Reduced artemether-lumefantrine exposure in HIV-infected Nigerian subjects on nevirapine-based antiretroviral therapy

FA Fehintola, L Huang, KK Scarsi, KM Darin, GD Morse, OO Akinyinka, FT Aweeka, S Parikh

May 19, 2014
15th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy

Background

- Artemesinin-based combination therapies (ACT) are standard treatment for malaria
  - Artemether/lumefantrine is the most widely used ACT
- Nevirapine (NVP) is routinely co-prescribed with ACTs in HIV/malaria endemic regions
- Existing data about the impact of NVP-based ART on artemether/lumefantrine exposure are variable

	Artemether	Dihydroartemisinin	Lumefantrine	NVP
Byakika-Kibwika et al. JAC 2012:69:2213-21	↓ 70%	↓ 38%	↓ (NS)	↓ 46%
Kredo et al. AAC 2011;55:5616-23	↓ (NS)	↓ 25%	↑ 37%	n/a
Chijioke-Nwauche et al. AAC 2013;57(9):4146	n/a	n/a	↑ 29%*	n/a

NS = non-significant

*7 day concentration, in subjects with malaria

WHO. Guidelines for the treatment of malaria.

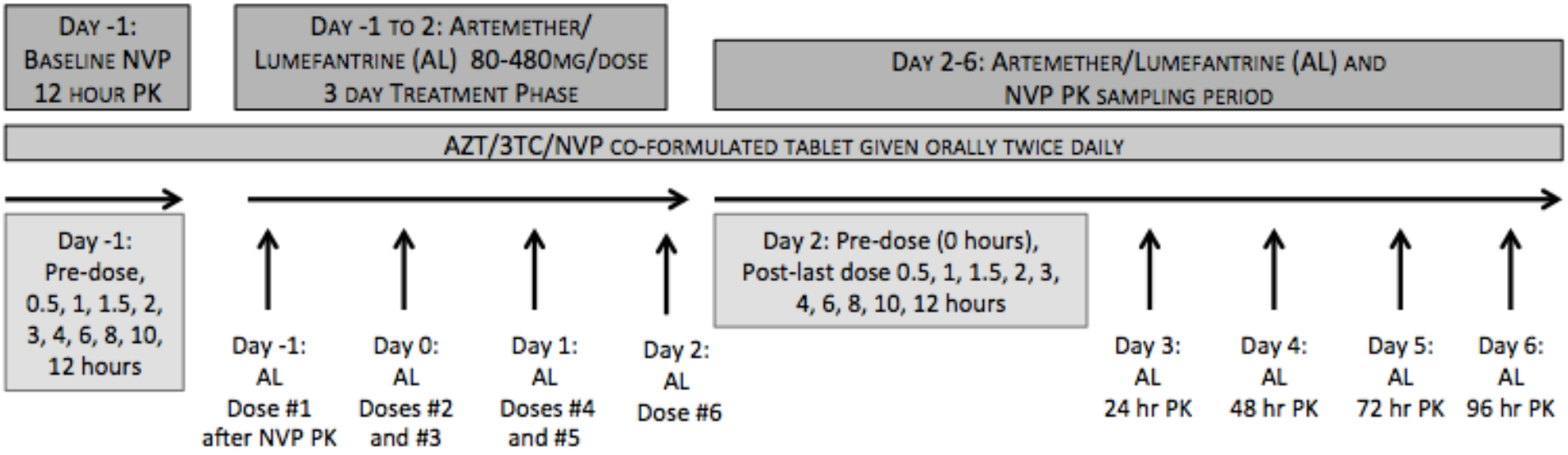
Pharmacokinetic properties

- **Artemether:** quickly metabolized to an active metabolite, **dihydroartemisinin (DHA),** predominately by CYP3A4
  - DHA is subsequently conjugated by UGT1A1, 1A8/9, and 2B7[2]
  - Artemether may also induce CYP3A4 activity
- **Lumefantrine:** long-acting component of the ACT; metabolized by CYP3A4
- **NVP**: Metabolite and inducer of CYP3A4 and 2B6
- Exposure-response relationship: lumefantrine concentrations correlate with malaria recurrence
- **Study objective**: Determine the exposure of artemether, DHA and lumefantrine in combination with NVP-based ART

