Spotlight on HIV

THE UNIVERSITY OF SYDNEY

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65/277 UNAIDS Declaration - 2011
Intensifying our Efforts to Eliminate HIV/AIDS

- HIV/AIDS constitute a global emergency, posing a formidable challenge to the development, progress and stability of our respective societies …
- Remains an unprecedented human catastrophe … >30 million deaths, another 33 million people living with HIV

>16 million children have been orphaned because of AIDS

>7,000 new HIV infections occur every day

<50% of people living with HIV are aware of their infection

- HIV and AIDS affect every region of the world … the number of new HIV infections is increasing in parts of Asia and the Pacific

- **NEW YORK 9 June 2011**—World leaders gathered in New York to launch a Global Plan

– to eliminate new HIV infections among children by 2015

- "Nearly every minute, a child is born with HIV. Preventing new HIV infections among children is truly a smart investment …"

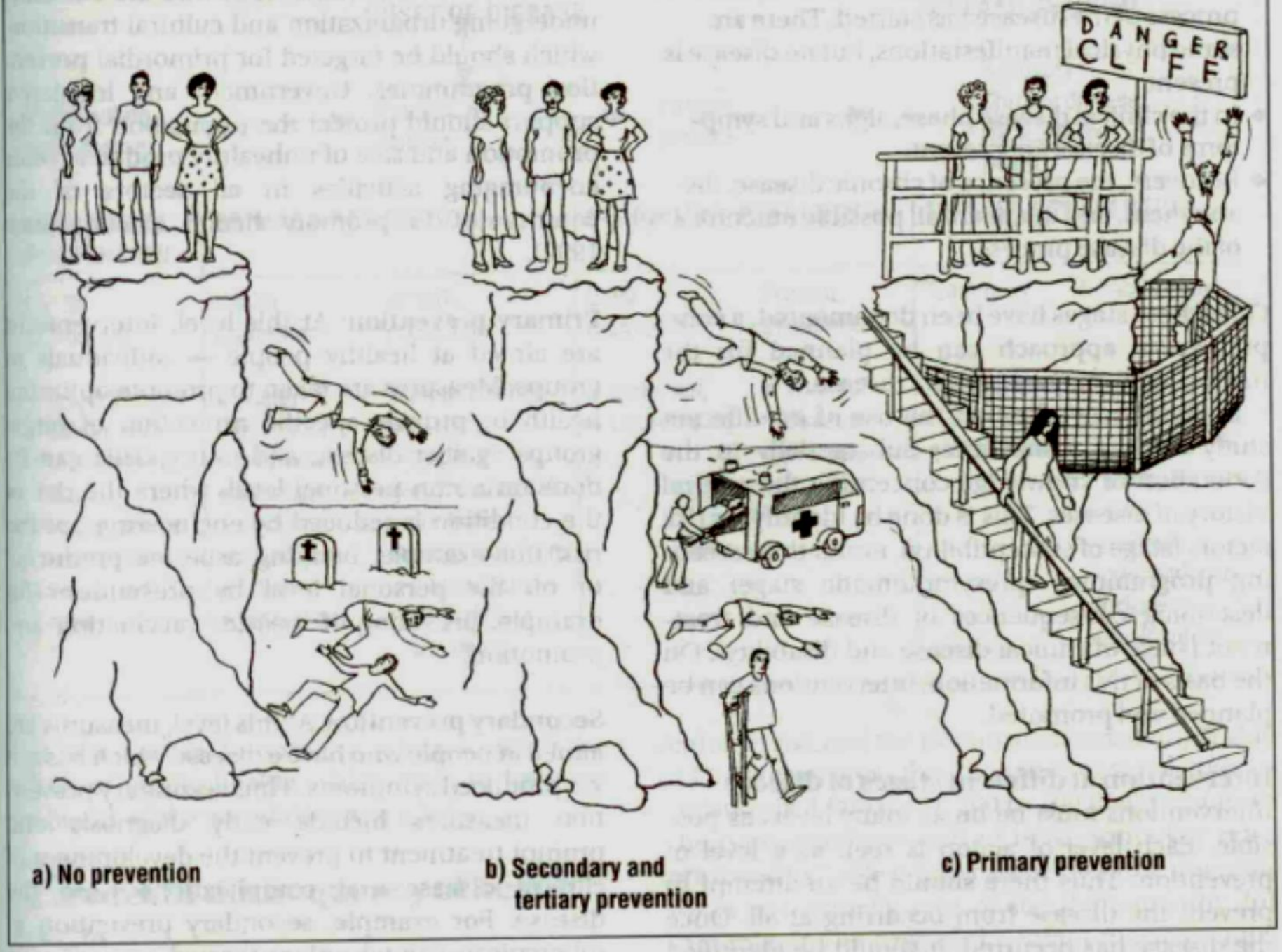
- What is needed is leadership, shared responsibility and concerted action … to make an AIDS-free generation a reality.

ZERO NEW INFECTIONS

USAID - Health Services to Pregnant Women

Inadequate antenatal care, poor knowledge of the danger signs of pregnancy, and lack of quick and appropriate response when emergencies occur are major contributing factors in many maternal and newborn deaths in the Philippines. …. government has committed to support more health activities in the future and has incorporated a series of integrated safe motherhood events …

Is HIV testing standard of care for all pregnant mothers in the Philippines?



From Epidemiology. Katzenellenbogen et al. OUP

Prevention of mother to child transmission of HIV (PMTCT)

2006 WHO Immunological Staging

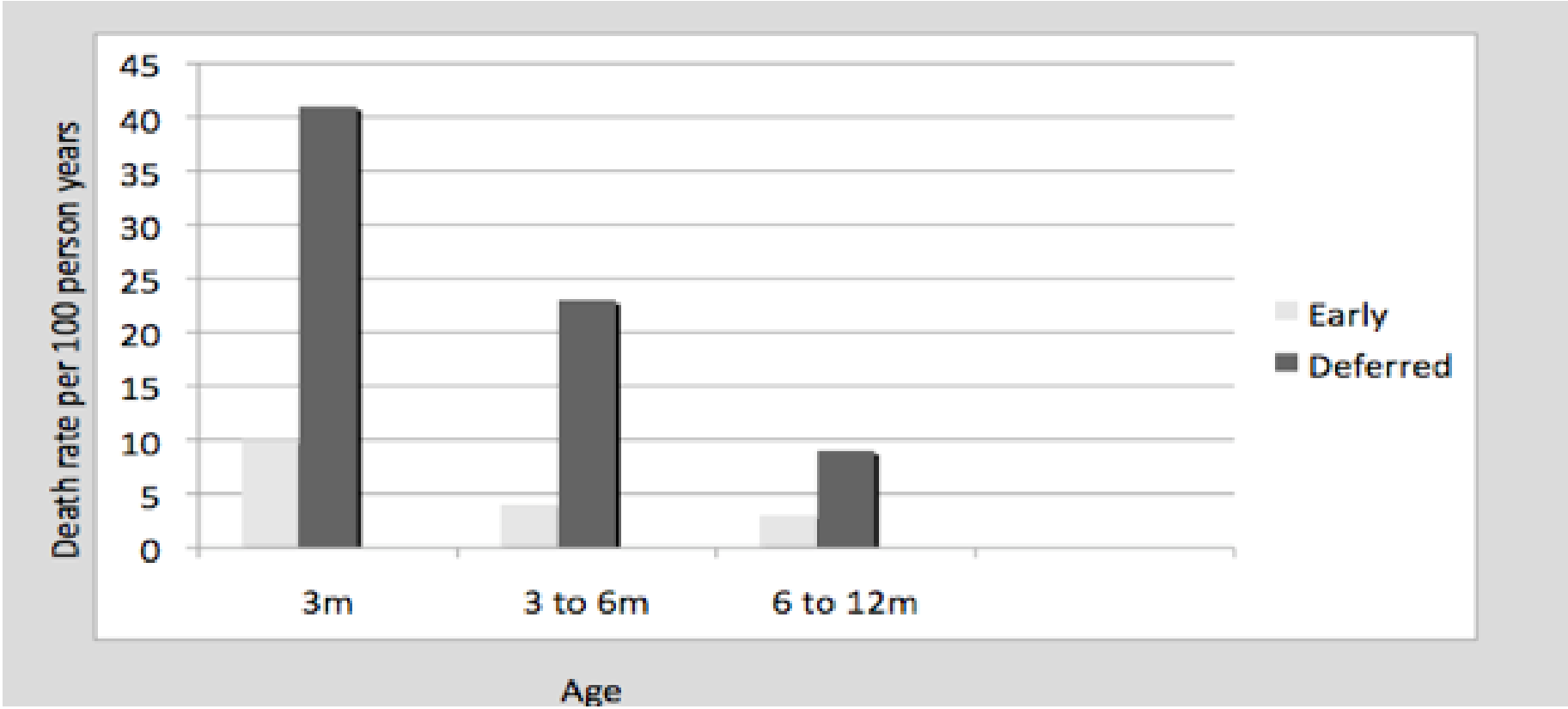
Immune Classification	≤1yr (%)	1-2yrs (%)	3-5yrs (%)	≥5 years (cells/mm^3)
No suppression	>35	>30	25	>500
Mild Suppression	30-35	25-30	20-25	350-499
Advanced Suppression	**25-30**	**20-25**	**15-20**	**200-349**
Severe Suppression	**<25**	**<20**	**<15**	**<200**

