based ART + DP (Sequence 3)**	**DTG-based ART alone (Sequence 2)**	**(Sequence 3 / Sequence 2)**	**P-value***
$AUC_{0\text{-}24hr}$ (ng.hr/mL)	42,374 (38,132-47,088)	30,647 (25,787-36,423)	**1.38 (1.13-1.70)**	**0.013**	46,348 (38,507-55,785	40,227 (37,510-43,141)	1.15 (0.93-1.43)	0.167
C_{max} (ng/mL)	3,233 (2,908-3,594)	2,296 (1,949-2,706)	**1.41 (1.16-1.72)**	**0.003**	3,346 (2,983-3,753)	2,977 (2,776-3,193)	1.12 (0.97-1.30)	0.201
C_{24} (ng/mL)**	666 (545-814)	437 (339-564)	**1.52 (1.10-2.12)**	**0.031**	778 (546-1,108)	633 (463-865)	1.23 (0.74-2.03)	0.077
T_{max} (hr)	2.4 (1.9-3.2)	2.3 (1.6-3.5)	1.04 (0.65-1.69)	0.796	3.1 (1.9-5.0)	2.4 (1.7-3.3)	1.29 (0.70-2.46)	0.203
$t_{1/2}$ (hr)	9.9 (8.4-11.6)	8.7 (7.8-9.7)	1.14 (0.93-1.38)	0.089	9.8 (8.4-11.5)	9.6 (7.5-12.2)	1.02 (0.76-1.39)	0.486
CL/F (litres/hr)	1.18 (1.06-1.31)	1.63 (1.37-1.94)	**0.72 (0.59-0.89)**	**0.013**	1.08 (0.90-1.30)	1.24 (1.16-1.33)	0.87 (0.70-1.08)	0.167

GM: Geometric Mean, DTG: Dolutegravir, ART: Antiretroviral therapy, CI: Confidence interval

Bold represents statistical significance

* Paired t-test

** One participant had an implausible dolutegravir trough concentration due to dosing prior to 24-hour sample. This value was imputed to the previous pre-dose concentration

FIGURE LEGENDS

Figure 1. Study design. Fixed sequence study switching from efavirenz- to dolutegravir-based antiretroviral therapy. Intense plasma pharmacokinetic sampling of dolutegravir was done at 4 weeks post-initiation of daily dose of 50 mg of dolutegravir-based antiretroviral therapy and conducted in two sequences- when dolutegravir-based ART was administered alone (sequence 2) and following coadministration with a three-day treatment course of dihydroartemisinin-piperaquine [DP] (sequence 3).

Figure 2. Plasma dolutegravir concentration-time profile following administration of dolutegravir (DTG) -based antiretroviral therapy alone (red line) and with a treatment course of dihydroartemisinin-piperaquine [DP] (black line) in 12 pregnant women. Data are presented as medians (interquartile ranges [IQR]).

Figure 3. Plasma dolutegravir concentration-time profile following administration of dolutegravir-based antiretroviral therapy alone (red line) and with a treatment course of dihydroartemisinin-piperaquine (black line) in 8 pregnant women who were not on daily isoniazid prophylaxis (graph plots on the left), and in 4 pregnant women who were on isoniazid prophylaxis (graph plots on the right). Data are presented as medians (interquartile ranges [IQR]).

SUPPLEMENTARY INFORMATION TITLES

Supplementary Figure 1: Study profile

Supplementary Table 1: Dolutegravir exposure when administered as dolutegravir-based antiretroviral therapy alone compared to coadministration with dihydroartemisinin-piperaquine (DP), stratified by concomitant intake of isoniazid prophylaxis (N=12).

Supplementary Text 1: Dolutegravir assay details

Dolutegravir was analysed with a validated liquid chromatography-tandem mass spectrometry assay developed at the Division of Clinical Pharmacology, University of Cape Town. Samples were processed with a liquid-liquid extraction method using dolutegravir-d4 as the internal standard, followed by high-performance liquid chromatography with tandem mass spectrometry detection using an AB SCIEX API 4000 instrument. The analyte and internal standard were monitored at mass transitions of the protonated precursor ions m/z 420.1 and m/z 424.2 to the product ions m/z 277.2 and m/z 279.1, respectively. The calibration curve fitted a quadratic regression over the range 0.030 – 10.0 µg/mL. The combined accuracy (%Nom) and precision (%CV) statistics of the quality control samples during validation were between 103.5% and 106.0%, and 4.6% and 6.1%, respectively.

Appendix 1: Questionnaire and data capture instruments/tools

Screening Form - All Sequences

Screening ID No:	S			

Participant initials			

D D M M M Y Y Y Y

Demographic information

DATE OF BIRTH:	D D M M M Y Y Y Y	OR AGE: YEARS

ONLY CONTINUE IF: Age ≥ 18 years

Informed consent

Time informed consent obtained (hh/mm)	
Questions asked, with answers given	

Pregnancy history

Gravidity		Parity	
Last Menstrual Period (DD/MMM/YYYY)			
Have you experienced any problems during this pregnancy, or in previous pregnancies?			

HIV history

When did you first test positive for HIV? (DD/MMM/YYYY)			
What antiretroviral medicines are you taking currently?	☐ Efavirenz-based ART	☐ Dolutegravir-based ART	☐ Other ART
Please tell me the dates you started these medicines and how often you take them	Complete concomitant medication log with details		
Do you take other medicines?	☐ Cotrimoxazole ☐ Isoniazid ☐ Other	☐ Ferrous Folate ☐ Pyridoxine	
Please tell me the dates you started these medicines and how often you take them	Complete concomitant medication log with details		
Do you have any problems with taking any of these medicines?			

ONLY CONTINUE TO SEQUENCE 1 IF ON EFAVIRENZ-BASED ART FOR MORE >3 MONTHS, ONLY CONTINUE TO SEQUENCE 2 IF ON DOLUTEGRAVIR BASED ART FOR >1 MONTH (ask to return)

Staff initials_____ Checked by _____ on _____

Screening Form - All Sequences

Screening ID No:	S			

Participant initials			

Other Previous and current medical, social and surgical history

Do you currently have, or have a you previously had, any other diseases? Check all that apply:

	Yes	No		Yes	No
Allergies	☐	☐	Gynaecological	☐	☐
Significant current / recurrent infections	☐	☐	Dermatological	☐	☐
Gastrointestinal	☐	☐	Neurological	☐	☐
Pulmonary	☐	☐	Renal / urinary	☐	☐
Hepatic	☐	☐	Mental health problems	☐	☐
Diabetes, thyroid, other endocrine	☐	☐	Cardiac (e.g. fainting, palpitations)	☐	☐
History of smoking	☐	☐	If Yes, number of pack-years (= Number of packs smoked per day x Number of smoking years) _____		
History of alcohol consumption	☐	☐	If Yes, how much? _____		
History of any substance abuse	☐	☐	Details of substances (more details can be provided under additional notes) _____		
Family history of long QT syndrome / sudden death	☐	☐	Other _____		

If yes to any of the above questions, supply details below, noting approximate start date and stop date / on-going condition and clinical relevance.			**Clinically relevant?** (Lead Investigator to complete/initial)	
Medical history	Start date (DD/MMM/YYYY)	Stop date / ongoing	Yes	No
			☐	☐
			☐	☐
			☐	☐

Staff initials_____ Checked by _____ on _____

Screening Form - All Sequences

Screening ID No:	S			

Participant initials			

Have you had any surgical procedures? If yes, supply details below:	☐ Yes	☐ No
Procedure:	Date:	
Have you used prescription medicines, herbal supplements, over-the-counter (OTC) medication or dietary supplements (vitamins included) or vaccines in the past four weeks?	Yes ☐ No ☐ If yes, complete Concomitant Medication log or note reason for exclusion	

Height and weight

Body weight	_____.___ kg	Initials: Comments:
Height	_____ cm	

Vital signs

Supine BP	_____ / _____ mmHg	Initials: Comments:
Supine pulse	_____ bpm	
Temperature	_____ °C	

Staff initials_____ Checked by _____ on _____

Screening Form - All Sequences

Screening ID No:	S			

Participant initials			

Body system examination conducted by doctor (signature: _____)

Body System Checked	Normal	Abnormal	Not Done
General appearance (including JACCOL)	☐	☐	☐
Head and neck (including thyroid)	☐	☐	☐
Eyes, ears, nose, throat, mouth	☐	☐	☐
Dermatological	☐	☐	☐
Respiratory	☐	☐	☐
Cardiovascular	☐	☐	☐
Abdomen	☐	☐	☐
Fundal height	_____ cm		
Lie	Longitudinal ☐ Transverse ☐ Oblique ☐		
Presentation	Cephalic ☐ Breech ☐ Shoulder ☐		
FHR	_____ beats/min		
Musculoskeletal	☐	☐	☐
Neurological (gross assessment)	☐	☐	☐
Other	☐	☐	☐
Peripheral venous access	Good	Poor	

Abnormality	Clinically significant? Yes	No
	☐	☐
	☐	☐
	☐	☐

Staff initials_____ Checked by _____ on _____

Screening Form - All Sequences

Screening ID No:	S			

Participant initials			

Obstetric ultrasound

Gestational age	☐☐ weeks ☐☐ days
Any severe malformations, non-viable pregnancy or multiple. If yes indicate: _____	☐ Yes ☐ No

Baseline laboratory investigations for eligibility

Investigation	Initials of person collecting sample	Value	Normal	Abnormal*	Initials of person reviewing result
Haemoglobin (g/dL)		☐☐.☐	☐	☐ <8g/dL	
Recorded CD4 count (cells/mm^3)		☐☐☐☐	☐	☐ <100 cells/mm^3	
*Viral load (copies/mL)		☐☐☐☐☐	☐	☐ ≥50 copies/ML in Plasma ≥839 copies/ML on DBS	

***Remember to also complete viral load monitoring log**

Staff initials_____ Checked by _____ on _____

Screening Form - All Sequences

Screening ID No:	S			

Participant initials			

Inclusion Criteria	
Written informed consent prior to any study procedures.	Yes ☐ No ☐
Living with HIV and on efavirenz-based ART regimen for at least 3 months or dolutegravir-based ART for at least a month	Yes ☐ No ☐
Adult pregnant women (≥18 years of age) without any impaired decision-making capacity	Yes ☐ No ☐
22 ± 6 weeks of gestation estimated by ultrasound scan	Yes ☐ No ☐
Willing to adhere to scheduled and unscheduled study visit procedures and to attend follow up visits.	Yes ☐ No ☐
Resident of the study area	Yes ☐ No ☐
Willing to deliver at the study hospital and have a maternal plasma, placental and cord blood samples collected at delivery	Yes ☐ No ☐
Virologically suppressed (viral load <50 copies/mL)	Yes ☐ No ☐
CD4 cell count > 100 cells/mm^3	Yes ☐ No ☐
Exclusion criteria	
Haemoglobin value of <8.0 g/dL	Yes ☐ No ☐
Multiple pregnancies (i.e. twin/triplets)	Yes ☐ No ☐
Severe malformations or non-viable pregnancy observed by ultrasound	Yes ☐ No ☐
Known allergy or contraindication to any of the study drug (dihydroartemisinin-piperaquine)	Yes ☐ No ☐
On other medications that are known to have clinically significant interactions with efavirenz, dolutegravir or piperaquine such as rifampicin	Yes ☐ No ☐
Medical history of comorbidities that can influence the pharmacokinetic parameters of a study drug, such as clinically significant renal, liver or cardiac diseases	Yes ☐ No ☐

Is this volunteer ELIGIBLE* to participate in the study? Yes ☐ No ☐

*Volunteer is eligible to participate in the study if all inclusion criteria are met and does not meet any of the exclusion criteria. Complete all boxes above

STUDY CLINICIAN SIGNATURE	Date

Staff initials_____ Checked by _____ on _____

Screening Form - All Sequences

Screening ID No:	S			

Participant initials			

Additional notes (including any reasons for exclusion where applicable)

Staff initials_____ Checked by _____ on _____

Sequence 1 Enrolment (Day 0) Form
For Participants Enrolled on EFV-based ART

Participant ID No:	D	D	I		

Participant initials			

D	D	M	M	M	Y	Y	Y	Y

Medical History

How have you been since your last visit?	Record any symptoms reported
Provide participants with feedback regarding special investigation results not given at screening (e.g. Viral load, CD4 Count) and study eligibility.	Record any questions and responses given: *NOTE: Do not proceed with enrolment if any exclusion criteria met*
What medicines have you taken since your last visit?	Efavirenz-based ART: Date and time of last dose? DATE ☐☐☐☐☐☐☐☐ TIME ☐☐:☐☐ D D M M M Y Y Y Y H H M M
Have you used prescription medicines, herbal supplements, over-the-counter (OTC) medication or dietary supplements (vitamins included) or vaccines since your last visit?	Yes ☐ No ☐ If yes, complete or update the Concomitant Medication log (or note reason for exclusion)

Staff initials_____ Checked by _____ on _____

Sequence 1 Enrolment (Day 0) Form
For Participants Enrolled on EFV-based ART

Participant ID No:	D	D	I		

Participant initials			

Vital signs

BP	_____ / _____ mmHg	Initials: Comments:
Pulse	_____ bpm	
Temperature	_____ °C	
Weight	_____Kg	

Body system examination by doctor (signature: _____)

Body System Checked	Normal	Abnormal	Not Done
Symptom directed examination	☐	☐	☐
Abdomen	☐	☐	☐
Fundal height	_____ cm		
Lie	Longitudinal ☐ Transverse ☐ Oblique ☐		
Presentation	Cephalic ☐ Breech ☐ Shoulder ☐		
FHR	____ beats/min		

	Clinically significant?	
Abnormality	Yes	No
	☐	☐
	☐	☐
	☐	☐

Staff initials_____ Checked by _____ on _____

Sequence 1 Enrolment (Day 0) Form
For Participants Enrolled on EFV-based ART

Participant ID No:	D	D	I		

Participant initials			

Sample time in relation to first DP dose	**Protocol time** (HH:MM)	**Dosing**	**Bloods**		**Comment** (e.g. problems sampling, observations post-dose)	**Initials**
		Actual time (HH:MM)	**Actual time** (HH:MM)	**Piperaquine PK sample No.**		
Pre-dose PK sample			:	**S1d0H00**		
First DP dose given (Observed)		:				

Staff initials_____ Checked by _____ on _____

Sequence 1 Enrolment (Day 0) Form
For Participants Enrolled on EFV-based ART

Participant ID No:	D	D	I		

Participant initials			

Patient instructions:

	Completed (tick)
Demonstration on the use of the WisePill dispenser	
WisePill dispenser filled for Days 1 to 7	
Dosing instructions including self-administration of 2nd DP dose on Day 1 at time: _____:_____ hh : mm	
Provide appointment card with instructions to return on Day 2 for full day admission at time: _____:_____ hh : mm	

Staff initials_____ Checked by _____ on _____

Sequence 1 Enrolment (Day 0) Form
For Participants Enrolled on EFV-based ART

Participant ID No:	D	D	I		

Participant initials			

Comments and additional notes	
***Source reviewed by* Clinician**	Check any new or updated AEs (reported by participant, or observed from examinations, lab, ultrasound etc. results have been documented/interpreted on the AE form) ☐ Check any new or updated medications (ART, cotrimoxazole, concomitant [no study] medications have been documented/interpreted on the relevant form) ☐ _____ Initials _____/_____/_____ Date

Staff initials_____ Checked by _____ on _____

Sequence 1: Day 2 Form

Participant ID No:	D	D	I		

Participant initials			

D	D	M	M	M	Y	Y	Y	Y

Medical History

How have you been since your last visit?	Record any symptoms reported
Did you vomit following intake of DP at home on day 1	Yes ☐ No ☐ If yes: approximately, after how many minutes did you vomit when you took DP _____mins (if in hours, convert to minutes)
What medicines have you taken since your last visit?	Efavirenz-based ART: Date and time of last dose?* DATE |									TIME			:		| D D M M M Y Y Y Y H H M M Isoniazid: Date and time of last dose? DATE |									TIME			:		| D D M M M Y Y Y Y H H M M
Have you used prescription medicines, herbal supplements, over-the-counter (OTC) medication or dietary supplements (vitamins included) or vaccines since your last visit?	Yes ☐ No ☐ If yes, complete Concomitant Medication log (check if prohibited medicine and or note reason for withdrawal if necessary)

Sequence 1: Day 2 Form

Participant ID No:	D	D	I		

Participant initials			

Did you have breakfast/meal before coming to the hospital today?	Yes ☐ No ☐ If yes: approximately what time did you have the meal? _____:_____ hh : mm What kind of meal was it? (state in few words the meal and particularly probe for fatty food intake) _____

Vital signs

Supine BP	_____ / _____ mmHg	Comments:
Supine Pulse	_____ bpm	
Temperature	_____ °C	_____ Initials

Body system examination by doctor (signature: _____)

Body System Checked	Normal	Abnormal	Not Done
Symptom directed examination	☐	☐	☐
Abdomen	☐	☐	☐
Fundal height	_____ cm		
Lie	Longitudinal ☐ Transverse ☐ Oblique ☐		
Presentation	Cephalic ☐ Breech ☐ Shoulder ☐		
FHR	_____ beats/min		

Staff initials_____ Checked by _____ on _____

Sequence 1: Day 2 Form

Participant ID No:		D	D	I		

Participant initials			

Abnormality	Clinically significant? Yes	No
	☐	☐
	☐	☐
	☐	☐
Conducted by medical doctor	_____ (initials)	

Staff initials_____ Checked by _____ on _____

Sequence 1: Day 2 Form

Participant ID No:	D	D	I		

Participant initials			

Pharmacokinetic sampling for piperaquine while on EFV-based ART

Sample time in relation to DP dose	Protocol time (HH:MM)	Dosing Actual time (HH:MM)	Bloods		Comment (e.g. problems sampling, observations post-dose)	Initials
			Actual time (HH:MM)	Piperaquine PK sample No.		
Pre-dose sample			:	**S1d2H00**		
Final DP dose (observed)		:				
2h post-dose	:		:	**S1d2H02**		
4h post-dose	:		:	**S1d2H04**		
6h post-dose	:		:	**S1d2H06**		
8h post-dose	:		:	**S1d2H08**		

Staff initials_____ Checked by _____ on _____

Sequence 1: Day 2 Form

Participant ID No:	D	D	I		

Participant initials			

Patient instructions:

Instruction/reminder	Completed (tick and initial last row)
Review use of the WisePill dispenser	
Provide appointment card with instructions to return on Day 3 on the following date: _____/_____/_____ At time: _____:_____ hh : mm	
Remind participant not to take any of their medications before coming to the hospital on day 3 including ART, iron, isoniazid or antacids. These will be taken after blood sampling	

Sequence 1: Day 2 Form

Participant ID No:	D	D	I		

Participant initials			

Comments and additional notes	
Source Reviewed by Study Clinician	Check any new or updated AEs (reported by participant, or observed from examinations, lab, ultrasound etc. results) have been documented/interpreted on AE form ☐ Check any new or updated medications (ART, cotrimoxazole, concomitant medications) have been documented/interpreted on relevant medication form) ☐ _____ Initials _____/_____/_____ Date

Staff initials_____ Checked by _____ on _____

Sequence 1: Day 3

Participant ID No:	D	D	I		

Participant initials			

D	D	M	M	M	Y	Y	Y	Y

Medical History

How have you been since your last visit?	Record any symptoms reported
What medicines have you taken since your last visit?	Efavirenz-based ART: Date and time of last dose?*
	DATE (D D M M M Y Y Y Y) TIME (H H : M M)
	Isoniazid: Date and time of last dose?
	DATE (D D M M M Y Y Y Y) TIME (H H : M M)
Have you used prescription medicines, herbal supplements, over-the-counter (OTC) medication or dietary supplements (vitamins included) or vaccines since your last visit?	Yes ☐ No ☐ If yes, complete Concomitant Medication log (or note reason for exclusion)