Kiang et al. Clin Pharmacokinet. 2014 53:151-53

Methods

- Open label, study of 11 HIV-infected, otherwise healthy Nigerian subjects already receiving NVP-based ART (**NVP group**)
- Co-formulated artemether/lumefantrine (AL) 80/480mg was given twice daily for 3 days (6 doses)
- Subjects received a traditional Nigerian meal with each AL dose



Methods

- **Nevirapine concentrations** were compared within the NVP group before and during artemether/lumefantrine therapy
- **Artemether, DHA, and lumefantrine concentrations** were compared to HIV-uninfected historical controls (**Control group**) [1]
- Drug concentrations were quantified using validated LC-MS[2] (artemether, DHA, and lumefantrine) and HPLC-UV (nevirapine) methods
- PK parameters were determined using non-compartmental analysis WinNonlin/Phoenix (Pharsight Corporation, Mountain View, CA).

1. Huang et al. JAIDS. 2012; 61:210-6.
2. Huang et al. J Pharm Biomed Ana. 2009;50:959-65.

Demographics

	Control group (n=16)	NVP group (n=11)	p-value
Female sex	4 (25%)	9 (81.8%)	<0.01
Age, years	33 (24-53)	37 (31 – 59)	0.13
Weight, kg	77 (86-93)	66 (56 – 92)	0.5
Time on NVP, years	---	3.5 (2 – 5.6)	---
HIV-RNA, % undetectable	---	9 (81.8%)	---
CD4, cells/mm^3	---	388 (218 – 549)	---

Sex and HIV-RNA presented as n (%).
Age, weight, time on NVP, CD4 presented as median (range).

Artemether/DHA pharmacokinetic parameters

	Control Group n=16	NVP Group n=11	% Change (p-value)
Artemether			
C_{max} (ng/mL)	19.1 [13.2, 27.5]	6.0 [4.1, 9.0]	**↓ 68 (<0.01)**
T_{max} (hr)	1.0 (0.5)	1.5 (2.5)	↑ 50 (0.12)
AUC_{last} (hr•ng/mL)	53.9 [35.0, 83.0]	18.9 [11.9, 30.0]	**↓ 65 (0.02)**
$t_{1/2}$ (hr)	3.9 (3.8), n=12	2.2 (3.3), n=6	↓ 44 (0.16)
DHA			
C_{max} (ng/mL)	61.4 [47.7, 78.9]	47.3 [35.5, 63.1]	↓ 23 (0.37)
T_{max} (hr)	1.0 (1.0)	1.5 (2.0)	↑ 50 (0.54)
AUC_{last} (hr•ng/mL)	177 [142, 222]	180 [143, 227]	↑ 2 (0.88)
$t_{1/2}$ (hr)	1.9 (2.2)	2.6 (1.8)	↑ 37 (0.37)

