

Altered plasma levels of nevirapine after commencing rifampicin containing TB regimens in Malawi

Mas Chaponda,

W Nyirenda, V Watson, S White, JJ van
Oosterhout, J Kumwenda, D G Lalloo, M Pirmohamed,
R Heyderman, H Mwandumba, S H Khoo



The ARV scale up in Malawi

- 1 million of the total 12 million population are HIV-1 infected
- Massive scale up in provision
End 2009: 250,840 started
- Fixed dose Combination
Triomune®
- TB is the most common route of presentation in adults
- 80% of TB cases HIV Positive



WHO 2009 Recommendation

All HIV-TB patients to start ART during TB therapy
EFV-containing regimens preferred
(In Malawi, nevirapine based ART is used with no dose modification)

**The reduction in nevirapine exposure (AUC
↓36-42%) by rifampicin is well characterised**

Manosuthi, CID, 2009,
Boulle JAC 2008
Riberia, JAIDS, 2001

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Dose Increment

Thai data [Ruxrungtham, Antiviral therapy 2008,13:539-536]

- N=32
- NVP 400mg/day: 6/16 suboptimal
- NVP 600mg/day: 4/16 developed hypersensitivity

South African data [McIlleron, EJCP 2009, 65:71-80]

- N=27,
- RiF + NVP: C_{min} was 39% lower with co-administration
- Simulation 300 mg bd likely to provide adequate exposure

India data [Rachachanran JAIDS 2006, 41:36-41]

- N=13
- C_{trough} <MEC in 8/13 patients
- Dose increment to 300mg bd restored NVP troughs to therapeutic range in 7/7 patients
- No toxicity observed

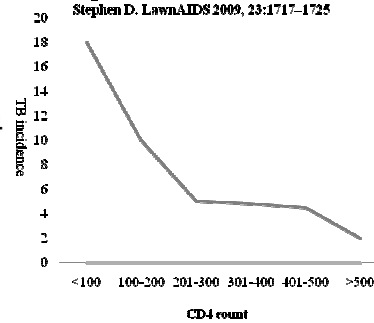
Incident TB whilst on ART

ART reduces, but does not eliminate TB in high prevalence settings

Different treatment scenario

- No lead in dose
- Risk of HSR lower
- Induction is taking place over 10-14 days
- ? Increase NVP dose
- ?If so, when ?

Tuberculosis incidence rates cases/100 person-years against serially updated CD4 cell counts
Stephen D. Lawn AIDS 2009, 23:1717-1725



WHO 2009 Recommendation

Continue ART and start TB treatment

Limited data on the impact of rifampicin on patients stable on nevirapine containing ART who develop TB.

AIMS

Primary

- To determine the effect of rifampicin on plasma nevirapine AUC in patients on steady-state nevirapine containing ART who are commencing TB Rx

Secondary

- Proportion of C_{trough} below MEC
- Sequential trough sampling at day 3 and 7 to determine the optimal time for dose increment (if indicated)
- Safety

Methods

- A prospective cohort study
- 10 male, 10 female patients
- Stable on NVP containing ART (200mg twice daily greater than 1 month)
- Starting rifampicin containing TB treatment
- Exclusion age < 18, NVP < 1 month, abnormal LFTs
- Nevirapine levels were measured by LC-MS at the University of Liverpool.