Vital signs

BP	_____ / _____ mmHg	Comments:
Pulse	_____ bpm	
Temperature	_____ °C	_____ Initials

Staff initials_____ Checked by _____ on _____

Sequence 1: Day 3

Participant ID No:	D	D	I		

Participant initials			

D	D	M	M	M	Y	Y	Y	Y

Body system examination

Body System Checked	Normal	Abnormal	Not Done
Symptom directed examination	☐	☐	☐
Abdomen	☐	☐	☐
Fundal height	_____ cm		
Lie	Longitudinal ☐ Transverse ☐ Oblique ☐		
Presentation	Cephalic ☐ Breech ☐ Shoulder ☐		
FHR	____ beats/min		

Abnormality	Clinically significant? Yes	No
	☐	☐
	☐	☐
	☐	☐
Conducted by Medical Doctor	_____	Initials

Staff initials_____ Checked by _____ on _____

Sequence 1: Day 3

Participant ID No:	D	D	I		

Participant initials			

D D M M M Y Y Y Y

Pharmacokinetic sample (s) and DP dose

Sample time in relation to DP dose	Protocol time (HH:MM)	Dosing	Bloods			Comment (e.g. problems sampling, observations post-dose)	Initials
		Actual time (HH:MM)	Actual time (HH:MM)		Piperaquine sample No		
24h (after last DP dose and before DTG dose)	:		:		**S1d3H24**		

Staff initials_____ Checked by _____ on _____

Sequence 1: Day 3

Participant ID No:	D	D	I		

Participant initials			

D	D	M	M	M	Y	Y	Y	Y	

Patient instructions:

Instruction/reminder	Completed (tick and initial the last cell)
Check appointment card with instructions to return on Day 7 at time: _____:_____ hh : mm	
Remind participant not to take any of their medications before coming to the hospital on day 7 including ART, iron, isoniazid or antacids. These will be taken after blood sampling	

Staff initials_____ Checked by _____ on _____

Sequence 1: Day 3

Participant ID No:	D	D	I		

Participant initials			

D	D	M	M	M	Y	Y	Y	Y	

Comments and additional notes

Source Reviewed by Study Clinician	Check any new or updated AEs (reported by participant, or observed from examinations, lab, ultrasound etc. results) have been documented/interpreted on AE form ☐ Check any new or updated medications (ART, cotrimoxazole, concomitant medications) have been documented/interpreted on relevant medication form) ☐ _____ Initials _____/_____/_____ Date

Staff initials_____ Checked by _____ on _____

Sequence 1: Day 7

Participant ID No:	D	D	I		

Participant initials			

D	D	M	M	M	Y	Y	Y	Y

Medical History

How have you been since your last visit?	Record any symptoms reported
What medicines have you taken since your last visit?	Efavirenz-based ART: Date and time of last dose?*
	DATE ☐☐☐☐☐☐☐☐ TIME ☐☐:☐☐
	D D M M M Y Y Y Y H H M M
	Isoniazid: Date and time of last dose?
	DATE ☐☐☐☐☐☐☐☐ TIME ☐☐:☐☐
	D D M M M Y Y Y Y H H M M
Have you used prescription medicines, herbal supplements, over-the-counter (OTC) medication or dietary supplements (vitamins included) or vaccines since your last visit?	Yes ☐ No ☐ If yes, complete Concomitant Medication log (check if prohibited medicine and or note reason for withdrawal if necessary)

Vital signs

Supine BP	_____ / _____ mmHg	Comments:
Supine Pulse	_____ bpm	
Temperature	_____ °C	_____ Initials

Sequence 1: Day 7

Participant ID No:	D	D	I		

Participant initials			

D	D	M	M	M	Y	Y	Y	Y

Body system examination

Body System Checked	Normal	Abnormal	Not Done
Symptom directed examination	☐	☐	☐
Abdomen	☐	☐	☐
Fundal height	_____ cm		
Lie	Longitudinal ☐ Transverse ☐ Oblique ☐		
Presentation	Cephalic ☐ Breech ☐ Shoulder ☐		
FHR	____ beats/min		

Abnormality	Clinically significant? Yes	No
	☐	☐
	☐	☐
	☐	☐
Conducted by Medical Doctor	_____	Initials

Staff initials_____ Checked by _____ on _____

Sequence 1: Day 7

Participant ID No:	D	D	I		

Participant initials			

D	D	M	M	M	Y	Y	Y	Y

Pharmacokinetic sample (s) for piperaquine

Sample time in relation to DP dose	Protocol time (HH:MM)	DOSING	Bloods			Initials
		Actual time (HH:MM)	Actual time (HH:MM)	Piperaquine PK sample No.	Comment (e.g. problems sampling, observations post-dose)	
168h (after first DP dose)	:		:	**S1d7H168**		

Staff initials_____ Checked by _____ on _____

Sequence 1: Day 7

Participant ID No:		D	D	I		

Participant initials			

D	D	M	M	M	Y	Y	Y	Y	

Patient instructions:

Instruction/reminder	Completed (Tick and initial the last row)
Check appointment card with instructions to return on Day 14 on: _____ At time _____:_____ hh : mm	
Remind participant not to take any of their medications before coming to the hospital on day 14 including ART, iron, isoniazid or antacids. These will be taken after blood sampling	

Staff initials_____ Checked by _____ on _____

Sequence 1: Day 7

Participant ID No:	D	D	I		

Participant initials			

D	D	M	M	M	Y	Y	Y	Y	

Comments and additional notes

Source Reviewed by Study Clinician	Check any new or updated AEs (reported by participant, or observed from examinations, lab, ultrasound etc. results) have been documented/interpreted on AE form ☐ Check any new or updated medications (ART, cotrimoxazole, concomitant medications) have been documented/interpreted on relevant medication form) ☐ _____ Initials _____/_____/_____ Date

Staff initials_____ Checked by _____ on _____

Sequence 1: Day 14

Participant ID No:	D	D	I		

Participant initials			

D	D	M	M	M	Y	Y	Y	Y

Medical History

How have you been since your last visit?	Record any symptoms reported
What medicines have you taken since your last visit?	Efavirenz-based ART: Date and time of last dose?*
	DATE ☐☐☐☐☐☐☐☐ TIME ☐☐:☐☐
	D D M M M Y Y Y Y H H M M
	Isoniazid: Date and time of last dose?
	DATE ☐☐☐☐☐☐☐☐ TIME ☐☐:☐☐
	D D M M M Y Y Y Y H H M M
Have you used prescription medicines, herbal supplements, over-the-counter (OTC) medication or dietary supplements (vitamins included) or vaccines since your last visit?	Yes ☐ No ☐ If yes, complete Concomitant Medication log (check if prohibited medicine and or note reason for withdrawal if necessary)

Vital signs

Supine BP	_____ / _____ mmHg	Comments:
Supine Pulse	_____ bpm	
Temperature	_____ °C	_____ Initials

Staff initials_____ Checked by _____ on _____

Sequence 1: Day 14

Participant ID No:	D	D	I		

Participant initials			

Body system examination

Body System Checked	Normal	Abnormal	Not Done
Symptom directed examination	☐	☐	☐
Abdomen	☐	☐	☐
Fundal height	_____ cm		
Lie	Longitudinal ☐ Transverse ☐ Oblique ☐		
Presentation	Cephalic ☐ Breech ☐ Shoulder ☐		
FHR	____ beats/min		

Abnormality	Clinically significant? Yes	No
	☐	☐
	☐	☐
	☐	☐
Conducted by Medical Doctor	_____	Initials

Staff initials_____ Checked by _____ on _____

Sequence 1: Day 14

Participant ID No:	D	D	I		

Participant initials			

Pharmacokinetic sample (s) for piperaquine

Sample time in relation to DP dose	Protocol time (HH:MM)	DOSING	Bloods		Comment (e.g. problems sampling, observations post-dose)	Initials
		Actual time (HH:MM)	Actual time (HH:MM)	Piperaquine PK sample No.		
336h (after first DP dose)	:		:	**S1d14H336**		

Staff initials_____ Checked by _____ on _____

Sequence 1: Day 14

Participant ID No:	D	D	I		

Participant initials			

Patient instructions:

	Completed (tick)
Patient information on switch from efavirenz-based ART to dolutegravir based ART	
Updated ART medication log with switch	
WisePill dispenser filled for Days 14 - 28	
Dosing instructions on self-administration of dolutegravir based ART	
Provide diary card with instructions to return on Day 28 at time: _____:_____ hh : mm	

Sequence 1: Day 14

Participant ID No:	D	D	I		

Participant initials			

Comments and additional notes	
Source Reviewed by Study Clinician	Check any new or updated AEs (reported by participant, or observed from examinations, lab, ultrasound etc. results) have been documented/interpreted on AE form ☐ Check any new or updated medications (ART, cotrimoxazole, concomitant medications) have been documented/interpreted on relevant medication form) ☐ _____ Initials _____/_____/_____ Date

Staff initials_____ Checked by _____ on _____

Sequence 1: Day 28

Participant ID No:	D	D	I		

Participant initials			

D	D	M	M	M	Y	Y	Y	Y

Medical History

How have you been since your last visit?	Record any symptoms reported
What medicines have you taken since your last visit?	Dolutegravir-based ART: Date and time of last dose?* DATE ☐☐☐☐☐☐☐☐ TIME ☐☐ : ☐☐ D D M M M Y Y Y Y H H M M Isoniazid: Date and time of last dose? DATE ☐☐☐☐☐☐☐☐ TIME ☐☐ : ☐☐ D D M M M Y Y Y Y H H M M
Have you used prescription medicines, herbal supplements, over-the-counter (OTC) medication or dietary supplements (vitamins included) or vaccines since your last visit?	Yes ☐ No ☐ If yes, complete Concomitant Medication log (or note reason for exclusion)

Vital signs

BP	_____ / _____ mmHg	Comments:
Pulse	_____ bpm	
Temperature	_____ °C	_____ Initials

Staff initials_____ Checked by _____ on _____

Sequence 1: Day 28

Participant ID No:	D	D	I		

Participant initials			

Body system examination

Body System Checked	Normal	Abnormal	Not Done
Symptom directed examination	☐	☐	☐
Abdomen	☐	☐	☐
Fundal height	_____ cm		
Lie	Longitudinal ☐ Transverse ☐ Oblique ☐		
Presentation	Cephalic ☐ Breech ☐ Shoulder ☐		
FHR	____ beats/min		

Abnormality	Clinically significant? Yes	No
	☐	☐
	☐	☐
	☐	☐
Conducted by Medical Doctor	_____	Initials

Pharmacokinetic sample (s) for piperaquine

Sequence 1: Day 28

Participant ID No:	D	D	I		

Participant initials			

Sample time in relation to DP dose	Protocol time (HH:MM)	DOSING	Bloods		Comment (e.g. problems sampling, observations post-dose)	Initials
		Actual time (HH:MM)	Actual time (HH:MM)	Piperaquine PK sample No.		
672h (after first DP dose)	__:__		__:__	**S1d28H672**		

Pharmacokinetic sample (s) for piperaquine

Staff initials_____ Checked by _____ on _____

Sequence 1: Day 28

Participant ID No:	D	D	I		

Participant initials			

Patient instructions:

	Completed (Tick)
Check appointment card and instruct to return at 6 weeks post start of study, after completing 4 weeks of dolutegravir-based ART, for sequence 2 sampling on: _____/_____/_____ At time: _____:_____ hh : mm	
Ensure Wise pill device is filled with dolutegravir-based ART	
Remind participant about not taking ART medication and other medications when they come to the hospital as these will be taken in hospital	

Staff initials_____ Checked by _____ on _____

Sequence 1: Day 28

Participant ID No:	D	D	I		

Participant initials			

Comments and additional notes

Staff initials_____ Checked by _____ on _____

Sequence 1: Day 28

Participant ID No:	D	D	I		

Participant initials			

Source Reviewed by Study Clinician	Check any new or updated AEs (reported by participant, or observed from examinations, lab, ultrasound etc. results) have been documented/interpreted on AE form ☐ Check any new or updated medications (ART, cotrimoxazole, concomitant medications) have been documented/interpreted on relevant medication form) ☐ _____ Initials _____/_____/_____ Date

Sequence 2: Enrolment / Day 0 Form

Participant ID No:	D	D	I		

Participant initials			

D	D	M	M	M	Y	Y	Y	Y

Medical History

How have you been since your last visit?	Record any symptoms reported
For participants enrolled on DTG-based ART: Provide feedback regarding special investigation results not given at screening (e.g. Viral load, CD4 Count) and study eligibility.	Record any questions and responses given: *NOTE: Do not proceed with enrolment if any exclusion criteria met*
How long have you been on DTG-based ART?	_____ weeks / months / years *NOTE: Do not proceed with enrolment if < 4 weeks*
What medicines have you taken since your last visit?	Dolutegravir-based ART: Date and time of last dose? DATE										TIME			:		| D D M M M Y Y Y Y H H M M Isoniazid: Date and time of last dose? DATE										TIME			:		| D D M M M Y Y Y Y H H M M
Have you used prescription medicines, herbal supplements, over-the-counter (OTC) medication or dietary supplements (vitamins included) or vaccines since your last visit?	Yes ☐ No ☐ If yes, complete Concomitant Medication log (check if prohibited medicine and note reason for exclusion/withdrawal if necessary)

Staff initials_____ Checked by _____ on _____

Sequence 2: Enrolment / Day 0 Form

Participant ID No:	D	D	I		

Participant initials			

Vital signs

Supine BP	_____ / _____ mmHg	Initials: Comments:
Supine pulse	_____ bpm	
Temperature	_____ °C	

Body system examination by doctor (signature: _____)

Body System Checked	Normal	Abnormal	Not Done
Symptom directed examination	☐	☐	☐
Abdomen	☐	☐	☐
Fundal height	_____ cm		
Lie	Longitudinal ☐ Transverse ☐ Oblique ☐		
Presentation	Cephalic ☐ Breech ☐ Shoulder ☐		
FHR	____ beats/min		

	Clinically significant?	
Abnormality	Yes	No
	☐	☐
	☐	☐
	☐	☐

Sequence 2: Enrolment / Day 0 Form

Participant ID No:	D	D	I		

Participant initials			

Pharmacokinetic sampling and Dolutegravir dosing

Sample time in relation to DTG dose	Protocol time (HH:MM)	Dosing Actual time (HH:MM)	Bloods		Comment (e.g. problems sampling, observations post-dose)	Initials
			Actual time (HH:MM)	Dolutegravir PK sample No		
Pre-dose			:	S2d0H00		
DTG dose		:				
1h	:		:	S2d0H01		
2h	:		:	S2d0H02		

Staff initials_____ Checked by _____ on _____

Sequence 2: Enrolment / Day 0 Form

Participant ID No:	D	D	I		

Participant initials			

			Actual time (HH:MM)	Dolutegravir PK sample No		
3hr	:		:	**S2d0H03**		
4hr			:	**S2d0H04**		
6h	:		:	**S2d0H06**		
8h	:		:	**S2d0H08**		

Staff initials_____ Checked by _____ on _____

Sequence 2: Enrolment / Day 0 Form

Participant ID No:	D	D	I		

Participant initials			

Patient instructions:

	Completed (Tick)
Demonstration on the use of the WisePill dispenser	
WisePill dispenser filled with DTG for Days 1 to 14. Remind patient NOT to take Day 1 DTG dose at home – this dose will be administered during Day 1 visit.	
Remind participant not to take their Isoniazid, iron or antacids tablets on day 1, these will be taken in the evening after day 1 sample.	
Provide appointment card with instructions to return on Day 1 on date below: _____ At time: _____:_____ hh : mm	

Sequence 2: Enrolment / Day 0 Form

Participant ID No:	D	D	I		

Participant initials			

Comments and additional notes

Source Reviewed by Study Clinician	Check any new or updated AEs (reported by participant, or observed from examinations, lab, ultrasound etc. results have been documented/interpreted on the AE form) ☐ Check any new or updated medications (ART, cotrimoxazole, concomitant [no study] medications have been documented/interpreted on the relevant form) ☐ _____ Initials _____/_____/_____ Date

Staff initials_____ Checked by _____ on _____

Sequence 2: Day 1 Form ☐
Sequence 3: Day 0 Form ☐

(Tick all which apply)

Participant ID No:	**D**	**D**	**I**		

Participant initials			

D	**D**	**M**	**M**	**M**	**Y**	**Y**	**Y**	**Y**

Medical History

How have you been since your last visit?	Record any symptoms reported
What medicines have you taken since your last visit?	Dolutegravir-based ART: Date and time of last dose?* DATE | | | | | | | | | | TIME | | | : | | | D D M M M Y Y Y Y H H M M Isoniazid: Date and time of last dose? DATE | | | | | | | | | | TIME | | | : | | | D D M M M Y Y Y Y H H M M
Have you used prescription medicines, herbal supplements, over-the-counter (OTC) medication or dietary supplements (vitamins included) or vaccines since your last visit?	Yes ☐ No ☐ If yes, complete Concomitant Medication log (check if prohibited medicine and note reason for exclusion/withdrawal if necessary)

Staff initials_____ Checked by _____ on _____

Sequence 2: Day 1 Form ☐
Sequence 3: Day 0 Form ☐

(Tick all which apply)

Participant ID No:	**D**	**D**	**I**		

Participant initials			

Did you have breakfast/meal before coming to the hospital today?	Yes ☐ No ☐ If yes: approximately what time did you have the meal? _____:_____ hh : mm What kind of meal was it? (state in few words the meal and particularly probe for fatty food intake) _____

Vital signs

Supine BP	_____ / _____ mmHg	Comments:
Supine Pulse	_____ bpm	
Temperature	_____ °C	

Body system examination by doctor (signature: _____)

Body System Checked	Normal	Abnormal	Not Done
Symptom directed examination	☐	☐	☐
Abdomen	☐	☐	☐
Fundal height	_____ cm		
Lie	Longitudinal ☐ Transverse ☐ Oblique ☐		
Presentation	Cephalic ☐ Breech ☐ Shoulder ☐		
FHR	_____ beats/min		

Staff initials_____ Checked by _____ on _____

Sequence 2: Day 1 Form ☐
Sequence 3: Day 0 Form ☐

(Tick all which apply)

Participant ID No:	**D**	**D**	**I**		

Participant initials			

		Clinically significant?
Abnormality	Yes	No
	☐	☐
	☐	☐
	☐	☐

Sequence 2: Day 1 Form □
Sequence 3: Day 0 Form □

(Tick all which apply)

Participant ID No:	**D**	**D**	**I**			**Participant initials**			

Sample time in relation to day 0 DTG dose	**Protocol time (HH:MM)**	**Dosing Actual time** (HH:MM)	**Bloods**			**Comment** (e.g. problems sampling, observations post-dose)	**Initials**
			Actual time (HH:MM)	**Piperaquine PK sample No.**	**Dolutegravir & piperaquine PK sample No.**		
24h (before next DTG-based ART dose and before start of DP dose)	:		:		**S2d1H24 + S3d0H00***		
DP & DTG-based ART doses		:					

* Same sample draw, but of 4mL (not usual 2mL) as will be split in the laboratory as Sequence 2 dolutegravir sample for d1H24 and the Sequence 3 piperaquine sample for d0H00 If Sequence 2 D1. However, if Sequence 2 D1 and Seq3 D0 do not occur on the same day, label vacutainer as Seq3 D0 using spare labels.

