Effect of obesity on dolutegravir exposure in Black Southern African adults living with HIV

by

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Date of submission: 14-02-2022

Supervisor: Prof Phumla Zuleika Sinxadi

Co-supervisor Professor: Gary Maartens

Division of Clinical Pharmacology University of Cape Town

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ABSTRACT

Background: Dolutegravir, a component of the preferred first-line antiretroviral therapy (ART) regimen has been associated with increased weight gain, which is markedly higher when combined with tenofovir alafenamide (TAF), the newer tenofovir prodrug instead of tenofovir disoproxil fumarate (TDF). South Africa has a high prevalence of obesity, especially among women. Understanding dolutegravir exposure in the patients with obesity is important for dose optimisation.

Aims: We compared the pharmacokinetic parameters of dolutegravir in Southern African adults living with HIV with and without obesity.

Methods: Blood samples were collected at various time points over a 24 hour-period for dolutegravir assays. Non-compartmental analysis was conducted and geometric mean ratios (GMRs), with 90% confidence intervals (CIs), were generated to compare dolutegravir pharmacokinetic parameters between the groups. Regression analyses to assess predictors of dolutegravir exposure were done.

Results: 40 participants were enrolled, 26 were women and 10 had obesity. Dolutegravir area under the concentration-time curve to 24-hours ($AUC_{0\text{-}24hr}$) and the maximum concentrations (C_{max}) were marginally lower in participants with obesity: GMR 0.91 (90% CI, 0.71-1.16) and GMR 0.86 (90% CI, 0.68-1.07), respectively. In a multivariate linear regression analysis adjusting for age, sex, body mass index (BMI), creatinine clearance and randomisation arm (TAF or TDF), a unit increase in BMI was associated with 1.2% lower dolutegravir $AUC_{0\text{-}24h}$, (P = 0.035).

Conclusion: Dolutegravir exposure was marginally lower in participants with obesity, but this is not clinically significant. Our findings suggest that there is no need to dose adjust dolutegravir in people with obesity.

Author contributions

E.M was responsible for the study design, data analysis including the non-compartmental analysis, data interpretation, drafting and revising the manuscript. P.Z.S was responsible for supervision and study design and critically revising the manuscript. C.B was responsible for data analysis including the non-compartmental analysis in parallel with EM, drafting and revising manuscript content. G.M contributed to study concept and design, critical reviewed of the manuscript content. L.W supervised the pharmacokinetic assays and critically reviewed the manuscript. N.C, S.S contributed to study design, study conduct, data collection and critically reviewed the manuscript. F.V is the principal investigator of the ADVANCE RCT (parent study), and he critically reviewed the manuscript.

TABLE OF CONTENTS **Page**

APPENDICES

List of Tables

List of Figures

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DTG	dolutegravir
TFV	tenofovir
TDF	tenofovir disoproxil fumarate
TAF	tenofovir alafenamide
FTC	emtricitabine
$C_{(max)}$	maximum concentration
$C_{(0-24)}$	trough concentrations
AUC_{0-24hr}	area under the concentration-time curve to the last measurable time point at 24 hours post dosing
$T_{(max)}$	time to maximum concentration
$t_{(1/2)}$	terminal elimination half-life
GMRs	geometric mean ratios
CI	confidence interval
BMI	body mass index
INSTIs	integrase strand transfer inhibitors
PLWH	people living with HIV
MC4R	melanocortin-4-receptor

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TABLE OF CONTENTS **Page**

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Conclusion: Dolutegravir exposure was marginally lower in participants with obesity, but this is not clinically significant. Our findings suggest that there is no need to dose adjust dolutegravir in people with obesity.

Keywords: Pharmacokinetics, Dolutegravir, Obesity; South Africa; Antiretroviral treatment optimisation; HIV

INTRODUCTION

Antiretroviral therapy (ART) has reduced morbidity and mortality in patients living with HIV (1). ART regimens with durable efficacy, better tolerability and long-term safety are now preferred. (2). In all HIV treatment guidelines, second generation integrase strand transfer inhibitors (INSTI), such as dolutegravir, are included in first-line ART regimens owing to excellent tolerability and high resistance barrier (3,4). Dolutegravir is often administered as a fixed-dose combination together with lamivudine or emtricitabine and a tenofovir prodrug (tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF)).

More weight gain has been associated with the use of INSTIs in ART-naïve people living with HIV (PLWH) than with other classes of antiretrovirals (5), or in people switching from – efavirenz to INSTI-based ART (6). In sub-Saharan Africa, two randomised controlled trials of dolutegravir versus efavirenz (standard versus low-dose in ADVANCE (8) and NAMSAL (9), respectively) in ART-naïve PLWH, reported more weight gain and treatment-emergent obesity, especially among women, in participants treated with dolutegravir compared with efavirenz. Furthermore, participants randomised to the TAF arm of the ADVANCE study experienced more weight gain than those treated with TDF(8). In the OPERA cohort of PLWH, it has been showed that switching from TDF to TAF was associated with pronounced weight gain immediately after switch regardless of the core class or core agent(10).

Obesity, itself associated with poor health outcomes, is a common outcome of all modern ART regimens, especially among Black women (5,11,12). In South Africa, there are 7.8 million PLWH, with 230 000 new HIV infections reported in 2020 (13). South Africa also has a high levels of pre-existing obesity: 68% of women and 31% of men were overweight or obese in a 2016 survey (14). Obesity affects several physiological processes relevant to drug exposure (e.g. gut permeability, gastric emptying, cardiac output, liver and renal function) (15). It is important to determine if drug exposure is sub-optimal in obese individuals as they are usually excluded in drug development studies that inform dosing (16,17).

It has been postulated that dolutegravir could cause weight gain by off-target effects through inhibition of the melanocortin-4 receptor (MC4R) pathway, affecting appetite and energy balance (18,19). However, *in vitro* studies have shown that the concentrations needed for the direct inhibition of MC4R that would explain clinically important weight gain are much higher than those achieved with the currently recommended daily dose of 50 mg (20). In a sub-study of ADVANCE, our group has recently shown that weight gain differences between dolutegravir and efavirenz are driven by impaired weight gain in participants who are genetic slow metabolisers of efavirenz (21)– this finding suggests that dolutegravir is not causing weight gain but that efavirenz is impairing weight gain in slow metabolisers who have high efavirenz concentrations. The reason for the contributory effect of TAF on weight gain is still unclear, and may reflect weight loss effects of TDF (11,22).

As marked weight gain is increasingly reported in patients treated with dolutegravir, especially when co-administered with TAF (8,23), understanding the effects of obesity on dolutegravir exposure is important for dose optimisation to ensure the effective and safe of dolutegravir in obese people (16,24,25). We hypothesised that dolutegravir exposure would be lower in obese compared with non-obese participants due to the pharmacokinetic changes in obesity. We compared the pharmacokinetic parameters of dolutegravir administered in obese versus non-obese Southern African PLWH enrolled in the ADVANCE randomised clinical trial. We also explored covariates associated with overall dolutegravir exposure.

