

The pharmacokinetics of lopinavir in South African HIV-infected volunteers receiving rifampicin with adjusted doses of lopinavir/ritonavir

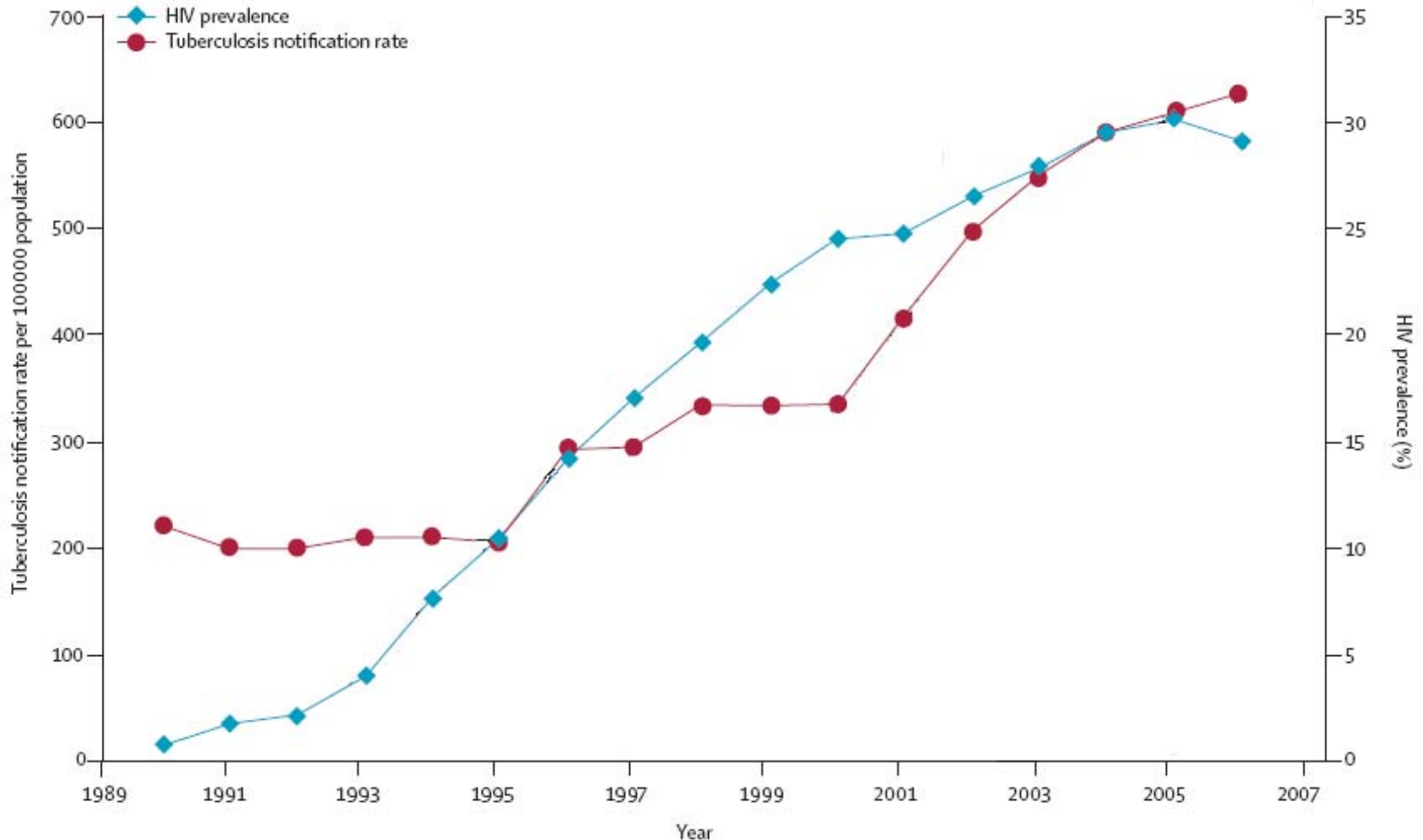


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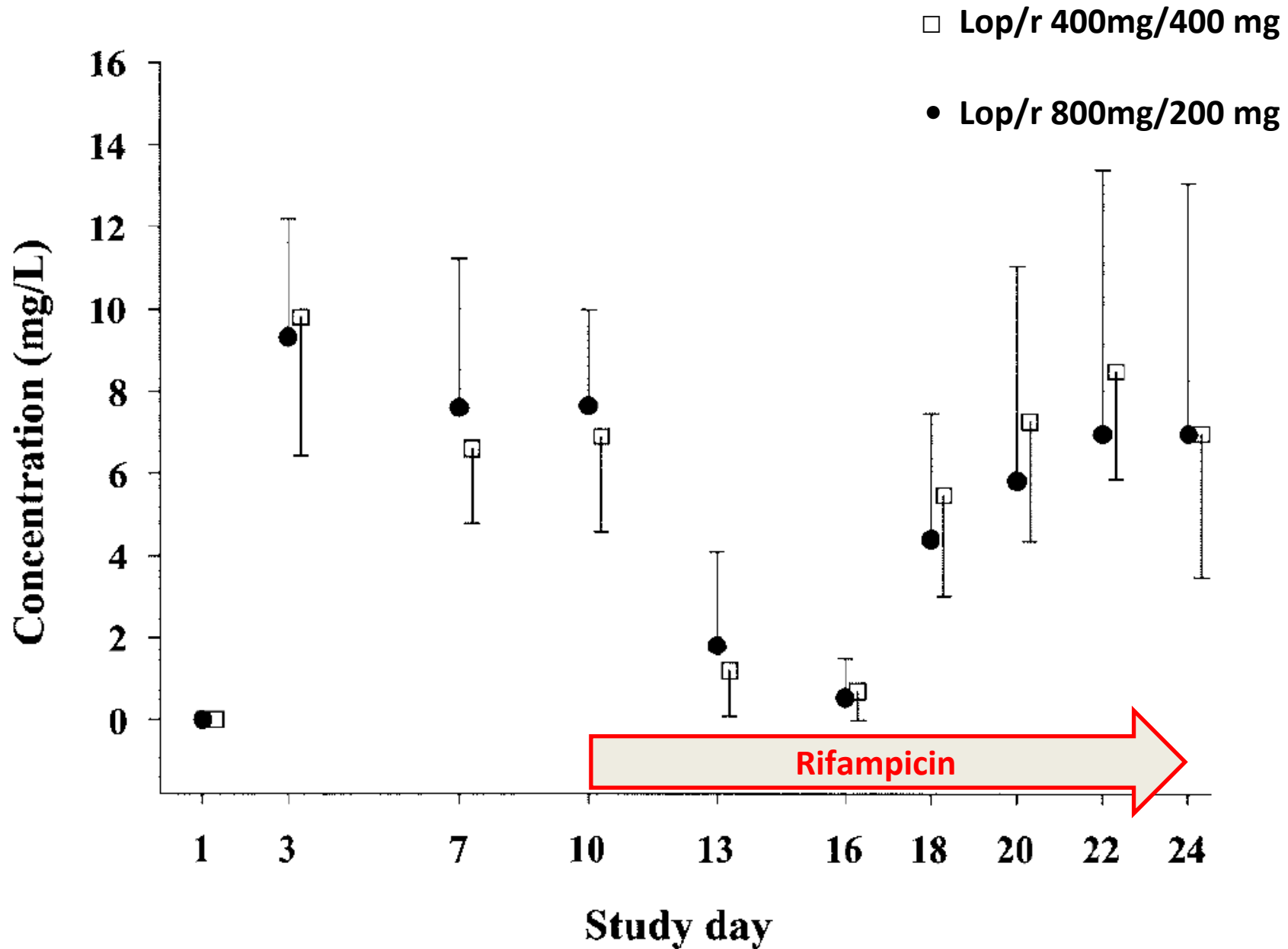
HIV & TB epidemics in South Africa