Staff initials_____ Checked by _____ on _____

Sequence 2: Day 1 Form □
Sequence 3: Day 0 Form □

(Tick all which apply)

Participant ID No:	D	D	I		

Participant initials			

Patient instructions:

Instruction/reminder	Completed (tick)
Remind participant about DTG-based ART and DP dosing recommendations and use of WisePill	
Remind participant about DP dosing recommendations and use of WisePill	
Check appointment card with instructions to return on Day 2 of sequence 3 (2 days from this date) on: _____/_____/_____ At time: _____:_____ hh : mm	
Remind participant about fasting for day 2 of sequence 3. Participant not to take any of their medications before coming to the hospital on day 2 of sequence 3 including ART, iron, isoniazid or antacids. These will be taken at the hospital after blood sampling	

Staff initials_____ Checked by _____ on _____

Sequence 2: Day 1 Form □
Sequence 3: Day 0 Form □

(Tick all which apply)

Participant ID No:	**D**	**D**	**I**		

Participant initials			

Comments and additional notes

Staff initials_____ Checked by _____ on _____

Sequence 2: Day 1 Form ☐
Sequence 3: Day 0 Form ☐

(Tick all which apply)

Participant ID No:	**D**	**D**	**I**		

Participant initials			

Source Reviewed by Study Clinician	Check any new or updated AEs (reported by participant, or observed from examinations, lab, ultrasound etc. results have been documented/interpreted on the AE form) ☐ Check any new or updated medications (ART, cotrimoxazole, concomitant [no study] medications have been documented/interpreted on the relevant form) ☐ _____ _____/_____/_____ Initials Date

Sequence 3: Day 2 Form

Participant ID No:	D	D	I		

Participant initials			

D	D	M	M	M	Y	Y	Y	Y

Medical History

How have you been since your last visit?	Record any symptoms reported
Did you vomit following intake of DP at home on day 1	Yes ☐ No ☐ If yes: approximately, after how many minutes did you vomit when you took DP _____mins (if in hours, convert to minutes)
What medicines have you taken since your last visit?	Dolutegravir-based ART: Date and time of last dose?* DATE D D M M M Y Y Y Y TIME H H : M M Isoniazid: Date and time of last dose? DATE D D M M M Y Y Y Y TIME H H : M M
Have you used prescription medicines, herbal supplements, over-the-counter (OTC) medication or dietary supplements (vitamins included) or vaccines since your last visit?	Yes ☐ No ☐ If yes, complete Concomitant Medication log (check if prohibited medicine and or note reason for withdrawal if necessary)

Sequence 3: Day 2 Form

Participant ID No:	D	D	I		

Participant initials			

Did you have breakfast/meal before coming to the hospital today?	Yes ☐ No ☐ If yes: approximately what time did you have the meal? _____:_____ hh : mm What kind of meal was it? (state in few words the meal and particularly probe for fatty food intake) _____

Vital signs

Supine BP	_____ / _____ mmHg	Comments:
Supine Pulse	_____ bpm	
Temperature	_____ °C	_____ Initials
Weight	_____Kg	

Body system examination by doctor (signature: _____)

Body System Checked	Normal	Abnormal	Not Done
Symptom directed examination	☐	☐	☐
Abdomen	☐	☐	☐
Fundal height	_____ cm		
Lie	Longitudinal ☐ Transverse ☐ Oblique ☐		
Presentation	Cephalic ☐ Breech ☐ Shoulder ☐		
FHR	_____ beats/min		

Staff initials_____ Checked by _____ on _____

Sequence 3: Day 2 Form

Participant ID No:	D	D	I		

Participant initials			

	Clinically significant?	
Abnormality	Yes	No
	☐	☐
	☐	☐
	☐	☐
Conducted by medical doctor	_____ (initials)	

Sequence 3: Day 2 Form

Participant ID No:	D	D	I		

Participant initials			

Pharmacokinetic sampling, DP and Dolutegravir dosing

Time in relation to DP & DTG-based ART dose	Protocol time (HH:MM)	Dosing	Actual time (HH:MM)	DTG and Piperaquine PK sample No.	Comment (e.g. problems sampling, observations post-dose)	Initials
Pre-dose			:	**S3d2H00**		
DP & DTG dose		:				
1h	:		:	**S3d2H01**		

Staff initials_____ Checked by _____ on _____

Sequence 3: Day 2 Form

Participant ID No:	D	D	I		

Participant initials			

2h	:		:	**S3d2H02**		
3h	:		:	**S3d2H03**		
4h	:		:	**S3d2H04**		
6h	:		:	**S3d2H06**		
8h	:		:	**S3d2H08**		

Staff initials_____ Checked by _____ on _____

Sequence 3: Day 2 Form

Participant ID No:	D	D	I		

Participant initials			

Patient instructions:

Instruction/reminder	Completed (tick and initial last row)
Review use of the WisePill dispenser	
Provide appointment card with instructions to return on Day 3 on the following date: _____/_____/_____ At time: _____:_____ hh : mm	
Remind participant not to take any of their medications before coming to the hospital on day 3 including ART, iron, isoniazid or antacids. These will be taken after blood sampling	

Sequence 3: Day 2 Form

Participant ID No:	D	D	I		

Participant initials			

Comments and additional notes	
Source Reviewed by Study Clinician	Check any new or updated AEs (reported by participant, or observed from examinations, lab, ultrasound etc. results) have been documented/interpreted on AE form ☐ Check any new or updated medications (ART, cotrimoxazole, concomitant medications) have been documented/interpreted on relevant medication form) ☐ _____ Initials _____/_____/_____ Date

Staff initials_____ Checked by _____ on _____

Sequence 3: Day 3

Participant ID No:	D	D	I		

Participant initials			

D	D	M	M	M	Y	Y	Y	Y	

Medical History

How have you been since your last visit?	Record any symptoms reported
What medicines have you taken since your last visit?	Dolutegravir-based ART: Date and time of last dose?* DATE _ _ _ _ _ _ _ _ TIME _ _ : _ _ D D M M M Y Y Y Y H H M M Isoniazid : Date and time of last dose? DATE _ _ _ _ _ _ _ _ TIME _ _ : _ _ D D M M M Y Y Y Y H H M M
Have you used prescription medicines, herbal supplements, over-the-counter (OTC) medication or dietary supplements (vitamins included) or vaccines since your last visit?	Yes ☐ No ☐ If yes, complete Concomitant Medication log (or note reason for exclusion)

Vital signs

BP	_____ / _____ mmHg	Comments:
Pulse	_____ bpm	
Temperature	_____ °C	_____ Initials

Staff initials_____ Checked by _____ on _____

Sequence 3: Day 3

Participant ID No:	D	D	I		

Participant initials			

Body system examination

Body System Checked	Normal	Abnormal	Not Done
Symptom directed examination	☐	☐	☐
Abdomen	☐	☐	☐
Fundal height	_____ cm		
Lie	Longitudinal ☐ Transverse ☐ Oblique ☐		
Presentation	Cephalic ☐ Breech ☐ Shoulder ☐		
FHR	____ beats/min		

Abnormality	Clinically significant? Yes	No
	☐	☐
	☐	☐
	☐	☐
Conducted by Medical Doctor	_____	Initials

Staff initials_____ Checked by _____ on _____

Sequence 3: Day 3

Participant ID No:	D	D	I		

Participant initials			

Pharmacokinetic sample (s) and DP dose

Sample time in relation to DP dose	Protocol time (HH:MM)	Dosing	Bloods			Comment (e.g. problems sampling, observations post-dose)	Initials
		Actual time (HH:MM)	Actual time (HH:MM)		DTG and piperaquine sample No		
24h (after last DP dose and before DTG dose)	__:__		__:__		**S3d3H24**		

Staff initials_____ Checked by _____ on _____

Sequence 3: Day 3

Participant ID No:		D	D	I		

Participant initials			

Patient instructions:

Instruction/reminder	Completed (tick and initial the last cell)
Check appointment card with instructions to return on Day 7 at time: _____:_____ hh : mm	
Remind participant not to take any of their medications before coming to the hospital on day 7 including ART, iron, isoniazid or antacids. These will be taken after blood sampling	
Instruction Provided by (initials)	

Sequence 3: Day 3

Participant ID No:	D	D	I		

Participant initials			

Comments and additional notes	
Source Reviewed by Study Clinician	Check any new or updated AEs (reported by participant, or observed from examinations, lab, ultrasound etc. results) have been documented/interpreted on AE form ☐ Check any new or updated medications (ART, cotrimoxazole, concomitant medications) have been documented/interpreted on relevant medication form) ☐ _____ Initials _____/_____/_____ Date

Staff initials_____ Checked by _____ on _____

Sequence 3: Day 7

Participant ID No:	D	D	I		

Participant initials			

D	D	M	M	M	Y	Y	Y	Y

Medical History

How have you been since your last visit?	Record any symptoms reported
What medicines have you taken since your last visit?	Dolutegravir-based ART: Date and time of last dose?*
	DATE (D D M M M Y Y Y Y) TIME (H H : M M)
	Isoniazid: Date and time of last dose?
	DATE (D D M M M Y Y Y Y) TIME (H H : M M)
Have you used prescription medicines, herbal supplements, over-the-counter (OTC) medication or dietary supplements (vitamins included) or vaccines since your last visit?	Yes ☐ No ☐ If yes, complete Concomitant Medication log (check if prohibited medicine and or note reason for withdrawal if necessary)

Vital signs

Supine BP	_____ / _____ mmHg	Comments:
Supine Pulse	_____ bpm	
Temperature	_____ °C	_____ Initials

Staff initials_____ Checked by _____ on _____

Sequence 3: Day 7

Participant ID No:		D	D	I		

Participant initials			

Body system examination

Body System Checked	Normal	Abnormal	Not Done
Symptom directed examination	☐	☐	☐
Abdomen	☐	☐	☐
Fundal height	_____ cm		
Lie	Longitudinal ☐ Transverse ☐ Oblique ☐		
Presentation	Cephalic ☐ Breech ☐ Shoulder ☐		
FHR	____ beats/min		

Abnormality	Clinically significant? Yes	No
	☐	☐
	☐	☐
	☐	☐
Conducted by Medical Doctor	_____	Initials

Staff initials_____ Checked by _____ on _____

Sequence 3: Day 7

Participant ID No:		D	D	I		

Participant initials			

Pharmacokinetic sample (s) for piperaquine

Sample time in relation to DP dose	Protocol time (HH:MM)	DOSING	Bloods			Initials
		Actual time (HH:MM)	Actual time (HH:MM)	Piperaquine PK sample No.	Comment (e.g. problems sampling, observations post-dose)	
168h (after first DP dose)	__:__		__:__	**S3d7H168**		

Staff initials_____ Checked by _____ on _____

Sequence 3: Day 7

Participant ID No:		D	D	I		

Participant initials			

Patient instructions:

Instruction/reminder	Completed (Tick and initial the last row)
Check appointment card with instructions to return on Day 14 on: _____ At time _____:_____ hh : mm	
Remind participant not to take any of their medications before coming to the hospital on day 14 including ART, iron, isoniazid or antacids. These will be taken after blood sampling	
Instruction Provided by (initials)	

Sequence 3: Day 7

Participant ID No:	D	D	I		

Participant initials			

Comments and additional notes	
Source Reviewed by Study Clinician	Check any new or updated AEs (reported by participant, or observed from examinations, lab, ultrasound etc. results) have been documented/interpreted on AE form ☐ Check any new or updated medications (ART, cotrimoxazole, concomitant medications) have been documented/interpreted on relevant medication form) ☐ _____ Initials _____/_____/_____ Date

Staff initials_____ Checked by _____ on _____

Sequence 3: Day 14

Participant ID No:	D	D	I		

Participant initials			

D	D	M	M	M	Y	Y	Y	Y

Medical History

How have you been since your last visit?	Record any symptoms reported
What medicines have you taken since your last visit?	Dolutegravir-based ART: Date and time of last dose?*
	DATE D D M M M Y Y Y Y TIME H H : M M
	Isoniazid: Date and time of last dose?
	DATE D D M M M Y Y Y Y TIME H H : M M
Have you used prescription medicines, herbal supplements, over-the-counter (OTC) medication or dietary supplements (vitamins included) or vaccines since your last visit?	Yes ☐ No ☐ If yes, complete Concomitant Medication log (check if prohibited medicine and or note reason for withdrawal if necessary)

Vital signs

Supine BP	_____ / _____ mmHg	Comments:
Supine Pulse	_____ bpm	
Temperature	_____ °C	_____ Initials

Staff initials_____ Checked by _____ on _____

Sequence 3: Day 14

Participant ID No:	D	D	I		

Participant initials			

Body system examination

Body System Checked	Normal	Abnormal	Not Done
Symptom directed examination	☐	☐	☐
Abdomen	☐	☐	☐
Fundal height	_____ cm		
Lie	Longitudinal ☐ Transverse ☐ Oblique ☐		
Presentation	Cephalic ☐ Breech ☐ Shoulder ☐		
FHR	____ beats/min		

Abnormality	Clinically significant? Yes	No
	☐	☐
	☐	☐
	☐	☐
Conducted by Medical Doctor	_____	Initials

Sequence 3: Day 14

Participant ID No:	D	D	I		

Participant initials			

Pharmacokinetic sample (s) and DP dose

Sample time in relation to DP dose	Protocol time (HH:MM)	DOSING	Bloods		Comment (e.g. problems sampling, observations post-dose)	Initials
		Actual time (HH:MM)	Actual time (HH:MM)	Piperaquine PK sample No.		
336h (after first DP dose)	:		:	**S3d14H336**		

Staff initials_____ Checked by _____ on _____

Sequence 3: Day 14

Participant ID No:	D	D	I		

Participant initials			

Patient instructions:

Instruction/reminder	Completed (tick and initial last row)
Check diary card with instructions to return on Day 28 on _____ At time: _____:_____ hh : mm	
Remind participant not to take any of their medications before coming to the hospital on day 28 including ART, iron, isoniazid or antacids	
Instruction Provided by (initials)	

Sequence 3: Day 14

Participant ID No:	D	D	I		

Participant initials			

Comments and additional notes	
Source Reviewed by Study Clinician	Check any new or updated AEs (reported by participant, or observed from examinations, lab, ultrasound etc. results) have been documented/interpreted on AE form ☐ Check any new or updated medications (ART, cotrimoxazole, concomitant medications) have been documented/interpreted on relevant medication form) ☐ _____ Initials _____/_____/_____ Date

Staff initials_____ Checked by _____ on _____

Sequence 3: Day 28

Participant ID No:	D	D	I		

Participant initials			

D	D	M	M	M	Y	Y	Y	Y

Medical History

How have you been since your last visit?	Record any symptoms reported
What medicines have you taken since your last visit?	Dolutegravir-based ART: Date and time of last dose?* DATE ____ ____ ____ ____ ____ ____ ____ ____ TIME ____ ____ : ____ ____ D D M M M Y Y Y Y H H M M Isoniazid: Date and time of last dose? DATE ____ ____ ____ ____ ____ ____ ____ ____ TIME ____ ____ : ____ ____ D D M M M Y Y Y Y H H M M
Have you used prescription medicines, herbal supplements, over-the-counter (OTC) medication or dietary supplements (vitamins included) or vaccines since your last visit?	Yes ☐ No ☐ If yes, complete Concomitant Medication log (or note reason for exclusion)

Vital signs

BP	_____ / _____ mmHg	Comments:
Pulse	_____ bpm	
Temperature	_____ °C	_____ Initials

Staff initials_____ Checked by _____ on _____

Sequence 3: Day 28

Participant ID No:	D	D	I		

Participant initials			

Body system examination

Body System Checked	Normal	Abnormal	Not Done
Symptom directed examination	☐	☐	☐
Abdomen	☐	☐	☐
Fundal height	_____ cm		
Lie	Longitudinal ☐ Transverse ☐ Oblique ☐		
Presentation	Cephalic ☐ Breech ☐ Shoulder ☐		
FHR	____ beats/min		

Abnormality	Clinically significant? Yes	No
	☐	☐
	☐	☐
	☐	☐
Conducted by Medical Doctor	_____	Initials

Staff initials_____ Checked by _____ on _____

Sequence 3: Day 28

Participant ID No:		D	D	I		

Participant initials			

Sample time in relation to DP dose	Protocol time (HH:MM)	DOSING	Bloods		Comment (e.g. problems sampling, observations post-dose)	Initials
		Actual time (HH:MM)	Actual time (HH:MM)	Piperaquine PK sample No.		
672h (after first DP dose)	__:__		__:__	**S3d28H672**		

Pharmacokinetic sample (s) for piperaquine

Staff initials_____ Checked by _____ on _____

Sequence 3: Day 28

Participant ID No:	D	D	I		

Participant initials			

Patient instructions:

	Completed
Check appointment card and instruct to return at Date _____(34-36weeks gestation) on: _____/_____/_____ At time: _____:_____ hh : mm	
Instruction Provided by (initials)	

Staff initials_____ Checked by _____ on _____

Sequence 3: Day 28

Participant ID No:	D	D	I		

Participant initials			

Comments and additional notes

Staff initials_____ Checked by _____ on _____

Sequence 3: Day 28

Participant ID No:	D	D	I		

Participant initials			

Source Reviewed by Study Clinician	Check any new or updated AEs (reported by participant, or observed from examinations, lab, ultrasound etc. results) have been documented/interpreted on AE form ☐ Check any new or updated medications (ART, cotrimoxazole, concomitant medications) have been documented/interpreted on relevant medication form) ☐ _____ _____/_____/_____ Initials Date

Sequence 4: Day 0 Form (34-36 weeks gestation)

Participant ID No:	D	D	I		

Participant initials			

D	D	M	M	M	Y	Y	Y	Y

Medical History

How have you been since your last visit?	Record any symptoms reported
What medicines have you taken since your last visit?	Dolutegravir-based ART: Date and time of last dose? DATE D D M M M Y Y Y Y TIME H H : M M Isoniazid: Date and time of last dose? DATE D D M M M Y Y Y Y TIME H H : M M
Have you used prescription medicines, herbal supplements, over-the-counter (OTC) medication or dietary supplements (vitamins included) or vaccines since your last visit?	Yes ☐ No ☐ If yes, complete Concomitant Medication log (check if prohibited medicine and or note reason for withdrawal if necessary)

Staff initials_____ Checked by _____ on _____

Sequence 4: Day 0 Form (34-36 weeks gestation)

Participant ID No:	D	D	I		

Participant initials			

Vital signs

Supine BP	_____ / _____ mmHg	Initials: Comments:
Supine pulse	_____ bpm	
Temperature	_____ °C	
Weight	_____Kg	

Body system examination by doctor (signature: _____)

Body System Checked	Normal	Abnormal	Not Done
Symptom directed examination	☐	☐	☐
Abdomen	☐	☐	☐
Fundal height	_____ cm		
Lie	Longitudinal ☐ Transverse ☐ Oblique ☐		
Presentation	Cephalic ☐ Breech ☐ Shoulder ☐		
FHR	____ beats/min		

	Clinically significant?	
Abnormality	Yes	No
	☐	☐
	☐	☐
	☐	☐

Sequence 4: Day 0 Form (34-36 weeks gestation)

Participant ID No:	D	D	I		

Participant initials			

Laboratory investigations for continued eligibility in the study

Investigation	Yes	No	Initials of person collecting sample
*Viral load (copies/mL)	☐	☐	

Patient instructions:

Instruction to participants	Completed (tick and initial the last row)
Review the use of the WisePill dispenser	
WisePill dispenser filled for Days 1 to 14.	
Remind participant to take iron tablets and antacids in the evening and not together with their ART	
Remind participant to return to study hospital the following day for viral load result- **Day 1*** (if certain it will be available on the following day). ***Day 1 of this sequence is any day between 34-36 weeks when participant has a VL result**	
Instruction Provided by (initials)	

Sequence 4: Day 0 Form (34-36 weeks gestation)

Participant ID No:	D	D	I		

Participant initials			

Comments and additional notes	
Source Reviewed by Study Clinician	Check any new or updated AEs (reported by participant, or observed from examinations, lab, ultrasound etc. results have been documented/interpreted on the AE form) ☐ Check any new or updated medications (ART, cotrimoxazole, concomitant [no study] medications have been documented/interpreted on the relevant form) ☐ _____ _____/_____/_____ Initials Date

Sequence 4: Day 1 Form (34-36 weeks gestation)

Participant ID No:	D	D	I		

Participant initials			

D	D	M	M	M	Y	Y	Y	Y

Medical History

How have you been since your last visit?	Record any symptoms reported
Provide participants with any results not available at last visit, including VIRAL LOAD result.	Note any comments or questions from patient regarding the result/s.
What medicines have you taken since your last visit?	Dolutegravir-based ART: Date and time of last dose? DATE ☐☐☐☐☐☐☐☐ TIME ☐☐ : ☐☐ D D M M M Y Y Y Y H H M M Isoniazid: Date and time of last dose? DATE ☐☐☐☐☐☐☐☐ TIME ☐☐ : ☐☐ D D M M M Y Y Y Y H H M M
Have you used prescription medicines, herbal supplements, over-the-counter (OTC) medication or dietary supplements (vitamins included) or vaccines since your last visit?	Yes ☐ No ☐ If yes, complete Concomitant Medication log (check if prohibited medicine and or note reason for withdrawal if necessary)

Staff initials_____ Checked by _____ on _____

Sequence 4: Day 1 Form (34-36 weeks gestation)

Participant ID No:	D	D	I		

Participant initials			

Vital signs

Supine BP	_____ / _____ mmHg	Initials: Comments:
Supine pulse	_____ bpm	
Temperature	_____ °C	

Body system examination by doctor (signature: _____)

Body System Checked	Normal	Abnormal	Not Done
Symptom directed examination	☐	☐	☐
Abdomen	☐	☐	☐
Fundal height	_____ cm		
Lie	Longitudinal ☐ Transverse ☐ Oblique ☐		
Presentation	Cephalic ☐ Breech ☐ Shoulder ☐		
FHR	____ beats/min		

	Clinically significant?	
Abnormality	Yes	No
	☐	☐
	☐	☐
	☐	☐

Sequence 4: Day 1 Form (34-36 weeks gestation)

Participant ID No:	D	D			

Participant initials			

Review Eligibility Criteria:

Viral load result from day 0 visit **(Remember to complete viral load monitoring log)**	☐☐☐☐☐ (copies/mL)*	
*Does participant still meet ALL eligibility criteria (including having viral load <1000 copies/mL or undetectable (<50 copies/mL)?	Yes ☐	No ☐
Eligibility confirmed by	Initials _____	
*Dolutegravir blood sample collected if participant excluded on basis of VL >1000 copies/mL **(S4ExtraDTG)**	Yes ☐	No ☐

*** Viral load will be considered normal if <50 copies/mL. If viral load >50 copies but <1000 copies, participant should remain in the study and be referred for counselling. Exclude participant from the study if viral load is ≥ 1000 copies/mL. In such a scenario, remember to collect a blood sample for dolutegravir concentration measurement, flag participant for infant follow up by completing infant follow up log and scheduling a reminder for infant follow up at 6 weeks. Refer participant to Lighthouse for continued care with appropriate documentation. Complete AE log.**

DP dose administration (if eligible)

DP dose administered	Yes ☐	No ☐
Time dose given	**Actual time** (HH:MM) ☐☐:☐☐	Initials: _____

Staff initials_____ Checked by _____ on _____

Sequence 4: Day 1 Form (34-36 weeks gestation)

Participant ID No:	D	D	I		

Participant initials			

Estimated date of delivery or planned C-section:

D	D	M	M	M	Y	Y	Y	Y

Patient instructions:

Instructions to participant	Completed (tick and initial the last row)
Review the use of the WisePill dispenser	
WisePill dispenser filled for Days 1 to 14, and give participant instructions on how to refill. Remind participant to take DP tablets at home on Day 2 and Day 3	
Remind participant to take iron tablets and antacids in the evening and not together with DP tablets or their ART	
Remind participant to return to study hospital as soon as labour pains start.	
Instruction Provided by (initials)	

Sequence 4: Day 1 Form (34-36 weeks gestation)

Participant ID No:	D	D	I		

Participant initials			

Comments and additional notes	
Source Reviewed by Study Clinician	Check any new or updated AEs (reported by participant, or observed from examinations, lab, ultrasound etc. results have been documented/interpreted on the AE form) ☐ Check any new or updated medications (ART, cotrimoxazole, concomitant [no study] medications have been documented/interpreted on the relevant form) ☐ Check that any other appropriate forms/logs have been completed ☐ _____ Initials _____/_____/_____ Date

Staff initials_____ Checked by _____ on _____

Sequence 4: Delivery

Participant ID No:	D	D	I		

Participant initials			

D	D	M	M	M	Y	Y	Y	Y

Medical History

How have you been since your last visit?	Record any symptoms reported
When did your labour start?	Date and time Labour pains started? DATE D D M M M Y Y Y Y TIME H H : M M Date and time "Waters broke" (membranes ruptured)? DATE D D M M M Y Y Y Y TIME H H : M M
What medicines have you taken since your last visit?	Dolutegravir-based ART: Date and time of last dose? DATE D D M M M Y Y Y Y TIME H H : M M Isoniazid: Date and time of last dose? DATE D D M M M Y Y Y Y TIME H H : M M
Have you used prescription medicines, herbal supplements, over-the-counter (OTC) medication or dietary supplements (vitamins included) or vaccines since your last visit?	Yes ☐ No ☐ If yes, complete Concomitant Medication log (check if prohibited medicine and or note reason for withdrawal if necessary)

Sequence 4: Delivery

Participant ID No:	D	D	I		

Participant initials			

Vital signs

Supine BP	_____ / _____ mmHg	Initials: Comments:
Supine pulse	_____ bpm	
Temperature	_____ °C	

Body system examination by study personnel (Signature: _____)

Body System Checked	Normal	Abnormal	Not Done
Symptom directed examination	☐	☐	☐

	Clinically significant?	
Abnormality	Yes	No
	☐	☐
	☐	☐
	☐	☐

Sequence 4: Delivery

Participant ID No:	D	D	I		

Participant initials			

Labour and delivery details:

Duration of labour	_____	hours
Mode of delivery	SVD ☐	Caesarean Section ☐
Gestational age at delivery	_____	weeks
Birth weight	_____ . _____	Kgs
Any complications during delivery	Normal ☐	Adverse ☐
If yes, provide details and complete (S)AE form as necessary		
Surface examination of the baby (If any adverse outcome, complete [Serious] Adverse Event form with full details)	Normal ☐	Adverse outcome ☐
Records/Examination reviewed by Medical Doctor (With additional notes if needed-see additional notes section)	_____	Initials

Sequence 4: Delivery

Participant ID No:	D	D	I		

Participant initials			

PK sampling DTG and DP

DTG and DP PK samples collected		Maternal blood S4DMat ☐	Umbilical blood S4DUmb ☐
Comments:	Initials _____	**Actual time** (HH:MM)	**Actual time** (HH:MM)

Sequence 4: Delivery

Participant ID No:	D	D	I		

Participant initials			

Comments and additional notes	
Source Reviewed by Study Clinician	Check any new or updated AEs (reported by participant, or observed from examinations, lab, ultrasound etc. results have been documented/interpreted on the AE form) ☐ Check any new or updated medications (ART, cotrimoxazole, concomitant [no study] medications have been documented/interpreted on the relevant form) ☐ _____ Initials _____/_____/_____ Date

Staff initials_____ Checked by _____ on _____

IMPROVE DDI ADVERSE EVENT LOG

Patient Identity Number	D D I	**Participant's Initials**		**IMPROVE DDI STUDY**	
Health facility Site	Z O M B A	**Enrolment Date** DD-MMM-YYYY		**Form Number** *(01, 02, 03, etc...)*	

ADVERSE EVENT LOG

Line # e.g. 01	Description of Adverse Event	Date of onset DD-MMM-YYYY	Severity (Please refer to key text on page 2)	Relationship to study medication	Action taken	Out-come	Date of resolution DD-MMM-YYYY	Serious Adverse Event?
								☐ Yes ☐ No
								☐ Yes ☐ No
								☐ Yes ☐ No
								☐ Yes ☐ No

Staff initials	**Signature:**	**Date:**	D D M M M Y Y Y Y
Checked by	**Signature:**	**Date:**	D D M M M Y Y Y Y

Patient Identity Number	D D I	**Participant's Initials**		**IMPROVE DDI STUDY**	
Health facility Site	Z O M B A	**Enrolment Date** DD-MMM-YYYY		**Form Number** *(01, 02, 03, etc...)*	

ADVERSE EVENT LOG

Severity: 1=mild, 2=moderate, 3=severe, 4=life threatening.

Relationship to study medication: 1=definitely unrelated, 2=unlikely related, 3=possibly related, 4=probably related 5=definitely related

Action taken: 1=no action, 2=dosing interrupted, 3=dosing discontinued

Outcome: 1=recovered/resolved, 2=recovered/resolved with sequelae, 3=recovering/resolving, 4=not recovered/resolved, 5=died, 6=Not known

Serious Adverse Event: 1=death, 2=life threatening, 3=hospitalisation, 4=persistent/significant disability, 5=medically important, 6=congenital anomaly.

In case of an SAE, please complete the SAE form.

Staff initials	**Signature:**	**Date:**	D D M M M Y Y Y Y
Checked by	**Signature:**	**Date:**	D D M M M Y Y Y Y

Participant ID No:	D	D			

Participant initials			

Adverse event (AE) information

D D M M M Y Y Y Y *Start date of AE* : *Start time of AE*	Is the AE on-going at end of study (i.e. no stop date)? ☐ Yes ☐ No _____ Initials
D D M M M Y Y Y Y *Stop date of AE* : *Stop time of AE*	

To be completed by study doctor

AE term						
Severity	☐ Mild	☐ Moderate	☐ Severe	☐ Life threatening		
Outcome	☐ Recovered/resolved	☐ Recovered/resolved with sequalae	☐ Recovering/resolving	☐ Not recovered /resolved	☐ Died	☐ Not known
Relationship to DP	☐ Definitely unrelated	☐ Unlikely related	☐ Possibly related	☐ Probably related	☐ Definitely related	
Alternative cause						
Therapy? Check all that apply	☐ None	☐ Prescribed drug/self-medication (complete concomitant med form)		☐ Other _____ _____		
Was AE serious?	☐ Yes* ☐ No * complete remaining fields this section	☐ Hospitalisation ☐ Prolonged hospitalisation Date of admission: _____/_____/_____ Date of discharge: _____/_____/_____				
	☐ Fatal	☐ Life-threatening				
	☐ Persistent disability / incapacity	☐ Medically significant	☐ Congenital anomaly/ defect			
Action taken w.r.t. DP	☐ No action	☐ Dosing interrupted	☐ Dosing discontinued			
Brief comment for CRF						
Study Clinician signature		**Date:**	_____/_____/_____ _			

Staff initials_____ Checked by _____ on _____

Adverse event clinical notes

Date/time	Clinical notes (AE as described by volunteer, assessment and investigations, description of action taken with regard to participation, study drug and concomitant medications given)	Initials

Staff initials_____ Checked by _____ on _____

SAE Form

Participant ID No:	D	D	I		

Participant initials			

To be submitted with corresponding AE report form

Serious Adverse Events **SAE No.** |__|__| Participant ID: | D | D | I | __|__|__| Participant initials: |__|__|__|

1. Report Status

- ○ Initial report — **Date of Report** |__|__|-|__|__|__|-20|__|__| *(eg. 01-Jan-2013)*
- ○ Follow-up report — **Date of Report** |__|__|-|__|__|__|-20|__|__| *(eg. 01-Jan-2013)*
- ○ Follow-up report — **Date of Report** |__|__|-|__|__|__|-20|__|__| *(eg. 01-Jan-2013)*
- ○ Follow-up report — **Date of Report** |__|__|-|__|__|__|-20|__|__| *(eg. 01-Jan-2013)*
- ○ Final report — **Date of Report** |__|__|-|__|__|__|-20|__|__| *(eg. 01-Jan-2013)*

Subject Information

2a. Date of Birth |__|__|-|__|__|__|-|__|__|__|__| *(eg. 01-Jan-2013)* **OR** 2b. Age |__|__| years |__|__| months

3. Gender Female

Event Classification

4. Serious Adverse Event (provide key word or cause of death, **NB term should match corresponding AE page**):

5. Describe the serious adverse event ***(include all relevant laboratory results and add any further notes in the last section of the form as additional SAE notes)***

6. Relationship to study drug and action taken (To be completed by study doctor)

AE term						
Severity	☐ Mild	☐ Moderate	☐ Severe	☐ Life threatening		
Outcome	☐ Recovered/resolved	☐ Recovered/resolved with sequalae	☐ Recovering/resolving	☐ Not recovered /resolved	☐ Died	☐ Not known
Relationship to DP	☐ Definitely unrelated	☐ Unlikely related	☐ Possibly related	☐ Probably related	☐ Definitely related	
Alternative cause						
Therapy? Check all that apply	☐ None	☐ Prescribed drug/self-medication (complete concomitant med form)	☐ Other _____ _____			
Was AE serious?	☐ Yes* ☐ No * complete remaining fields this section	☐ Hospitalisation ☐ Prolonged hospitalisation Date of admission: _____/_____/_____ Date of discharge: _____/_____/_____				
	☐ Fatal	☐ Life-threatening				
	☐ Persistent disability / incapacity	☐ Medically significant	☐ Congenital anomaly/ defect			
Action taken w.r.t. DP	☐ No action	☐ Dosing interrupted	☐ Dosing discontinued			

Study Drug Detail

7. Study drug start date: |__|__|-|__|__|__|-20|__|__|
(eg. 01-Jan-2013)

7a. Date of last study drug taken |__|__|-|__|__|__|-20|__|__|
(eg. 01-Jan-2013)

7b. Time of last study drug taken |__|__|:|__|__| *(eg. 14:00)*

Therapy

8. Medication given to treat current event ○ Yes (if yes, please fill in below table) ○ No

Medication (Generic name)	Dose	Frequency	Route of administration	Start Date *(eg. 01-Jan-2013)*	End Date *(eg. 01-Jan-2013)*	Indication

Staff initials_____ Checked by _____ on _____

9. Serious adverse event clinical notes

Date/time	Clinical notes (SAE as described by volunteer, assessment and investigations, description of action taken with regard to participation, study drug and concomitant medications given)	Initials

Staff initials_____ Checked by _____ on _____

Investigator/Study Physician (print full name): _____

Signature: _____ Date: _____

Unscheduled Visit Form: All Sequences

Unscheduled Visit No:____

Study ID Number:	D	D	I		

D	D	M	M	M	Y	Y	Y	Y

Physical examination

Vital signs

Supine BP	_____ / _____ mmHg	Comments: _____ Initials
Supine pulse	_____ bpm	
Temperature	_____ °C	

Body system examination (symptom-directed)

Code	Body System Checked	Normal	Abnormal	Not Done
01	General appearance (including JACCOL)	☐	☐	☐
02	Head and neck (including thyroid)	☐	☐	☐
03	Eyes, ears, nose, throat, mouth	☐	☐	☐
04	Dermatological	☐	☐	☐
05	Respiratory	☐	☐	☐
06	Cardiovascular	☐	☐	☐
07	Abdomen	☐	☐	☐
07a	Fundal height	_____ cm		
07b	Lie	Longitudinal ☐ Transverse ☐ Oblique ☐		
07c	Presentation	Cephalic ☐ Breech ☐ Shoulder ☐		
07d	FHR	_____ b/min		

Staff initials _____ Checked by _____ on _____

Unscheduled Visit Form: All Sequences

Unscheduled Visit No:____

Study ID Number:	D	D	I		

D	D	M	M	M	Y	Y	Y	Y

08	Musculoskeletal, including back	☐	☐	☐
09	Neurological	☐	☐	☐
10	Urogenital	☐	☐	☐
11	Other	☐	☐	☐

Detail on abnormal findings above			**Clinically significant?**	
No.	Code	Abnormality	Yes	No
1			☐	☐
2			☐	☐
3			☐	☐

Physical exam findings	☐ Normal	☐ Abnormal	☐ Abnormal –
Conducted by doctor	_____ Initials		

AE and concomitant medications	Yes	No	**Initials**
Has participant reported any new AEs in this visit ***(If yes complete AE form)***	☐	☐	_____
Has participant reported previously documented AEs on this visit ***(If yes update AE form)***	☐	☐	_____
Any changes in Concomitant medication? ***If yes complete Concomitant medications form***	☐	☐	_____

Unscheduled Visit Form: All Sequences

Unscheduled Visit No:____

Study ID Number:	D	D	I		

D	D	M	M	M	Y	Y	Y	Y

Comments and additional notes (complete adverse event form, where appropriate)

Source Reviewed by Study Clinician	_____ Initials	_____/_____/_____ Date

Staff initials _____ Checked by _____ on _____

Any study, prescription/non-prescription/traditional meds, vitamins, herbal/dietary supplements, or vaccinations **from 3 months before screening (ANTIRETROVALS) or 4 weeks before screening (ALL OTHER)** and throughout the trial. **PLEASE CHECK ANY OTHER EXISTING HEALTH PASSPORTS AND CROSS-CHECK AGAINST ELIGIBILITY CRITERIA/PROHIBITED MEDICINES LIST**							Use additional forms as required if medications stop and re-start	
Medication name	**Taking medication?**	**Start date** *(dd/mm/yyyy)*	**Stop date** *(dd/mm/yyyy)*	**Route of administration**	**Dose and dose unit (e.g. 1 tablet or 500mg)**	**Frequency**	**Indication (s)**	**Initials**
Dolutegravir-based ART TDF 300mg / 3TC 300mg / DTG 50mg	☐ Yes ☐ No			Oral	1 tablet	Once daily	HIV treatment	
Efavirens-based ART TDF 300mg/ 3TC 300mg/ EFV 600mg	☐ Yes ☐ No			Oral	1 tablet	Once daily	HIV treatment	
Cotrimoxazole preventive therapy 960mg	☐ Yes ☐ No			Oral	1 tablet	Once daily	Opportunistic infections prophylaxis	
Isoniazid preventive prophylaxis 300mg	☐ Yes ☐ No			Oral	1 tablet	Once daily	TB prophylaxis	
Ferrous folate (FeFol) or Ferrous Sulphate	☐ Yes ☐ No			Oral	1 tablet	Once daily	Anaemia prevention	
Pyridoxine 25mg	☐ Yes ☐ No			Oral	1 tablet	Once daily	Peripheral neuropathy prevention	
Antacids (indicate name below) _____	☐ Yes ☐ No			Oral				

*e.g. unit (such as 500mg) or number of tablets (if only combination)

Participant ID No:	D	D	I		

Participant initials			

Medication name	**Start date** *(dd/mm/yyyy)*	**Stop date** *(dd/mm/yyyy)*	**Route of administration**	**Dose and dose unit (e.g. 1 tablet or 500mg)**	**Frequency**	**Indication(s)**	**Initials**
			☐ Oral ☐ Respiratory ☐ Intravenous ☐ Intramuscular ☐ Nasal ☐ Vaginal ☐ Rectal ☐ Topical Other: ____________	______________ ☐ Tablet/capsule ☐ g ☐ mg ☐ µg Other:	☐ Once daily ☐ BD ☐ TID ☐ QID ☐ PRN Other:		
			☐ Oral ☐ Respiratory ☐ Intravenous ☐ Intramuscular ☐ Nasal ☐ Vaginal ☐ Rectal ☐ Topical Other: ____________	______________ ☐ Tablet/capsule ☐ g ☐ mg ☐ µg Other:	☐ Once daily ☐ BD ☐ TID ☐ QID ☐ PRN Other:		
			☐ Oral ☐ Respiratory ☐ Intravenous ☐ Intramuscular ☐ Nasal ☐ Vaginal ☐ Rectal ☐ Topical Other: ____________	______________ ☐ Tablet/capsule ☐ g ☐ mg ☐ µg Other:	☐ Once daily ☐ BD ☐ TID ☐ QID ☐ PRN Other:		
			☐ Oral ☐ Respiratory ☐ Intravenous ☐ Intramuscular ☐ Nasal ☐ Vaginal ☐ Rectal ☐ Topical Other: ____________	______________ ☐ Tablet/capsule ☐ g ☐ mg ☐ µg Other:	☐ Once daily ☐ BD ☐ TID ☐ QID ☐ PRN Other:		

Staff initials________ Checked by ________ on ______________

Viral load monitoring log

Study ID Number:	D	D	I		

Viral load monitoring

	Visit	Description of visit	Date of visit	Value (copies/mL)	Normal	Abnormal*	PK sample collected if abnormal	Initials
1	Screening	Baseline sample before enrolment.	D D M M Y Y		☐	☐		
2	Sequence 2: Before DTG sampling (if enrolled on efavirenz-based ART	As part of screening process (Baseline sample) if enrolling while on DTG ART	D D M M Y Y		☐	☐	Yes ☐ No ☐	
3	Sequence 4: Day 0	Before last course of DP	D D M M Y Y		☐	☐	Yes ☐ No ☐	

*Participant should not be enrolled if virologically unsuppressed; >50 copies/mL; and should be withdrawn from the study if there is a viral load measurement of >1000 copies/mL after enrolment or intake of study drug.