MATERIALS AND METHODS

Study population and study design

The ADVANCE study (NCT03122262) was a phase 3 clinical trial conducted in South Africa, which randomised 1,053 ART-naïve participants to one of three treatment arms: 1) dolutegravir, TAF and emtricitabine; 2) dolutegravir, TDF and emtricitabine; or 3) efavirenz, TDF and emtricitabine (5). The present pharmacokinetic sub-study included participants from the ADVANCE study who were older than18 years of age, weighed 40 kg or more,

were randomized to the dolutegravir arms, and consented to the intensive pharmacokinetic sub-study. We excluded those who missed any ART doses within 3 days before the pharmacokinetic sampling, smokers, and participants who needed concomitant medications with a potential for drug-drug interactions with dolutegravir. Participants were categorised into obese (≥30 kg/m^2) and non-obese (<30 kg/m^2) groups using the World Health Organization definition (26).

This sub-study was approved by the University of the Witwatersrand Human Research Ethics Committee (Wits HREC 160606B) and the University of Cape Town Human Research Ethics Committee (HREC REF: 224/2021). All participants provided additional informed consent to participate in the pharmacokinetic sub-study.

Pharmacokinetic sampling and analysis

Enrolled participants had a standardised meal prior to observed oral administration of study medication. Blood sampling was done at 0 (pre-dose), 1, 2, 4, 6, 8 and 24-hours post dosing. An intravenous cannula was inserted and remained in situ for serial sampling up to 8 hours. At each time point, 4 mL of venous blood was collected in an EDTA tube, centrifuged, plasma pipetted, and stored at -80ºC until analysis.

Dolutegravir was quantified with a validated 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 an internal standard, followed by high performance liquid chromatography with tandem mass spectrometry detection (LC/MS/MS) using an AB SCIEX API 4000 instrument. 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 to 10.0 µg/mL. Combined accuracy and precision statistics of quality control samples during validation were between 103.5% and 106.0%, and 4.6% and 6.1%, respectively (18). The laboratory participated in the Clinical Pharmacology Quality Assurance external quality control program under a contract with the Division of

AIDS of the National Institute of Allergy and Infectious Diseases, through which this assay was approved.

Statistical analysis

Baseline characteristics were described using medians (interquartile ranges [IQRs]) and proportions (%) for non-parametric continuous variables and categorical variables, respectively.

Using non-compartmental analysis, employing the trapezoidal rule with cubic splines, the following pharmacokinetic parameters were estimated for dolutegravir: 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 dose. Pharmacokinetic data were log-transformed to calculate the geometric mean ratio (GMR) of the pharmacokinetic parameters of dolutegravir comparing obese to non-obese groups 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 arms were considered statistically significant when the 90% CI of the GMR did not cross the value of one. Multivariate linear regression was used to explore and determine covariates associated with overall drug exposure (AUC_{0-24}). The covariates explored were age, sex, BMI, creatinine clearance and ART regimen group (TAF versus TDF). A p-value of < 0.05 will be considered as significant. There was no correction for multiple testing. All the analyses were conducted in Stata® (version 16.0, StataCorp LLC, College Station, Texas, USA).

RESULTS

Forty participants were enrolled into the intensive pharmacokinetic sub-study. The participant flow chart is shown in **Figure 1.** Ten participants were classified as obese, and their baseline characteristics are summarised in **Table 1.**

Pharmacokinetic profile of dolutegravir in patients with versus without obesity

Pharmacokinetic parameters of dolutegravir when administered in obese compared with non-obese participants are summarised in **Table 2**. Modest reductions in the $AUC_{0\text{-}24hr}$ (9%) and C_{max} (14%) were observed in the obese group. However, this was not statistically significant. The T_{max} was significantly prolonged (62%) in the obese. There were no differences in apparent dolutegravir clearance between the two groups. The median (IQR) concentration-time profiles of dolutegravir in obese and non-obese participants are shown in **Figure 2**. In both groups, dolutegravir trough concentrations were above the pre-specified minimum effective concentration of 300 ng/mL (27,28).

Predictors of overall dolutegravir exposure

In a multivariate linear regression analysis to investigate covariates associated with dolutegravir $AUC_{0\text{-}24h}$ in the whole group, a unit increase in BMI was associated with 1.2% lower dolutegravir exposure (beta coefficient of -1838.66 (95% CI: -3540.85, -136.46, p-value = 0.035) - see **Table 3)**. Other covariates tested (age, sex, creatinine clearance, and treatment groups (TDF or TAF) were not associated with dolutegravir exposure **(Table 3).**

DISCUSSION

We investigated the effects of obesity on dolutegravir pharmacokinetics among participants enrolled into the intensive pharmacokinetic sampling sub-study of the ADVANCE study. We investigated predictors of dolutegravir exposure in the whole group using multivariate regression analyses adjusting for age, sex, BMI, creatinine clearance, and tenofovir prodrug: only BMI was independently associated with higher dolutegravir $AUC_{0\text{-}24hr}$. In the group with obesity, we found that $AUC_{0\text{-}24hr}$ and C_{max} were marginally lower. However, this was not

178 statistically significant. We also observed that the T_{max} was significantly prolonged in the
179 obese group. However, these observed minor differences in pharmacokinetic parameters in
180 participants with obesity are not clinically significant.

181 Obesity is associated with various physiological changes that can affect drug
182 pharmacokinetics. These include changes in plasma proteins, drug metabolizing enzymes,
183 drug transporters and blood flow (15). In our study, we observed a marginal, non-significant,
184 decrease in overall dolutegravir exposure in the group with obesity. T_{max} was significantly
185 prolonged in the group with obesity, which was a surprising finding as drug absorption is not
186 generally affected by obesity (15,25,29).

187 Similar observations were made in the Swiss HIV cohort study using a physiologically based
188 pharmacokinetic (PBPK) modelling, where obesity was predicted to reduce dolutegravir C_{max}
189 and AUC by 13% and 3%, respectively (30). The observed marginal reduction in dolutegravir
190 exposure in our study is not clinically significant as all participants had concentrations above
191 the purported minimum effective concentration of 300 ng/mL (27,28). We investigated
192 predictors of dolutegravir and found a unit increase in BMI was associated with a
193 significantly lower dolutegravir $AUC_{0\text{-}24hr}$. However, this small difference is not clinically
194 significant.

195 Our study has limitations. First, this was a post hoc analysis, and we did not do formal
196 sample size calculation. The sample size of 10 participants with - and 30 without obesity had
197 limited power to detect small differences in overall dolutegravir exposure. The post hoc
198 sample estimation showed that a sample size that included 10 participants with obesity and
199 30 without would provide 80% power if the relative difference in AUC between these groups
200 was 30%. Second, we classified our participants into with versus without obesity; however,
201 the group without obesity also included 17 participants who were overweight (BMI >25 to
202 <30 kg/m^2). This may have underestimated the impact of obesity on dolutegravir exposure.
203 In a sensitivity analysis comparing the 10 participants with obesity and 13 adults with BMI ≤
204 25 kg/m^2 dolutegravir PK profile was similar to that seen when comparing obese and non-

obese participants (data not shown). Third, all our participants were Africans; our findings may, therefore, not be generalisable to other populations.

