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DOLUTEGRAVIR INTERACTIONS WITH ARTEMETHER-LUMEFANTRINE AND AMODIAQUINE-ARTESUNATE

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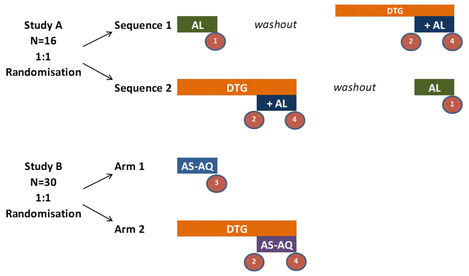
INTRODUCTION

In Sub-Saharan Africa artemisinin-containing therapies (ACTs) for malaria treatment are often co-administered with antiretrovirals. We investigated the drug-drug interaction between the most commonly used ACTs artmether-lumefantrine (AL) or artesunate -amodiaquine (AS-AQ) versus dolutegravir (DTG).

METHODS

Two intensive pharmacokinetic (PK) studies were undertaken in healthy Ugandan volunteers, using standard treatment doses of AL and AS-AQ with 50 mg DTG once daily given with moderate fat meal.

Rich PK sampling was performed after the final doses of AL or AS-AQ, with sampling schedules indicated in schema below.



Study A: The **DTG/AL interaction** was evaluated using a two-way cross-over study design (n=16) with 1:1 randomisation. After 21 days (washout period), the opposite drug regimen was administered.

Study B: The **DTG/AS-AQ interaction** was evaluated with 1:1 randomization using a parallel study design (n=30) due to the long half-life of the AQ metabolite, desethylamodiaqine [DEAQ]).

PK sampling

1. **AL-** 0,1,2,3,4,8,12,24,48,72,96,168,264 h post 6th dose
2. **DTG-** 0,1,2,3,4,8,12,24 h
3. **AS-AQ-** 0,1,2,3,4,8,12,24,48,72,96,120,228,624h post 3rd dose
4. **DTG and ACT-** time points detailed above

LABORATORY AND CLINICAL ASSESSMENTS

Clinical and laboratory adverse events (AE) were reported using DAIDS criteria. Artemether (ARM), dihydroartemisinin (DHA), lumefantrine (LF), desbutyl- lumefantrine (DBL), artesunate (ARS), amodiaquine (AQ) and DEAQ were measured over 0-264h (Study A) and 0-624h (Study B) using validated LC-MS/MS. Noncompartmental analysis was performed using WinNonlin (Phoenix, version 6.1, Pharsight, CA). Geometric mean ratios (GMR; 90% CI) for antimalarials +/- DTG for C_{max}, T_{max} and AUC to last measurable time point (AUC_{last}) were computed in Study A, and Mann Whitney U tests (SPSS, version 22; Chicago, IL) compared these parameters in Study B.

RESULTS

Study A (ARM/DHA/LF/DLF/DTG)

N=14: No statistical differences were seen between sequences 1 and 2.

Impact of DTG on AL Pharmacokinetics: Addition of DTG did not result in significant changes in pharmacokinetic (PK) parameters (C_{max}, T_{max}, AUC_{0-t}) for ARM, DHA, LF, and DBL.

A) **Artemether**

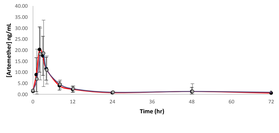


Fig 1

B) Dihydroartemisinin (DHA)

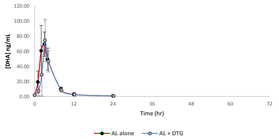


Fig 2

C) Lumefantrine

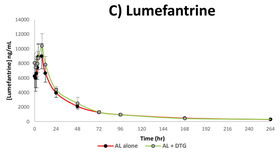


Fig 3

D) Desbutyl-lumefantrine (DBL)