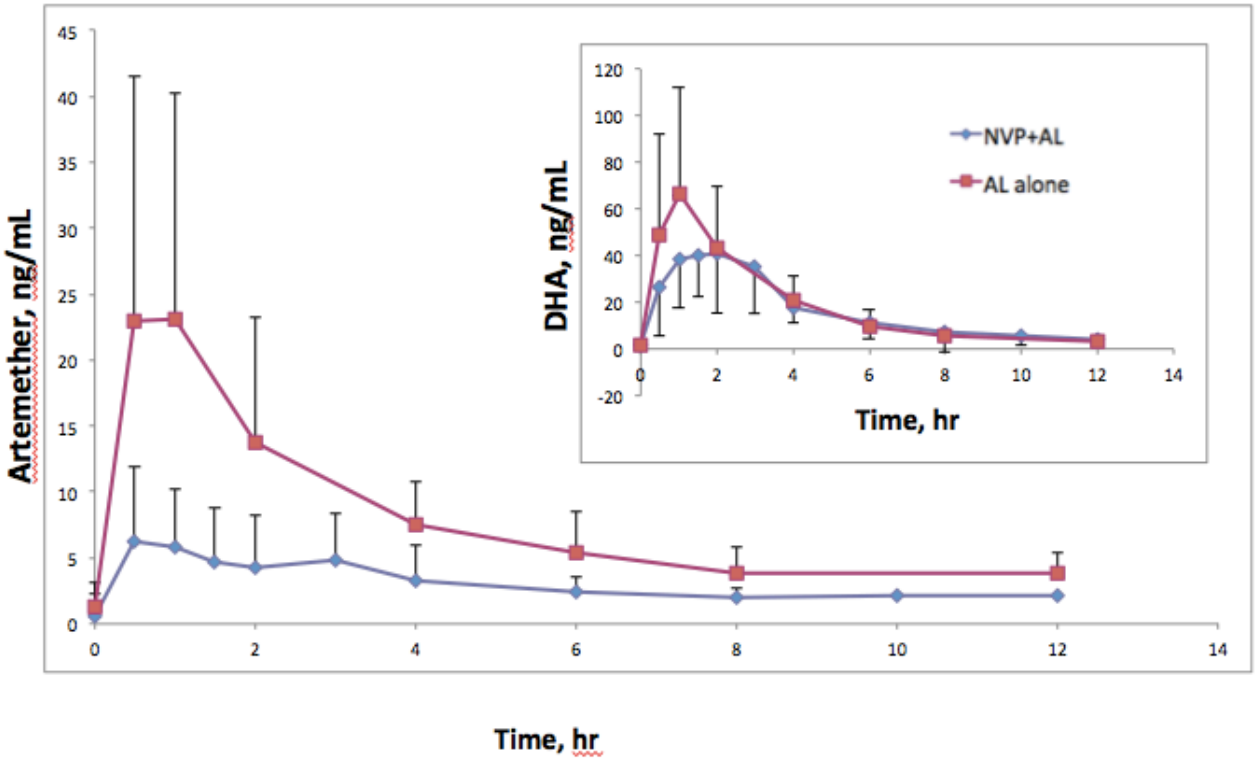
C_{max} and AUC_{last} are presented as geometric mean with 90% confidence intervals
T_{max} and $t_{1/2}$ are presented as median (IQR)
Patients with a minimum of 3 samples in the elimination phase were used to calculate $t_{1/2}$

Artemether/DHA

	Control Group n=16	NVP Group n=11	% Change (p-value)
Artemether			
AUC_{last} (hr•ng/mL)	53.9 [35.0, 83.0]	18.9 [11.9, 30.0]	**↓ 65 (0.02)**
DHA			
AUC_{last} (hr•ng/mL)	177 [142, 222]	180 [143, 227]	↑ 2 (0.88)

