IMPAACT P1106
ARV AND TB PHARMACOKINETICS (PK) IN PREMATURE/ LOW BIRTH WEIGHT (LBW) INFANTS

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Vice-Chair: Adrie Bekker
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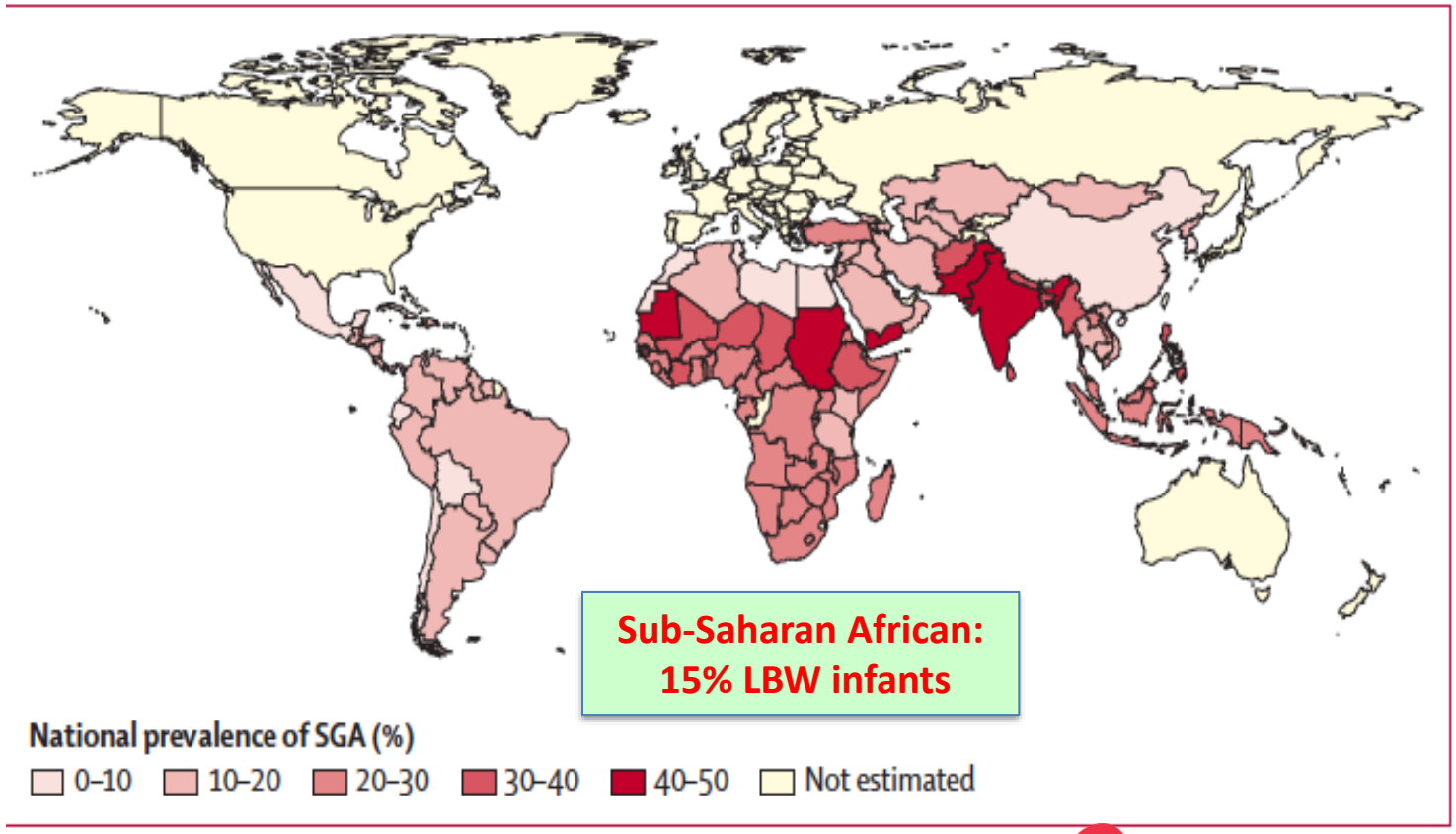
SGA births is common in LMIC settings 2010