Staff initials_____

Checked by _____ on _____

IMPROVE DDI STUDY EXIT FORM

Participant ID	D D I	**Participant Initials**		**EXIT CHECKLIST**	
Health Facility	ZCH	**Date of visit** *(DD-MMM-YYYY)*			

1	How did the participant leave the study? *(Note: "completed" includes treatment failures and adequate responses)*	☐ Completed ☐ Withdrawn consent ☐ Withdrawn for safety reasons ☐ Lost to follow up ☐ Screening failure ☐ Death
2	Date of last contact	
3	Last contact visit	Sequence 1 Day ☐ Sequence 2 Day ☐ Sequence 3 Day ☐ Sequence 4 Day ☐
4	Are all adverse event forms signed off?	Yes ☐ No ☐
5	Are all concomitant forms signed off?	Yes ☐ No ☐
Notes		

Study Staff Initials ☐☐☐	**Signature**_____	D D M M M Y Y Y Y
Checked by ☐☐☐	**Signature**_____	D D M M M Y Y Y Y

Appendix 2: Consent forms and participant information sheets

Informed Consent Form	Screening ID Number:	D	D	I			

Impact of dolutegravir-based antiretroviral therapy on the pharmacokinetic profile of piperaquine administered as dihydroartemisinin-piperaquine for intermittent preventive treatment of malaria in pregnant women living with human immunodeficiency virus in Malawi: a fixed sequence cohort study.

Investigators

1. **Chief Investigator:** Dr Feiko ter Kuile, MD, MSc, PhD; Professor and Chair of Tropical Epidemiology, Liverpool School of Tropical Medicine

2. **Overall Principal Investigator:** Dr Karen Irma Barnes, MBChB, MMed; Professor of Clinical Pharmacology, Division of Clinical Pharmacology, University of Cape Town

3. **Site Principal Investigator:** Dr Clifford George Banda, MBBS, MSc; Specialist Registrar in Clinical Pharmacology, Division of Clinical Pharmacology University of Cape Town & Career Development Fellow in Clinical Pharmacology, College of Medicine, University of Malawi.

Co-Investigators

4. Dr Gary Maartens, MBChB, MMed, FCP; Professor of Clinical Pharmacology, Division of Clinical Pharmacology, University of Cape Town

5. Dr Victor Mwapasa, MBBS, MPH, PhD; Professor of Public Health and Epidemiology, Department of Epidemiology, College of Medicine, University of Malawi & Senior Research Fellow, Malawi-Liverpool-Wellcome Trust Clinical Research Programme.

6. Dr Mwayiwawo Madanitsa, MD, PhD, Post-Doctoral Research Fellow, College of Medicine, University of Malawi.

Introduction

You are invited to take part in a research study on how best to prevent malaria in pregnant women living with HIV. Before you decide whether or not you want to take part, you need to know what the study is about, the possible risks and benefits of being in this study, and what you will need to do if you choose to be part of this study. You may also want to discuss it with your family, friends, or the healthcare workers at the clinic you normally visit.

If you are considering being part of the study, it is important you read the information in this document and ask the study doctor or nurse if there is anything that you do not understand. Being part of the study is voluntary and you can take time to decide. If you agree, you will be asked to sign this form. A copy of this information and your signed Informed Consent Form will be given to you to keep.

Why are we doing this research study? What is the purpose of this study?

As you may know, malaria is still a big problem in Malawi. During pregnancy, malaria infection in the mother, even if she doesn't feel sick, can affect her baby and may sometimes result in a lower birth weight, anaemia ("thin blood") in both the mother and the baby or still births. Malaria treatments are given to pregnant women to prevent these problems. The medicine currently used to prevent malaria in pregnant women living with HIV, cotrimoxazole, is becoming less effective at preventing malaria. So, we need to find better ways of preventing malaria in pregnancy in women living with HIV.

A new malaria medicine, dihydroartemisinin-piperaquine (DP), has been shown generally to work well in pregnant women. However, HIV treatment containing efavirenz (called "efavirenz-based HIV treatment") seems to lower the amount of DP in the blood, so there may not be enough DP left to prevent malaria in pregnant women who are on efavirenz-based HIV treatment.

Fortunately, there is now a new HIV treatment regimen, called "dolutegravir based HIV treatment" that is now being rolled out in Malawi and elsewhere in the world, and the Ministry of Health in Malawi is switching those living with HIV to this new regimen. Dolutegravir based HIV treatment reduces the HIV infection more quickly and may have fewer side effects than the older efavirenz-based treatment. In this study in pregnant women living with HIV in Malawi, we would like to find out if the amount of the malaria treatment in DP called piperaquine, is better for preventing malaria when given with the new the dolutegravir-based HIV treatment than the older efavirenz-based HIV treatment.

Why am I being asked to volunteer? Who else is being invited to take part in this study?

You are being asked to participate in this study because you are pregnant, living with HIV and receiving HIV treatment. We are inviting women like you who are 18 years of age or older, pregnant for 4 months or more, and who attend antenatal care at health facilities around Zomba Central Hospital whether they would like to take part. We hope to include 22 pregnant women in total.

What HIV and malaria treatments will be given during the study?

Women on efavirenz-based HIV treatment who are willing to participate in the study will first receive a 3-day course of the malaria preventive treatment, DP, together with their efavirenz-based HIV treatment. Two weeks later, the efavirenz-based HIV treatment will be switched to the new dolutegravir-based HIV treatment, according to the new national guidelines for treating HIV in pregnant women. Once you are on the new dolutegravir-based HIV treatment for at least 4 weeks, you will be given another course of DP, and then this will be repeated in the 8th month of your pregnancy.

If you are already taking the new dolutegravir-based HIV treatment you will skip Part 1 of the study and stay on your dolutegravir-based HIV treatment throughout the study. You will receive a 3-day course of the malaria preventive treatment, DP, soon after you start the study and again in the 8th month of your pregnancy.

What procedures will happen in the study?

You will be given a diary card that shows when you need to come back to the hospital. Below, we describe the different parts of the study. If you are currently on efavirenz-based HIV treatment or antiretroviral therapy (ART), there will be four parts to the study before your baby is born. Those already on dolutegravir-based ART will skip Part 1 and start with Part 2. In total, you will need to come back to the hospital up to 13 more times if you are still on efavirenz based ART (or 8 more times if you are already on dolutegravir-based ART). Most visits will last about one hour, but on three visits (or two visits if you are already on dolutegravir-based ART) you will be asked to stay at the hospital for most of the day (about 8 hours). On these "Day admission" days we will provide lunch for you as you will be at the hospital during lunch time, and we will drop you at your home afterwards, using the study vehicle, to avoid you getting home late.

PART 1 (First DP malaria preventive treatment – only if on the old efavirenz-based HIV treatment):

- After receiving the first DP treatment dose on day 0, you will be given another dose to take at home on the next day (day 1). You will then be asked to come back to the hospital on days 2, 3, 7, 14 and 28 after the first dose of DP. Each visit will last about one hour with the exception on day 2, where you will spend about 8 hours (approximately 9am to 5pm) at the hospital. The day admission on day 2 is needed for us to measure how much of the malaria preventive treatment piperaquine is in your blood over that period.
- On day 14 (2 weeks after taking the first dose of the DP malaria treatment), your efavirenz-based HIV treatment will be switched to the new dolutegravir-based HIV treatment, which youwill continue to take once a day throughout the study and thereafter.

PART 2 (On dolutegravir-based HIV treatment):

- After you have been taking the new dolutegravir-based HIV treatment for at least 4 weeks, you will have a day admission for about 8 hours (approximately 9am to 5pm) so we can measure how much of the new HIV treatment dolutegravir is in your blood over that period.
- The next day you will come to the hospital again for one blood sample. You will then be started on a 3-day course of the malaria preventive treatment. You will be given one dose of DP and will be given another dose to take at home on the next day (day 1).

PART 3 (First DP malaria preventive treatment on the new dolutegravir-based HIV treatment

- You will be asked to come back to the hospital 2, 3, 4, 7, 14 and 28 days after the start of the DP malaria treatment. Each visit will last about one hour, except on day 2 when you will spend about 8 hours (approximately 9am to 5pm) at the hospital so we can collect several blood samples to measure how much of the new HIV treatment, dolutegravir, and the malaria preventive treatment, piperaquine, is in your blood over that period.

PART 4 (Second DP malaria preventive treatment on the new dolutegravir-based HIV treatment):

- We will give you another course of the DP malaria preventive treatment when you are 8 months (34-36 weeks) pregnant

DELIVERY

- You will be asked to deliver your baby at Zomba Central Hospital so that we can see how you and your baby are and measure how much of the DP is left in your and your baby's blood (for which a small blood sample will be taken from the umbilical cord after your baby is born).
- After your baby is born, you will remain on the new dolutegravir-based HIV treatment as it is now the recommended HIV treatment in Malawi

Each blood draw will be approximately equal to half a teaspoon (2 ml). You will contribute approximately twelve teaspoons (60 ml) in total for all the blood draws in this study when enrolled into the study while on efavirenz-based HIV treatment, and approximately eight teaspoons (38 ml) when enrolled while already on dolutegravir-based ART.

Table 1 below shows the calendar of your visits and what will happen at each visit when enrolled into the study while on efavirenz-based HIV treatment. You will spend approximately 36 hours in total in study related hospital visits. NOTE: you may also come back to the hospital any other day if you feel unwell and we may ask you to come back for extra visits if we think that is best for you or your baby.

Table 1: Calendar and outline of procedures for participants on efavirenz-based ART who will get switched to dolutegravir based ART during the study.

		Week 1				Week 2	Week 4
PART 1	**Day 0**	**Day 1**	**Day 2: DAY ADMISSION**	**Day 3**	**Day 7**	**Day 14**	**Day 28**
Physical examination	X	**Take DP dose at home (no hospital visit)**	X	X	X	X	X
Blood sampling for piperaquine concentrations	X		X	X	X	X	X
DP malaria prevention treatment	X		X				
Monitoring for any possible side effects	X		X	X	X	X	X
HIV Viral load monitoring & CD4 count	X						
Ultrasound	X						
Haemoglobin measurement	X						
Switch to daily Dolutegravir-based ART						X	

	Week 6	
PART 2	**Day 42: DAY ADMISSION**	**Day 43**
Physical examination	X	X
Blood sampling for piperaquine concentrations		X
Blood sampling for dolutegravir concentrations	X	X
DP malaria prevention treatment		X
Monitoring for any possible side effects	X	X
HIV Viral load monitoring	X	

	Week 6 (continued)			Week 7	Week 8	Week 10
PART 3	**Day 44**	**Day 45 DAY ADMISSION**	**Day 46**	**Day 49**	**Day 56**	**Day 70**
Physical examination	**Take DP dose at home (no hospital visit)**	X	X	X	X	X
Blood sampling for piperaquine concentrations		X	X	X	X	X
Blood sampling for dolutegravir concentrations		X	X			
DP malaria prevention treatment		X				
Monitoring for any possible side effects		X	X	X	X	X

PART 4	**34-36 weeks**	**At delivery (in labour ward)**
Physical examination (including vital signs)	X	X
Venous and cord blood sampling for piperaquine PK analysis		X
Venous and cord blood sampling for dolutegravir PK analysis	X	X
DP oral administration treatment course for 3 days	X	
Viral load monitoring	X	
Monitoring of adverse events	X	X

Table 2 below shows the calendar of your visits and what will happen at each visit when enrolled into the study while on dolutegravir-based HIV treatment. You will spend approximately 24 hours in total in study related hospital visits. NOTE: you may also come back to the hospital any other day if you feel unwell and we may ask you to come back for extra visits if we think that is best for you or your baby.

Table 2: Calendar and outline of procedures for participants who are already on dolutegravir-based ART

PART 1	Not applicable

	Week 1		
PART 2	**Screening**	**Day 0: DAY ADMISSION**	**Day 1**
Physical examination	X	X	X
Blood sampling for piperaquine concentrations			X
Blood sampling for dolutegravir concentrations		X	X
DP malaria prevention treatment			X
Monitoring for any possible side effects		X	X
Haemoglobin measurement	X		
HIV Viral load monitoring & CD4 count	X		
Ultrasound	X		

	Week 1 continued			Week 2	Week 3	Week 5
PART 3	**Day 2**	**Day 3 DAY ADMISSION**	**Day 4**	**Day 7**	**Day 14**	**Day 28**
Physical examination		X	X	X	X	X
Blood sampling for piperaquine		X	X	X	X	X
Blood sampling for dolutegravir	**Take DP dose at home (no hospital visit)**	X	X			
DP malaria prevention treatment		X				
Monitoring for any possible side effects		X	X	X	X	X
HIV Viral load monitoring						X

PART 4	**34-36 weeks**	**At delivery (in labour ward)**
Physical examination (including vital signs)	X	X
Blood and umbilical cord sampling for piperaquine		X
Blood and umbilical cord sampling for dolutegravir		X
DP malaria prevention treatment (for 3 days)	X	
Viral load monitoring	X	
Monitoring of adverse events	X	X

What are the possible risks or discomforts?

Possible Risks from study drug/s to you and the baby
There is no known risk of the study drugs (DP and DTG) for the baby when administered to women who are between 4 and 9 months pregnant. However, the two clinical trials that are currently going on in Malawi (IMPROVE studies) will be the first studies where these two medicines are given together. While no interaction between these medicines is expected, we will do blood tests regularly to make sure your HIV infection is controlled, that you have not been infected with malaria, and to see how much of these medicines remain in your blood.

We will test your HIV viral load three times during your pregnancy. In the unlikely event of a significant increase in viral load (>1000 copies/ml), we will:

- Withdraw you from the study and you will not receive any further DP malaria preventive treatments.
- Offer you counselling about HIV treatment adherence, and refer you to a clinic where, if needed, blood tests will be conducted to make sure the HIV is not resistant to the currently recommended HIV treatment and arrange for appropriate care for you.
- We will also follow you (and your baby) up until 6 weeks after delivery when an HIV test on your baby will be done to see if he or she is infected so that s/he will receive appropriate HIV treatment if needed.

Although not common, you may experience some side effects after taking the malaria preventive treatment, DP. Side effects that have been reported include nausea and vomiting, feeling dizzy (light-headed), headache, itching (skin irritation) or stomach pains. You should tell the study doctor or nurse if you have any of these or other medical problems during the study, so that we can take care of you.

It is possible that the study may involve risks that are not known at this time. Should any new information be reported during this study about the study medicines that could be important to you, you will be informed, and you will be asked if you still want to be part of the study.

Possible Risks from Study Procedures
Pain, bruising or numbness of the arm may occasionally result from the blood collections during this study. These may occasionally also cause dizziness or fainting. These reactions are usually mild and last a short time. We try and prevent these by using a little cannula (like the ones used to put up a drip) to take repeated blood samples during the day admission days when you spend the whole day (about 8 hours) at the hospital. You should tell the study doctor or nurse if you have any of these or other medical problems during the study, so that we can take care of you.

Potential Benefits from being part of the study
We expect that DP will be a better treatment against malaria in pregnant women. DP is more likely to clear any malaria infection that you may have which could be harmful to your unborn baby - even if it is not giving you any malaria symptoms. DP is also expected to be better at preventing you getting a new malaria infection while you are pregnant. You may receive improved antenatal care during the study since you will be reviewed by a study medical doctor at every antenatal visit. Furthermore, if you get sick, you will be attended to by a study medical doctor and will not have to wait to be seen at the hospital outpatient clinic. Lastly, an ultrasound scan of your baby will be done when you join the study; this is an antenatal service that is not routinely offered in Malawi.

Benefits to the community
The study will help the Ministry of Health in Malawi and other countries where malaria and HIV are common to understand if DP malaria preventive treatment should also be given to pregnant women on dolutegravir-based HIV treatment, which is now part of the national HIV treatment policy in Malawi.

Will I be paid for being in the study?

You will not be given any money or gifts to join this research study. However, on each visit to the hospital you will be given 7300 Malawi Kwacha and on the three days when you will spend at least 8 hours at the hospital, this amount will be increased to 11000 Malawi Kwacha. This money is aimed at covering any travel costs, inconvenience, loss of work time or other related expenses.

When is the study over?

This study is expected to end after all participants have completed all visits, and all information has been collected, so after your baby is born or 4 weeks after the last DP malaria preventive treatment dose is given, whichever occurs last.

This study may also be stopped at any time without your consent if:

- The study doctor feels it is necessary for your health or safety or the health or safety of your baby. This would not require your consent, but you will be told about this and given the reason for this decision.
- You have not followed study instructions.
- The Sponsor, the study doctor or the regulatory bodies decide to stop the study.

If the study has to be stopped before its completion for any reason, your study doctor will discuss with you any further follow up needed and your return to routine antenatal and HIV care.

What happens if I decide not to be part of the study?

It is important you you understand that your participation in this study is voluntary (entirely your choice). If you decide not to take part, you will still be given the usual treatment for preventing malaria in those living with HIV, cotrimoxazole. The cotrimoxazole you are already taking is the current standard of care for prevention of malaria and other opportunistic infections in individuals living with HIV.

Even if you decide to take part in the study, you may change your mind later and stop being in the study. This will not in any way affect the health care that you receive at this hospital or any other health facility. If you decide you do not want to be part of the study, you should tell the study doctor or nurse and let him/her perform the appropriate final assessments. Any information (data) that you share with us or samples that you have contributed will not be further used for the purposes of this study or shared with anyone after you decide to stop being in the study.