Adapted from Karim et al *Lancet* 2009

- Protease inhibitors
 - are key components of second line ART regimen
 - Lopinavir/ritonavir (LPV/r)
- LPV/r are substrates of CYP 3A4 & p-glycoprotein
- Rifampicin is a potent inducer of CYP 3A4 & p-glycoprotein
- Rifampicin & LPV/r co-administration causes marked reductions in LPV/r concentrations
- Rifabutin not currently an option for resource limited countries

BACKGROUND



La Porte et al *Antimicrob Agents Chemother* 2004

- High incidence of hepatotoxicity experienced in healthy volunteers on adjusted dose PIs & rifampicin
 - Follow-up LPV/r tablet formulation
 - Atazanavir & saquinavir
 - FDA warning
- Sequence of drug initiation important
 - risk higher when rifampicin given first
- Hepatotoxicity risk may be different in HIV+
 - risk of hepatotoxicity with rifampicin + PZA for latent TB very high in HIV negative, but not HIV positive

Nijland et al *AIDS* 2008

Haas et al *J Acquir Immune Defic Syndr* 2009

Grange et al *6th Int Workshop on Clin Pharm of HIV Ther* 2005

Gordon et al *Clin Infect Dis* 2004

- Study rationale:
 - Increasing use of second line ART
 - Need data from HIV+ patients
 - Additional ritonavir more complex than double doses

- Cohort HIV-infected adults:
 - Established on LPV/r (400 mg / 100 mg) + 2 NRTIs
 - Undetectable viral load
 - Medically well without acute or other chronic illness
- Evaluated steady state pharmacokinetics of LPV under 4 sequential treatment conditions:

Study week	LPV/r dose (12 hourly)	Rifampicin dose (daily)
1	400 mg / 100 mg	Not given
2	400 mg / 100 mg	600 mg
3	600 mg / 150 mg	600 mg
4	800 mg / 200 mg	600 mg

1. Describe steady state LPV pharmacokinetics at each study week

Intensive sampling:

