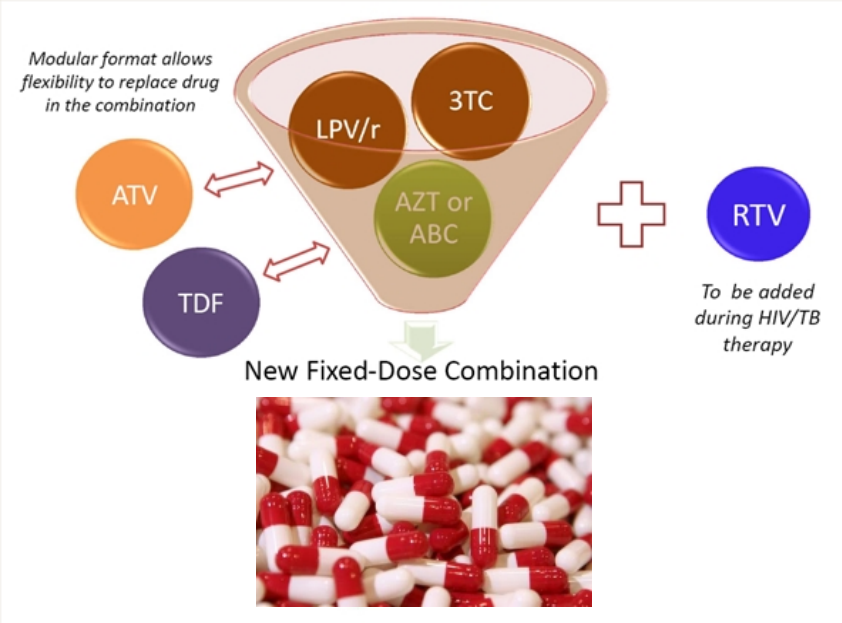
ACCELERATING OPTIMAL TREATMENT FOR PAEDIATRIC AIDS OCTOBER 2016



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I. Andrieux-Meyer. M. Lallemant JR.Kiechel
13.10.2016

2016 WHO ARV Consolidated Guidelines

Test earlier and closer

Treat earlier and better

Tailor service delivery

Treat more newborns

Introduce new drugs

Simplify strategies

World Health Organization

Treat earlier and better

Offer optimal regimens in age-appropriate formulations

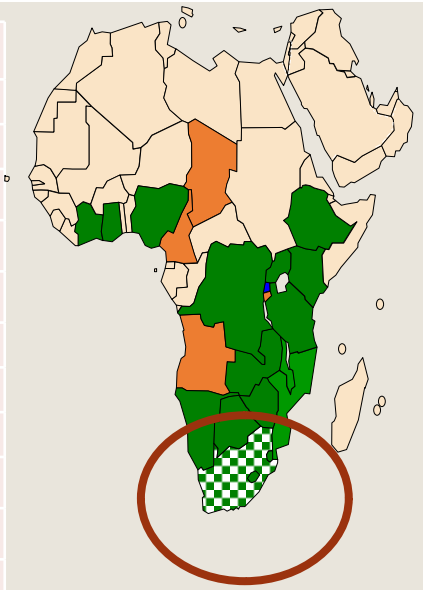
	Age at first line failure	First-line ART regimen	Second-line ART regimen
LPV/r-based first line	Younger than 3 years	ABC + 3TC + LPV/r	AZT or ABC + 3TC + RAL
		AZT + 3TC + LPV/r	
	3 years and older	ABC + 3TC + LPV/r	AZT + 3TC + EFV or RAL
		AZT + 3TC + LPV/r	ABC or TDF + 3TC + EFV or RAL
NNRTI-based first-line regimen	All ages	ABC + 3TC + EFV (or NVP)	AZT + 3TC + ATV/r or
		TDF + 3TC + EFV (or NVP)	AZT + 3TC + LPV/r
		AZT + 3TC + EFV (or NVP)	ABC or TDF + 3TC + ATV/r or LPV/r

- Simplification strategy: substitute LPVr with EFV at 3 years
- RAL first line in special circumstances
- DRV/r and DTG most appropriate for 3rd line use.