OLD DOGMA TREAT ONLY IF CLINICAL STAGE 3 OR 4

Aim: Treat ALL <2yrs of age, anyone with advanced suppression

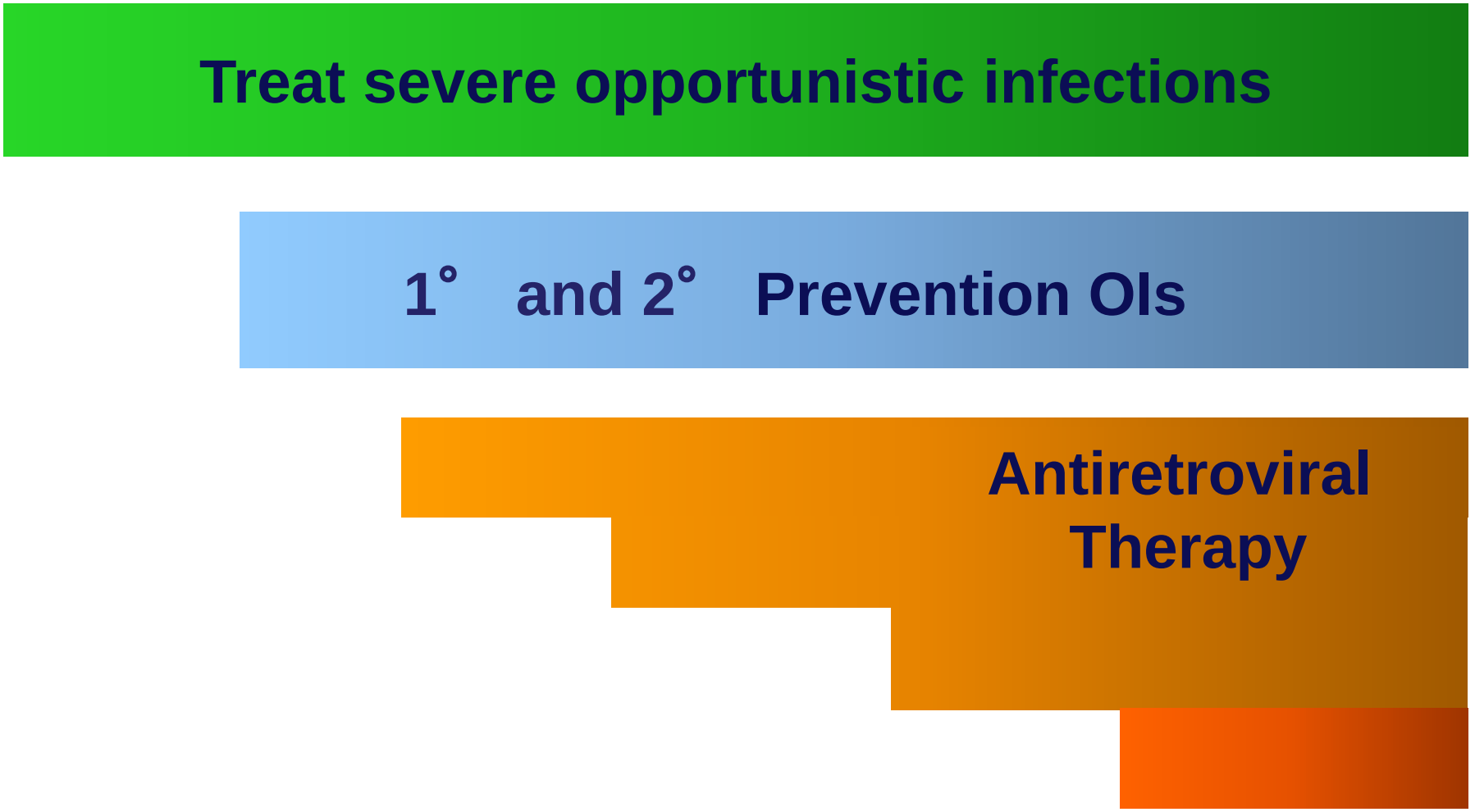
Death rate / 100 person-years

Early vs Deferred ART in infancy



Violari et.al. N Engl J Med 2008;359: 2233-44

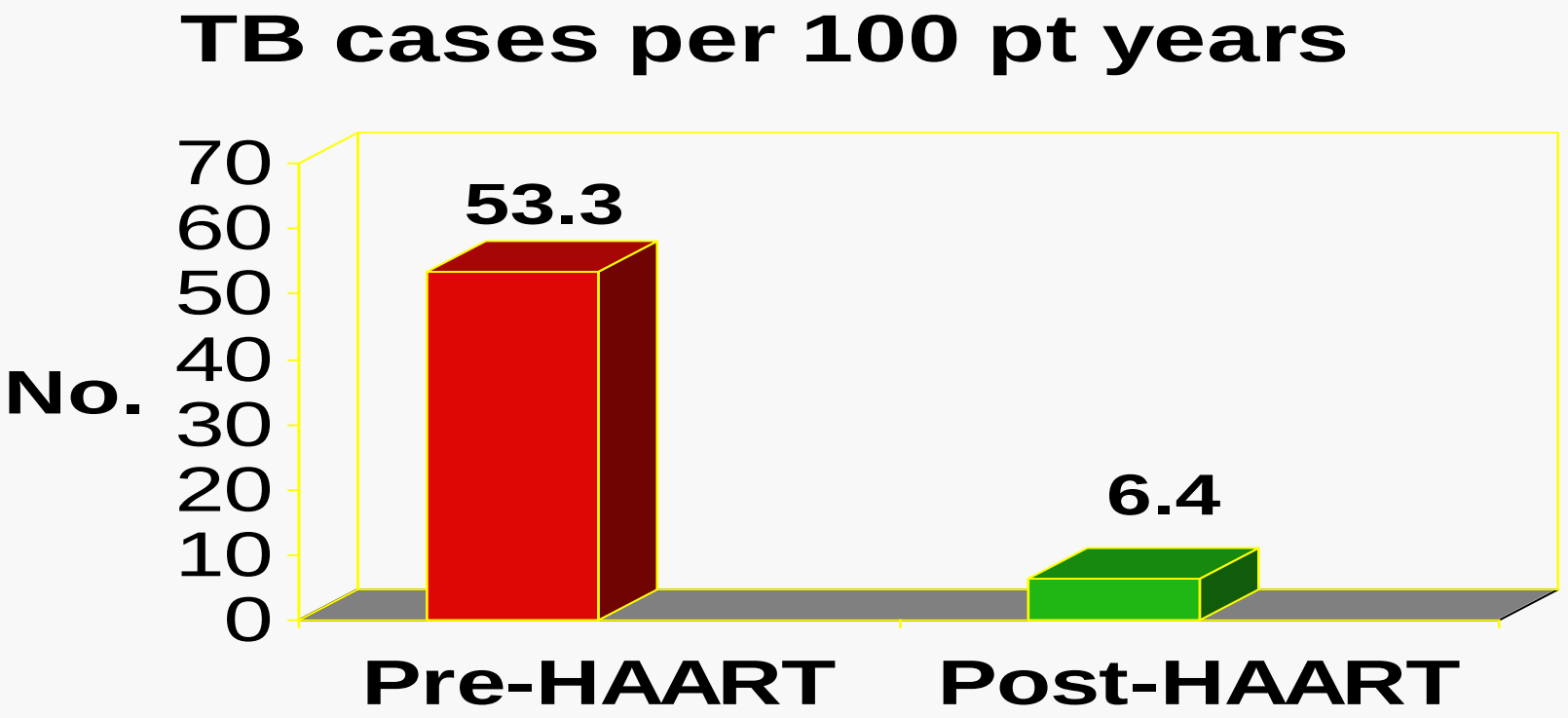
Progress in HIV management



Goals of treatment

- ➔Prevent death
- ➔Reduce the risk of infection by improving the immune function
- ➔Reverse complications of HIV/AIDS
- ➔Achieve normal growth as well as physical and intellectual development
- ➔Ensure long term health and well being
- ➔To reduce HIV transmission

Impact of HAART on child TB



- Retrospective study at TCH (2003-2005)
- 136 episodes TB in 290 children
- Pre-HAART - 9m period before HAART initiation