Lee et al Lancet Global Health 2013; 1: 26 - 36

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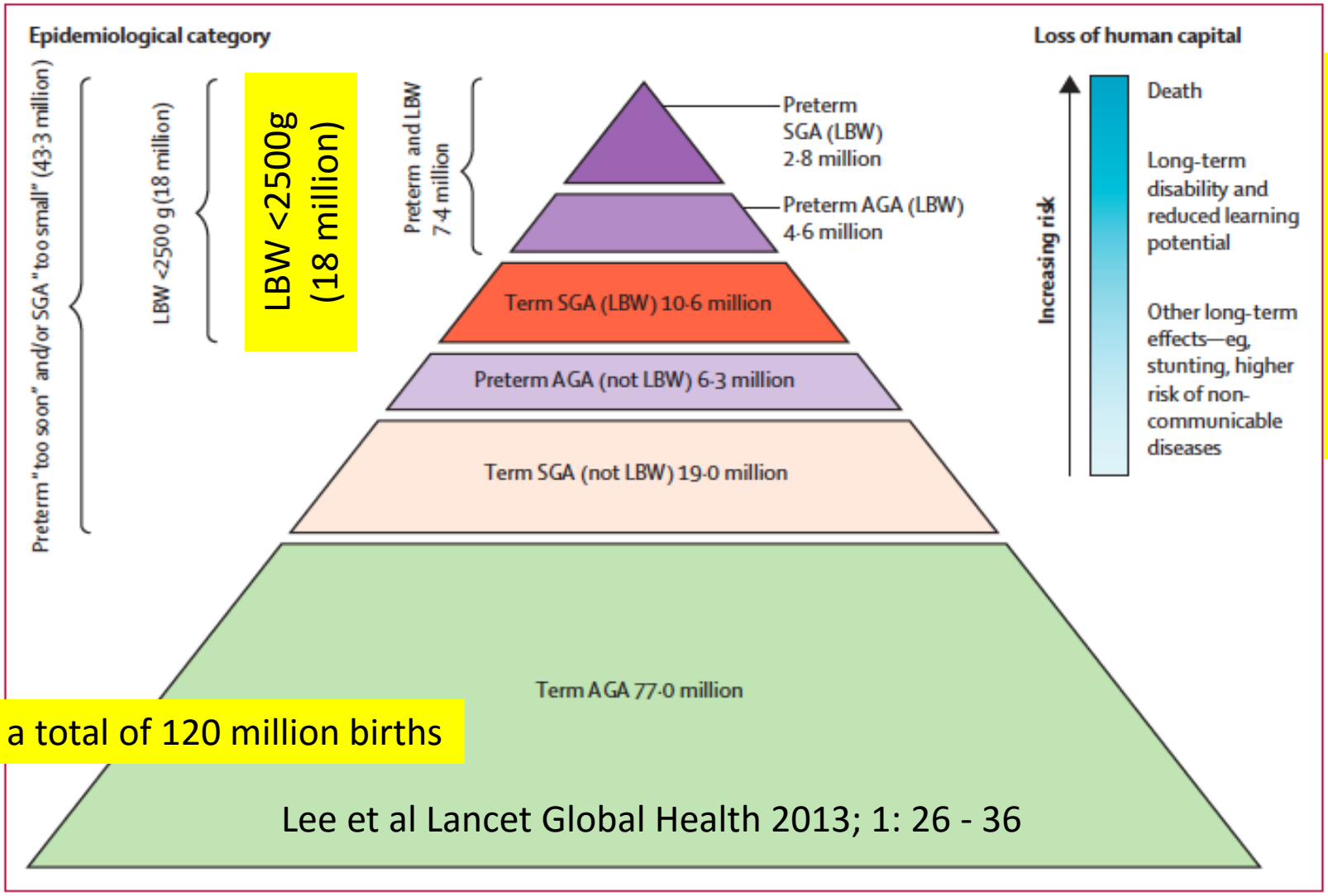
Burden of premature and SGA births in LMIC settings (2010)



From a total of 120 million births

Lee et al Lancet Global Health 2013; 1: 26 - 36

Rationale

- Increased risk of LBW (≤ 2500 g) infants in pregnant HIV (+/-TB) women
- LBW infants need access to ARV and TB drugs
- Developmental changes in premature infants affect pharmacokinetics (PK)
- **VERY** limited PK and safety data available for these drugs in LBW infants to guide dosing