World Health Organization

Paediatric treatment needs and coverage in South Africa

	2010	2011	2012	2013	2014
Outputs for NICD, generated using Thembisa 2.4 on 1 Nov 2015 South Africa					
HIV-positive					
<1	20260	14992	13435	11585	**10107**
1	33471	26168	20621	19514	**17712**
2-4	126625	115060	100861	84448	**72178**
5-9	171883	173809	173126	171625	166110
10-14	98017	109857	119901	127810	134556
On ART					
<1	2693	3470	3422	3126	**2586**
1	4099	4812	4881	4649	**4084**
2-4	22419	27076	28021	25364	**21930**
5-9	49317	63371	74071	81084	83488
10-14	29338	42332	54871	65660	75143
Coverage					
<1	0.13	0.23	0.25	0.27	**0.26**
1	0.12	0.18	0.24	0.24	**0.23**
2-4	0.18	0.24	0.28	0.30	**0.30**
5-9	0.29	0.36	0.43	0.47	0.50
10-14	0.30	0.39	0.46	0.51	0.56



In 2014: 18% of children were reported to be on LPV/r first line.
Of children on second line, 91% were on a LPV/r base regimen.

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From nevirapine (NVP) to lopinavir (LPV/r)

NVP based ART

Fixed dose combinations (FDCs) available
Baby and junior dosing
Scored tablets
Can be crushed/dispersed
Easy dosing
But
Sub-optimal
Resistance mutations

LPV/r + 2 NRTIs

Liquid only currently
Bitter taste
Neurotoxic excipients
- 42% ethanol
- 15% propylene glycol

Needs cold chain
Heavy to carry, hard to hide
Difficult dosing
Need for RTV super-boosting in TB/HIV co-infection

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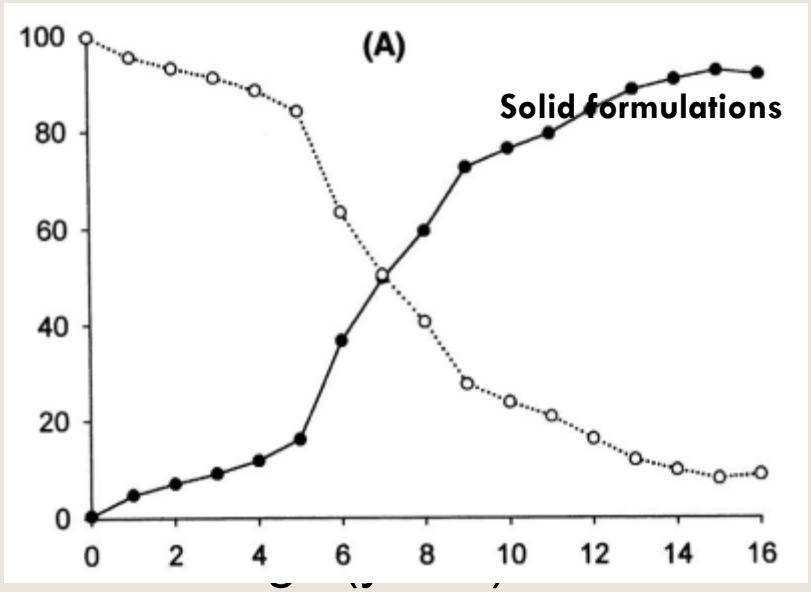
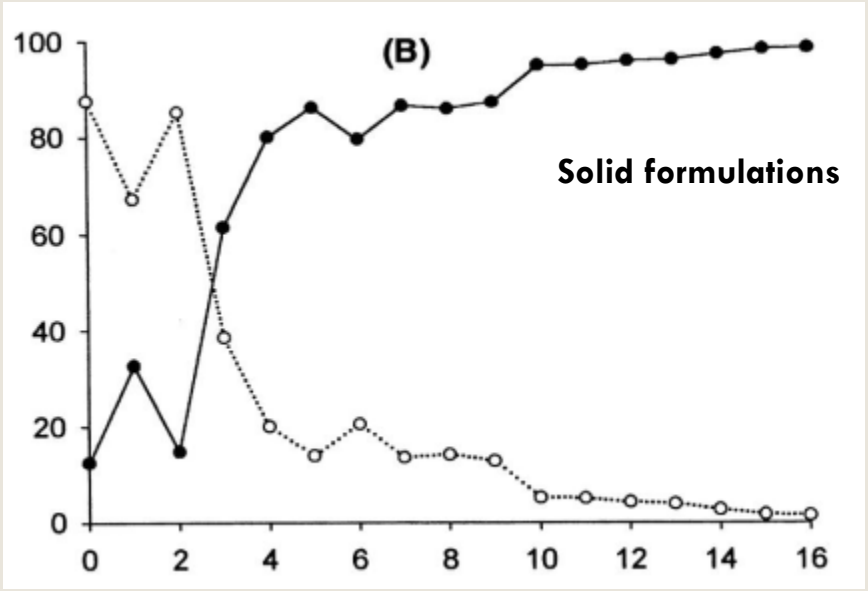
Tablets vs. liquid formulations