CONCLUSION

Dolutegravir exposure was marginally lower in participants with obesity, but this is not clinically significant given that trough concentrations were above a purported minimum effective concentration. Our findings suggest that there is no need to dose adjust dolutegravir in patients with obesity. However, future research studies with larger sample size are warranted.

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Data availability: The data that support the findings of this study are available from the corresponding author P.Z.S upon reasonable request

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REFERENCES

1. Ray AS, Fordyce MW, Hitchcock MJM. Tenofovir alafenamide: A novel prodrug of tenofovir for the treatment of Human Immunodeficiency Virus. Antiviral Res. 2016;125:63–70. Available from: http://dx.doi.org/10.1016/j.antiviral.2015.11.009

2. Ruane PJ, Dejesus E, Berger D, Markowitz M, Bredeek UF, Callebaut C, et al. Antiviral activity, safety, and pharmacokinetics/pharmacodynamics of tenofovir alafenamide as 10-day monotherapy in HIV-1-positive adults. J Acquir Immune Defic Syndr. 2013;63(4):449–55.

3. National Department of Health. 2019 ART Clinical Guidelines. 2019(14-February 2022);https://www.nicd.ac.za/wp-content/uploads/2019/11/2019-ART-Clinical-Guidelines-25-Nov.pdf

4. Walmsley SL, Antela A, Clumeck N, Duiculescu D, Eberhard A, Gutiérrez F, et al. Dolutegravir plus Abacavir–Lamivudine for the Treatment of HIV-1 Infection. N Engl J Med. 2013;369(19):1807–18.

5. Sax PE, Erlandson KM, Lake JE, McComsey GA, Orkin C, Esser S, et al. Weight gain following initiation of antiretroviral therapy: Risk factors in randomized comparative clinical trials. Clin Infect Dis. 2020;71(6):1379–89.

6. Leonard MA, Cindi Z, Bradford Y, Bourgi K, Koethe J, Turner M, et al. Efavirenz Pharmacogenetics and Weight Gain Following Switch to Integrase Inhibitor-Containing Regimens. Clin Infect Dis. 2021;73(7):e2153–63.

7. Mallon PWG, Brunet L, Hsu RK, Fusco JS, Mounzer KC, Prajapati G, et al. Weight gain before and after switch from TDF to TAF in a U.S. cohort study. J Int AIDS Soc. 2021;24(4):25–30.

8. Venter WDF, Moorhouse M, Sokhela S, Fairlie L, Mashabane N, Masenya M, et al. Dolutegravir plus two different prodrugs of tenofovir to treat HIV. N Engl J Med. 2019;381(9):803–15.

9. Calmy A, Tovar Sanchez T, Kouanfack C, Mpoudi-Etame M, Leroy S, Perrineau S, et al. Dolutegravir-based and low-dose efavirenz-based regimen for the initial treatment of HIV-1 infection (NAMSAL): week 96 results from a two-group, multicentre, randomised, open label, phase 3 non-inferiority trial in Cameroon. Lancet HIV. 2020;7(10):e677–87.

10. Mallon PWG, Brunet L, Hsu RK, Fusco JS, Mounzer KC, Prajapati G, et al. Weight gain before and after switch from TDF to TAF in a U.S. cohort study. J Int AIDS Soc. 2021 Apr 1;24(4).

11. Shah S, Hindley L, Hill A. Are New Antiretroviral Treatments Increasing the Risk of Weight Gain? Drugs. 2021 Feb 1;81(3):299–315.

12. Mabaso M, Makola L, Naidoo I, Mlangeni LL, Jooste S, Simbayi L. HIV prevalence in South Africa through gender and racial lenses: results from the 2012 population-based national household survey. Int J Equity Health. 2019;18(1):167.

13. United Nations Programme on HIV/aids. UNAIDS 2021;4–38.(14 February

2022)https://www.unaids.org/sites/default/files/media_asset/JC3032_AIDS_Data_book_2021_En.pdf

14. StatsSA SSA. South Africa demographic and health survey 2016: Key indicator report Statistics South Africa. 2017. 1–57 p. (14 February 2022)https://www.statssa.gov.za/publications/Report 03-00-09/Report 03-00-092016.pdf

15. Jain R, Chung SM, Jain L, Khurana M, Lau SWJ, Lee JE, et al. Implications of obesity for drug therapy: Limitations and challenges. Clin Pharmacol Ther . 2011;90(1):77–89. Available from: http://dx.doi.org/10.1038/clpt.2011.104/nature06264

16. EMA. Reflection paper on investigation of pharmacokinetics and pharmacodynamics in the obese population.2018;44(0):1–11.

17. Madelain V, Le MP, Champenois K, Charpentier C, Landman R, Joly V, et al. Impact of obesity on antiretroviral pharmacokinetics and immuno-virological response in HIV-infected patients: a case-control study. J Antimicrob Chemother 2017 Apr 1;72(4):1137-1146. doi: 10.1093/jac/dkw527

18. Griesel R, Kawuma AN, Wasmann R, Sokhela S, Akpomiemie G, Venter WDF, et al. Concentration-Response Relationships of Dolutegravir and Efavirenz With Weight Change After Starting Antiretroviral Therapy. Br J Clin Pharmacol. 2022 Mar;88(3):883-893. doi: 10.1111/bcp.15177. Epub 2022 Jan 26

19. Adan RAH, Tiesjema B, Hillebrand JJG, La Fleur SE, Kas MJH, De Krom M. The MC4 receptor and control of appetite. Br J Pharmacol. 2006;149(7):815–27.

20. McMahon C, Trevaskis JL, Carter C, Holsapple K, White K, Das M, et al. Lack of an association between clinical INSTI-related body weight gain and direct interference with MC4 receptor (MC4R), a key central regulator of body weight. PLoS One 2020 Feb 28;15(2):e0229617. doi: 10.1371/journal.pone.0229617. eCollection 2020

21. Griesel R, Maartens G, Chirehwa M, Sokhela S, Akpomiemie G, Moorhouse M, et al.

CYP2B6 Genotype and Weight Gain Differences Between Dolutegravir and Efavirenz. Clinical Infectious Diseases, Volume 73, Issue 11, 1 December 2021, Pages e3902–e3909, https://doi.org/10.1093/cid/ciaa1073

22. Lake JE, Trevillyan J. Impact of Integrase inhibitors and tenofovir alafenamide on weight gain in people with HIV. Curr Opin HIV AIDS. 2021;16(3):148–51.

23. Eckard AR, McComsey GA. Weight gain and integrase inhibitors. Curr Opin Infect Dis. 2020;33(1):10–9.

24. Cho SJ, Yoon IS, Kim DD. Obesity-related physiological changes and their pharmacokinetic consequences [Internet]. Vol. 43, Journal of Pharmaceutical Investigation. Elsevier BV; 2013 [cited 2021 Sep 29]. p. 161–9. Available from: http://link.springer.com/10.1007/s40005-013-0073-4

25. Schachter M. Clinical pharmacology. Clin Pharmacol Elev Ed. 2012;24(7):2–4.

26. WHO Consultation on Obesity (1997: Geneva S, Diseases WHOD of N, World Health Organization. Programme of Nutrition F and RH. Obesity : preventing and managing the global epidemic : report of a WHO Consultation on Obesity, Geneva, 3-5 June 1997 [Internet]. Geneva PP - Geneva: World Health Organization; Available from: https://apps.who.int/iris/handle/10665/63854

27. Walimbwa SI, Lamorde M, Waitt C, Kaboggoza J, Else L, Byakika-Kibwika P, et al. Drug interactions between dolutegravir and artemether-lumefantrine or artesunate-amodiaquine. Antimicrob Agents Chemother 2019 Jan 29;63(2):e01310-18. doi: 10.1128/AAC.01310-18. Print 2019 Feb.