Methods

Day 0

- Truncated NVP AUC_{0-8hrs}

Day 3,7

- Day 3 + NVP trough
- Day 7 + NVP trough

Day 14

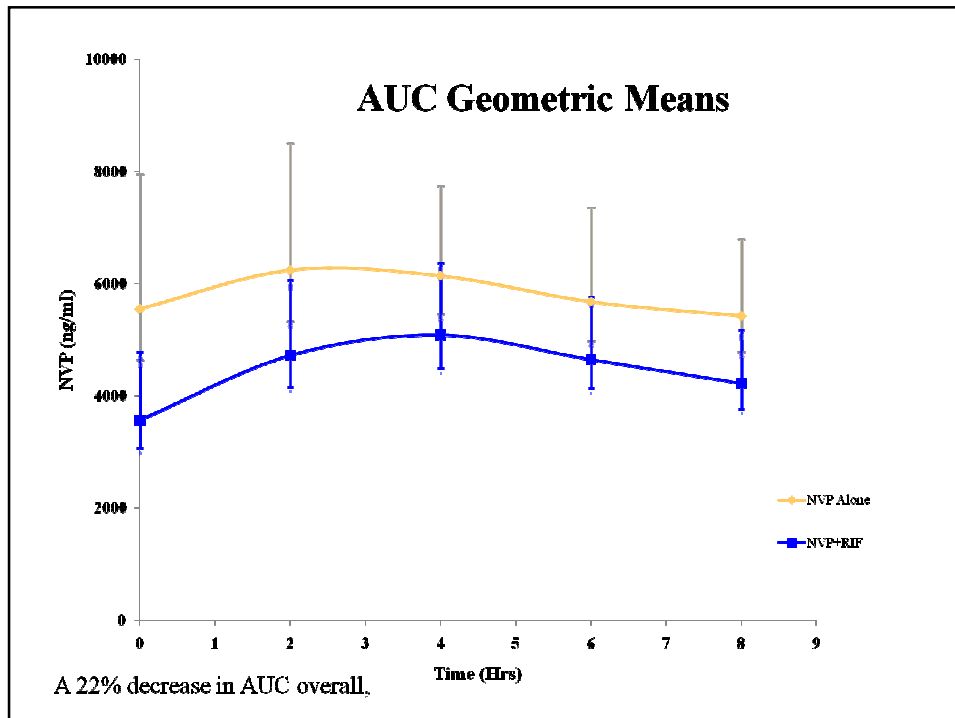
- Truncated NVP AUC_{0-8hrs}

Demographics

- Gender 10 Male, 10 Female
- Median CD4 206
- BMI average 19.4
- ART Duration 1.5 Months
- WT<50kg 9 patients

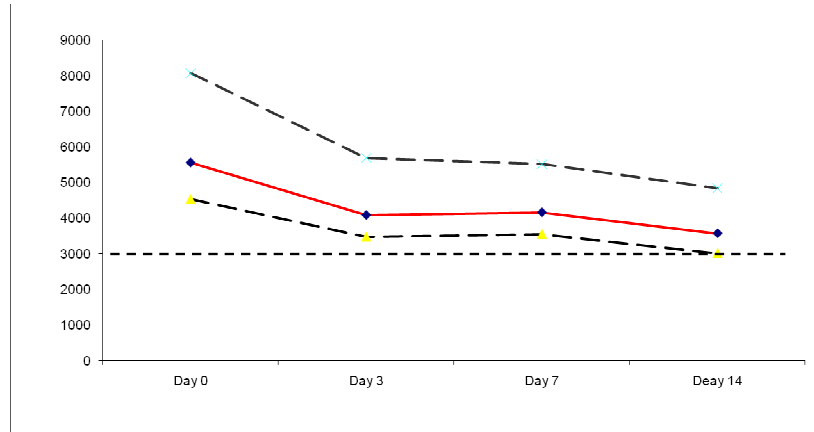
NVP PK

	-RIF	+RIF	GMR	90% CI
AUC0-8 (ng.h/ml)	47325	36839	0.78	0.72,0.89
Cmax (ng/ml)	6672	5223	0.78	0.72,0.91
Tmax (h)	3.15	4.11	1.31	1.17,2.05
C ₀ (ng/ml)	5552	3568	0.64	0.59,0.79



Change in NVP troughs with Rif over 14 days

Day 3 gives the greatest mean drop in NVP levels of 21.3 %



6 patients (30%) troughs <MEC 3000 by day 14

Day 0	Day 3	Day 7	Day 14
19446	10129	10692	10161
5174	3659	3345	3686
7889	4824	4317	3669
3292	4538	5330	4565
6287	3929	3983	4308
7219	6329	6707	6463
9230	5528	4863	4734
5203	4454	2855	3018
3713	2861	2367	3052
8533	7423	6865	6457
5945	3515	2958	2936
10210	9852	7190	3278
4618	3527	3569	2903
2563	2895	3208	2763
2820	2016	2787	1883
4208	2659	2432	1985
6918	1581	6203	3475
5034	2599	2893	1606
4291	5963	4311	3897
3371	3366	3738	3632

Sub therapeutic patients

- Gender 3 male, 3 female
- BMI
17.25, 18.89, 25.26,
24.97, 18.20, 18.63
- Compliance by pill count deemed to be good

Safety

- LFTs Normal at baseline and day 14
in all 20pts, no grade 2/3 rise
- HSR No skin hypersensitivity reactions

Conclusion

- 22% decrease AUC
- 30% sub therapeutic
- Decrease in exposure apparent by day 3
- No increase in liver toxicity observed

Planned study

RCT of 200/200mg vs 400/200mg
Increment at day 3

Outcomes

- PK
- Safety / tolerability
- Viral load, resistance, CD4 count

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