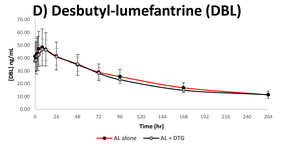


Fig 4

Artemether and Lumefantrine PK parameters

Study A (n=14)	AL alone [GM (90% CI)]	AL+ DTG [GM (90% CI)]	GMR (90%CI)
Artemether			
C_{max} (ng/mL)	31.93 (20.60, 43.26)	27.88 (10.30, 45.47)	0.87 (0.67, 1.14)
T_{max} (h)	2.03 (1.64, 2.43)	2.16 (1.75, 2.56)	1.06 (0.84, 1.34)
AUC_{0-t} (ng.h/mL)	129.58 (79.35, 179.82)	136.44 (60.29, 212.59)	1.05 (0.84, 1.32)
Dihydroartemisinin			
C_{max} (ng/mL)	110.43 (92.86, 127.99)	89.91 (71.07, 108.74)	0.81 (0.64, 1.03)
T_{max} (h)	2.31 (1.98, 2.64)	2.70 (1.99, 3.42)	1.17 (0.92, 1.49)
AUC_{0-t} (ng.h/mL)	389.26 (344.52, 434.01)	357.26 (274.89, 439.63)	0.92 (0.79, 1.07)
Lumefantrine			
C_{max} (ng/mL)	9975 (8318, 11633)	11203 (9533, 12873)	1.12 (0.97, 1.29)
T_{max} (h)	3.92 (2.49, 5.35)*	6.48 (1.43, 11.54)#	**1.65 (1.02, 2.69)**
AUC_{0-t} (ng.h/mL)	389350 (333607, 445092)	429736 (379911, 479561)	1.10 (0.96, 1.27)
Desbutyl-lumefantrine			
C_{max} (ng/mL)	51 (37, 66)	49 (41, 58)	0.97 (0.79, 1.18)
T_{max} (h)	4.78 (3.43, 6.12)	9.52 (4.48, 14.56)#	**3.00 (2.06, 4.36)**
AUC_{0-t} (ng.h/mL)	6299 (4803, 7795)	6048 (5235, 6862)	0.96 (0.80, 1.15)

**one subject had a T_{max} at 0 hours; # one subject had a T_{max} at 48 hours as a secondary peak*

Impact of AL on DTG exposure

A) Dolutegravir ± AL

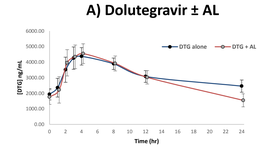


Fig 5 Summary PK data

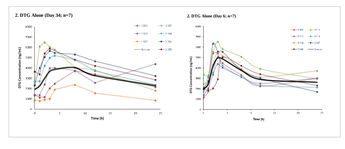


Fig 6 Individual PK profiles

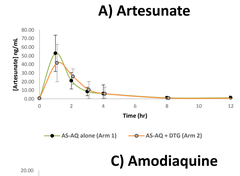
Study A (n= 14)	DTG alone [GM (90% CI)]	DTG+ AL [GM (90% CI)]	GMR (90%CI)
C_{24} (ng/mL)	2456.50 (2062.40, 2850.61)	1543.11 (1121.59, 1964.64)	**0.63 (0.48, 0.82)**
C_{max} (ng/mL)	5018.44 (4511.68, 5525.19)	5216.45 (4623.51, 5809.38)	1.04 (0.92, 1.18)
T_{max} (h)	3.94 (1.41, 6.46)	3.00 (1.89, 4.10)	0.90 (0.66, 1.24)
AUC_{0-24} (h.ng/mL)	78753 (70615, 86891)	73738 (63420, 84056)	0.94 (0.86, 1.02)

The 37% decrease in DTG C_{24} when given with AL may have been driven in part by an unexplained rise in C_{24} in some subjects on DTG only *(Fig 6)* . No significant changes were observed for DTG AUC_{0-24} or C_{max}.

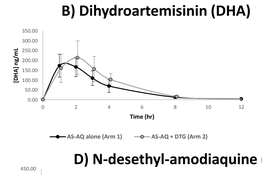
Study B ARM/DHA/AQ/DEAQ/DTG:

Impact of DTG on AS-AQ Pharmacokinetics: There were no statistically significant differences in AUC_{0-t} for ARS (p=0.77), DHA (p=0.28), AQ (p=0.17) and DEAQ (p=0.69) between subjects administered AS-AQ alone (N=13) and those receiving DTG(N=12).