28. Dooley KE, Savic R, Gupte A, Marzinke MA, Zhang N, Edward VA, et al. Once-weekly rifapentine and isoniazid for tuberculosis prevention in patients with HIV taking dolutegravir-based antiretroviral therapy: a phase 1/2 trial. Lancet HIV. 2020;7(6):e401–9.

29. Smit C, De Hoogd S, Brüggemann RJM, Knibbe CAJ. Obesity and drug pharmacology: a review of the influence of obesity on pharmacokinetic and pharmacodynamic parameters. Expert Opin Drug Metab Toxicol [Internet]. 2018;14(3):275–85. Available from: https://doi.org/10.1080/17425255.2018.1440287

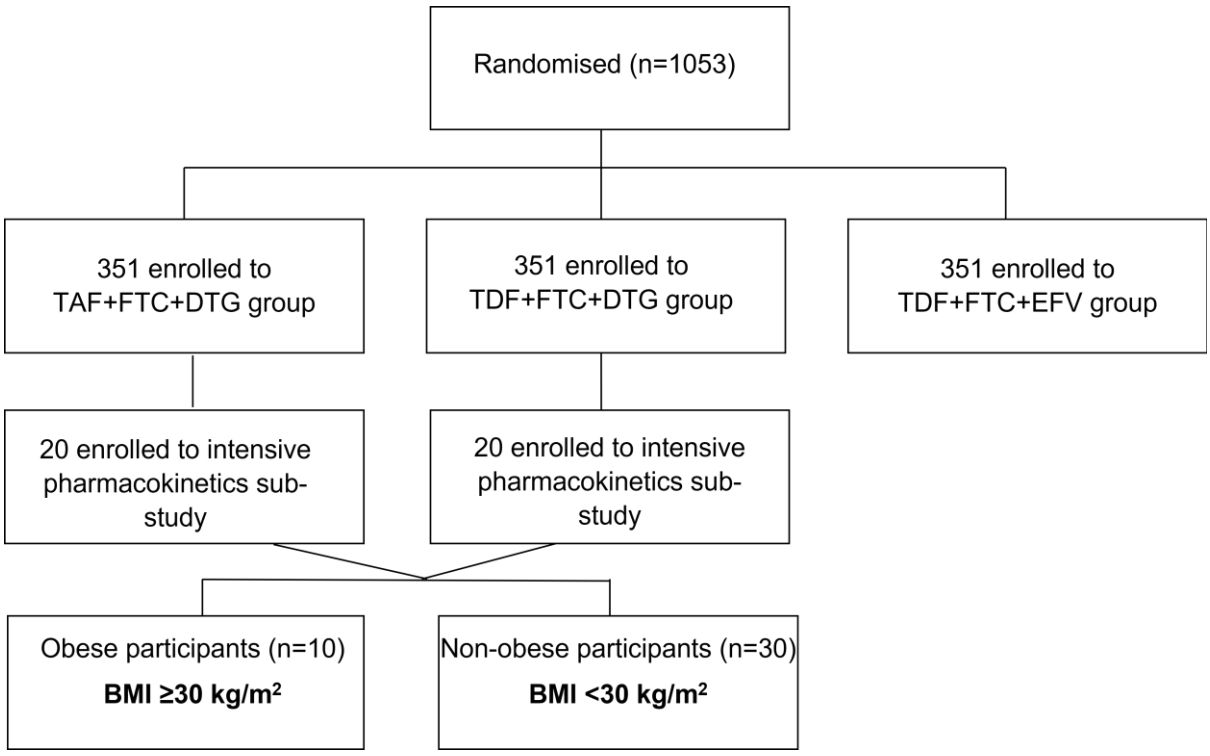
30. Mattia Berton , Sara Bettonte , Laurent Decosterd , Manuel Battegay , Matthias Cavassini F, 2 1 1 2 1, Stader CM. Pharmacokinetics of dolutegravir and bictegravir in obese people living with HIV. CROI February 2022;30–2.

Figure legends

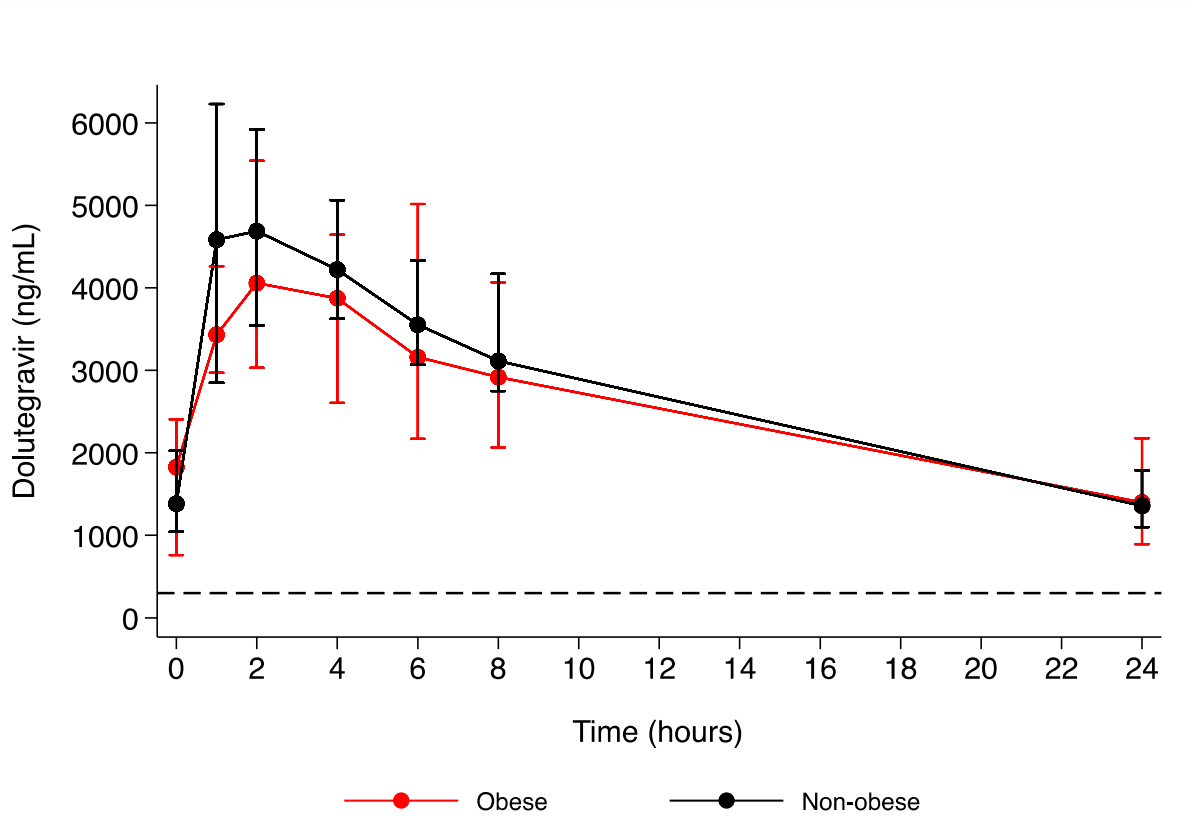
Figure 1: Participant flow chart

Figure 2: Median concentration-time of dolutegravir administered in obese (red line plot, n=10) and non-obese participants (black line plot, n=30. Data are represented as median (IQR). The black dashed horizontal line represents the purported minimum effective dolutegravir concentration of 300 ng/mL.