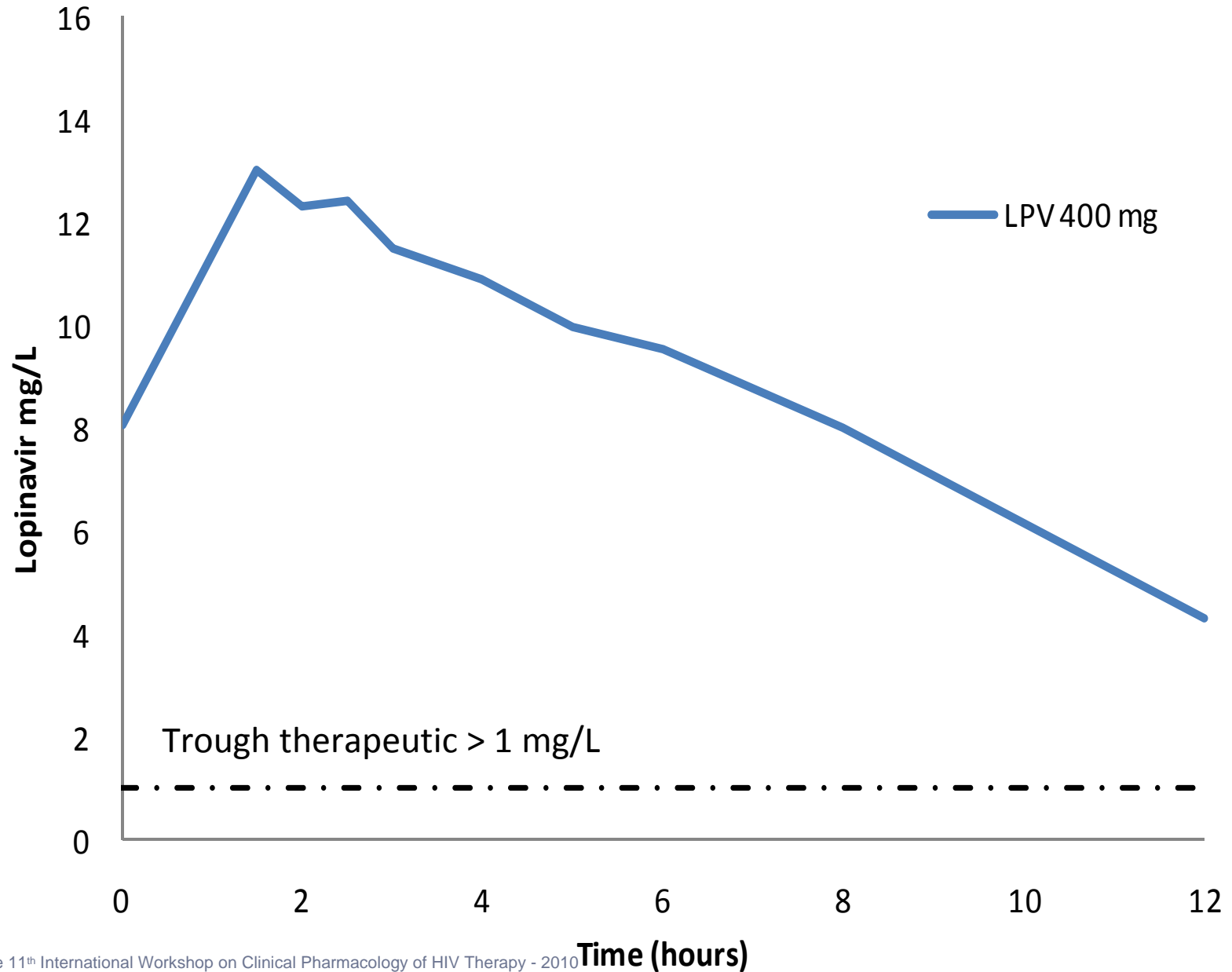
pre-dose, 1.5 h , 2 h, 2.5 h , 3 h, 4 h, 5 h, 6 h, 8 h 12 h