- Licensed



- Off label use



E. Schirm et al., Acta Paediatr. 92: 1486-1489 (2003)

- Lopinavir/ritonavir tablets cannot be used in young children as crushed they loose up to 50% bioavailability

Pharmacokinetics of Lopinavir/Ritonavir Crushed Versus Whole Tablets in Children

Brookie M. Best, PharmD, MAS,† Edmund V. Capparelli, PharmD,*† Huy Diep, BS,* Steven S. Rossi, PhD,† Michael J. Farrell, RN,† Elaine Williams, RN, MSN,‡§ Grace Lee, BS,‡ John N. van den Anker, MD, PhD,‡§ and Natella Rakhmanina, MD, PhD‡§*

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Cipla meltrex pellets

- Adult bioequivalence study presented at CROI 2012

Pharmacokinetics of a novel pediatric formulation, Lopinavir/ritonavir sprinkles in healthy human subjects: A pilot study. Jaideep A Gogtay Milind Gole Abhishek Khanna Raghu Naidu Geena Malhotra Shrinivas Purandare

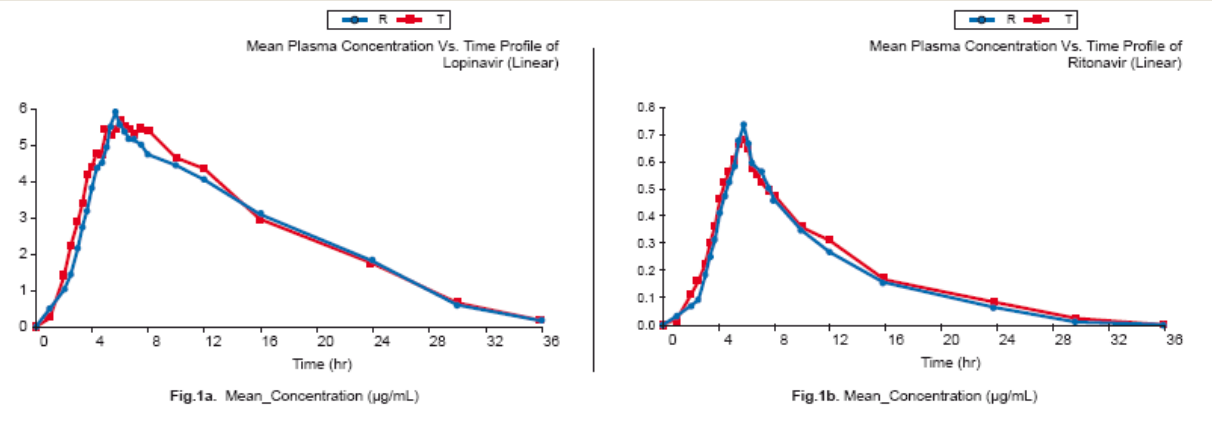
Cipla Limited, Mumbai, India; Sitec Labs, India

2015

Pharmacokinetic parameters

Table 2: Pharmacokinetic parameters of Lopinavir and Ritonavir administered as oral solution and as sprinkles.