Walters et.al. BMC Pediatrics 2008

Monitoring

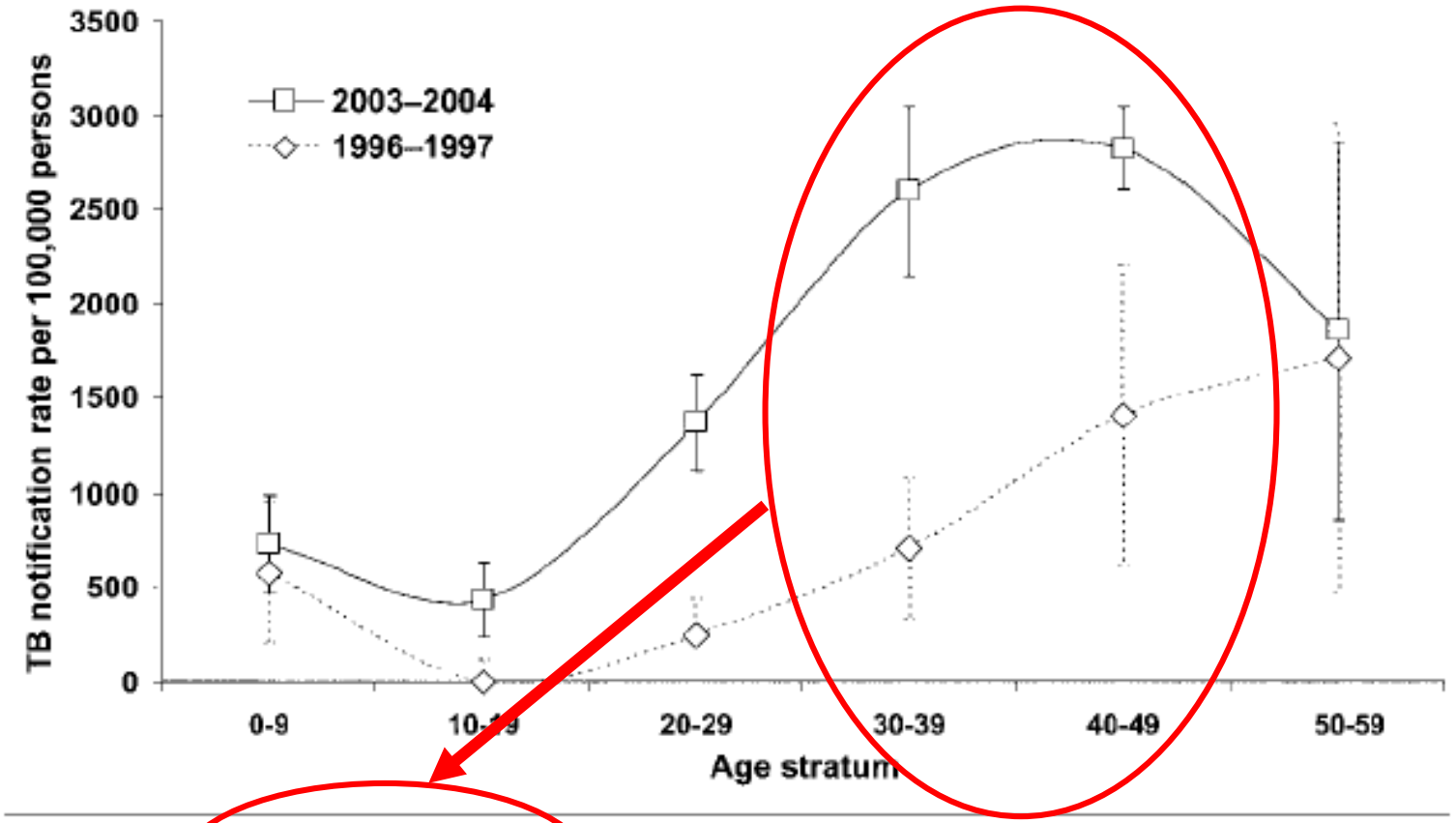
- Adherence NB!!!!
- High index of suspicion for side effects
- FBC: Baseline, 1 month, 6 monthly
- ALT: Baseline 1 month, 6 monthly
- Random glucose lipids: Baseline and annually (PI)
- CD4 & Viral load: Baseline, 6 monthly
- **TB exposure / disease screening at every clinical visit**

When to provide IPT?

Poor TST Reactivity in HIV-infected Children With TB

Study	HIV infected	HIV non-infected	P value
South Africa Jeena et al IJTLD 1994	15/40 (38%)	35/40 (88%)	<0.001
Cote d'Ivoire Mukadi et al. AIDS 1995	9/24 (38%)	74/106 (88%)	<0.01
Dominican Rep. Espinal et al. 1994	5/26 (20%)	124/178 (70%)	<0.001
South Africa Madhi SA et al. IJTLD 2000	12/100 (12%)	83/110 (76%)	<0.001
Ethiopia Palme at el. 2002	12/58 (21%)	354/438 (80%)	<0.001

TB - Age & Gender shift



2003–2004	731	436	1369	2599	2824	1856
1996–1997	582	0	245	706	1405	1708

HIV prevalence in general population: **3-4% 0-9y** **25% 20-39y**

Lawn SD et al. CID 2006; 42: 1040-7

TB exposure
(at 3-4 months of age)

	Pre-Screened (nurses)	Screened (doctors)	Total
	769	658	769
Close TB contact	49	25	74 (9.6%)

Cotton M et al. IJTLD 2009

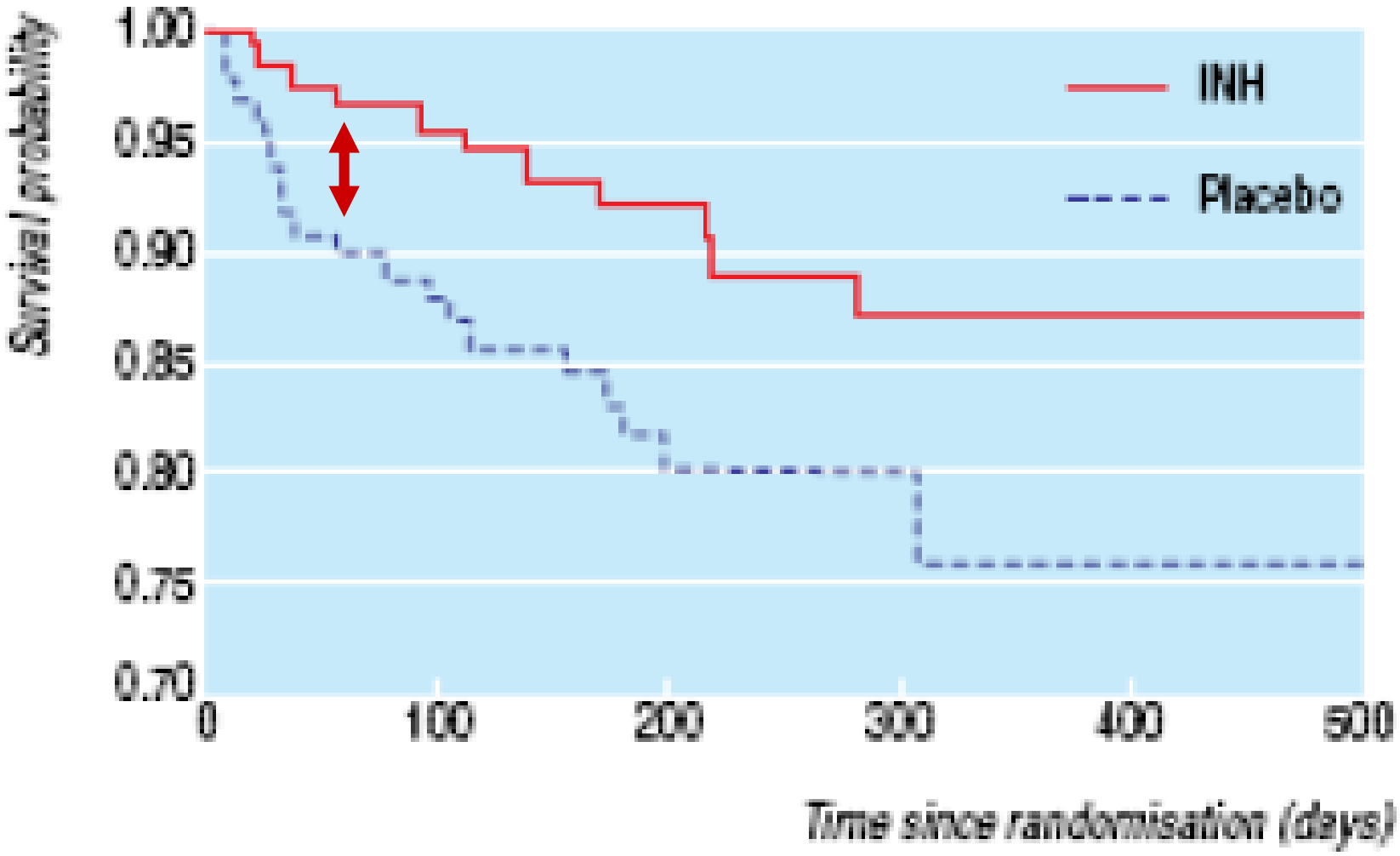
Incidence of culture positive TB in HIV+/- infants (per 100 000 population)

	All infants	HIV -	HIV +	RR
All TB	**83.1** (72.9-93.7)	**65.9** (56.7-75.3)	**1595.9** (1151.3-2131.5)	**24.2** (16.9-33.6)
Pulmonary tuberculosis	**78.7** (68.6-89.0)	**62.5** (53.3-71.7)	**1505.6** (1075.2-2022.8)	**24.1** (16.7-33.7)
Extrapulmonary tuberculosis	**28.2** (22.2-34.4)	**22.9** (17.5-28.6)	**481.8** (257.0-750.8)	**21.0** (10.7-35.0)
Disseminated tuberculosis	**16.6** (11.9-21.2)	**14.1** (9.7-18.3)	**240.9** (86.6-431.7)	**17.1** (6.0-33.7)
Miliary tuberculosis	**10.9** (7.2-14.7)	**9.3** (5.8-12.7)	**150.6** (30.8-301.0)	**16.2** (3.4-37.1)
Tuberculosis meningitis	**9.2** (5.8-12.6)	**7.9** (4.7-11.1)	**120.1** (27.7-257.9)	**15.2** (2.9-38.7)

Hesseling et al, Clin Infect Dis, 2009

Should pre-exposure INH be given routinely to all HIV-infected infants?

Universal INH preventive therapy to all HIV-infected infants??