Figure 1.


Randomised (n=1053)
351 enrolled to TAF+FTC+DTG group
351 enrolled to TDF+FTC+DTG group
351 enrolled to TDF+FTC+EFV group
20 enrolled to intensive pharmacokinetics sub-study
20 enrolled to intensive pharmacokinetics sub-study
Obese participants (n=10)
BMI ≥30 kg/m2
Non-obese participants (n=30)
BMI <30 kg/m2

352 **Figure 2**



353

Table 1. Baseline characteristics of study participants included in analysis (N=40)

Variables	All	Obese (n=10)	Non-obese (n=30)
Age in years	32 [29 to 37]	35 [31 to 44]	31 [28 to 36]
Sex			
Female	26 [65]	8 [80]	18 [60]
Weight (kg)	73.7 [67.3 to 85.6]	90.6 [86.0 to 95.3]	69.1 [62.1 to 75.5]
Height (cm)	166.5 [160 to 173.5]	165 [159.0 to 172.0]	167 [161 to 175]
Body mass index (kg/m^2)	27.1 [23.4. to 30.19]	32.8 [31.7.8 to 34.4]	25.3 [22.6 to 27.9]
Antiretroviral therapy regimen			
Tenofovir alafenamide/emtricitabine/dolutegravir	20 [100]	5 [50]	15 [50]
Tenofovir disoproxil fumarate/emtricitabine/dolutegravir	20 [100]	5 [50]	15 [50]
Baseline creatinine (µmol/L)	70 [56.0 to 76.0]	73 [56.0 to 75.0]	67.0 [56.0 to 77.0]
Baseline creatinine clearance (mL/ min)	130.5 [104.5 to 148.5]	135.6 [126,3 to 181.0]	119.5 [103.8 to 145.6]

Medians (IQR) were used to describe continuous variables. Proportions (n, [%]) were used to describe categorical variables

354

Table 2. Dolutegravir (DTG) exposure profile in obese compared with non-obese participants [N=40]

	Geometric Mean (GM) (90% CI)		GM Ratio (90% CI)	
Pharmacokinetic parameter	**DTG in obese participants (Group 1)**	**DTG in non-obese participants (Group 2)**	**Group 2/Group 1**	**P-value***
$AUC_{0\text{-}24hr}$ (ng.hr/mL)	62,502 (50,178 to 77,852)	68,491 (62,153 to 75,475)	0.91 (0.71 to 1.16)	0.529
C_{max} (ng/mL)	4,268 (3,502 to 5,201)	4,985 (4,504 to 5,518)	0.86 (0.68 to 1.07)	0.251
C_{24} (ng/mL)	1,433 (1,073 to 1,912)	1,444 (1,263 to 1,650)	0.99 (0.72 to 1.37)	0.968
T_{max} (hr)	2.4 (1.8 to 3.3)	1.5 (1.3 to 1.7)	**1.62 (1.15 to 2.27)**	**0.023**
$t_{1/2}$ (hr)	16.4 (13.2 to 20.3)	14.7 (13.1 to 16.5)	1.11 (0.87 to 1.42)	0.470
CL/F (litres/hr)	0.80 (0.64 to 1.00)	0.73 (0.66 to 0.80)	1.10 (0.86 to 1.40)	0.529

* t-test $C_{max:}$ maximum concentration * $C_{24:}$ trough concentrations * $T_{max;}$ time to maximum concentration * $t_{1/2:}$ terminal elimination half-life* CL/F: oral clearance

$AUC_{0\text{-}24:}$ area under the concentration-time curve to the last measurable time point at 24 hours post dosing

Bold represents statistical significance

Table 3. Association between AUC exposure and various predictive covariates

	Unadjusted		Adjusted	
Variable	Beta coefficient (95% CI)	p-value	Beta coefficient (95% CI)	p-value
BMI	-1343.60 (-2889.39 to 202.18)	0.087	**-1838.66 (-3540.85 to -136.46)**	**0.035**
ART treatment group (TDF)	-5458.93 (-20341.69 to 9423.84)	0.462	-4835.94 (-19222.67 to 9550.78)	0.499
Age	-652.87 (-1632.07 to 326.32)	0.185	83.94 (-1055.50 to 1223.38)	0.882
Sex (Male)	-12537.39 (-27702.57 to 2627.78)	0.102	-14975.44 (-39693.31 to 9742.42)	0.227
Creatinine clearance	-373.78 (-787.00 to 39.46)	0.075	-108.51 (-700.92 to 483.90)	0.712

Bold represents statistical significance.

TDF: tenofovir disoproxil fumarate

355

INTENSIVE PHARMACOKINETIC(PK) SAMPLING SUBSTUDY INFORMATION LEAFLET AND INFORMED CONSENT (OPTIONAL)

Each **participant** must receive, read and understand this document

Before any study-related procedure

STUDY NUMBER:	WRHI060
STUDY TITLE:	A 96-week Randomised, Phase 3 Non-inferiority Study of DTG+TAF+FTC Compared with DTG+TDF+FTC and EFV+TDF+FTC in Patients Infected with HIV-1 Starting First-line Antiretroviral Therapy
SPONSOR:	Wits Reproductive Health and HIV Institute (Wits RHI)
INVESTIGATOR (NATIONAL & SITE):	Prof. WD Francois Venter
INSTITUTION:	Wits Reproductive Health and HIV Institute (Wits RHI)
DAYTIME AND AFTER HOURS TELEPHONE NUMBER(S):	011 358 5583 or 082 618 7851

To the potential participant: *This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home* ***an unsigned copy of this consent*** *form to think about or discuss with family or friends* ***before making your decision.***

ICF administration starting time: _____ **ICF administration finish time: _____**

INTRODUCTION

Your study doctor has established that you are a suitable patient to take part in the ADVANCE clinical trial, whose purpose is to test whether two potential new combinations using newly available drugs [tenofovir alafenamide (TAF) and dolutegravir (DTG)], are both safer and more effective when compared to the current South African standard of care [tenofovir (TDF) + emtricitabine (FTC) or lamivudine (3TC) + efavirenz (EFV)]. You're now invited to take part in an additional substudy, whose aim is to collect more blood samples to measure the levels of the medicines in your blood.

WHY ARE YOU INVITED?

You are invited to take part in the substudy because you have already agreed to take part in the ADVANCE study, where you will be given study medicines, undergo medical examinations and procedures at scheduled visits. We now invite you to take part in the substudy (another part of the study), where we ask for permission to take more

blood samples at specific times over a two day period (before you take your morning pills (hour 0) and then 1, 2, 4, 6, 8, 10 and 24 hours after you take your morning pills).