		AUC_{0-t} (hr. μg/ml)	$AUC_{0-\infty}$ (hr. μg/ml)	C_{max} (μg/ml)	T_{max} (hr)
Lopinavir	Sprinkles	86.98±19.95	92.99±21.96	6.82±1.3	6.26±2.17
	Solution	84.57±26.48	89.26±27.83	6.28±1.77	5.99±0.65
	Ln-transformed 90 % Confidence intervals (T/R)	87.19-120.52	87.76 –122.54	91.31 – 131.02	
Ratio of Least square means T/R	Ln-transformed	102.51	103.71	109.38	
Ritonavir	Sprinkles	6.69±2.45	6.86±2.51	0.79±0.23	6.08±1.95
	Solution	6.23±2.22	6.38±2.24	0.77±0.34	5.72±0.59
	Ln-transformed 90 % Confidence intervals (T/R)	88.23-125.15	88.63–124.6	80.4 – 135.96	
Ratio of Least square mean T/R	Ln-transformed	105.08	105.09	104.55	



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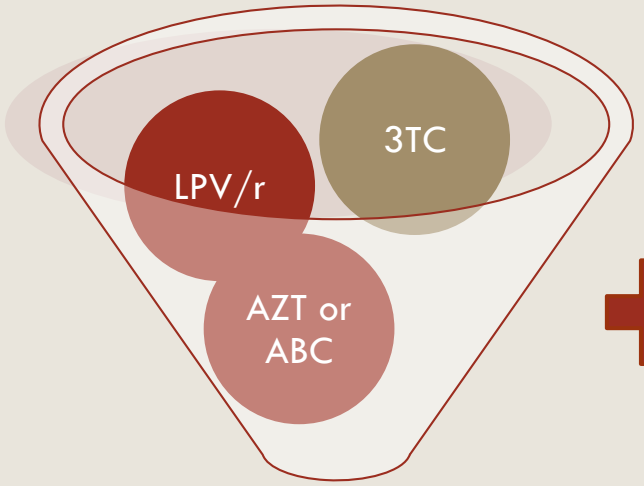
DNDi-Cipla Target Product
The Right Dose, The Right Taste

- 4 products in 1: granules (FDC) in a capsule
- Capsule simple to open and use with water, milk, food
- Well taste masked
- No cold chain
- Suitable for infants < 2 mos-3 yrs (& children who cannot swallow pills)
- TB-treatment manageable (additional RTV booster)
- Affordable



Modular format allows flexibility to replace drug in the combination

To be added during HIV/TB therapy

4-in-1 in Fixed-Dose Combinations

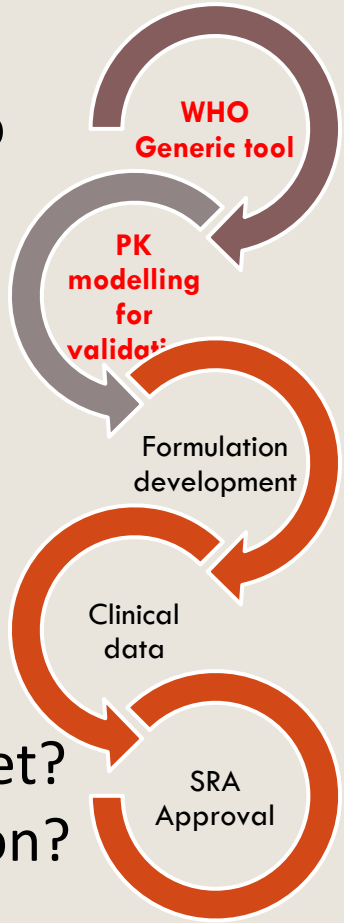
4-in-1 initial questions

R&D questions

- Are the four molecules compatible?
- What amount of each drug is needed per unit dose to cover all weight bands?
- How to taste mask without losing bioavailability?
- How likely is the new formulation bioequivalent to originator products?
- What paediatric clinical data will be necessary for registration?

IP and Market shaping questions

- How to deal with IP issues, for research and for market?
- What needs to be done to assist in country registration?
- How to facilitate adoption in national guidelines and procurement by national treatment programs