2. Evaluate adverse events throughout study period

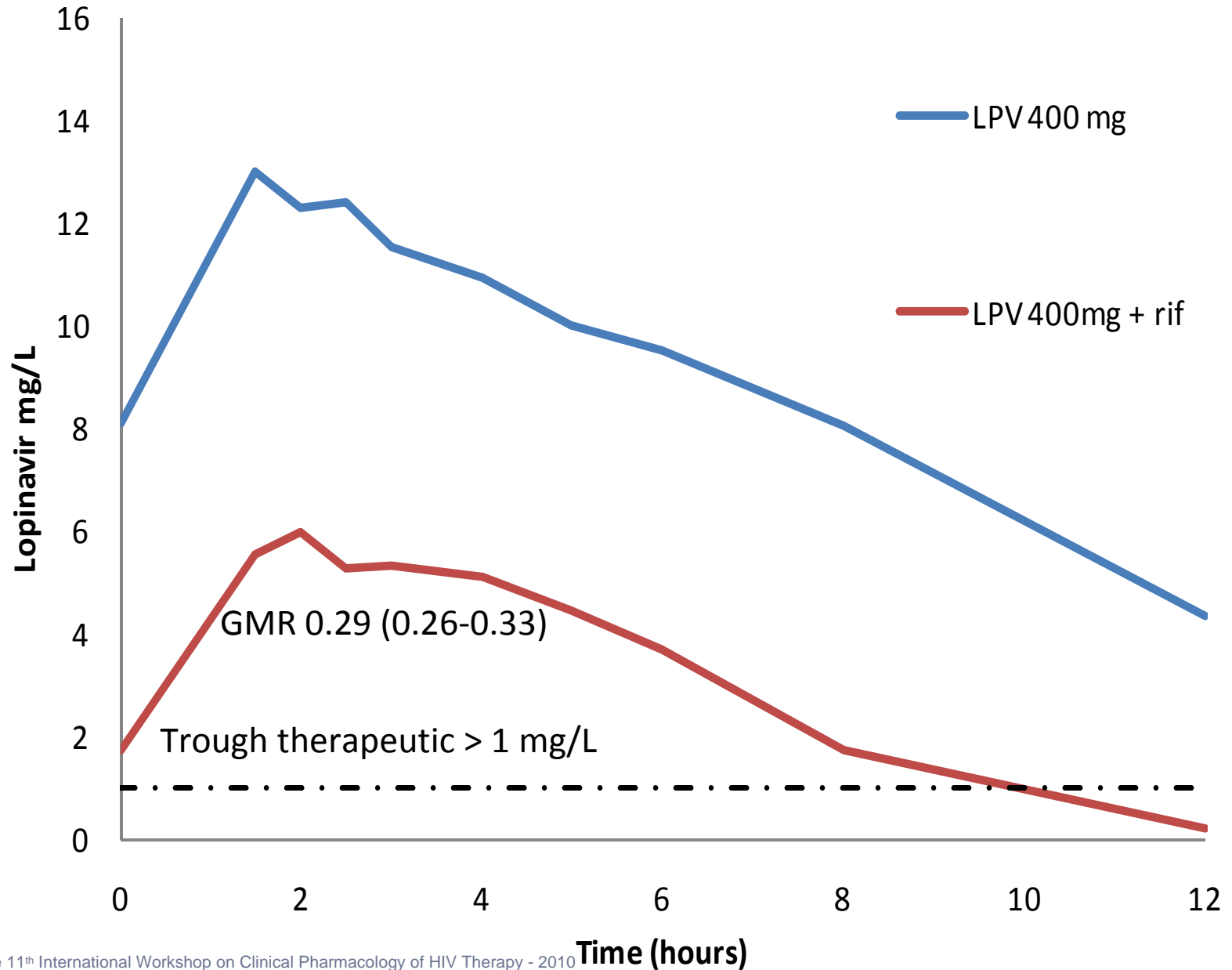
BASELINE CHARACTERISTICS (n =21)

Age	36.1 ± 7.1 years
Female	18/21 (86%)
Body mass index	26.2 ± 5.8 kg/m ²
CD4+ count	543 ± 216 cells/mm ³
Creatinine	63.6 ± 16.0 µmol/L
Albumin	41.2 ± 2.7 g/L
Random cholesterol	5.1 ± 1.2 mmol/L