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Challenges to overcome

To design a feasible study for LBW infants

- Strategy to minimize the blood volumes (sparse sampling with population PK design)
- PK assays on tiny plasma volumes
- How to provide real-time PK results to clinicians managing these infants
- How to manage adverse events

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Phase IV Prospective PK Study

Primary Objective

To describe PK and safety of ARV and TB drugs in LBW infants

Study Arms		(planned n=158)
1	NVP	40
2	NVP + INH	18
3	NVP + INH + RIF	28
4	INH ± RIF	18-36
5	LPV/r + 2NRTIs ± INH	24
6	LPV/r + 2NRTIs +RIF ± INH	12

Opportunistic study design (infant dosing – clinician choice)

PK visits at Entry and Weeks 4, 6, 10, 16, and 24

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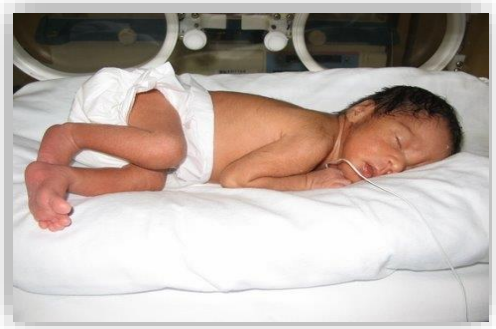
Safety Study Visits

- **Ex**pected adverse events

  To provide a snapshot of the infant's overall clinical condition at visit



- **Un**expected adverse events

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Expected Adverse Event Parameters

Parameters	
Apnea	Neonatal abstinence syndrome
Anemia	Neurologic compromise (including HIE)
Congenital abnormalities	Neutropenia
Congenital Heart disease (not PDA)	Patent Ductus Arteriosus
Electrolyte or metabolic disorder	Persistent Pulmonary Hypertension
GI dysfunction (including NEC)	Renal dysfunction
Hypertension	Respiratory insufficiency
Hypotension	Retinopathy of prematurity
Intravascular hemorrhage	Sepsis
Jaundice	Thrombocytopenia

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2 South African sites
(FAM-CRU - Cape Town; PHRU - Johannesburg)

Accrual per arm

From 4 August 2015 - 02 May 2017 (18 months)

Study Arms		Accrual target (PK evaluable infants)	Current Accrual
1	**NVP**	**40**	**40**
2	NVP + INH	18	9
~~3~~	~~NVP + INH + RIF *~~	~~28~~	~~0~~
4	INH ± RIF	18 - 36	5
5	**LPV/r + 2NRTIs ± INH**	**24**	**15**
6	LPV/r + 2NRTIs +RIF ± INH	12	1
	New total	Max of 130	**70**

* Arm 3 was closed on November 2016 – due to changes in clinical practice

** One Arm 5 infant was excluded from both PK and safety analysis

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Baseline Characteristics (n=70)

Infant Characteristics (n=70)	
Male (n, %)	30 (43%)
Race (Black African) (n,%)	60 (86%)
Birth weight, g (median, Q1-Q3)	1815 (1490 - 2165)
Gestational age, weeks (median, Q1-Q3)	34 (32 - 36) *
Enrollment age, days (median, Q1-Q3)	12 (10 – 14)

*missing data (gestational age) for 4 infants

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Preliminary PK results

Arm 1 - NVP (n=40) - prevention

Arm 5 – LPV (n=16) - treatment

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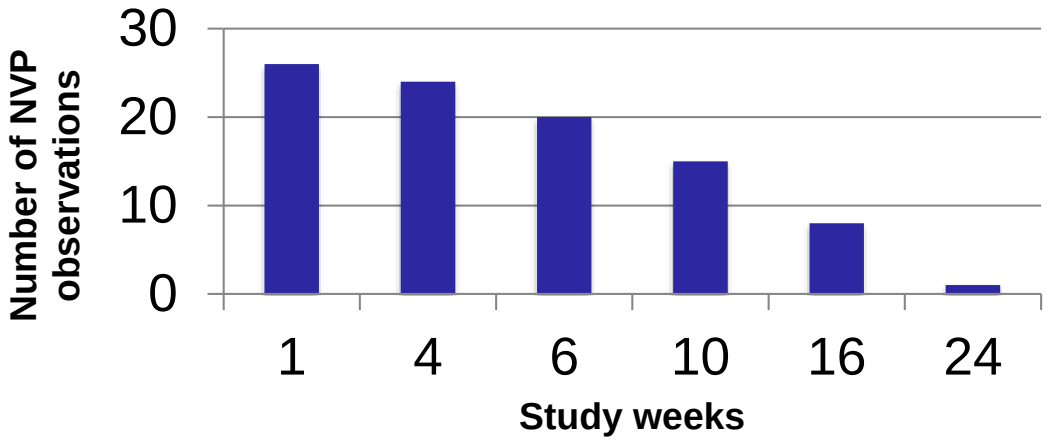
NVP PK results (Arm 1) – August 2016