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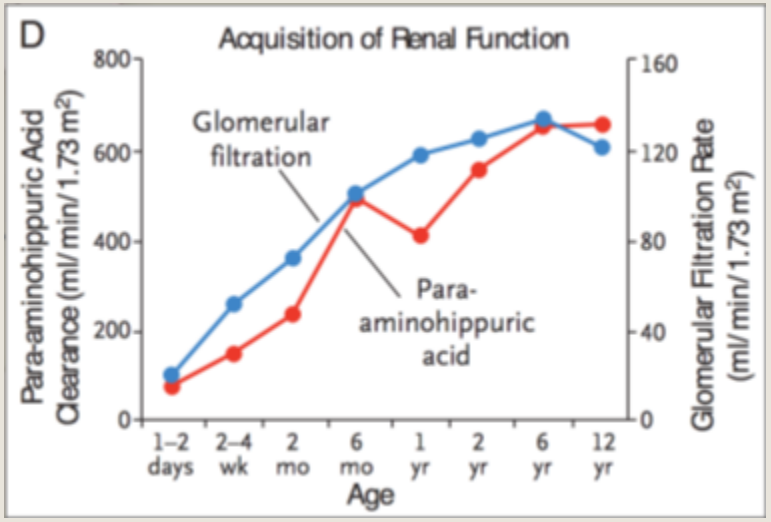
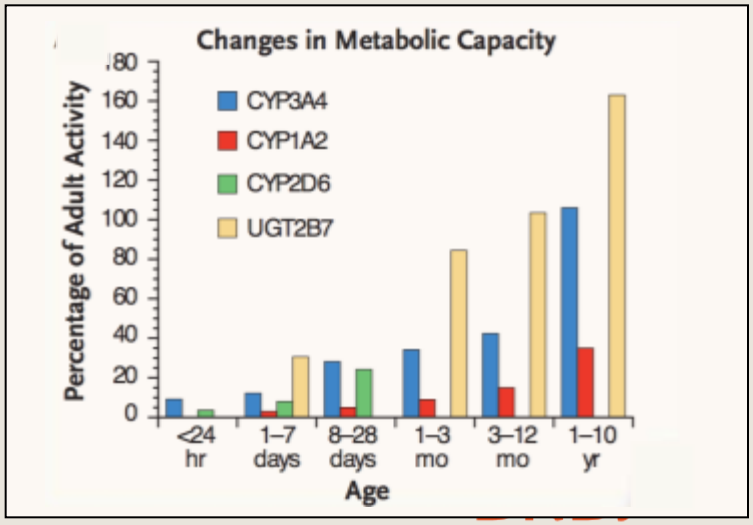
Lopinavir based fixed dose combinations: ratios, strengths, weight bands

- Four drugs that are absorbed and metabolized through different mechanisms which mature at different paces

ZDV: glucuronyl transferase + renal excretion
3TC: 5% transsulfoxide; unchanged renal elimination
ABC: alcohol dehydrogenase and glucuronyl transferase
LPV: Oxidation by CYP3A enzymes





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Lopinavir based fixed dose combinations: ratios, strengths, weight bands

- PK analysis of 25 datasets (INSERM, IMPAACT and PENTA)
- Nonlinear mixed effect modelling

Drug	Dose
LPV	40 mg
AZT or ABC	30 mg
3TC	15 mg

	No. of capsules (2x per day)
4 – 5.9 kg	2
6 – 9.9 kg	3
10 – 13.9 kg	4
14 - 19.9 kg	5
20 -24.9 kg	6

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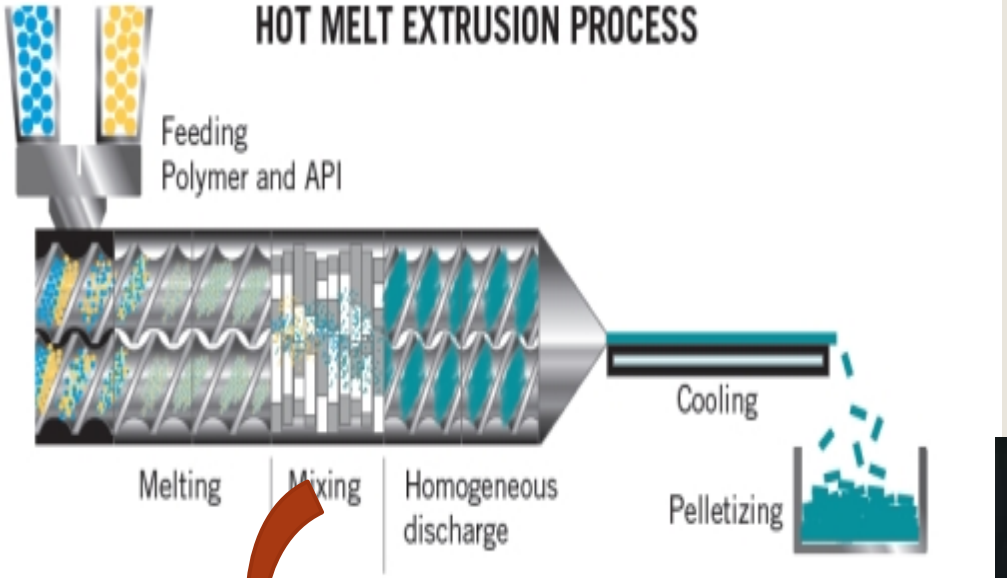
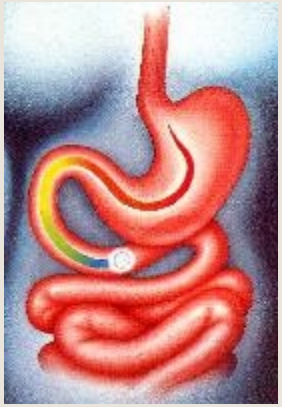
Taste masking lopinavir