Zar & Cotton et al. BMJ Jan 2007

IMPAACT INH Prophylaxis Study P1041

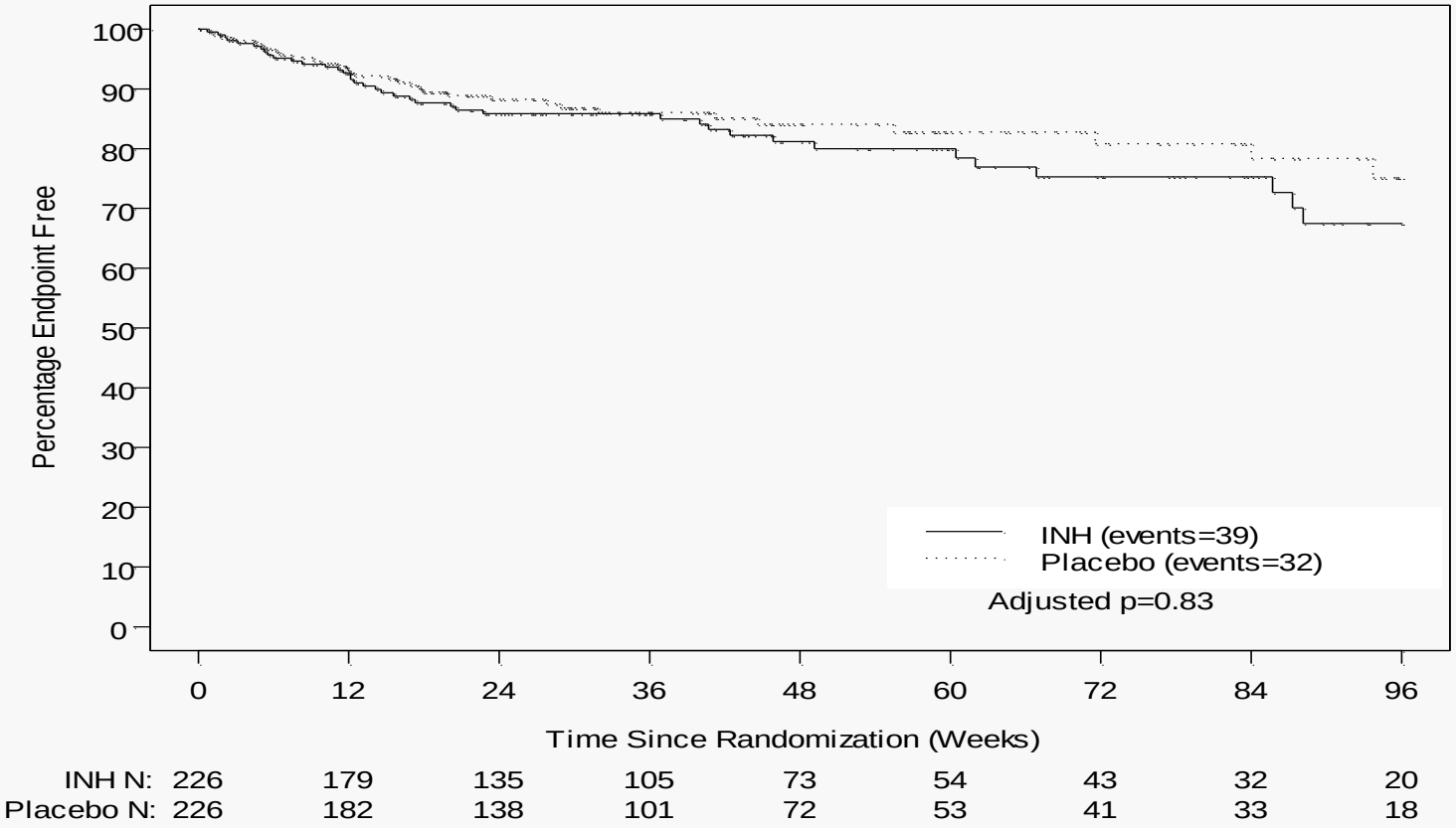
Daily INH or placebo, 10-20 mg/kg/dose

- 2 years on study medication
- 2 years follow-up off study medication

➢ Primary objective

- To determine whether INH prophylaxis decreases the incidence of TB disease, among HIV-infected study participants

Pre-exposure IPT Does Not Increase TB Free Survival in HIV-infected Children



Kaplan-Meier Estimate of Percentage Disease Free Survival

Madhi SA et al. 48th ICAAC/IDSA 46th annual meeting 2008

Greatest Reduction TB: Both HAART & INH

Observational study in >11,000 pts in Rio de Janeiro both interventions better than either alone

Exposure Category	Person-Years	TB Incidence Rate/100 Person-Years
Naive	3865	4.06 (3.54-4.75)
HAART only	11,629	1.97 (1.72-2.24)
INH prophylaxis only	395	1.27 (0.41-2.95)
HAART + INH	1253	1.04 (0.55-1.78)

Golub JE, et al AIDS 2007; 41: 1441-8

IPT conclusion

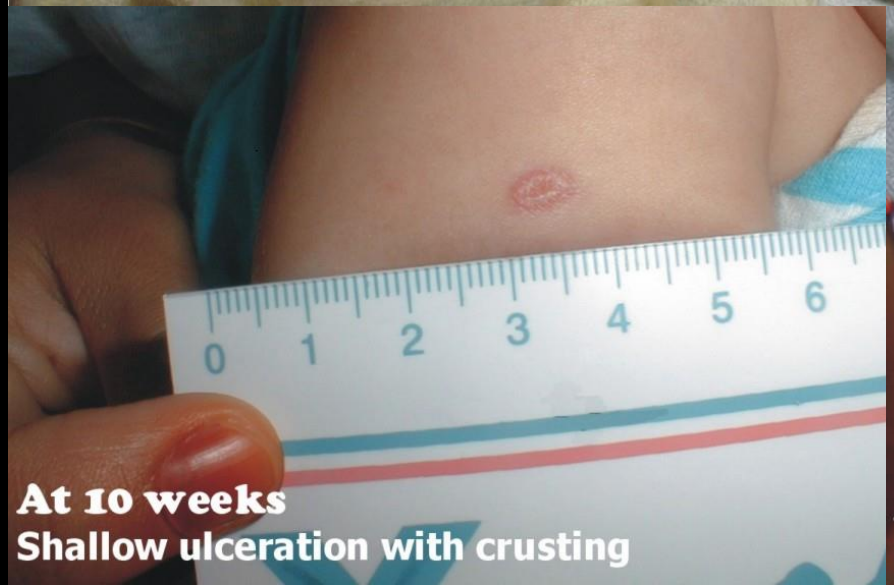
- **Children are at high risk to become infected with *M.tb* in areas with poor epidemic control**
- **The very young and/or HIV-infected are particularly vulnerable**
- **Early ART reduce TB risk in HIV-infected children, BUT it remains high**
- **<u>Post-exposure prophylaxis</u> NB!!**
  Repeated as necessary

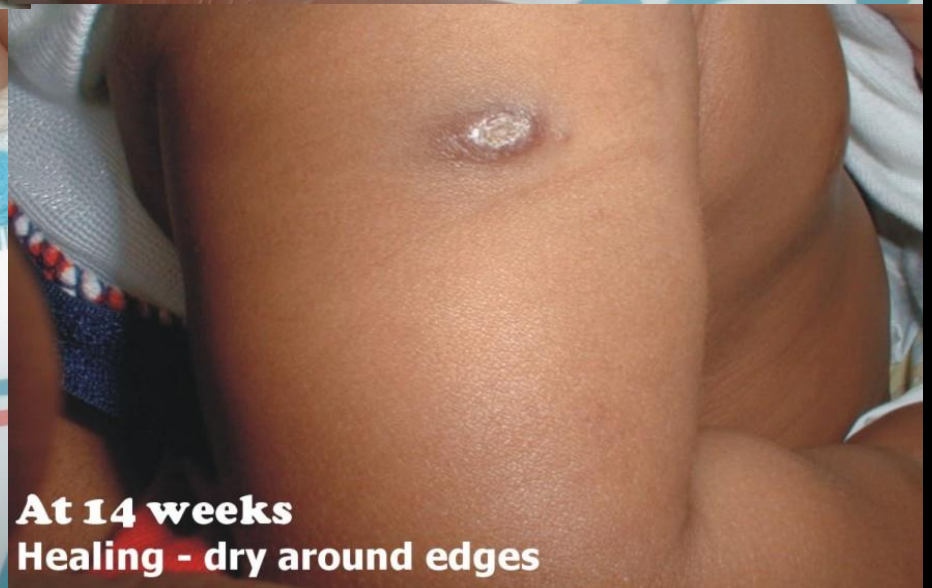
<u>Remaining question</u>

Should all HIV-infected children receive IPT during the first 1-2yrs of life as part of a comprehensive package of care? (ART + Bactrim + IPT)

Natural history of BCG vaccination

G. Hussey,
SATVI, UCT

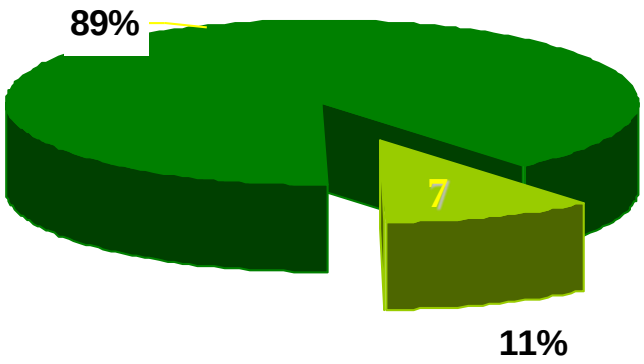




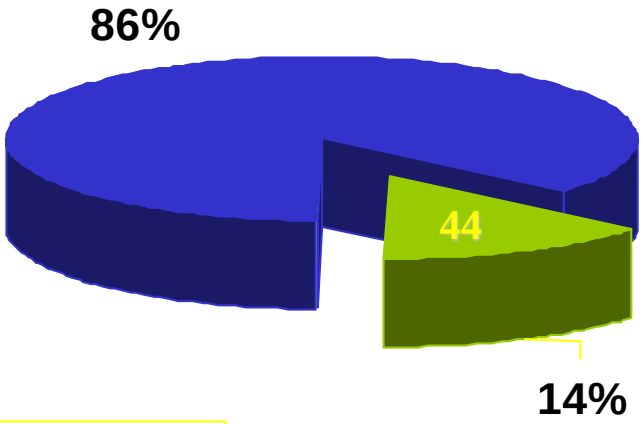
BCG Ineffective in Preventing TB in HIV-Infected Children

n = 51/374 (12.5%)