- NVP dosed at 2 mg/kg (0-14 days) and then 4 mg/kg dly

Weight Band	N=40
<1400 gm	12 infants
1400 - <1800 gm	12 infants
1800 - <2500 gm	16 infants

- ***94 NVP*** trough levels in 27 infants

  across study visits from day 7 to week 24



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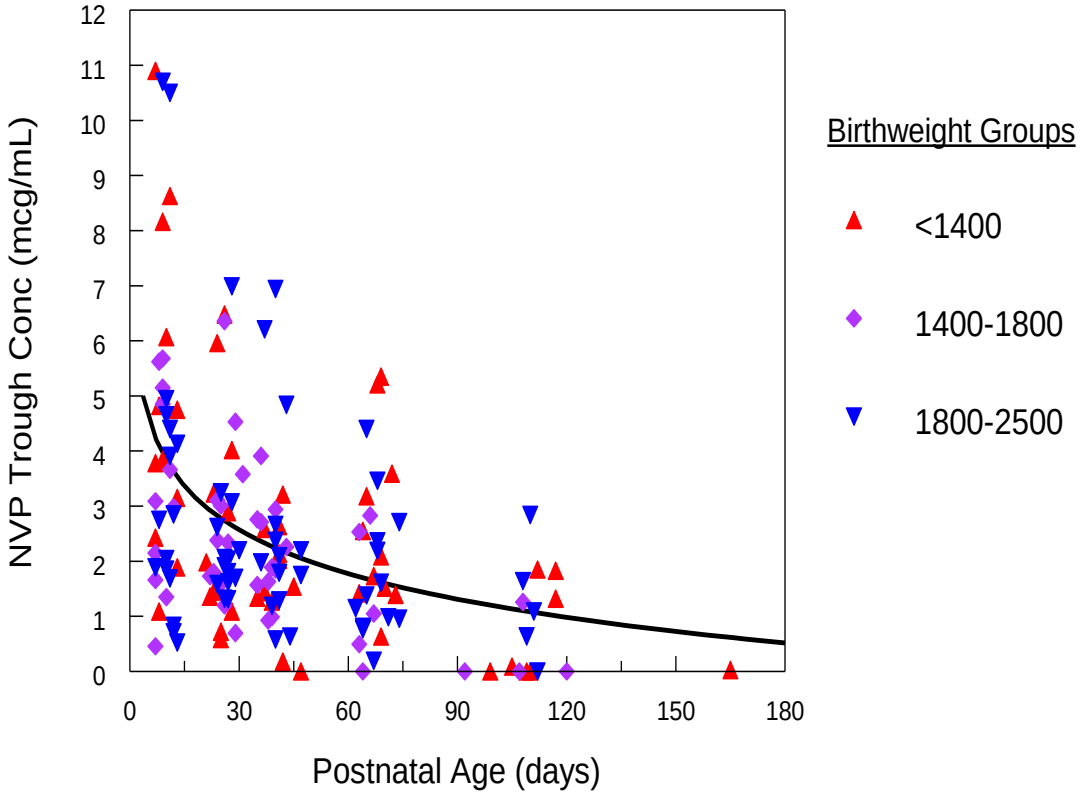
94 Observed NVP concentrations versus postnatal age in days over study period (n=40)