Forty participants from groups 1 (20 participants) and 2 (20 participants), who have completed 24 weeks, will be invited to participate in this substudy.

WHAT DO WE WANT TO DO WITH YOUR BLOOD SAMPLES AND INFORMATION FROM YOUR STUDY RECORDS?

Information that is in your blood can tell us how well your body deals with the medicine after you swallow it. It will tell us how quickly the the medicine is absorbed from the intestines, how long it takes to reach the highest levels in the blood before it is broken down and cleared from the body. This information will allow us to be able to estimate what levels of the medicines are to be expected at specific times after medicines are swallowed, even when we have limited information. We can then be able to tell whether the levels of the medicines in the blood determine how well the drug works, or cause side effects.

WHAT WILL HAPPEN TO YOU IF YOU TAKE PART?

You will be asked to sign this form to show that you understand what the substudy is about and that you agree to take part. Before we include you in the substudy, we need to make sure you understand the substudy including what will happen, any possible risks and what is required of you. If you decide to take part, you have to sign the consent form to show your willingness to take part. The study staff will give you a date and time to come to the clinic. On the day before you come to the clinic, you are required to write down the date and time when you took your pills in the morning. On the day you do come to the clinic, you are required to not take your pills in the morning, and bring your pill containers with you to the clinic. When you arrive at the clinic, we will put a cannula (a flexible plastic needle like those used to give fluids to patients in hospital) into one of your arm veins from which we will collect as many of the blood samples as possible to avoid having to prick you more than . The first blood sample will be taken before you take your pills (this will be called the predose sample). You will then take your pills under supervision and the date and time will be recorded. Six more blood samples (at 1, 2, 4, 6, 8 and 10 hours after you swallowed your pills) will be drawn from the cannula already in your arm to avoid pricking you more than is needed. After the last dose of your medicine, the cannula will be taken out and you will be asked to return to the clinic the next morning. On the next day, you will be required to not take your morning pills until your last blood sample is taken directly from the arm vein, and to bring your pills containers with you to the clinic. Your can then take your pills after the last blood sample is taken and you can come back to the clinic on the next scheduled date for the main study. For example, if you arrive at the clinic on the first day of your appointment at 7:45 am, and the cannula is put in your arm by 7:55 am, your predose sample can be taken at 7:55 am. If you then swallow your medicine at 8:00am, the plan will be to take the next blood samples at 9:00am, 10:00am, 12:00pm, 2:00pm, 4:00pm, 6:00pm and the last blood sample taken at 8:00am the next day. It is important to return early the next day, so that the last sample can be taken in time. Each blood sample will be about one teaspoon of blood (5 milliliters).

Your choice to take part in this optional substudy does not affect your participation in the ADVANCE study.

POTENTIAL BENEFITS

There is no benefit to you from being in this substudy. Results of these studies are for research purposes only and are not expected to benefit you directly. Therefore, you or your doctor will not have access to the results. Your taking part may help patients with HIV in the future.

RISKS AND INCONVENIENCES

This is a minimal risk study. The risks of taking blood or inserting a cannula may include fainting, pain and/or bruising. For this substudy, the total amount of blood to be taken from you will be approximately 100ml (less than half a cup).

CONFIDENTIALITY

To make sure all information remains confidential, the blood samples will be labelled with study numbers only, and none of the information that could identify you will be put on the samples. Your information will be kept confidential within the limits of the law and used only for research purposes mentioned above. If the results of this study are published or presented in a meeting, you will not be named and nobody will be able to tell that you were in the study from the publication or presentation.

VOLUNTARY PARTICIPATION

Taking part in this study is your choice. If you decide not to take part, this will not affect the medical care you receive from your study doctor or the clinic, or your participation in the main study.

AUTHORISATION TO USE AND DISCLOSE RECORDS FOR RESEARCH

By signing this form you give consent to take part in this substudy, you are agreeing that the study doctor, the research team, the institution, study monitors/inspectors/auditors, and one or more central laboratories may use and disclose your information, together with your study subject number, to the Institutional Review Board overseeing this study, and to governmental authorities if appropriate. These uses and disclosures are necessary to conduct the study and to ensure its integrity.

Your participation in this substudy is entirely voluntary and you can decide not to participate, or stop at any time, without stating any reason. Your withdrawal will not affect your participation in the ADVANCE study or access to other medical care. However, if you do cancel your consent, the samples collected will be used to maintain the integrity of the study.

WILL YOU BE COMPENSATED FOR YOUR TRAVEL COSTS, TIME AND INCONVENIENCE?

You will be compensated for time,inconvenience and travel. An amount of R950 will be given to you after all blood samples are collected on day 2.

ETHICAL APPROVAL:

- This clinical study protocol has been submitted to the University of the Witwatersrand, **Human Research Ethics Committee (HREC)** and written approval has been granted by that committee.
- The study has been structured in accordance with the **Declaration of Helsinki** (last updated: October 2013), which deals with the recommendations guiding doctors in biomedical research involving human participants. A copy may be obtained from me should you wish to review it.

SOURCE OF ADDITIONAL INFORMATION:

- For the duration of the study, you will be under the care of qualified medical doctors and nurses. If at any time between your visits, you feel that any of your symptoms are causing you any problems, or you have any questions during the study, please do not hesitate to contact the study staff.
- **The 24-hour telephone number** through which you can reach me or another authorised person is 082 618 7851.
- If you want any information regarding your **rights as a research participant, or complaints regarding this research study**, you may contact Prof. Clement Penny, Chairperson of the University of the Witwatersrand, Human Research Ethics Committee (HREC), which is an independent committee established to help protect the rights of research participants at (011) 717 2301.
- For **research information** you can contact Prof Francois Venter at **011 358 5568**

MEDICINES CONTROL COUNCIL-SOUTH AFRICA - MCC

- If you have questions about this trial, you should first discuss them with your doctor or the ethics committee (contact details as provided on this form). After you have consulted your doctor or the ethics committee and if they have not provided you with answers to your satisfaction, you should write to the South African Health Products Regulatory Authority at:

  The Registrar, South African Health Products Regulatory Authority,
  Department of Health, Private Bag X828, PRETORIA, 0001
  Tel: (012) 395 8126
  Fax: (012) 395 9201
  E-mail: portia.nkambule@health.gov.za

PARTICIPANT QUESTIONS:

Did the participant raise any questions? **YES ☐ / NO ☐**

If YES – What were they:

_____

_____

_____

_____

_____

_____

INFORMED CONSENT:

- I hereby confirm that I have been informed by the study staff about the nature, conduct, benefits and risks of clinical study and have agreed to participate in the substudy.
- I have read this document/had its contents explained to me.
- I have been given the opportunity to ask any questions about the research study procedures
- I have been given time to discuss with others to decide whether or not to take part.
- I understand that blood samples will be taken and will be analysed at the end of the study and I will not have access to the results.
- It has been explained to me that I am free to leave the substudy at any time, without any disadvantage to my future care I do freely give my consent to join in this substudy, as described to me in this document.
- By signing this consent form I authorise that, for conducting research related to HIV, my blood sample may used by and transported to other collaborators, including sites outside South Africa. If any of the sample remains after analysis, it may be stored for up to 15 years after the results have been released and confirmed. This consent is valid until I revoke it by notifying the study doctor in writing.
- By signing this consent form I authorise use and sharing of my medical information as described under section "AUTHORISATION TO USE AND DISCLOSE RECORDS FOR RESEARCH" to ensure the study is conducted with integrity. This consent is valid until I revoke it.
- I understand that I will receive a copy of this document as signed below.