NON - VACCINATED 64



BCG VACCINATED: 310



TB disease

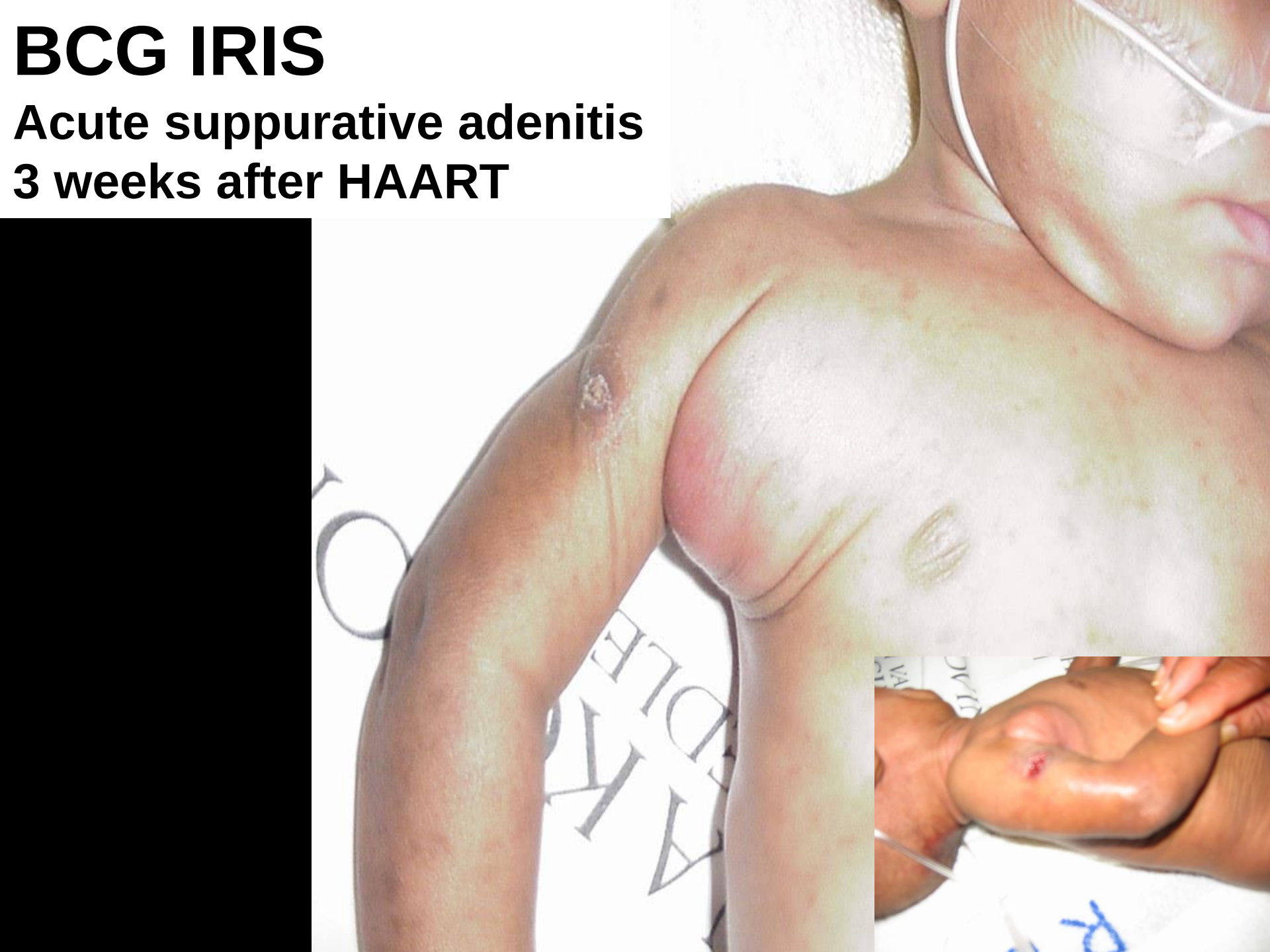
- 7.7% of vaccinated children developed local complications of BCG
- 1.3% of vaccinated children developed disseminated BCG disease

Fallo et al. IJID 2005; 9: 96-103

BCG IRIS

Acute suppurative adenitis

3 weeks after HAART



Calculated risk of distant/disseminated BCG disease in HIV-infected children

Risk scenarios of disseminated BCG disease	**Cases/year 2002**	**Cases/year 2003**	**Cases/year 2004**
Actual cases/year	2	2	3
Risk of disseminated BCG disease Case scenario 1, assuming 5% total vertical HIV infection	2/571= **350/100 000/year**	2/608= **329/100 000**/year	3/719= **417/100 000**/year
Case scenario 2, assuming 10% total vertical HIV infection	2/1142= **175/100 000/year**	2/1217= **164/100 000**/year	3/1439= **208/100 000**/year
Case scenario 3, assuming 15% total vertical HIV infection	2/1713= **117/100 000/year**	2/1825= **110/100 000**/year	3/2158= **139/100 000**/year

Hesseling et al, Vaccine 2007

Revised BCG vaccination guidelines for infants at risk for HIV infection

Background

Following a review of relevant data, the Global Advisory Committee on Vaccine Safety (GACVS) has revised its previous recommendations[1] concerning bacille Calmette-

[1] See No. 3, 2007, 82, pp. 18–24.

Révision des lignes directrices relatives à la vaccination par le BCG des nourrissons exposés au risque d'infection par le VIH

Généralités

Suite à un examen des données pertinentes, le Comité consultatif mondial de la Sécurité vaccinale (GACVS) a révisé ses recommandations antérieures[1] relatives à la vac[illegible]ation par le

[1] Voir N° 3, 2007, 82, pp. 18-24.

- **Benefits usually outweigh risks fo[illegible]**
  for: infants whose HIV infe[illegible]wn and who demonstrate [illegible]mptoms suggestive of HI[illegible] are born to known HI[illegible]se infants should be imm[illegible]ion of the aforementioned [illegible]ctors.
  [illegible] benefits for BCG vaccination for [illegible]ho are known to be HIV infected with or [illegible]out signs or reported symptoms of HIV infection. These infants should **not** be immunized.

??Defer vaccination of HIV exposed children if early HIV testing available
NB!! Optimal MTCT program

Co-Treatment TB and HIV

Issues to consider

- Pharmacokinetics mainly drug-absorption & drug-drug interactions
- Overlapping drug toxicities
- Paradoxical reactions (IRIS)
- Adherence with multiple medications
- Timing of initiation of HAART

Drug-Drug Interactions

- The rifamycins induce the cytochrome P450 system also P-glycoprotein (RMP most potent inducer)

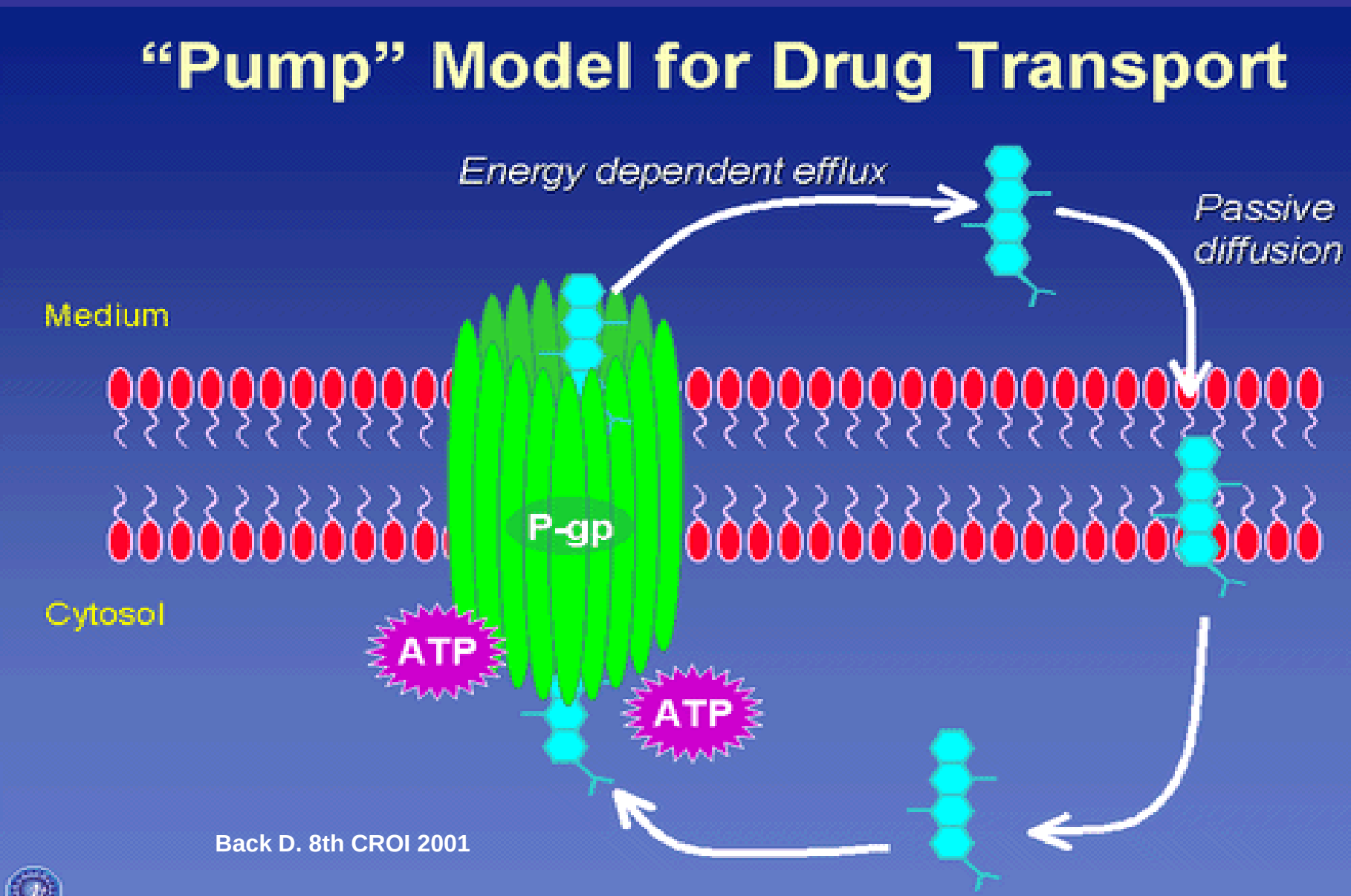
  decrease serum concentrations of PIs and NNRTIs
- Serum concentrations of all PIs, except ritonavir (35%) reduced by 75-95%
- NNRTIs: AUC for efavirenz reduced by 22% and that of nevirapine by 37-58%