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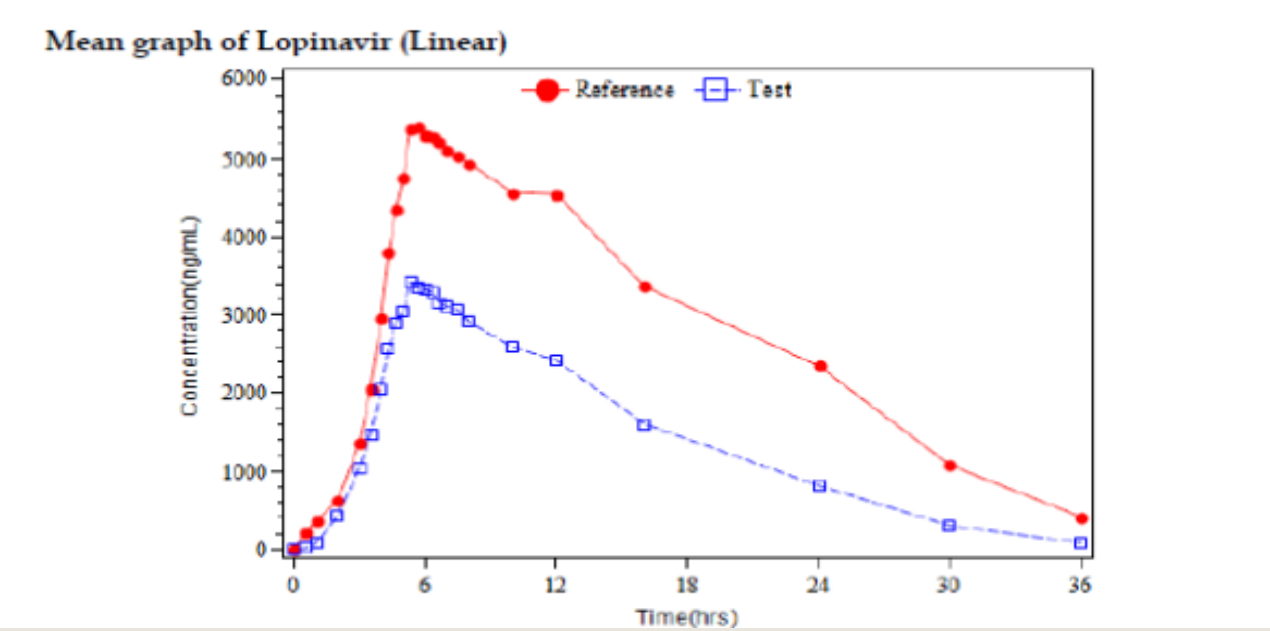
The challenge of taste masking: loss of bioavailability and high variability of lopinavir plasma levels



Screen new formulations in dogs in order to select formulations to be evaluated in adult volunteers