PARTICIPANT:

_____

Printed Name(s) and Surname

_____

Signature / Mark or Thumbprint Date and Time

I herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above study.

INFORM CONSENT ADMINISTRATOR:

_____

Printed Name(s) and Surname

_____

Signature / Mark or Thumbprint Date and Time

STUDY DOCTOR/INVESTIGATOR:

_____

Printed Name(s) and Surname

_____

Signature / Mark or Thumbprint Date and Time

WITNESS (If applicable)**:**

Printed Name(s) and Surname

Signature / Mark or Thumbprint Date and Time

University of the Witwatersrand, Johannesburg

Human Research Ethics Committee: (Medical)
FWA Registered No IRB 00001223

SECRETARIAT: Suite 189, Private Bag x2600, Houghton 2041, South Africa Tel: +27-11-274 9200 Fax: +27-11-274 9281

Prof WDF Venter,

EMAILED & COURIERED

Wits Reproductive Health and HIV Institute
Hillbrow Health Precinct
Hugh Solomon Building
Esselen Street, Hillbrow
2001

14 February 2019

Fax: 011 358 5439

Dear Prof Venter,

PROTOCOL: WRHI 060 - A 96-WEEK RANDOMISED, PHASE 3 NON-INFERIORITY STUDY OF DTG + TAF + FTC COMPARED WITH DTG + TDF + FTC AND EFV + TDF+FTC IN PATIENTS INFECTED WITH HIV-1 STARTING FIRST-LINE ANTIRETROVIRAL THERAPY

ETHICS REFERENCE NO: 160606B

RE : APPROVAL FOR INTENSIVE PHARMACOKINETIC (PK) SAMLING SUB-STUDY ENGLISH INFORMATION LEAFLET AND INFORMED CONSENT FORM (ICF) ADULTS, VERSION 1.0

We acknowledge receipt of your letter dated 13 February 2019 with the following documentation pertaining to the above-captioned trial.

Amendment Date:	11-Feb-2019	Amendment Version:	Version 1.0
Amendment Number:		Received Date:	13-Feb-2019

The following has been approved by the Wits Human Research Ethics Committee: (Medical):

* Intensive Pharmacokinetic(PK) Sampling Substudy Information Leaflet and Informed Consent (Optional), Version 1.0 dated 11 February 2019

Ethics Approval Date: Thursday, 14 February, 2019

The University of the Witwatersrand, Human Research Ethics Committee Approval Granted for the above mentioned study is valid for five years. Where required by Sponsor to have approval on a more frequent basis it remains the responsibility of the Sponsor and Investigator to apply for continuing review and approval, or for the duration of the Trial.

.

1. THIS APPROVAL IS SUBJECT TO THE FOLLOWING PROVISOS:

* A copy of the SAHPRA Approval and/or SAHPRA Notification letter must be submitted to the Ethics Regulatory Office Secretariat before the study commences / or where an Amendment may be implemented (IF SAHPRA APPROVAL / NOTIFICATION IS APPLICABLE). It remains the responsibility of the Principal Investigator and/or Sponsor to ensure that the relevant approvals are in place.

.

* The study is conducted according to the protocol submitted to the University of the Witwatersrand, Human Research Ethics Committee. Any amendments to the protocol must first be submitted to the Human Research Ethics Committee for approval.

.

* During the study, the University of the Witwatersrand, Human Research Ethics Committee is informed immediately of :

- Any Unexpected Serious Adverse Events or Unexpected Adverse Drug Reactions, which, in the Investigator and/or the Sponsor's opinion are suspected to be related to the study drug. (Refer to POL-IEC–001 and SOP-IEC–005, Item 3.4).
- Any data received during the trial which, may cast doubt on the validity of the continuation of the study .

.

" The University of the Witwatersrand, Human Research Ethics Committee is notified of any decision to discontinue the study and the reason stated.

" The Investigators authorised by this approval participate in this study. Additional Investigators shall be submitted to the University of the Witwatersrand, Human Research Ethics Committee for approval prior to their participation in the study.

" In the event of an authorised Investigator ceasing to participate in the study, the University of the Witwatersrand, Human Research Ethics Committee must be informed and the reason for such cessation given.

2. PRINCIPLES OF INFORMED CONSENT:

" The University of the Witwatersrand, Human Research Ethics Committee requires that in all studies, the Principles of Informed Consent are adhered to. This applies to volunteers as well as patients.

3. PROGRESS REPORTS:

. The University of the Witwatersrand, Human Research Ethics Committee requests that the MCC Progress Reports be submitted twice a year either in March and September or six monthly from start of study to the HREC Secretariat Office - 011 274 9281 and a report of the final results, at the conclusion of the study. (IF APPLICABLE)

4. REIMBURSEMENT TO PATIENTS FOR TRANSPORT:

" The Human Research Ethics Committee: (Medical) is in agreement that reimbursement per visit is according to the South African Health Products Regulatory Authority and that reimbursement should be appropriate according to the situation.

5. TRANSPORT AND STORAGE OF BLOOD AND TISSUE SAMPLES IN SOUTH AFRICA:

" If blood specimens are to be stored for future analysis and is planned that such analysis will be done outside Wits, then the blood must be stored at a facility in South Africa agreed with the relevant IRB, with release of sub-samples only once projects have been approved by the local Research Ethics Committee applicable to where the analysis will be done as well as by the Wits Human Research Ethics Committee: (Medical).

6. GENETIC TESTING

. The Human Research Ethics Committee: Medical; will not approve open-ended genetic testing as this does not fit the Human Research Ethics Committee criteria.

7. GOOD CLINICAL PRACTICE

The South African Department of Health, South African Health Products Regulatory Authority requires Good Clinical Practice (GCP) Training for all Investigators in Clinical Trials, and that GCP training be renewed every three (3) years.

As yet, there are no National Guidelines for the content of GCP courses. Until these are available the Wits Human Research Ethics Committee (Medical) will note courses completed by Investigators without approval of the content of the individual courses.

The above has been noted for the Ethics Committee information and records.

KINDLY FORWARD TO THE RELEVANT INVEST/GA TORS I CRA I STUDY CO-ORD/NA TORS

of the Human Research Ethics Committee: (Medical)

Processed by: Tania Booysen -Tel: 0112749279

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

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submisisons@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

09 April 2021

HREC REF: 224/2021

Prof P Sinxadi
Division of Pharmacology
K-45 OMB
Email: phumla.sinxadi@uct.ac.za
Student: enkosi.mondleki@uct.ac.za

Dear Prof Sinxadi

PROJECT TITLE: PHARMACOKINETIC ANALYSIS OF DOLUTEGRAVIR AND TENOFOVIR IN HIV-POSITIVE SOUTH AFRICANS-MMED CANDIDATE-DR ENKOSI MONDLEKI-SUB-STUDY LINKED TO 403/2019 & 571/2019

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

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

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & 06 July 2020.