AUC_{last} ratio of DHA:artemether =

Control group = 3.3
NVP group = 9.5

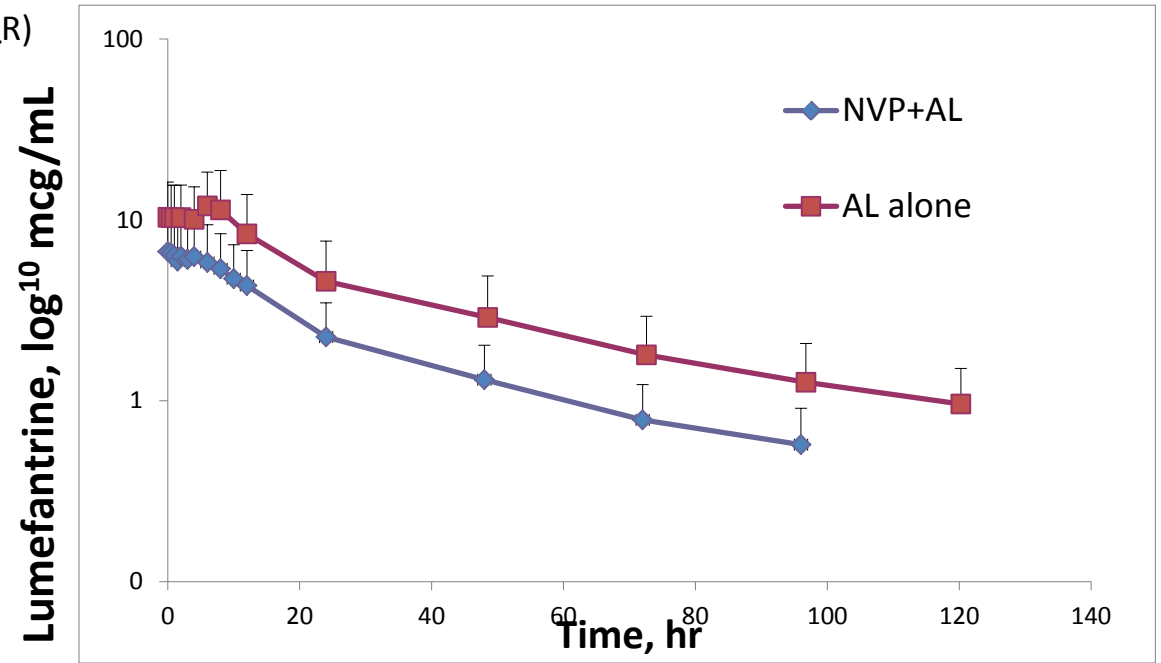


Lumefantrine pharmacokinetic parameters

	Control Group n=16	NVP Group n=11	% Change (p-value)
C_{max} (mcg/mL)	11.0 [8.0, 15.0]	5.81 [3.50, 9.65]	↓ 47 (0.07)
T_{max} (hr)	2.0 (4.0)	2.0 (6.0)	---
$AUC_{0-\infty}$ (hr•mcg/mL)	426 [298, 609]	180 [117, 278]	**↓ 58 (0.016)**
$t_{1/2}$ (days)	4.8 (3.0)	1.6 (0.6)	**↓ 66 (<0.01)**

C_{max} and $AUC_{0-\infty}$ are presented as geometric mean with 90% confidence intervals
T_{max} and $t_{1/2}$ are presented as median (IQR)

- Lumefantrine exposure was reduced 58% in subjects receiving NVP-based ART.



Nevirapine pharmacokinetic parameters

	Pre- AL n=11	Concurrent AL n=11	% Change (p-value)
C_{max} (mcg/mL)	6.4 [5.4, 7.4]	6.3 [5.3, 7.4]	↓ 2 (0.86)
T_{max} (hr)	1.5 (0.5)	2 (0.5)	↑ 33 (0.07)
AUC_{last} (hr•mcg/mL)	52.1 [39.9, 64.4]	54.2 [42.0, 66.5]	↑ 4 (0.25)
C_{12h} (mcg/mL)	3.7 [2.7, 4.7]	3.7 [2.5, 4.8]	--- (0.48)

C_{max}, AUC_{last}, and C_{12h} are presented as geometric mean with 90% confidence intervals
T_{max} is presented as median (IQR)
AL: artemether/lumefantrine

- No change was observed in NVP exposure.

Discussion

- **Artemether and lumefantrine exposure**: significantly lower in subjects receiving NVP-based ART
- **DHA or NVP exposure**: no change observed

	Artemether	DHA	Lumefantrine	NVP
Byakika-Kibwika et al. JAC 2012:69:2213-21	↓ 70%	↓ 38%	↓ (NS)	↓ 46%
Kredo et al. AAC 2011;55:5616-23	↓ (NS)	↓ 25%	↑ 37%	n/a
Chijioke-Nwauche et al. AAC 2013;57(9):4146	n/a	n/a	↑ 29%*	n/a
Fehintola et al.	**↓ 65%**	**No change**	**↓ 60%**	**No change**

NS = non-significant

*7 day concentration, in subjects with malaria

Discussion

- **Potential limitations**
  - Historical control group, not HIV-infected, with dietary, gender and racial differences
  - Unable to compare our results to those with 7 day (120 hour) lumefantrine concentration results
  - Subjects with malaria may have variable artemether/lumefantrine exposure

- **Future directions**
  - Compartmental analysis to further elucidate metabolite pharmacokinetics
  - Urgent need to evaluate the impact of decreased ACT exposure on malaria outcomes

Acknowledgements

- We gratefully acknowledge the time and commitment of the study participants who made this evaluation possible.

- The study team:
  - University of Ibadan and the University College Hospital, Ibadan, Nigeria
  - Northwestern University, Chicago, IL, USA
  - University at Buffalo, Translational Pharmacology Research Core, Buffalo, NY, USA
  - UCSF, Drug Research Unit, San Francisco, CA, USA

- Supported by the Fogarty International Center, NIH
  - Grant # 1D43TW007995 and 1D43TW007991