Ineffective ART levels

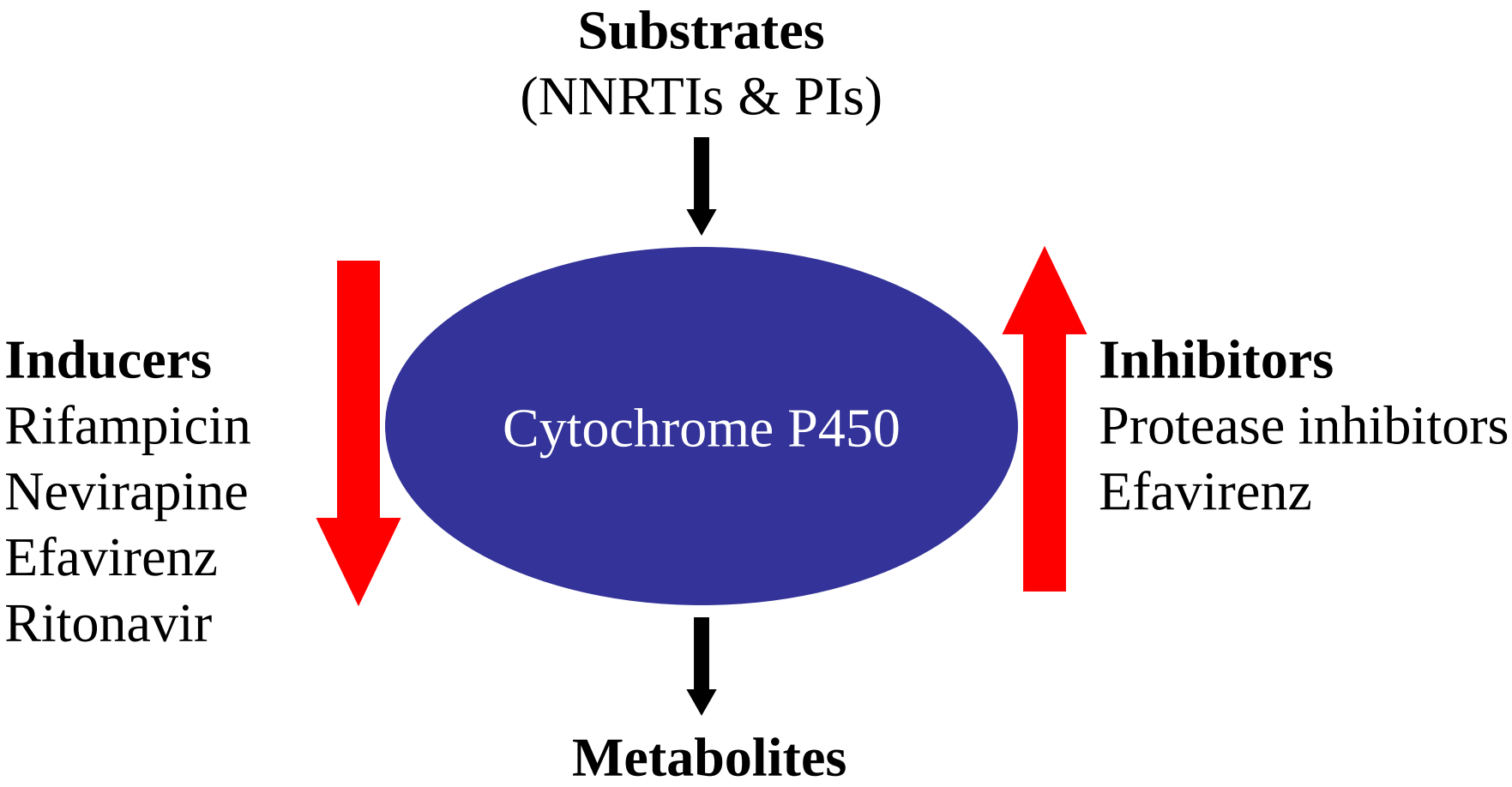
NB! risk for developing drug resistance

Need for accurate pharmacokinetic data in children

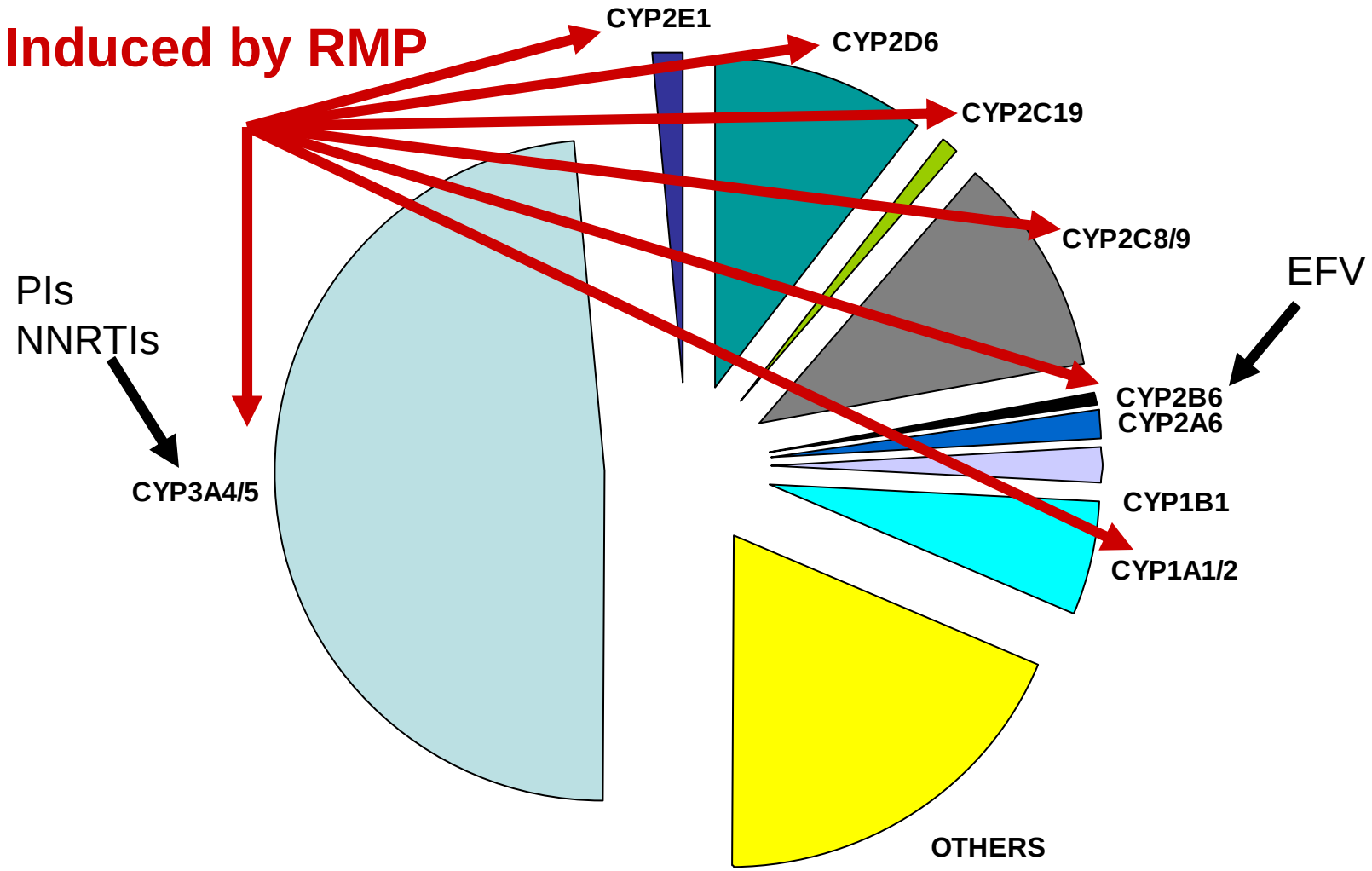
P Glycoprotein



ART drug interactions

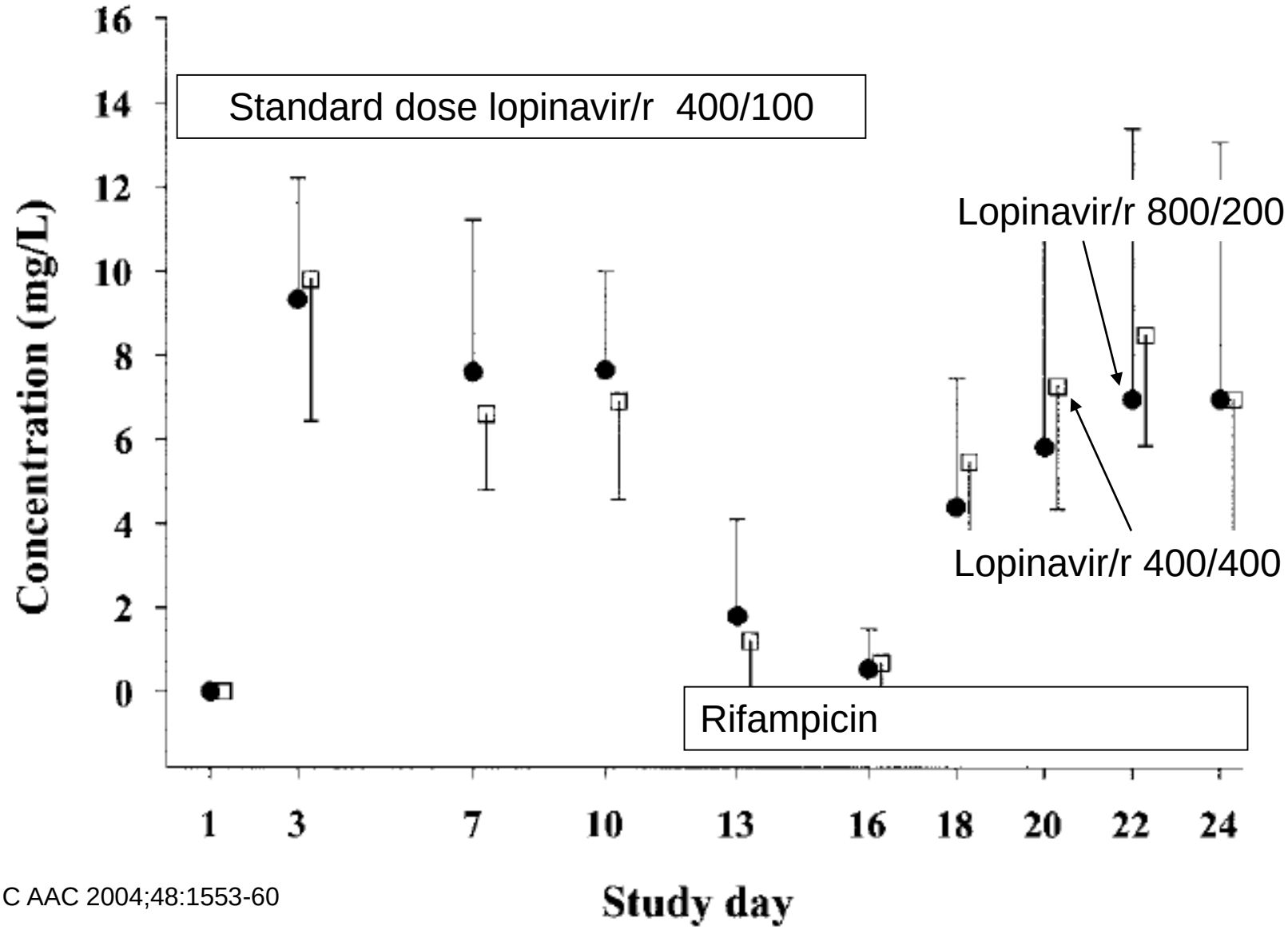


The cytochrome p-450 system (phase 1 enzymes)