Approval is granted for one year until the 30 April 2022.

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)

The HREC acknowledge that the student: - Dr Enkosi Mondleki will also be involved in this study.

Please quote the HREC REF 224/2021 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.

Yours sincerely

Prof Marc Blockman

Digitally signed by Prof Marc Blockman
Date: 2021.04.09 14:54:11 +02'00'

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

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 Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: 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.

SUBMISSION GUIDELINES

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INPAGE MENU

Abridged structure

- Original Research Article
- Editorial
- Case Report
- Clinical Images
- Review Article
- Scientific Letter
- Guidelines
- Obituaries
- Opinion Papers
- Conference Abstracts
- Corrections
- Cover Letter

Full structure

- Original Research Article
- Case Report

Overview

The author guidelines include information about the types of articles received for publication and preparing a manuscript for submission. Other relevant information about the journal's policies and the reviewing process can be found under the about section. The **compulsory cover letter** forms part of a submission and must be submitted together with all the required **forms.** All forms need to be completed in English.

Original Research Article

An original article provides an overview of innovative research in a particular field within or related to the focus and scope of the journal, presented according to a clear and well-structured format.

Word limit	3500-5500 words (excluding the structured abstract and references)
Structured abstract	250 words to cover a Background, Objectives, Method, Results and Conclusion
References	60 or less
Tables/Figures	no more than 7 Tables/Figure

Ethical statement	should be included in the manuscript
Compulsory supplementary file	ethical clearance letter/certificate

Original Research Article full structure

Title: The article's full title should contain a maximum of 95 characters (including spaces).

Abstract: The abstract, written in English, should be no longer than 250 words and must be written in the past tense. The abstract should give a succinct account of the objectives, methods, results, and significance of the matter. The structured abstract for an Original Research article should consist of five paragraphs labelled Background, Objectives, Method, Results and Conclusion.

- Background: *Why do we care about the problem?* State the context and purpose of the study. (What practical, scientific, or theoretical gap is your research filling?)
- Objectives: *What problem are you trying to solve*? What is the scope of your work (e.g., is it a generalised approach or for a specific situation)? Be careful not to use too much jargon.
- Method: *How did you go about solving or making progress on the problem*? State how the study was performed, and which statistical tests were used. (What did you actually do to get the results?) Clearly express the basic design of the study; name or briefly describe the basic methodology used without going into excessive detail. Be sure to indicate the key techniques used.
- Results: *What is the answer*? Present the main findings (that is, as a result of completing the procedure or study, state what you have learnt, invented, or created). Identify trends, relative change, or differences on answers to questions.
- Conclusion: *What are the implications of your answer*? Briefly summarise any potential implications. (What are the larger implications of your findings, especially for the problem or gap identified in your motivation?)

Do not cite references and do not use abbreviations excessively in the abstract.

Introduction: The introduction must contain your argument for the social and scientific value of the study, as well as the aim and objectives:

- Social value: The first part of the introduction should make a clear and logical argument for the importance or relevance of the study. Your argument should be supported by use of evidence from the literature.
- Scientific value: The second part of the introduction should make a clear and logical argument for the originality of the study. This should include a summary of what is already known about the research question or specific topic and should clarify the knowledge gap that this study will address. Your argument should be supported by use of evidence from the literature.
- Conceptual framework: In some research articles it will also be important to describe the underlying theoretical basis for the research and how these theories are linked together in a conceptual framework. The theoretical evidence used to construct the conceptual framework should be referenced from the literature.
- Aim and objectives: The introduction should conclude with a clear summary of the aim and objectives of this study.

Research methods and design: This must address the following:

- Study design: An outline of the type of study design.

- Setting: A description of the setting for the study; for example, the type of community from which the participants came or the nature of the health system and services in which the study is conducted.
- Study population and sampling strategy: Describe the study population and any inclusion or exclusion criteria. Describe the intended sample size and your sample size calculation or justification. Describe the sampling strategy used. Describe in practical terms how this was implemented.
- Intervention (if appropriate): If there were intervention and comparison groups, describe the intervention in detail and what happened to the comparison groups.
- Data collection: Define the data collection tools that were used and their validity. Describe in practical terms how data were collected, and any key issues involved, e.g., language barriers.
- Data analysis: Describe how data were captured, checked, and cleaned. Describe the analysis process, for example, the statistical tests used, or steps followed in qualitative data analysis.
- Ethical considerations: Approval must have been obtained for all studies from the author's institution or other relevant ethics committee and the institution's name and permit numbers should be stated here.

Results: Present the results of your study in a logical sequence that addresses the aim and objectives of your study. Use tables and figures as required to present your findings. Use quotations as required to establish your interpretation of qualitative data. All units should conform to the **SI convention** and be abbreviated accordingly. Metric units and their international symbols are used throughout, as is the decimal point (not the decimal comma).

Discussion: The discussion section should address the following four elements:

- Key findings: Summarise the key findings without reiterating details of the results.
- Discussion of key findings: Explain how the key findings relate to previous research or to existing knowledge, practice, or policy.
- Strengths and limitations: Describe the strengths and limitations of your methods and what the reader should take into account when interpreting your results.
- Implications or recommendations: State the implications of your study or recommendations for future research (questions that remain unanswered), policy or practice. Make sure that the recommendations flow directly from your findings.

Conclusion: Provide a brief conclusion that summarises the results and their meaning or significance in relation to each objective of the study.

Acknowledgements: Those who contributed to the work but do not meet our authorship criteria should be listed in the Acknowledgments with a description of the contribution. Authors are responsible for ensuring that anyone named in the Acknowledgments agrees to be named. Refer to the acknowledgement structure guide on our *Formatting Requirements* page.

Also provide the following, each under their own heading:

- Competing interests: This section should list specific competing interests associated with any of the authors. If authors declare that no competing interests exist, the article will include a statement to this effect: *The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.* Read our **policy on competing interests**.
- Author contributions: All authors must meet the criteria for authorship as outlined in the **authorship** policy and **author contribution** statement policies.
- Funding: Provide information on funding if relevant

- Data availability: All research articles are encouraged to have a data availability statement.
- Disclaimer: A statement that the views expressed in the submitted article are his or her own and not an official position of the institution or funder.

References: Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests. Refer to the journal referencing style downloadable on our *Formatting Requirements* page.

Style and format

File format

- Manuscript files can be in the following formats: DOC, DOCX, or RTF. Microsoft Word documents should not be locked or protected.
- LaTeX documents (.tex) should be converted into Microsoft Word (.doc) before submission online.
- Rich Text Format (RTF): Users of other word processing packages should save or convert their files to RTF before uploading. Many free tools are available that will make this process easier.

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Identify eight keywords that represent the content of your manuscript and are specific to your field or sub-field. Test your keywords: when you enter your keywords into the various journal and academic databases like Google Scholar, do the results include papers similar to your topic? If not, revise the terms until they do.

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AOSIS house style
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References

Referencing style guide
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