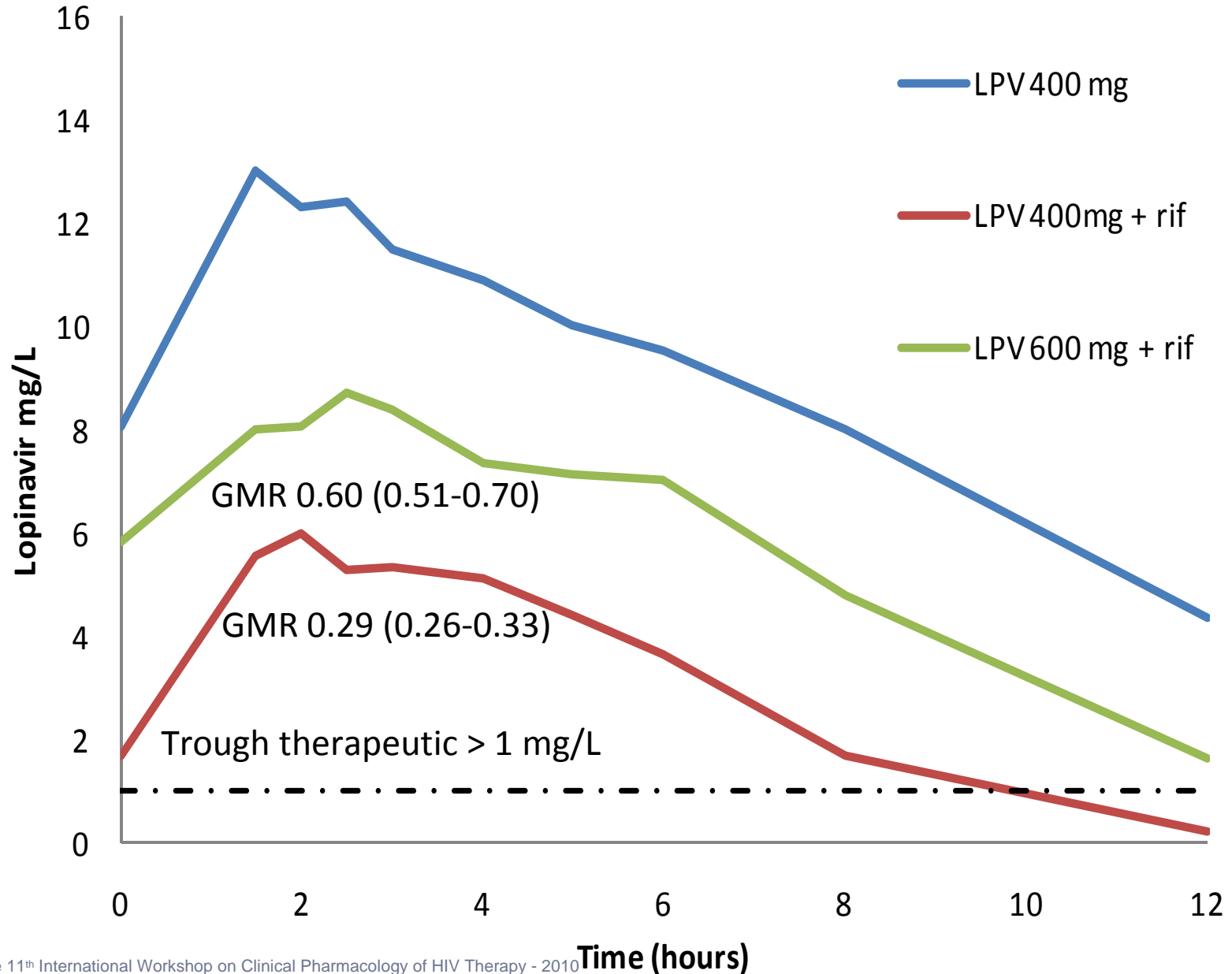
Median LPV concentration versus time: baseline