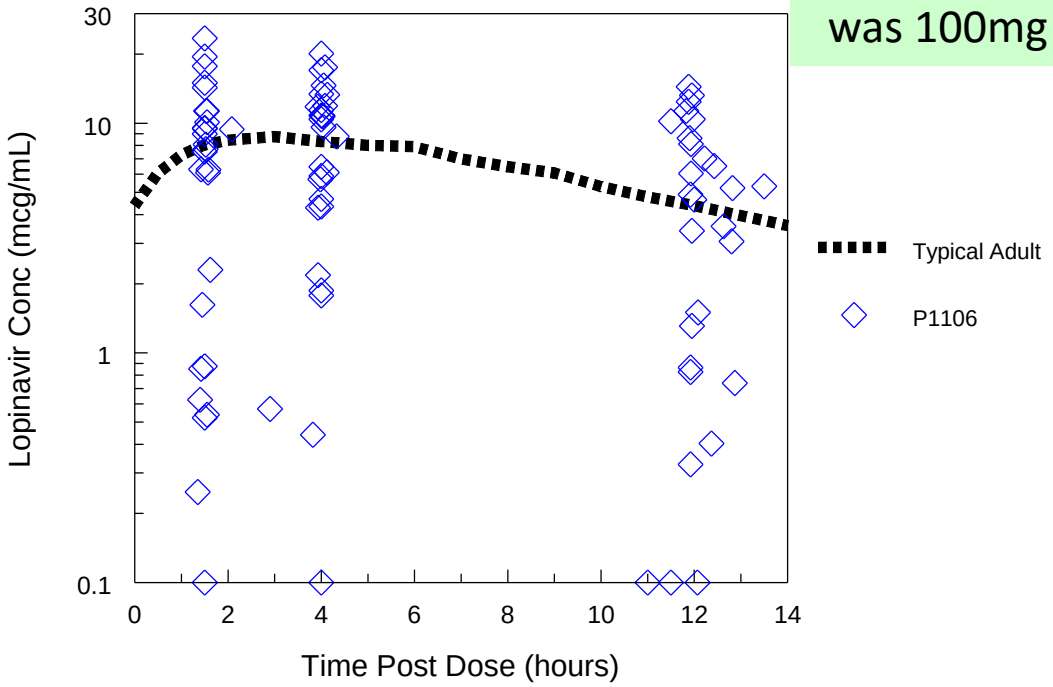
NVP trough concentrations were **> 0.1 µg/mL prophylaxis target**

NVP concentrations **decreased with increasing postnatal age**

LPV PK results (Arm 5) – May 2017 (n=16)

LPV was prescribed by clinicians using +/- 300 mg/m^2/dose twice daily

Median LPV dose for all infants was 100mg (range 48-200mg)



	Number	Mean	SD range
Pre-Dose (mcg/mL)	35	4.14	(0.4 – 7.88)
1.5 hr Post Dose	29	6.70	(1.48 - 11.92)
4 hr Post Dose	29	7.62	(2.77 - 12.47)

Adverse Events

All AEs were **unrelated** to study drugs

Expected Adverse Events
14 infants had Grade 3/4 expected AEs that commonly occur in premature infants, most common being presumed or confirmed sepsis (n=8)
All grade 3/4 expected AEs **resolved** or were downgraded to a Grade 1/2 by study end
Unexpected Adverse Events
16 infants had Grade 3/4 unexpected AEs, most common being pneumonia (n=6)
All grade 3/4 unexpected AEs **resolved** or were downgraded to a Grade 1/2 by study end (except for the infant that died from septicemia)

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Deaths

Five infants died during the study period:

Total deaths	Cause	Age of death (weeks)
3	Sudden unexpected death in infancy	7, 13 ,17
1	*Acinetobacter baumannii* septicemia	4
1	Bronchopneumonia	6

All deaths were unrelated to study drugs

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Summary

- Successfully enrolled 70 LBW infants on ARV and TB drugs
- NVP concentrations were within the target range for prophylaxis
- Subsequent NVP trough levels decreased with postnatal age
- LPV concentrations were similar to adult LPV target values (safety)
- No treatment related adverse events were observed

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ACKNOWLEDGEMENTS

NIH National Institutes of Health

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

- P1106 teams at PHRU & FAM-CRU
- Mae Cababasay and Jiajia Wang
- Bobbie Graham, Stephanie Popson and Chris Hensel
- Katie McCarthy

Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network was provided by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) under Award Numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC) and UM1AI106716 (IMPAACT LC), with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.