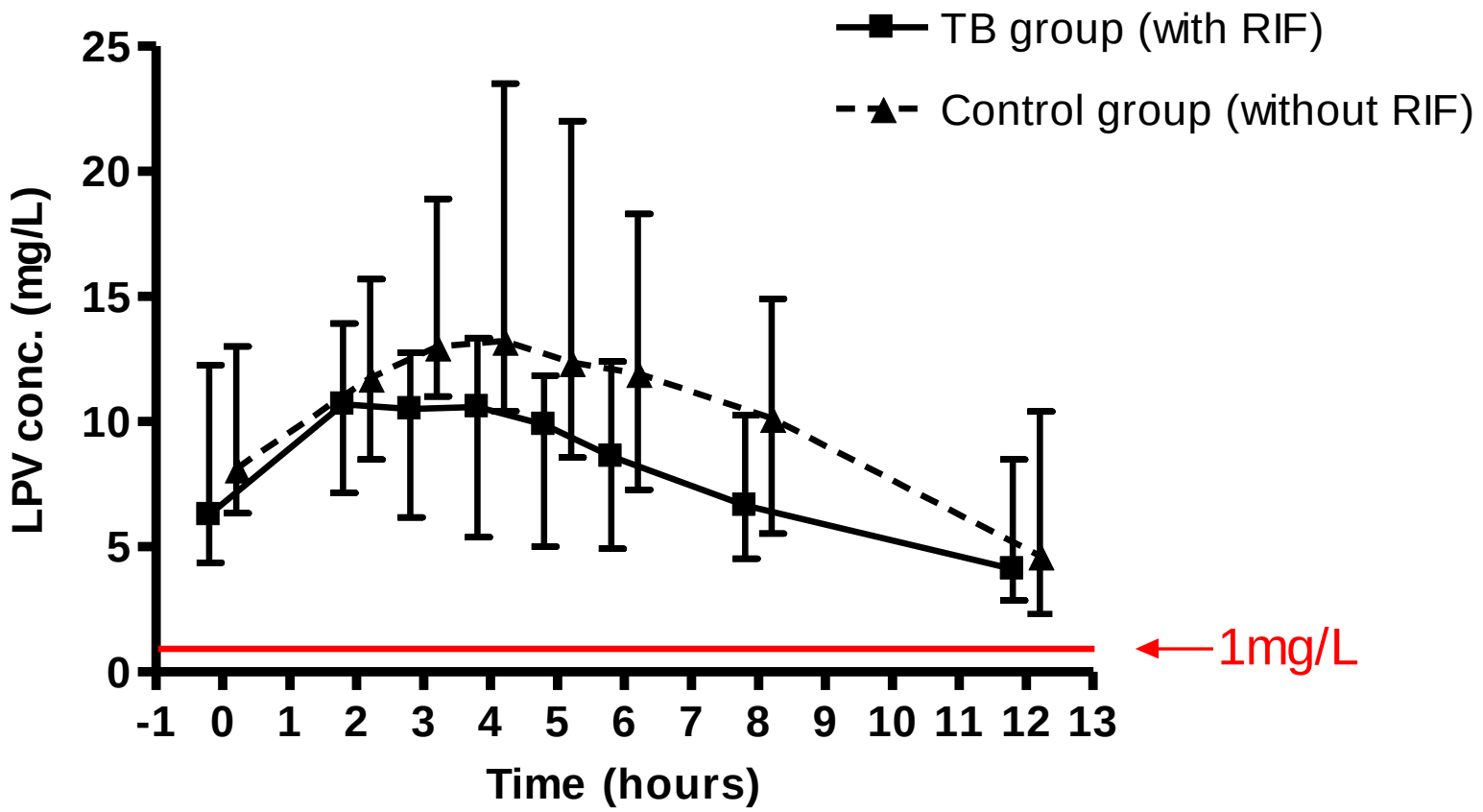


Gary Maartens

RMP & trough lopinavir concentrations: Healthy adult volunteers

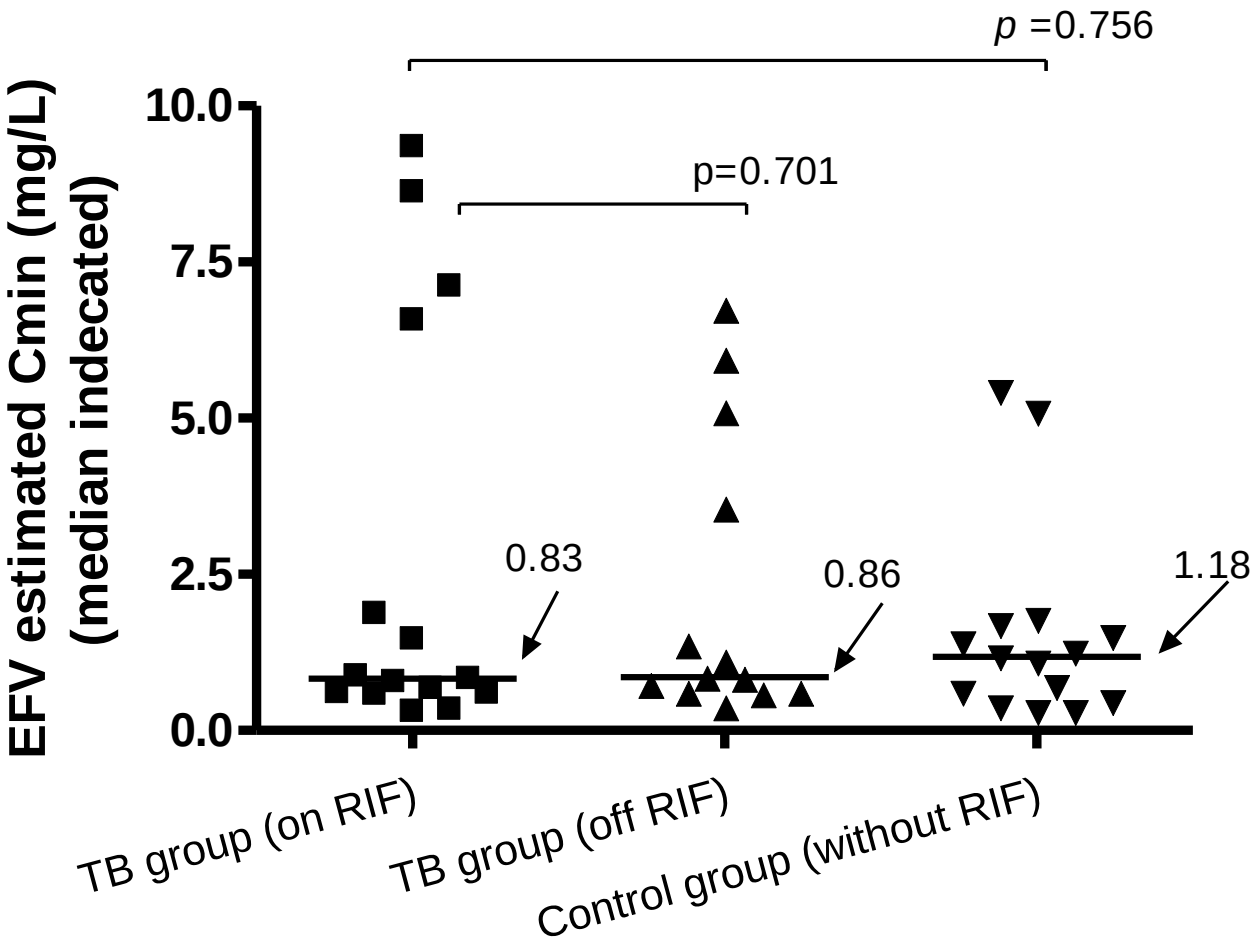


La Porte C AAC 2004;48:1553-60



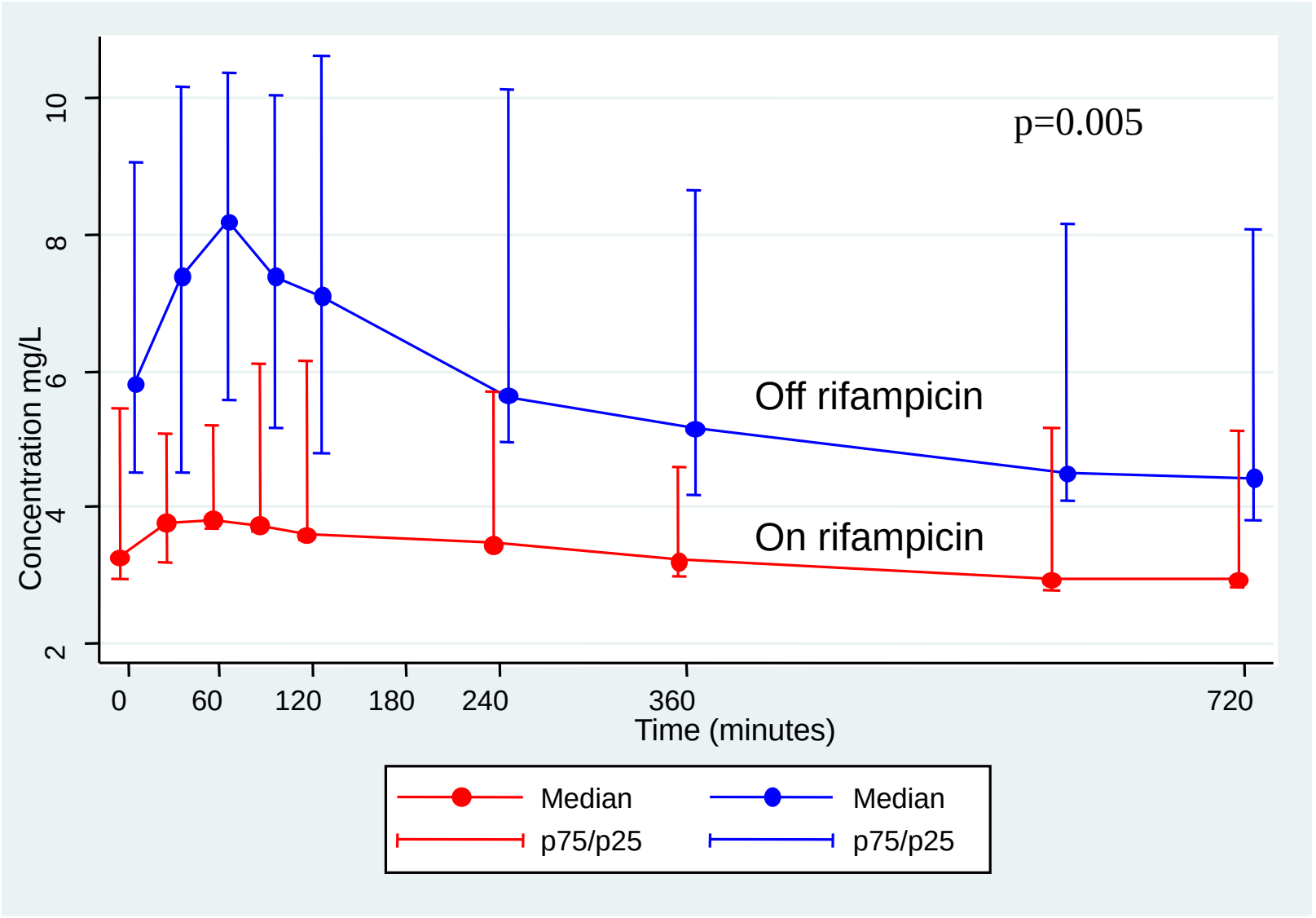
PK measures Median (IQR)	**TB Group LPV:RTV=1:1**	**Control Group LPV:RTV=4:1**	***p* value**
T_{max} (hr)	3.0 (2.0, 4.07)	3.92 (2.78, 4.0)	0.660
C_{max} (mg/L)	11.9 (7.24, 14.3)	14.2 (11.9, 23.5)	0.038
C_{min} (mg/L)	4.12 (2.89, 7.66)	4.64 (2.32, 10.4)	**0.872**
AUC_{0-12}	84.29 (53.51, 113.37)	113.70 (78.81, 168.61)	0.056
Half life (hr)	10.98 (5.44, 16.61)	4.86 (3.82, 8.29)	0.062

Efavirenz – high variability



- 50% had estimated Cmin < 1mg/L (lower limit of the recommended therapeutic range)

NVP concentrations in adult patients before and after stopping RMP-based TB therapy



Cohen, SAPS Congress 2005

Rifampicin & increased NVP dose

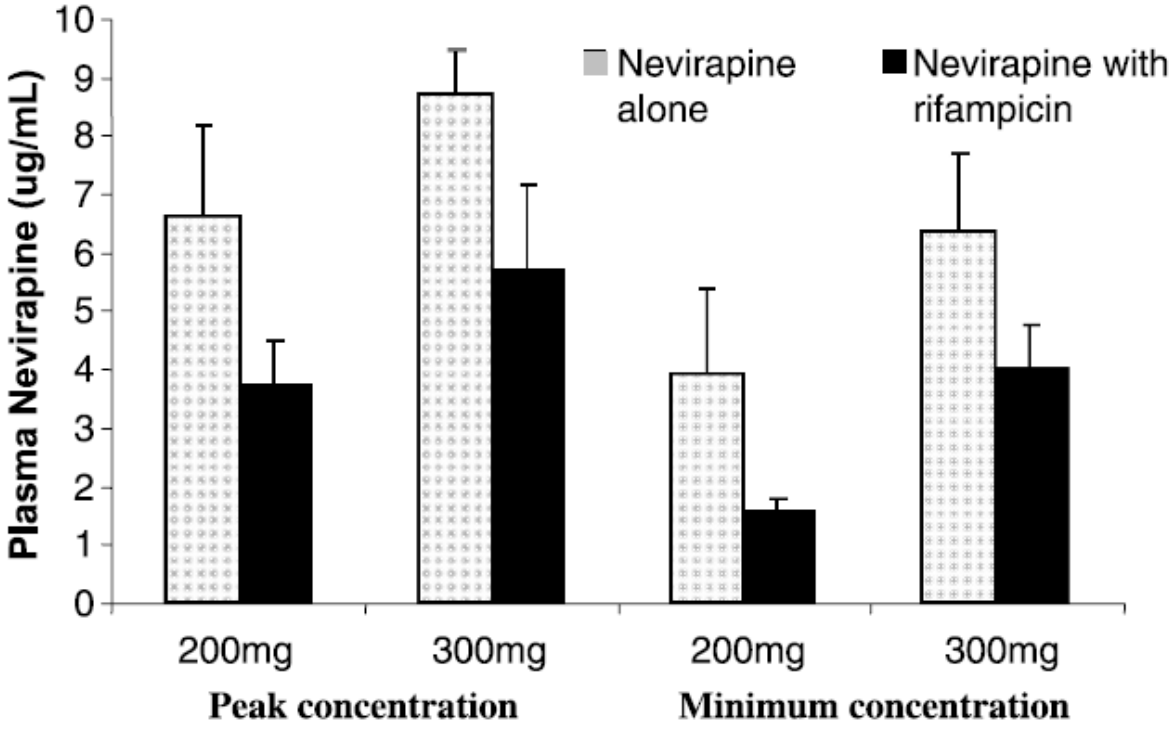


FIGURE 2. Comparison of peak (C_{max}) and minimum (C_{min}) concentrations of nevirapine at 200- and 300-mg doses twice daily. Values are represented as mean ± SD calculated in 7 patients.

Ramachandran JAIDS 2006;41:1-6

Triple NRTIs

- Seems to be no significant interaction between NRTIs and rifampicin
- Triple NRTI regimens associated with higher failure rates than standard HAART
- Could be considered in selected cases (viral load <100 000)

Rifabutin & ART

- Used in developed countries, now also on WHO essential meds list
- Rifabutin levels are increased by PIs & decreased by NNRTIs
- No FDCs available
- No paediatric formulation

ART for children on TB Rx

- <3 years of age:
  abacavir or zidovudine (AZT) + lamivudine (3TC) + lopinavir/ritonavir (Kaletra)
  - Ritonavir boosted Kaletra
  - Double dose Kaletra (no longer recommended)

- >3 years of age:
  abacavir or zidovudine (AZT) + lamivudine (3TC) + efavirenz

- NVP may be also be effective (depending on PMTCT exposure), check LFTs monthly, consider increasing NVP dose (30%)

Summary

TB & HIV remain difficult diseases to deal with in children

BUT

They are both preventable and treatable

We should do everything within our power to reduce missed opportunities for:

- **prevention**
- **early initiation of treatment**