Reduced Metformin Concentrations in Obese Women with HIV Treated with Dolutegravir

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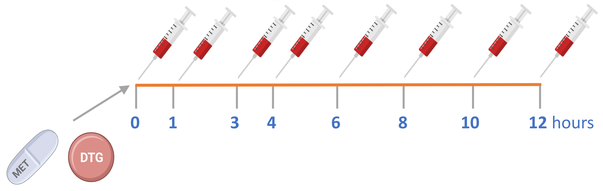
BACKGROUND

- 1 in 3 PWH in sub-Saharan Africa are overweight or obese (BMI ≥30 kg/m^2).
- Obesity is nearly 2-fold higher among women with HIV (WWH) than in men.
- Obesity is closely associated with dysglycemia, and frequently necessitates the co-administration of dolutegravir (DTG) and metformin in PWH.
- A drug interaction study by Song et al in 15 non-obese healthy volunteers showed that DTG 50 mg/day increased the exposure of metformin 1,000 mg/day by **79%**, due to the renal inhibition of metformin excretion.
- **Based on this study, clinical guidelines and drug interaction tools currently recommend that when co-administered with DTG, metformin should be limited to a total dose of 1,000 mg/day.**
- Obesity has been linked to lower metformin exposures, and to date this recommendation for the metformin dose limitation has not been verified in a study in the target population of PWH, many who are obese and female.

Primary aim: To verify metformin plasma concentrations in the increasing population of obese WWH on DTG.

METHODS

- 15 obese, virally suppressed WWH were enrolled.
- At steady-state, Metformin XR 1,000 mg/day and DTG 50 mg/day were administered with a standardised meal after an overnight fast.
- Intensive plasma sampling over 8 timepoints:



- **Primary endpoints:** Area under the concentration-time curve (AUC_{0-24}) and clearance (CL) using non-compartmental analysis in Phoenix WinNonlin.
- **Secondary endpoints:** Associations of plasma concentrations with: ● Body fat composition using dual-energy X-ray absorptiometry (DEXA); ● Renal function; ● Single nucleotide polymorphisms (SNPs) of metformin transporters (OCT2, MATE-1, and MATE2-K).

Limiting metformin to 1,000 mg/day leads to underdosing in obese women with HIV on dolutegravir

RESULTS

- In obese WWH, metformin and dolutegravir plasma concentrations were **approximately half of those observed in the comparator study**.
- Metformin and dolutegravir clearance were 1.7- and 2.2-fold higher, respectively.

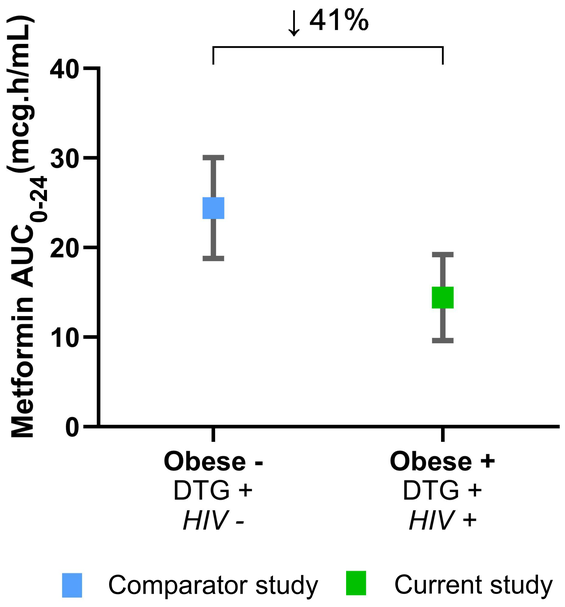


Figure: Comparative metformin area under the concentration-time curves over 24 hours (AUC_{0-24})

	Current study	Comparator study	Difference
N	15	14	
Age (years)	43.8 ± 11.5	37.7	
Female sex, n (%)	15 (100)	27%	
BMI (kg/m^2)	45.6 ± 6.6	18.5–31.0	
Metformin pharmacokinetics			
AUC_{0-24} (mcg.h/mL)	14.42 (33.35)	24.4 (23.1)	**↓40.9%**
CL/F (L/h)	69.33 (33.35)	40.9 (23.1)	**↑69.5%**
DTG pharmacokinetics			
AUC_{0-24} (mcg.h/mL)	24.9 (39.9)	54.6 (25.7)	**↓54.4%**
CL/F (L/h)	2.01 (39.88)	0.91 (26.7)	**↑120%**
C_{trough} (mcg/mL)	0.30 (153.87)	1.25 (33.7)	**↓76%**

- Linear regression did not reveal any associations of body composition, renal function, or SNPs of OCT2, MATE-1, and MATE2-K, with metformin or dolutegravir concentrations.
- The uniform morbidly obese group likely precludes clear associations between plasma concentrations and body composition.

CONCLUSIONS

- The increase in metformin plasma concentrations in obese WWH on DTG were less than previously reported.
- DTG plasma concentrations were also substantially lower versus the comparator, but participants remained virally suppressed.
- Lower drug exposures appear to be primarily due to obesity-related pharmacokinetic changes.
- Restricting metformin to 1,000 mg daily is likely to lead to subtherapeutic concentrations in obese PWH on DTG.
- Additional studies incorporating a wider range of body mass indices and modelling approaches are needed to establish optimal metformin dosing in obese PWH on DTG.
- Our evidence suggests that the uniform metformin dose restriction is inappropriate for the obese population, given metformin's wide therapeutic index and established safety profile.
- Our data support the revision of the current maximum dose restriction of metformin in the target population of obese PWH.

ADDITIONAL KEY INFOMRATION

Body composition on DEXA	**Mean (SD)**
Total mass (kg)	114.1 (13.9)
Fat mass (kg)	60.2 (9.4)
Lean mass (kg)	51.6 (6.7)
Total body fat percentage (%)	52.6 (3.9)
Waist-to-hip circumference ratio	0.86 (0.10)
Renal function	**Mean (SD)**
Serum creatinine (mcmol/L)	73.5 (7.7)
Estimated glomerular filtration rate (mL/min/1.73 m^2)	86.4 (11.6)

- Metformin volume of distribution (Vd/F) was **↑240%** in the current study vs the comparator: **613.6 vs 255.6 L**.

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Acknowledgements:
We gratefully acknowledge the Community and participants of this study, and the staff of FAMCRU and DTHF.