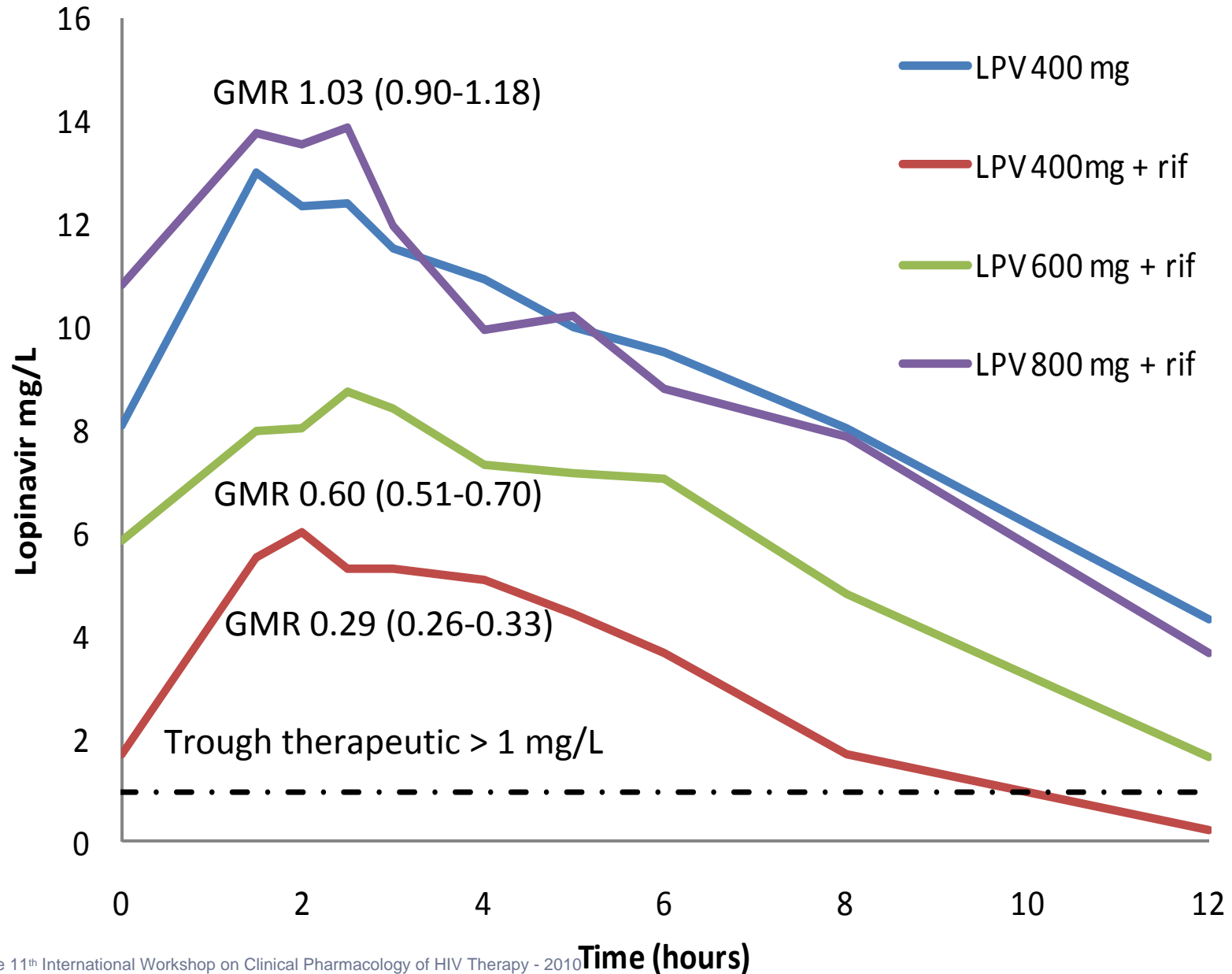
Median LPV concentration versus time: LPV 400 mg + rifampicin



Median LPV concentration versus time: LPV 600 mg + rifampicin



Median LPV concentration versus time: LPV 800 mg + rifampicin



RESULTS

Occasion	C ₀ mg/L (IQR)	LPV < 1 mg/L	C ₁₂ mg/L (IQR)	LPV < 1 mg/L
1	8.1 (6.2 – 9.8)	0 %	4.3 (3.5 – 6.5)	10%
2	1.7* (0.3 – 3.0)	48%	0.2* (0.1 – 0.4)	86%
3	5.9 (2.1 – 9.9)	10%	1.6* (0.1 – 4.4)	50%
4	10.8 (7.0 – 13.1)	0 %	3.7 (1.2 – 7.7)	22%

Compared with baseline *p-value < 0.001

RESULTS

Adverse event	Grade	Number	
Transaminitis	1	4	
	2	2	
	3/4	2	2 x discontinued
Hyperbilirubinaemia	1	2	
Nausea	1	6	
	2	2	1 x withdrew consent

- Double dose LPV/r sufficiently overcomes the induction effect of rifampicin
- Double dose LPV/r reasonably tolerated
- Limitation – not done in patients with TB

- Division of Pharmacology, UCT
- European and Developing Countries Clinical Trials Partnership (EDCTP)
- Volunteers
- Staff from the Hannan Crusaid Treatment Centre, Gugulethu