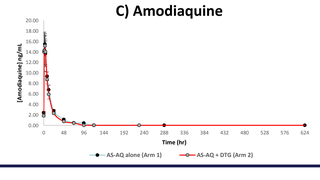
A) Artesunate



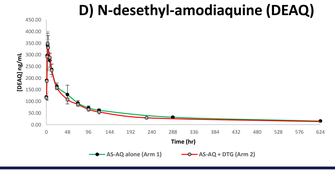
B) Dihydroartemisinin (DHA)



C) Amodiaquine



D) N-desethyl-amodiaquine (DEAQ)



Artesunate-Amodiaquine PK parameters

Study B	AS-AQ alone (Arm 1, n=13) [GM (90% CI)]	AS-AQ + DTG (Arm 2, n=12) [GM (90% CI)]	P value
Artesunate			
C_{max} (ng/mL)	61.29 (41.54, 81.04)	52.01 (31.70, 72.33)	0.650
T_{max} (h)	1.17 (0.78, 1.56)	1.66 (1.14, 2.17)	0.106
AUC_{0-t} (ng.h/mL)	128.38 (90.81, 165.94)	115.71 (83.22, 148.21)	0.768
Dihydroartemisinin			
C_{max} (ng/mL)	217.66 (157.37, 277.95)	290.43 (197.26, 383.59)	0.205
T_{max} (h)	1.58 (1.16, 2.00)	2.02 (1.52, 2.52)	0.277
AUC_{0-t} (ng.h/mL)	788.25 (622.06, 954.43)	946.78 (760.15, 1133.40)	0.270
Amodiaquine			
C_{max} (ng/mL)	17.79 (14.91, 20.68)	19.17 (15.95, 22.39)	0.639
T_{max} (h)	2.36 (1.06, 3.65)	1.97 (1.43, 2.51)	0.635
AUC_{0-t} (ng.h/mL)	256.14 (222.52, 289.76)	225.02 (198.93, 251.10)	0.137
N-desethylamodiaquine			
C_{max} (ng/mL)	393.96 (325.91, 462.01)	385.57 (346.81, 424.33)	0.883
T_{max} (h)	2.68 (1.88, 3.49)	3.38 (2.41, 4.36)	0.449
AUC_{0-t} (ng.h/mL)	31492 (28720, 34264)	26943 (22913, 30973)	0.689

Impact of AS-AQ on DTG exposure

B) Dolutegravir ± AS-AQ

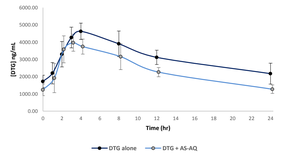


Fig 7

Co -administration of DTG with AS/AQ resulted in a statistically significant decrease of approximately 42% and 24% in DTG C_{24} and AUC_{0-24}

Study B (n=12)	DTG alone [GM (90% CI)]	DTG + AS-AQ [GM (90% CI)]	GMR (90%CI)
C_{24} (ng/mL)	2174.32 (1567.34, 2781.30)	1271.93 (1025.47, 1518.40)	**0.58 (0.50, 0.69)**
C_{max} (ng/mL)	5114.41 (4562.16, 5666.66)	4666.70 (3940.04, 5393.36)	0.91 (0.80, 1.04)
T_{max} (h)	3.69 (2.72, 4.65)	2.66 (1.82, 3.50)	0.72 (0.50, 1.04)
AUC_{0-24} (h.ng/mL)	77936 (67804, 88068)	59490 (52479, 66502)	**0.76 (0.69, 0.84)**

Safety and Tolerability

All AEs were Grade 1 or 2 in severity with more predominantly gastro-intestinal AEs, among participants who received AS-AQ. No serious adverse events were reported.

CONCLUSION

- **Standard doses of AL and AS-AQ should be used in patients receiving DTG.**
- **The combination with ACTs was well tolerated.**
- **The statistically significant decreases in DTG C_{trough} with AL and in DTG C_{trough} and AUC with AS-AQ is unexplained, but unlikely to be of clinical significance. In every participant, C_{24} was comparable to or above 1100ng/mL, which is the mean C_{trough} observed in prior DTG Phase 3 trials of non-pregnant women, and considerably above the protein adjusted IC_{90} of DTG (64ng/mL). Moreover, any impact on DTG exposure is likely to be brief given the short duration of antimalarial therapy.**

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