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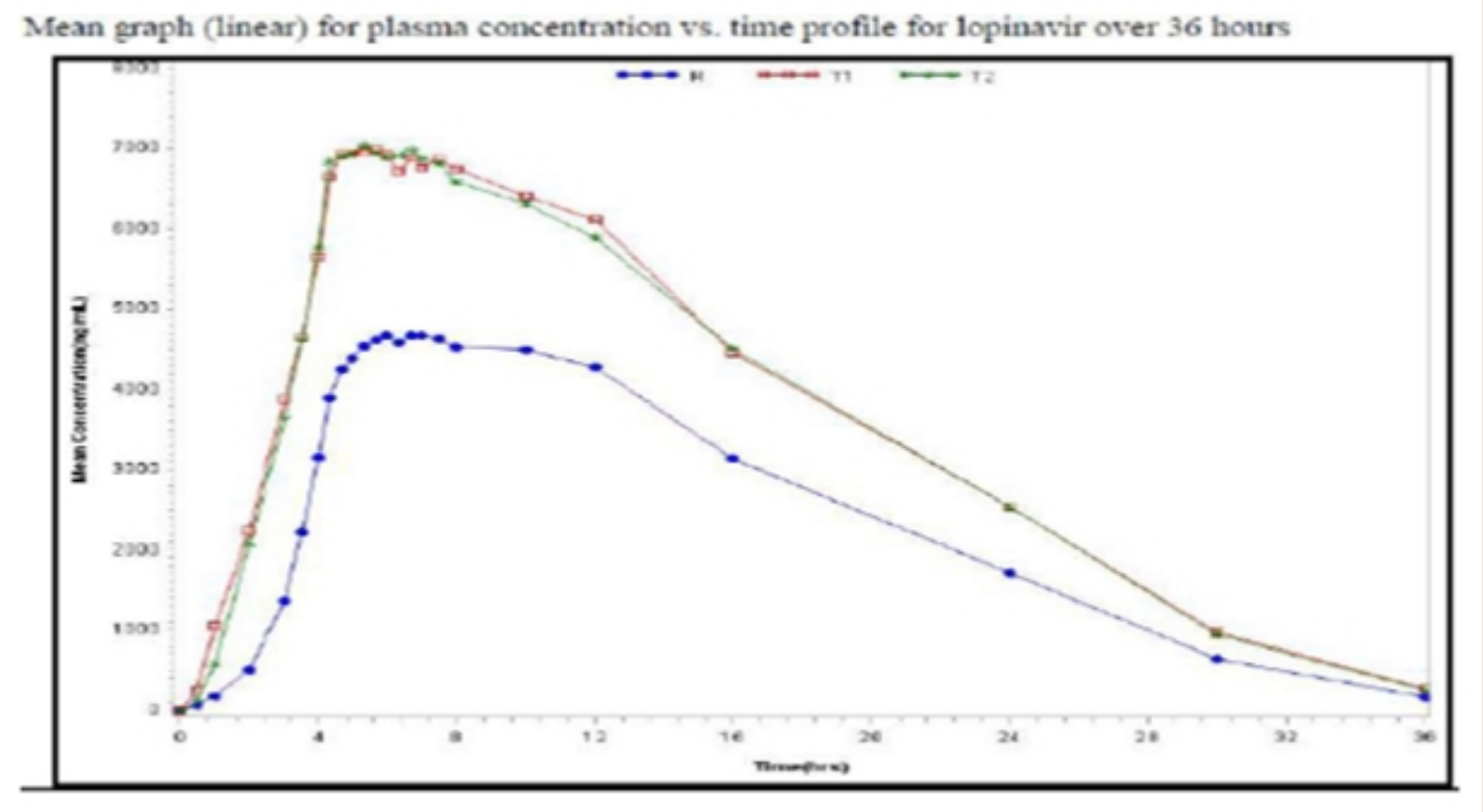
5% or 8% coated pellets vs. Solution – Fed state