What if something goes wrong during the study?

If you become ill or injured while in this study, you should come to Zomba Hospital as soon as possible for medical assessmeny and treatment, which will be provided free of charge. The study doctors will be available in the hospital every day to attend to you, if needed. This research study is covered by an insurance policy taken out by the Sponsor, the Liverpool School of Tropical Medicine in the United Kingdom. If you suffer a bodily injury because you are taking part in the study, the insurer will pay all reasonable medical costs to treat that injury, without you having to prove that the study was responsible for your injury.

While you are part of this study, it is important that you discuss with us before taking any medications including traditional and herbal medicines.

If you are harmed and the insurer pays for the necessary medical costs, usually you will be asked to accept that insurance payment as full settlement of the claim for medical costs. However, accepting this offer of insurance cover does not mean you give up your right to make a separate claim for other losses based on negligence, in a Malawian court.

Who can see or use my information? How will my personal information be protected?
Your medical records and information collected during this study that show your name or address or contact details will be kept confidential at the hospital. These will only be seen by those organising the study and authorities who give us permission to conduct the study and make sure studies like ours are run properly. Some medical and other information about you from the study will also be put into a computer so that we can work out the results, but this will not include anything that would identify you, such as your name or address or phone number; you will only be identified by a number (we call this "anonymized"). So that other interested people may learn from this study, summaries of the anonymized study results will be presented at community and scientific meetings, shared with the Malawian and other malaria control programmes or the World Health Organization, and will be published in scientific / medical journals. You will never be identified by name in any of these meetings or reports.

Sharing of study data and results
Medical journals now expect us to share anonymised information from studies like ours to allow others to check the results, compare / combine these with results from similar studies and prevent studies having to be repeated unnecessarily. These shared / combined results may also be discussed at meetings or published in scientific / medical journals, but you will never be identified by name. So, we will ask whether you agree to us sharing your anonymised information in this way. This is useful for understanding more about the malaria and HIV treatments used in this study, and how best to prevent malaria in pregnant women living with HIV. Please note, if you withdraw your consent after the study, we may not be able to take back the data that has already been shared with others in this way.

Who has approved the study?
In Malawi, this study has been approved by the College of Medicine Research Ethics Committee and the Pharmacy Medicines and Poisons Board. The study has also been approved by the Human Research Ethics Committee at University of Cape Town in South Africa and the Liverpool School of Tropical Medicine Research Ethics Committee in the United Kingdom.

Contact for further information
If you have any questions about this study, you can contact **Dr. Clifford George Banda**, the Lead Investigator of the study on **+265 994 717 867**.

If you have a question about your rights as a research participant, you can contact **the Chairperson of the College of Medicine Research Ethics Committee** on Phone: +265 11 871 911

Please **do not sign this consent form unless you have had a chance to ask questions and have received a satisfactory answer or explanation.**

Informed Consent Form

Impact of dolutegravir-based antiretroviral therapy on the pharmacokinetic profile of piperaquine administered as dihydroartemisinin-piperaquine for intermittent preventive treatment of malaria in pregnant women living with human immunodeficiency virus in Malawi: a fixed sequence cohort study.

Participant's Name: _____**Initials**: _____

Initials	I confirm that I have read, understood and had the information about the above study explained to me on this day:
[__I__I__I__]	-------/--------/------- and have had the opportunity to ask questions and am satisfied by the answers given.
[__I__I__I__]	I understand that my participation in the study is entirely voluntary and that I am free to withdraw at any time, without giving a reason, and without my medical care or legal rights being affected.
[__I__I__I__]	I understand that the Sponsor, others working on the Sponsor's behalf, the Pharmacy Medicines and Poisons Board and the College of Medicine Research and Ethics Committee, the University of Cape Town Human Research Ethics Committee or the Liverpool School of Tropical Medicine Research Ethics Committee will not need my permission to look at my health records in respect of my current study, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.
[__I__I__I__]	I agree not to restrict use of any data or results that arise from this study or the sharing of my anonymised (de-identified) data as long as it is for scientific purposes.
[__I__I__I__]	I agree to storage of blood samples that I will contribute as part of this study and to not restrict use of any such samples arising from this study as along as it is aimed at further understanding the drug-drug interactions between antimalarial and antiretroviral drugs.
[__I__I__I__]	I agree to take part in the above study, including participating in all study procedures as explained to me.

Please insert initials in each set of boxes provided on the left column to indicate your agreement with each statement

Signature of the Participant: _____ OR Thumb print

Date: [__|__] [__|__] [__|__] **Time:** [__I__]: [__I__]
Day Month Year

Name of Participant: _____

Signature of Impartial witness (only for illiterate participants):

_____

Date: [__|__] [__|__] [__|__] **Time:** [__I__]: [__I__]
Day Month Year

Name of Impartial witness: _____

Declaration by Site Principal Investigator/Sub-Investigator: "I have administered the informed consent process by explaining the nature, purpose, possible hazards of the study and the written information provided, to the study participant."

Signature of the Site Principal Investigator/Sub-Investigator: _____

Date: [__|__] [__|__] [__|__]
Day Month Year

Name of Investigator/ Sub-Investigator: _____

Name of the Institution/Location: _____

Sponsor:
Liverpool School of Tropical Medicine (LSTM)
Pembroke Place, Liverpool L3 5QA, UK
Contact Person: Carl Henry, Head of Research Management
Tel: +44 151 705 3212
Fax: +44 151 705 3370
Email: Carl.Henry@lstmed.ac.uk

Appendix 3: Ethics approval letter from the UCT HREC, the Malawi College of Medicine Research Ethics Committee and the Liverpool School of Tropical Medicine Research Ethics Committee

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

02 August 2019

HREC REF: 266/2019

Prof Karen Barnes
Pharmacology
K-floor, OMB

Dear Prof Barnes

PROJECT TITLE: IMPACT OF DOLUTEGRAVIR-BASED ANTIRETROVIRAL THERAPY ON THE PHARMACOKINETIC PROFILE AND PLACENTAL PENETRATION OF PIPERAQUINE ADMINISTERED AS DIHYDROARTEMISININ-PIPERAQUINE FOR INTERMITTENT PREVENTIVE TREATMENT OF MALARIA IN PREGNANT WOMEN LIVING WITH HUMAN IMMUNODEFICIENCY VIRUS IN MALAWI: A FIXED SEQUENCE COHORT STUDY (MASTER CANDIDATE - DR CG BANDA)

Thank you for submitting your response to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 August 2020.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

The HREC acknowledge that the student, Dr Clifford George Banda will also be involved int this study.

The following documentation are noted and approved:

- IMPROVE-DDI Informed Consent Form English version 1.0 dated 18 July 2019
- IMPROVE – DDI Protocol version 1.0 dated 18 July 2019
- PI Synopsis version 1.0 dated 31 March 2019
- CV's, Declarations and Certificates of Investigators.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Form FHS006: Protocol Amendment

HREC office use only (FWA00001637; IRB00001938)		
☑ Approved	☑ Type of review: Expedited	☐ Full committee
This serves as notification that all changes and documentation described below are approved.		
Signature Chairperson of the HREC	Signed by candidate	Date 10/10/2019

Note: All major amendments must i local **PI Synopsis** justifying the changes for the amendment. Please note that incomplete amen ent submissions will not be reviewed.

Comments from the HREC to the Principal Investigator:
Note: The approval of this protocol amendment does not grant annual approval. Please complete the FHS016 / FHS017 form for annual approval at least one month before study expiration.

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	9th October 2019
HREC REF Number	266/2019
Protocol title	Impact of dolutegravir-based antiretroviral therapy on the pharmacokinetic profile and placental penetration of piperaquine administered as dihydroartemisinin-piperaquine for intermittent preventive treatment of malaria in pregnant women living with human immunodeficiency virus in Malawi: a fixed sequence cohort study
Protocol number (if applicable)	IMPROVE DDI
Principal Investigator	Professor Karen Barnes
Department / Office Internal Mail Address	Division of Clinical Pharmacology K Floor Old Main Building, Groote Schuur Hospital

1.1 Is this a major or a minor amendment? (see FHS006hlp) Major (tick box) Minor (tick box)	☐ Major	X Minor
1.2 Does this protocol receive US Federal funding?	☐ Yes	X No

1.3 If the amendment is a major amendment and receives US Federal Funding, does the amendment require full committee approval?	☐ Yes	X NA

2. List of Proposed Amendments with Revised Version Numbers and Dates

Please itemise on the page below, all amendments with revised version numbers and dates, which need approval.
This page will be detached, signed and returned to the PI as notification of approval. Please add extra pages if necessary.

The UCT HREC approved version 1.0_18Jul19 of the above titled protocol. Following this approval, the protocol was submitted to the local ethics committee in Malawi (College of Medicine Research Ethics Committee- COMREC) and the sponsor's REC, the Liverpool School of Tropical Medicine Research Ethics Committee (LSTM REC). LSTM REC approved version 1.1_05Aug19, while LSTM and COMREC approved version 2.0_23Aug19

We highlight the changes that were made from version 1.0 to version 1.1, and to the version approved by the local committee (version 2.0). We further highlight administrative changes that have been made from version 2.0 to version 2.1

- IMPROVE-DDI_Protocol_(v1.1-05Aug19)-tracked compared to v1.0-18Jul19.pdf
- IMPROVE-DDI_Informed Consent_(v1.1-05Aug19)-tracked compared to v1.0-18Jul19.pdf
- IMPROVE-DDI_Protocol_(v2.0-23Aug19)-tracked compared to v1.1-05Aug19.pdf
- IMPROVE-DDI_Informed Consent_(v2.0-23Aug)-tracked compared to v1.1-05Aug19.pdf
- IMPROVE-DDI_Protocol_(v2.0-23Aug19)-tracked compared to v1.1-05Aug19.pdf
- IMPROVE-DDI_Protocol_(v2.1-29Sep19)-tracked compared to v2.0-23Aug19.pdf
- IMPROVE-DDI_Protocol_(v2.1-29Sep19) -clean.pdf
- IMPROVE-DDI_Informed Consent_(v2.0-23Aug)-clean

3. Protocol status (tick ✓)

☐	Open to enrolment
x	No participants have been enrolled
☐	Closed to enrolment (tick ✓)
☐	Research-related activities are ongoing
☐	Research-related activities are complete, long-term follow-up only
☐	Research-related activities are complete, data analysis only

4. Proposed changes will affect: (tick ✓ all the categories that apply)

	Protocol
☐	Study objectives, design (including investigator's brochure, clinical activities, study length)
☐	Study instruments, questionnaires, interview schedules
☐	Sample size

☐	Recruitment methods
x	Eligibility criteria (inclusion and exclusion criteria)
☐	Drug/device (composition, amount, schedule, route of administration, combination with other drugs/devices, safety information)
☐	Data collection / analysis
☐	Principal Investigator. (Please attach revised conflict of interest and PI declaration statements. Refer: sections 7 and 8.4 in the New Protocol Application Form FHS013)
x	Consent form and information sheet
☐	Recruitment materials (e.g. advertisements)
X	Administrative (e.g. change in sponsor's name, change in contact information)
☐	Other. Please specify:

4.1 In your opinion, will there be any **increase** in risk, discomfort or inconvenience to participants?	☐ Yes	X No
If yes, please provide a detailed justification/explanation:		

4.2 What follow-up action do you propose for participants who are already enrolled in the study?	
☐	Inform current participants as soon as possible
☐	Re-consent current participants with revised consent/assent forms (append)
X	No action required
☐	Other. Please describe:

5. Detailed description of the change(s)

Please attach, for each amendment, a summary of all changes which clearly indicates:

i. Old wording (e.g. ~~strikethrough~~ text, CHANGED FROM and CHANGED TO)

ii. New wording (e.g. *italicized*, **bold**, tracked)

iii. Detailed rationale/ justification/ explanation for each change

6. Signature

My signature certifies that I will maintain the anonymity and/ or confidentiality of information collected in this research. If at any time I want to share or re-use the information for purposes other than those disclosed in the original approval, I will seek further approval from the HREC.			
Signature of PI	Signed by candidate	Date	9 OCT 2019.

CERTIFICATE OF ETHICS APPROVAL

This is to certify that the College of Medicine Research and Ethics Committee (COMREC) has reviewed and approved a study entitled:

P.07/19/2746 - Impact of dolutegravir-based antiretroviral therapy on the pharmacokinetic profile and placental penetration of piperaquine administered as dihydroartemisinin-piperaquine for intermittent preventine treatment of malaria in pregnant women living with human immunodeficiency virus in Malawi: a fixed sequence cohort study version 2.0 dated 23 August, 2019. by Clifford George Banda

On 23-Sep-19

As you proceed with the implementation of your study, we would like you to adhere to international ethical guidelines, national guidelines and all requirements by COMREC some of which are indicated on the next page for your study

Signed by candidate

23-Sep-19

Dr. YB. Mlombe - Chairperson (COMREC)

Date

Approved by
College of Medicine
24-Sep-2019
(COMREC)
Research and Ethics Committee

REQUIREMENTS FOR YOUR COMREC APPROVED RESEARCH PROTOCOL

1. Pay the research overhead fees to College of Medicine or Kamuzu College Of Nursing (depending on your affiliation) as required for all approved studies (except undergraduate studies).

2. You should note that the COMREC Sub-Committee on Research Participants' Safety will monitor the conduct of the approved protocol and any deviation from the approved protocol may result in your study being stopped.

3. You will provide an end of study (close-out) report.

4. All COMREC approvals of new applications and progress reports are valid for one year only. Therefore all approved studies running for more than one year are subject to continuing review annually. You are required to submit a progress report to COMREC within 90-30 days before the expiration date. Your current expiration date is 22-Sep-20. Studies shall be considered lapsed and inactive if continuing review application is not received one month after the expiry of the previous approval. In that case, all study related operations should cease immediately except those that are necessary for the welfare of subjects.

5. All investigators who are Medical Practitioners must be fully registered with the Medical Council of Malawi.

Professor Feiko ter Kuile
Liverpool School of Tropical Medicine
Pembroke Place
Liverpool
L3 5QA

LSTM
LIVERPOOL SCHOOL OF TROPICAL MEDICINE

Pembroke Place,
Liverpool, L3 5QA, UK
Tel: +44(0)151 705 3100
Fax: +44(0)151 705 3370

www.lstmed.ac.uk

Tuesday, 01 October 2019

Dear Professor ter Kuile,

Re. Research Protocol (19-039) 'Impact of dolutegravir-based antiretroviral therapy on the pharmacokinetic profile and placental penetration of piperaquine administered as dihydroartemisinin-piperaquine for intermittent preventive treatment of malaria in pregnant women living with human immunodeficiency virus in Malawi: a fixed sequence cohort study'

Thank you for your letter of 30 September 2019 providing the necessary in-country approval for this project. I can confirm that the protocol now has formal ethical approval from the LSTM Research Ethics Committee.

The approval is for a fixed period of three years and will therefore expire on 30th September 2022. The Committee may suspend or withdraw ethical approval at any time if appropriate.

Approval is conditional upon:

- Continued adherence to all in-country ethical requirements.
- Notification of all amendments to the protocol for approval before implementation.
- Notification of when the project actually starts.
- Provision of an annual update to the Committee.
  Failure to do so could result in suspension of the study without further notice.
- Reporting of new information relevant to patient safety to the Committee
- Provision of Data Monitoring Committee reports (if applicable) to the Committee

Failure to comply with these requirements is a breach of the LSTM Research Code of Conduct and will result in withdrawal of approval and may lead to disciplinary action. The Committee would also like to receive copies of the final report once the study is completed. Please quote your Ethics Reference number with all correspondence.

Yours sincerely

Professor Graham Devereux
Chair
LSTM Research Ethics Committee

Appendix 4: Instructions to Authors from the chosen journal

The manuscript was submitted to the **Journal of Antimicrobial Chemotherapy**. Instructions to authors from the journal are included below. Specific instructions on manuscript type are under the subsection of “Article types and formats”. These instructions can also be accessed using the following link: https://academic.oup.com/jac/pages/General_Instructions.

Instructions for Authors

Background and Scope of the Journal

Background

The *Journal of Antimicrobial Chemotherapy* was founded in 1975 by the British Society for Antimicrobial Chemotherapy (BSAC)

as part of its mission to facilitate the acquisition and dissemination of knowledge in the field of antimicrobial chemotherapy. Proceeds from the Journal are used by the BSAC to further these objectives. Articles are published continuously online in JAC Advance Access and assembled into monthly printed and online issues. The Journal has an Impact Factor of 5.071 (2016).

Aims

The Journal publishes articles that further knowledge and advance the science and application of antimicrobial chemotherapy with antibiotics and antifungal, antiviral and antiprotozoal agents. The Journal publishes primarily in human medicine, and articles in veterinary medicine likely to have an impact on global health.

Scope

The Journal particularly welcomes manuscripts on:

- the practice of evidence-based medicine relating to antimicrobials (clinical trials, systematic reviews and meta-analyses)
- antimicrobial treatment (pharmacokinetics, pharmacodynamics and prescribing practices)
- the action of antimicrobial agents and the mechanisms, genetics and epidemiology of antimicrobial resistance
- antimicrobial stewardship
- the genetic basis of antimicrobial resistance

- In addition, the Journal is very keen to publish articles that:
  - offer evidence-based synthesis of knowledge and data useful for clinical practice
  - analyse, reflect and comment on the current state of the art and practice
  - consolidate our knowledge of antimicrobial agents and their use
  - consider the future of antimicrobial chemotherapy

The Journal will consider publishing articles on:

- new approaches to improving antimicrobial chemotherapy
- new compounds provided evidence is offered of selective antimicrobial activity and comparative cytotoxicity data
- previously unreported antimicrobial activity relating to a marketed drug product but such studies must take into account the exposure to the drug that can be safely achieved with clinically acceptable doses
- articles reporting the activity of bacteriophages

The Journal will not usually consider publishing material on:

- the chemical synthesis or characterization of compounds. These are better suited to chemistry journals.
- the use and activity of biocides or disinfectants. These require specialist methodology and are generally better suited to more specialist journals.
- the process of turning antimicrobials into a medication i.e. pharmaceutics. These are better suited to a pharmacy journal
- drug stability studies
- naturally occurring substances or extracts that exhibit antimicrobial activity but for which no specific active ingredient has been chemically defined

Authors who are unsure about whether their intended submission meets the aims and scope of the Journal are welcome to contact directly the Editor-in-Chief (jac@bsac.org.uk).

Open Access

Authors can choose open access publication, otherwise journal articles are typically available only to subscribers for 12 months from the month of publication in print and online. Thereafter, all articles are freely available online. This balances the desire for broad access to research with the need to retain revenue for the Journal. JAC is compliant with the NIH funding mandate.

Acceptance rate and processing times

There are almost four times the number of submissions to the Journal than it can accommodate. Hence the rejection rate is high and is likely to remain so. Articles that are not judged to meet the aims and scope of the Journal, or which are judged from the beginning to be unlikely to achieve high enough priority for publication, will be returned to the authors without external peer review. All remaining submissions will be subjected to peer review as rapidly as possible. Our aim is to keep the time from submission to first decision within 4–6 weeks. Once accepted, the time from acceptance to publication online ahead of print is also around 4-5 weeks.

Appeals

Authors wishing to lodge an appeal against a decision can do so by contacting the Senior Editor responsible for the decision directly and by copying in the Editorial Office.

Editorial Office Contact Information

The contact details for the *JAC* Editorial Office are as follows:

Griffin House
53 Regent Place
Birmingham
B1 3NJ
UK

Tel: +44 121 262 1830
E-mail: jac@bsac.org.uk

Processing of Papers

Where to submit

All material to be considered for publication should be submitted in electronic form via the Journal's online submission system.

Given that you can produce a file of your paper through a word processing package of some description, you only need the three

following items to access and use the system: access to the website via a web browser, Adobe Acrobat Reader (which can be downloaded free of charge from Adobe) and an e-mail account. For more guidance see the section Online Submission Details.

Authors must comply with the stipulations in the Instructions to Authors. Signed submission forms will only be requested once an article has received a revision decision. The Editorial Office will supply an article-specific template to the Corresponding author shortly after the revision decision has been made. Please note that should any authors be removed between versions of an article, we will require evidence that these authors have agreed to the removal of their names.

Article types and format

All documents should be double spaced, and the margins should not be excessively wide. A clear, legible single font (which is readily available internationally) and point size should be employed throughout. For symbols, please use the 'insert symbol' function and ONLY select characters from the 'normal text' subset. All submitted articles should be line numbered (using continuous line numbers). To do this in Word, use File, Page Setup, Layout, Line Numbers and select continuous line numbering. Please DO NOT insert page numbers (as the pdf proof created by the online submission system will automatically be page numbered).

All articles should include a title page comprising: article title; author names and their affiliations (each affiliation address must be given separately and in full); telephone, fax and e-mail contact details for the corresponding author; and a short running title. In addition, all articles must include a Funding section (if reporting original research) and a Transparency declarations section.

Article titles. All articles reporting the results of original research must have a descriptive title. For example ‘Effect of streptomycin in tuberculosis’ is acceptable; ‘Streptomycin cures tuberculosis’ is not acceptable. Viewpoints, which are expressions of opinion, are permitted to have declarative titles. Please note that claims of priority are not permitted in article

titles as such claims are impossible to verify; only history will reveal the first example. For instance ‘First NDM-1 *Escherichia coli* isolated in Andorra’ would not be permitted. Authors are permitted to indicate in the article that, to the best of their knowledge, a finding is the first of its kind.

Original articles and Brief reports must have a structured synopsis. The headings for the structured synopsis are as follows: Background (optional), Objectives, Patients and methods (or Methods), Results, and Conclusions.

Original articles . There is a limit of 3500 words in the main text of the article (everything from the Introduction to the end of the Discussion). Papers must be written as concisely as possible. Original articles are divided into the following sections: Synopsis (250 words maximum), Introduction, Materials (or Patients) and methods, Results, Discussion, Acknowledgements, Funding, Transparency declarations and References. Repetition of content between sections must be avoided. A combined Results and Discussion section is acceptable.

Brief reports . These should have the same format as Original articles, but should have no more than two figures/tables, should have a maximum of 20 references and should not exceed 1500 words of main text.

Correspondence . Letters on topics of concern or interest in the field of antimicrobial chemotherapy, particularly arising from papers or letters already published in the Journal. These should be addressed to the Editor-in-Chief and must not exceed 800 words, one figure or table and 10 references.

Case reports. JAC will publish Case reports that are of sufficient calibre and potential importance, and they should be submitted in the form of Correspondence (see above). Please note that patient anonymity MUST be preserved in Case reports (see the later section on Ethics approval and patient consent/privacy).

Systematic review articles. There is no length limit for this format. A systematic review, as defined by the Cochrane Handbook, is ‘A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse

data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarize the results of the included studies.' They should include a structured synopsis (with appropriate headings; these may differ from the headings used for Original articles etc.).

Review articles . There is no length limit for this format. These generally aim to give an overview of a field suitable for a wide audience, and they should include a synopsis (250 words maximum). Most reviews are invited. We are pleased to consider unsolicited reviews, but authors are encouraged to consult the Editor-in-Chief in advance of writing to avoid duplicating commissioned material.

Viewpoint. These articles are usually in the region of 800-1000 words and may contain the expression of opinion as well as fact. They should address a topical subject, perhaps taking a particular viewpoint and throwing new light on a current debate. A Viewpoint should include a short synopsis (150 words maximum) that should convey the topics and ideas the article covers. Those wishing to contribute a Viewpoint are encouraged to contact the Editor-in-Chief to discuss their ideas before writing to prevent clashes with any articles already in the pipeline.

For debate. These articles should air contentious issues or discuss controversies so as to stimulate discussion in the Journal on any given topic on antimicrobial chemotherapy. Articles should be as clear and concise as possible, consist of 800-2500 words and must be accompanied by an unstructured synopsis of up to 150 words.

The Editor-in-Chief particularly welcomes pairs of For debate articles offering two opposing viewpoints that aim to persuade readers of their cases. The two resultant articles will be published side by side in the same issue.

Those wishing to contribute a For debate article should first contact the Editor-in-Chief to discuss their ideas and secure a clear agreement before submission. Unsolicited For debate articles will not be considered.

Please note that on publication all Original articles and Brief reports, as well as Antimicrobial practice papers, will be

published under the heading of Original research so that articles on similar topics can be grouped together when assigned to an issue. In addition each piece of Correspondence will be published as either a Research letter or a Letter to the Editor.

Peer review

After preliminary examination of the submission by Editorial Office staff to check that all the necessary elements are present, the paper is passed to the Editor-in-Chief. The Editor-in-Chief then assigns the paper to an appropriate Senior Editor. The Senior Editor is then responsible for selecting an Editor to handle the article. Articles can be rejected immediately by the Editor-in-Chief, a Senior Editor or an Editor without further peer review. The assigned Editor is responsible for selecting referees and obtaining referee reports.
The usual number of referees is two, however, the Editors reserve the right to make a decision on a paper on the basis of one referee report, or seek the opinion of more than two referees if they judge this to be necessary or desirable. Viewpoints and Correspondence are not routinely sent for external refereeing, but the Editor-in-Chief, Senior Editors and Editors reserve the right to seek the opinion of one or more external referees if they judge this to be necessary or desirable. Senior Editors, Editors and referees are asked to consider whether they have any conflicts of interest when they are assigned a paper, and if necessary to decline to handle the paper. See the section ‘Conflicts of interest’ for more information on this subject.

If an Editor decides upon rejection of a paper, it is passed back to the handling Senior Editor for approval of this decision. All rejection correspondence therefore originates from a Senior Editor. Authors should regard rejection as final and only resubmit if they have been invited to do so. Papers may be rejected for a number of reasons, including: (i) they may be of only peripheral interest and perhaps more suitable for submission to a different journal; (ii) they may be, in the opinion of the reviewers, scientifically flawed; (iii) they may be unclear or overly long; or (iv) they may not make a significant contribution to the literature.

Requests that a revised version of a paper be submitted for consideration are sent direct to the corresponding author from the Editor responsible. Any revised version should be submitted within 6 weeks of the revision request or the Journal reserves the right to consider the manuscript as a new submission that may be subject to further refereeing.

The Editor-in-Chief, Senior Editors and Editors reserve the right to request more rounds of revision and resubmission/refereeing, or reject a paper outright, if they judge that any revised version does not adequately address the concerns raised by the referees and the Editor. Once the Editor is satisfied that a revised version has adequately dealt with any points raised they may accept the paper.

Authors can appeal against a decision by contacting the handling Senior Editor, but unless there has been a gross misunderstanding of the submitted article by the Editor and referees, rejection appeals are not likely to be successful. Authors should appreciate that if they resubmit an article that has been rejected without substantially modifying it in line with the suggestions of the Editor and referees, it is almost certain to be rejected again.

After acceptance the paper is sent for copy-editing and typesetting prior to production of proofs for author correction. The Journal maintains the right to edit any paper to the extent necessary to achieve clarity and precision of expression and to conform with English usage and the Journal's conventions. Please note that if authors ignore requests to conform with Journal style at the revision stage, these changes may be enforced during copy-editing and proof production.

Articles submitted by Editors of the Journal

JAC does not bar Editors (including Senior Editors and the Editor-in-Chief) from submitting articles to the Journal. Articles submitted by Editors are handled in the same fashion as other articles subject to the following considerations: these articles are never assigned to the submitting Editor, or an Editor from the same institution; the submitting Editor is unable to access details of their article through the online submission system; and, like other authors, the submitting Editor will not

know the identity of the handling Editor (in cases of rejection) or referees.

Supplement articles

Supplement articles are subject to peer review and may be rejected. Unless specialist external expertise is required, this peer review is conducted among the team of Editors that is dealing with the Supplement.

Guidelines

Guidelines that have undergone proper public consultation will normally only be subjected to peer review by members of the Editorial Board.

Proofs

An e-mail containing a link to the proof is sent to the corresponding author. The proof should be read carefully, paying particular attention to any tables, figures and references, and corrections (and answers to any queries) should be submitted to the *JAC* Editorial Office as soon as possible. Authors should pay particular attention that they check any dosage directions, owing to the seriousness of any error entering the printed record. Extensive changes at the proof stage are not permitted. Authors may be charged for correction of their non-typographical errors. The Journal reserves the right not to comply with changes marked on the Author's proof if these are contrary to the style set down in the Instructions to Authors. In the event of important developments in a field that affect the paper arising after the final revision, a 'Note added in proof' may be permitted. Please note that Supplementary data files are largely unedited and are not proofed out.

Once all the corrections have been made by the typesetters, the article is then posted on JAC Advance Access

Late corrections, Advance Access and Errata

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After publication online, the only avenue available to correct an article is the publication of a linked Erratum. The purpose of an Erratum is to correct items that affect the scientific validity of a piece of research. The Journal will refuse to publish an Erratum if the correction requested does not affect the scientific validity of the article (hence requests to correct author names or address details, funding information, or collaborator names or locations, for example, will be refused). This is why it is of the utmost importance that authors pay the necessary attention to ensuring articles are correct at every stage and treat the proof as the last available opportunity for corrections.

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In-press papers or papers under editorial consideration

In-press and submitted papers that are important for the review of a paper MUST be uploaded when the paper is submitted and referred to in the covering letter that accompanies the submission. Authors should be aware of the issues of redundant/duplicate publication. For further information, please see the following Editorial:

Reeves DS, Wise R, Drummond CWE. Duplicate publication: a cautionary tale. *J Antimicrob Chemother* 2004; 53 : 411-2.

Sequence data

When reporting sequences they must be submitted to one of the three major databases and an accession number must be provided at latest in the first revised version.

If a sequence has been submitted but an accession number has not yet been provided or the sequence is not yet available to the public then authors must submit the annotated sequence data as Supplementary data for scrutiny by the Editor and referees. Articles will not be permitted to enter the review process without the sequence data.

Supplementary data

Please note that it is also possible to submit files containing Supplementary data. The Supplementary data (for example large tables of MICs, or a questionnaire) can be lodged with the version of the paper published online as an extra resource for readers. Supplementary data is largely unedited and is not proofed out so authors should ensure that they provide high quality, accurate files. In addition, authors must ensure that they cite the Supplementary data within the article. Please contact the Editorial Office if you require further details.

Authorship

The authorship of the paper should be confined to those who have made a significant contribution to the design and execution of the work described. In the case of clinical

trials/randomized control trials it is compulsory for the contribution of each author to be clearly stated in the Transparency declarations section, after the information on conflicts of interest. Authors of other types of article may indicate the contribution made by each author if they wish.

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'Umbrella' groups and authorship

Many large collaborative studies are organized under a group name that represents all of the participants. *JAC* will not accept a group name as an 'author' of an article. All articles must have at least one named individual as author. Authors of large

collaborative studies should list the author(s) of the article and follow this with 'on behalf of the [GROUP NAME]'. The names of all of the participants should then be listed in the Acknowledgements section.

Professional medical writers and editorial assistance

Professional medical writers and other forms of writing assistance have an important role to play in the clear communication of scientific results. However, unless this role is openly explained and acknowledged unfounded suspicions about this role will continue. *JAC* encourages the open and precise description of any such assistance received by authors in relation to any article. It is possible that writers may qualify for authorship of a manuscript, we recommend that authors review the ICMJE criteria for authorship before submission.

The precise role of the writer or service in the origin or preparation of the manuscript must be declared in the Transparency declarations section; we recommend that the name of the writer (and their agency where applicable) or the service is provided. If this support was funded, the source must be declared in the Funding section.

Responsibilities of the corresponding author

For each paper submitted to *JAC* there must be a single corresponding author. As the representative of the authors, the corresponding author must ensure that all authors are given access to submitted and revised versions of papers. The corresponding author is responsible for the collation of the authors' signatures on submission forms and also the collation and communication of proof corrections to the Journal. The corresponding author should be the signatory of the publication licence form. As the authors' nominated representative, the corresponding author will be held primarily accountable for any failure to comply with the Instructions to Authors or generally accepted standards of good practice. This does not absolve other authors of responsibility, however.

The corresponding author will act as the primary contact for correspondence regarding the paper, and as such authors should take care not to appoint a corresponding author likely to be absent for extended periods (such as a sabbatical) during the

consideration of the paper as this is likely to cause unacceptable delays.

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Ethics

All articles in *JAC* describing research in humans or animals must include an 'Ethics' heading as the first section in the Patients and methods or Methods section. Authors must include in this section all relevant statements regarding approvals, licences, informed consent and so on, as applicable.

Research involving humans

Authors must indicate in the Ethics section whether the research was conducted in accordance with the Declaration of Helsinki and national and institutional standards. If approval was obtained from an Ethics Committee the authors must clearly name the ethics committee responsible if more than one institution is involved. The approval/reference number must be listed in the Ethics section of the article. Written informed consent must be obtained from study participants and the existence of this consent must be stated in the article. Authors must supply the relevant approval numbers from Ethics committees or other bodies.

Patient privacy. Patients have a right to privacy. Any information that might result in identification of individuals must be omitted, especially if it is not directly clinically relevant. Patient age, sex, admission dates and co-morbidities should be removed as far as possible. If it is possible that a patient could be identified, the authors must obtain written informed consent from the individual(s) concerned and state

that this has been obtained in the article. Publication consent forms should be retained by the authors and not supplied to the Journal. If the patient is deceased the next of kin should be contacted. If consent cannot be obtained the authors must explain the circumstances briefly in the article, as well as in detail in the covering letter. In rare circumstances where relevant clinical details mean that the patient can be identified, the patient/next of kin must be shown the manuscript before submission and made aware as part of the informed consent process that the article may appear on the internet.

Case reports. Authors must avoid the temptation to recite the entire clinical history of the patient at the start of a case report and should retain only the clinical history that is pertinent. Reciting the entire clinical history greatly increases the chances that the patient could be identified. Date of treatment must be removed or converted to timespans for the same reason.

Research involving animals

Authors must state their compliance with relevant institutional and national standards for animal care and experimentation, together with the details of any authorities that licensed the experiments.

JAC supports the use of the ARRIVE Guidelines and articles reporting research in animals must include a completed ARRIVE checklist which must be uploaded with the article so it is available for the scrutiny of the Editor and referees.

Funding

ALL papers submitted to *JAC* reporting original research MUST include a ‘Funding’ section. This section should appear after the 'Acknowledgements' section.

Details of all funding sources for the work in question must be given.

Authors must list any internal funding. If no specific funding has been received then this should be clearly stated; equally if data have been generated as part of the routine work of an organization, this too should be stated. Ongoing financial

support for any of the authors should also be included under the Funding heading.

If a professional medical writer or similar service was involved in the origin or preparation of a manuscript and this support was funded, the source must be declared in the Funding section.

Sources of funding may of course still be thanked in the Acknowledgements section, but should not be listed again in the Transparency declarations (see below), unless there is an important reason for doing so. For example if the funder played any decision-making role in the research this must be stated.

The following rules should be followed:

The sentence should begin: 'This work was supported by ...'

- The full official funding agency name should be given, i.e. 'the National Cancer Institute at the National Institutes of Health' or simply 'National Institutes of Health' not 'NCI' (one of the 27 subinstitutions) or 'NCI at NIH' (full RIN-approved list of UK funding agencies)

- Grant numbers should be complete and accurate and provided in brackets as follows: '(grant number ABX CDXXXXXX)'

- Multiple grant numbers should be separated by a comma as follows: '(grant numbers ABX CDXXXXXX, EFX GHXXXXXX)'

- Agencies should be separated by a semi-colon (plus 'and' before the last funding agency)

- Where individuals need to be specified for certain sources of funding the following text should be added after the relevant agency or grant number 'to (author initials)'.

An example is given here: 'This work was supported by the National Institutes of Health (P50 CA098252 and CA118790 to R. B. S. R.) and the Alcohol & Education Research Council (HFY GR667789).

Crossref Funding Data Registry

In order to meet your funding requirements authors are required to name their funding sources, or state if there are none, during the submission process. For further information on this process or to find out more about CHORUS, visit the CHORUS initiative.

Conflicts of interest

Conflicts of interest have the potential to affect authors, referees and Editors (including Senior Editors and the Editor-in-Chief). *JAC* has the following systems in place to deal with conflicts of interest:

Authors. Authors are required to include a Transparency declarations section in every submission to the Journal (for details see below).

Referees. When invited to act, and again when they agree to act, referees are reminded to consider whether they have any potential conflicts of interest. Referees are asked to discuss any perceived potential conflict with the Editor of the article who will reach a decision as to whether it is appropriate that the referee acts on the article or whether they should withdraw.

Editors . The Editor-in-Chief, Senior Editors and Editors register their interests (including personal and business interests) with the BSAC. The BSAC Register of Interests is held at BSAC Headquarters, is updated periodically and is available for inspection. When an article is assigned to a Senior Editor or an Editor they are reminded to consider whether there are any potential conflicts of interest, and if so, to discuss them with the handling Senior Editor or the Editor-in-Chief, who will come to a decision as to whether it is appropriate for them to act on the article, or whether it should be reassigned.

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In the interests of openness, ALL papers submitted to *JAC* MUST include a 'Transparency declarations' section (which should

appear at the end of the paper, before the ‘References’ section). We suggest authors concentrate on transparency declarations (i.e. conflicts of interest) of a financial nature, although relevant non-financial disclosures can also be made. Authors should consider making a declaration if they answer 'Yes' to any of the following questions:

1. Have you in the period of research leading up to this publication accepted any of the following from an organization (including government departments or granting bodies) that may in any way be financially affected by the conclusions of your article (e.g. reimbursement for attending a symposium, a fee for speaking, a consultancy fee, funds for research other than directly for this work, funds for a member of staff, any other substantial material benefit)?

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4. Have you received the assistance of a professional medical writer or similar service? [The precise role of the writer or service in the origin or preparation of the manuscript must be declared and we recommend that the name of the writer (and their agency where applicable) or the service is provided.]

5. Have you accepted any reimbursement for preparing your article?

Authors should either include appropriate declarations or state ‘None to declare’. Importantly, the declarations should be kept as concise as possible, should avoid giving financial details (e.g. sums received, numbers of shares owned etc.), and should be restricted to declarations that are specific to the paper in question. Authors will of course need to consider whether or not the transparency declarations need to be amended when revisions are submitted.

The burden of responsibility rests with all authors, who must ensure that appropriate declarations are included. The corresponding author will be responsible for obtaining the relevant information from all of their co-authors. By signing a

submission form each author is stating that they have made any necessary transparency declaration. All authors should carefully consider the embarrassment and potential damage to their reputation that could result should they fail to declare an interest that is revealed subsequently.

If only some authors need to make a declaration it must be made clear that the remaining authors have nothing to declare, for example:

'A.B. has received funds for speaking at symposia organized on behalf of Panacea Ltd and has also received funds for research from Panacea. C.D. is a member of the Panacea advisory board for fantastazole. All other authors: none to declare.'

All papers submitted to *JAC* must include a transparency declarations section; papers that do not include such a section will not enter the review process; they will be returned to the corresponding author so that the appropriate section can be added. Following resubmission the paper will then be progressed to peer review.

In the case of clinical trials/randomized control trials it is compulsory for the contribution of each author to be clearly stated in the Transparency declarations section, after the information on conflicts of interest. Authors of other types of article may indicate the contribution made by each author if they wish.

Other useful information

In some instances (often when the authors themselves have no interests to declare) it may be helpful to readers as background information to give brief details of organizations that do have an interest but do not appear elsewhere in the article, for example 'Fantastazole is owned by Wonder Pharmaceuticals'.

Misconduct

We will energetically pursue accusations of misconduct directed at authors, Editors or referees and have a number of sanctions at our disposal including the option to inform employers about accusations and ask them to mount their own internal

investigations. Accusations should not be made lightly or in the absence of the likelihood of supporting evidence being obtainable. The Journal may take the view that accusations are malicious if supporting evidence cannot be found and may direct sanctions against accusers in such cases. Any accusation of misconduct should be addressed to the Editor-in-Chief (unless it involves the Editor-in-Chief, in which case it should be directed to the President of BSAC). *JAC* is a member of COPE and will follow its guidelines on the handling of investigations into research misconduct.

Clinical trials/Randomized controlled trials

Registration and data publication

Authors must register their trials in one of the databases dedicated to registration of trials. In addition, authors must state the database and provide the unique registration number – both in the abstract and in the main body of the paper.

JAC will consider for publication clinical trials for which there has been prior publication of trial data in results databases (such as Clinical Study Results or others), however, authors MUST declare in the covering letter and the Acknowledgements section of the article that they have previously published data in a results database.

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The contribution of each author must be clearly stated in the Transparency declarations section, after the information on conflicts of interest.

Reporting standards

All involved in the publication of health intervention research have a duty to patients and society at large to ensure that this research is reported in a complete, accurate and transparent fashion. This includes authors, referees, Editors and Journals. *JAC* takes this responsibility seriously and endorses the work of organizations such as the EQUATOR network, an international

initiative that seeks to improve the reliability and value of the medical research literature.

There is a wide range of reporting guidelines, each specific for different types of study. Some of those for study types that are frequent in *JAC* are mentioned specifically below. Authors should consult the EQUATOR network website for links to the latest versions of guidelines, which are organized by the study type.

Randomized controlled trials

Authors should comply with the Consolidated Standards of Reporting Trials (CONSORT) statement and use the resources within it (for example the checklist and flow diagram) to ensure they have addressed potential criticisms and provided all necessary information. Authors should include a CONSORT flow diagram in their article, and provide a copy of the completed checklist.

Systematic reviews and meta-analyses

For systematic reviews and meta-analyses of randomized controlled trials authors should comply with the PRISMA statement (which replaces the QUORUM statement), which consists of a checklist and flow diagram. Authors should include a PRISMA flow diagram in their article, and provide a copy of the completed checklist.

Outbreaks and intervention studies in nosocomial infection

Authors should comply with the ORION statement, which is the CONSORT equivalent for infection control studies. Its purpose is to increase the quality of research and reporting in the area of nosocomial infection.

Economic evaluations

Authors of articles describing economic evaluations of antimicrobial interventions are encouraged to make use of the following resources, where applicable, in order to ensure that their work is both optimal and adequately described.

International Society of Pharmacoeconomics and Outcomes Research (ISPOR) Checklist for retrospective database studies.

Quality of Health Economic Studies (QHES) Instrument. See Table 1 on this page

Observational epidemiology studies

Authors of articles reporting observational epidemiology studies should follow the STROBE guidelines and complete the relevant checklist for the type of study they have conducted. The completed checklist should be supplied as part of the article submission process.

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Journal Style

General

In addition to reading the information provided here, authors should consult a recent issue of the Journal for the layout and conventions used.

The past tense should be used throughout for description of the results of the paper, the present tense should be used when referring to previously established and generally accepted results.

Where possible SI units should be used.

Please ensure that characters with a similar appearance are consistent throughout the document and not from different Unicode sub ranges as with the Greek Delta.

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Spelling

British spelling should be used. Spelling should follow that of the *Oxford Dictionary for Scientific Writers and Editors* and where

this gives no guidance the *Concise Oxford Dictionary* . Spelling of drug names should conform with that given in the latest edition of the *British National Formulary* (published by the British Medical Association and the Royal Pharmaceutical Society of Great Britain and available online), but please note that *JAC* will continue to use methicillin (not meticillin).

Abbreviations

Non-standard abbreviations should be defined at the first occurrence and introduced only where multiple use is made. See this document for abbreviations that may be used without definition, as well as antimicrobial abbreviations (which may be used in Tables and Figures).

Dosage frequencies and routes of administration

Latin dosage frequency abbreviations are not permitted (qd, bd, bid, tds etc.), however, constructions q12h, q8h and so on are permitted as there is less likelihood of confusion. . Routes of administration other than intramuscular (im) and intravenous (iv), which may be abbreviated after definition, should be given in full in English.

MICs

Please note that all MIC data in *JAC* must be expressed in terms of mg/L (not μg/mL).

Nomenclature

Authors are required to check and ensure that in all instances the most up to date nomenclature is being used.

Bacterial nomenclature

When genus and species are given together use a capital letter for the genus and a lowercase letter for the species and italicize both e.g. *Staphylococcus aureus* . After the initial use in the text of the full name of an organism the generic name should then be abbreviated to the initial letter, e.g. *E. coli.*

When the genus is used as a noun or adjective use lowercase roman unless the genus is specifically referred to e.g. 'staphylococci and streptococci' but 'organisms of the genera *Staphylococcus* and *Streptococcus* '.

The name of an order has an initial capital but is not italicized, e.g. Enterobacteriaceae. For genera in the plural, use lowercase roman, e.g. salmonellae.

When the species is used alone use lowercase e.g. viridans streptococci. For trivial names, use lowercase roman e.g. meningococcus.

Authors should use bacterial names present in the *Approved List of Bacterial Names, Amended Edition* (1989), Skermanm, V.B.D., McGowan, V. & Sneath, P.H.A., Eds, ASM Press, Washington, DC, USA (ISBN 1-55581-014-4), with subsequent alterations validly published by announcement in Validation Lists of the *International Journal of Systematic and Environmental Microbiology* (formally the *International Journal of Systematic Bacteriology*). A full list of validly published bacterial names is given on this page.

Genetic and amino acid nomenclature

Bacterial genetics. Genotype designations are indicated with italic lowercase three-letter locus codes (e.g. *par* , *his* , *ara*). If several loci are involved in a related function the individual loci are designated by the addition of an uppercase italic letter to the locus code (*parC* , *ompF*).

Phenotype designations (for example the protein product of a bacterial gene) are given in roman type with an initial capital letter (OmpF, LacZ).

Erythromycin gene nomenclature should follow that described in: Roberts MC, Sutcliffe J, Courvalin P, Jensen LB, Rood J & Seppala H. Nomenclature for macrolide and macrolide-lincosamide-streptogramin B resistance determinants. *Antimicrob Agents Chemother* 1999; 43 : 2823-30.

Yeast genetics. Wild-type alleles are all uppercase and italicized (*LEU2*), mutant alleles are all lowercase and italicized (*leu2*),

and gene products are capitalized on the first letter and are not italicized (Leu2).

General. Authors should ensure that they confine discussion of changes in amino acid sequence to the context of the protein (e.g. OmpF) and nucleotide changes to the context of the gene (e.g. *ompF*). Please also be aware of the difference between a mutant (a strain with one or more mutations) and a mutation (a change in the sequence of the genetic material).

Amino acids. The full residue names or three-letter abbreviations are preferred in the text (e.g. a methionine residue at position 184 should be symbolized Met-184). The single letter codes may be used in figures. Amino acid changes should be designated Met-184→Val or M184V.

When comparing nucleotide or amino acid sequences authors should exercise care in the use of the term homology. Homology should only be used when a common evolutionary origin is being implied; it is incorrect to give a percentage homology between two sequences. The wing of a bird and the human arm are homologous structures (they are believed to have a common evolutionary origin), homology cannot be quantified. For sequence comparison authors should use the terms identity and similarity. Sometimes 'equivalent' or 'counterpart' is more appropriate than 'homologue'.

Beta-lactamase nomenclature

Authors submitting articles reporting the identification of new beta-lactamases must provide evidence that they have contacted the relevant clearinghouse (Lahey) to deposit the new sequence data and receive a unique designation for the new enzyme.

Macrolide-lincosamide-streptogramin resistance determinant nomenclature

Nomenclature for macrolide-lincosamide-streptogramin resistance determinants should follow the structure suggested by: Roberts MC, Sutcliffe J, Courvalin P *et al* . Nomenclature for macrolide and macrolide-lincosamide-streptogramin B antibiotic resistance determinants. *Antimicrob Agents Chemother*

1999; 43 : 2823–30. A new gene must have ≤79% amino acid identity with all previously characterized MLS genes before receiving a new unique name. Adding subscripts or superscripts to established genes is not acceptable. See this page. Before submitting a sequence to GenBank or submitting a manuscript for publication, please contact Professor Marilyn Roberts (marilynr@u.washington.edu). Once a new name has been assigned you must indicate in your article that you have received approval by the nomenclature centre for the new gene name.

Tetracycline resistance determinant nomenclature

Nomenclature for tetracycline resistance determinants should follow that suggested by: Levy SB, McMurry LM, Barbosa TM *et al* . Nomenclature for new tetracycline resistance determinants. *Antimicrob Agents Chemother* 1999; 43 : 1523–4. A new gene must have ≤79% amino acid identity with all previously characterized *tet* genes before receiving a new unique name. Adding subscripts or superscripts to established genes is not acceptable. See this page. The Levy Group is responsible for coordinating the naming of new *tet* genes and before submitting a sequence to GenBank or submitting a manuscript for publication, please contact Laura McMurry (laura.mcmurry@tufts.edu). Once a new name has been assigned you must indicate in your article that you have received approval by the nomenclature centre for the new gene name.

qnr gene/allele nomenclature

Authors submitting articles reporting the identification of new *qnr* genes or alleles must provide evidence that they have contacted the relevant clearinghouse (Lahey) to deposit the new sequence data and receive a unique designation. Authors should consult Jacoby G, Cattoir V, Hooper D *et al* . *qnr* gene nomenclature. *Antimicrob Agents Chemother* 2008; 52 : 2297–9.

FICI data

Fractional inhibitory concentration index (FICI) experiments are performed in order to study drug interactions and they must be interpreted in the following way:

FICI<=0.5 = synergy

FICI>4.0 = antagonism

FICI>0.5-4 = no interaction

For further information please see the following Editorial:

Odds FC. Synergy, antagonism, and what the chequerboard puts between them. *J Antimicrob Chemother* 2003; 52 : 1.

Microarray data

Authors of articles containing microarray data must ensure that the full datasets are lodged with an appropriate publicly available online database (the data must not be supplied for publication as Supplementary data alongside the article). The data should be supplied with the submitted article if they are not already publicly available. The name of the database and the accession numbers should be provided in the article. Authors must ensure that their data are available for public scrutiny from the online publication date of their article at the latest.

Chemistry

General nomenclature . The IUPAC recommendations on chemical nomenclature should be followed (*IUPAC Compendium of Chemical Terminology* (1987, ISBN 0 632 01767 8, Blackwell Scientific Publications, Oxford). All chemical names are run together except those of acids, acetals, esters, ethers, glycosides, ketones and salts, which are printed as separate words; hyphens are used to separate numbers, Greek letters and some configurational prefixes, e.g. *p* -nitrophenol. Italics are used for certain prefixes, e.g. *cis* -, *trans* - and *N* . Small capitals are used for dextro- and laevo- prefixes, e.g. L -glutamine.

Drugs . Spelling of drug names should conform with that given in the latest edition of the British National Formulary. Chemical or generic names of drugs should be used; trade names may be referred to once only upon first use of the generic or chemical name. The content of proprietary formulations should be given if relevant. Generic names should not be abbreviated in the text; abbreviations may be used in Tables if there is limited space. If

compounds are referred to by code name or company number either the structure or a reference to a paper illustrating the structure must be given, any previous code names or designations should be given on first use.

Supplier locations are required for all smaller/local suppliers.

References

Authors are responsible for the accuracy of all references, which must be checked against the original material. Reference citations should be restricted to those that are essential for introducing the purpose and context of the paper, describing methods that are not given in detail, and for discussing the results and any relevant issues raised by them. Authors are responsible for ensuring that references are quoted accurately and not taken out of context. References must not be cited in the synopsis.

Where possible authors should avoid citing conference abstracts or posters (partly because they are not peer reviewed and also because they often report interim findings and the final published studies can often come to substantially different conclusions) and authors MUST NOT cite abstracts that are more than 2 years old without excellent justification for doing so. In addition, abstracts must only be cited if they appear in published abstract books, journal supplements or in a permanent online archive.

References should be cited in the text using sequential numbers. Superscript numbers should be used and should be placed after any punctuation. When referring to several references, separate individual numerals by a comma or a hyphen for a range greater than two references. For instance: This was first discovered by Jones, [1] and later confirmed by several other groups of investigators. [2,3,5–7]

Papers accepted for publication, but not yet published, may be included in the reference list; they should be listed as 'in press', with the name of the journal and the likely year of publication. Submitted work should be quoted as 'unpublished results'. Personal communications and unpublished results, which are permitted in the text only, must include the initials and

surnames of all the workers involved; for the former citation, the person's affiliation must be stated, e.g. '(J. Bloggs, NIH, personal communication)', and documentary evidence (an e-mail will suffice) from the person quoted, showing their agreement to be so quoted, must be provided (the agreement must include the exact wording that appears in the paper).

All references should be listed numerically at the end of the text. Each reference should be preceded by a bold number (not superscript). Please see the following examples. Failure to conform to Journal style will result in the manuscript being returned to authors.

Examples

Journal reference (<= three authors)
Sanschagrin F, Levesque RC. A specific peptide inhibitor of the class B metallo-B-lactamase L-1 from *Stenotrophomonas maltophilia* identified using phage display. *J Antimicrob Chemother* 2005; 55 : 252-5.

Journal reference (> three authors)
Williams I, Gabriel G, Cohen H *et al* . Zidovudine-the first year of experience. *J Infect* 1989; 18 Suppl 1: 23-31.

Journal reference (online journal)
Bell A, Lewandowski K, Myers R *et al* . Genome sequence analysis of Ebola virus in clinical samples from three British healthcare workers, August 2014 to March 2015. *Euro Surveill* 2015; 20 : pii=21131.

Whole book
Long HC, Blatt MA, Higgins MC *et al* . *Medical Decision Making* . Boston: Butterworth-Heinemann, 1997.

Book chapter
Manners T, Jones R, Riley M. Relationship of overweight to haitus hernia and reflux oesophagitis. In: Newman W, ed. *The Obesity Conundrum* . Amsterdam: Elsevier Science, 1997; 352-74.

NCCLS/CLSI methods
National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That*

Grow Aerobically—Sixth Edition: Approved Standard M7-A6 . NCCLS, Wayne, PA, USA, 2003.

Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing: Fifteenth Informational Supplement M100-S15* . CLSI, Wayne, PA, USA, 2005.

Meeting abstract
Hou Y, Qiu Y, Vo NH *et al* . 23-O derivatives of OMT: highly active against *H. influenzae* . In: *Abstracts of the Forty-third Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, 2003* . Abstract F-1187, p. 242. American Society for Microbiology, Washington, DC, USA.

Online material

References to online material should be given in the reference list. Please note that URLs for the suppliers of materials must not be given in either the text or the references. The Journal does not accept any responsibility for the content of web pages cited.

NB – it is no longer necessary to provide the 'date last accessed' for URLs.

Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* . Department of Health and Human Services.
http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf.

Tables

These should be employed sparingly and should be generally comprehensible without reference to the text. Each table should be supplied on a separate sheet and numbered consecutively using Arabic numerals in the order they are referred to in the text. Each must have a brief descriptive heading. Column headings must clearly explain the content of the column and indicate any units used. Footnotes should be kept to a minimum.

Tables must be created using the Table function in Word; they must not be inserted as images. Each data item should occupy a single cell and return characters should not be used within any Table. *JAC* reserves the right to move complicated Tables to online-only Supplementary data.

Figures

These must be employed sparingly to demonstrate important specific points. Figures should be numbered using Arabic numerals in the order in which they are referred to in the text. In figure LEGENDS, symbols should be described in words (e.g. filled circles, open squares etc.) .

Wherever possible, figures should be two-dimensional. Authors should NOT supply 'three-dimensional' figures unless this is actually necessary to represent the data.

The quality of reproduction in *JAC* is limited by the quality of the submitted material. All figures must be of high quality - they should be sharply focused, have good contrast and any lettering must be clear and legible.

Colour Figures

Figures supplied in colour will appear in colour in the online version of JAC; these Figures will be converted to black and white for the printed article unless the authors opt to pay the necessary fees for colour printing (£350/US$600/€525.00 per figure). We do not permit authors to submit different colour and black and white Figures for use in the online and printed articles, respectively.

Considerations for authors opting for online-only colour. The Journal takes no responsibility for online-only colour Figures that are confusing or uninterpretable in the black and white printed article. Careful choice of colours can maintain interpretability when reproduced in monochrome and authors are encouraged to consider this if they opt for online-only colour. For example, the use of different symbols or line styles can assist with maintaining interpretation after conversion from colour to black and white.

General considerations for colour Figures. Please use colours that can be easily distinguished from each other. In addition, please avoid the use of very pale colours (such as cyan and yellow) that may fail to provide a strong visual contrast on a white background. This problem is particularly acute for line graphs.

Guidance for preparation of Figures

Figures should be sized to fit a single column of the Journal where possible (88 mm) or a double column if necessary (180 mm). The preferred font for lettering is Times; lettering should have an upper case height of 2 mm and a lower case height of 1 mm at publication size (corresponding to point size 8). Line thickness should be set at 0.5 points. Shading used on line drawings should be clear and distinctive; shades of grey and heavy stippling do not reproduce well. Lines and symbols should be drawn boldly enough to withstand reduction. The preferred symbols are filled circles, open circles, filled squares, open squares, filled triangles and open triangles, and should be no smaller than 1 mm (height/diameter) at publication size. Part labels should be lower case letters within parentheses, e.g. (a), (b), (c) etc.

Authors must be ready to supply original gel pictures if requested to do so.

Online Submission Details

JAC′ s online submission and peer review site

For online submission instructions, please follow this link.

Availability of Data and Materials

Where ethically feasible, the *Journal of Antimicrobial Chemotherapy* strongly encourages authors to make all data and software code on which the conclusions of the paper rely available to readers. We suggest that data be presented in the main manuscript or additional supporting files, or deposited in a public repository whenever possible. For information on

general repositories for all data types, and a list of recommended repositories by subject area, please see Choosing where to archive your data.

Data Citation

Availability of Data and Materials

Where ethically feasible, *JAC* strongly encourages authors to make all data and software code on which the conclusions of the paper rely available to readers. We suggest that data be presented in the main manuscript or additional supporting files, or deposited in a public repository whenever possible. Information on general repositories for all data types, and a list of recommended repositories by subject area, are available on the Research Data Policy page.

Data Citation *JAC* supports the Force 11 Data Citation Principles and requires that all publicly available datasets be fully referenced in the reference list with an accession number or unique identifier such as a digital object identifier (DOI). Data citations should include the minimum information recommended by DataCite:

- [dataset]* Authors, Year, Title, Publisher (repository or archive name), Identifier

*The inclusion of the [dataset] tag at the beginning of the citation helps us to correctly identify and tag the citation. This tag will be removed from the citation published in the reference list.

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