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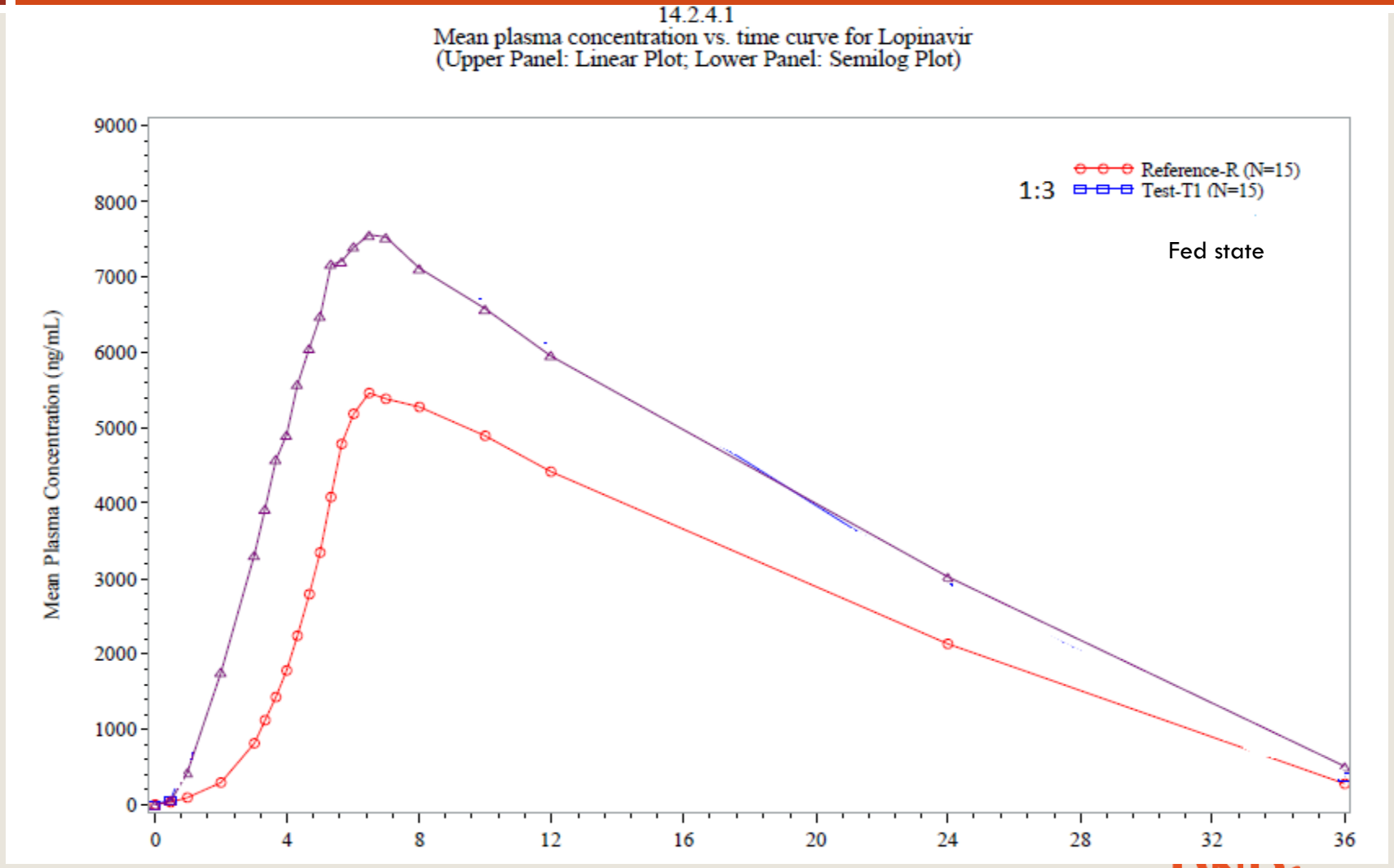
1:3 TMP granules vs. Liquid - Fed state



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Selection criteria for the final LPV/r formulation relevant for the targeted patient group

- Simplicity of the formulation process (compare minitablets ,coated granules and plain granules)
- Bioavailability
- Taste masking
- Size of granules versus minitablets
- Volume of dose to administer to babies
- "Mouthfeel"
- Visual aspect of the 4 in1
- Food effect

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Perspectives 1 : Global report on Early Warning Indicators of HIV drug resistance 2016

- LTFU at 12 months:20%,increased from 11.9% in 2004 to 24.5%in 2012.Retention on ART at M12:73.5%.
- Levels of pre-treatment HIVDR in LMIC have increased between 2004 and 2010, primarily driven by raised levels to NNRTIs in Africa.(14% in SA)
- The proportion of HIV new infections due to transmission from people with previous exposure to ARV drugs through PMTCT or previous treatment will increase. Therefore the risk of transmitted HIVDR among new-borns will increase. How do we anticipate this? In terms of early warning indicators, in terms of sequencing?

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Perspectives 2:the NRTIs?

- With increasing NNRTI HIVDR combined to use of Prep based on tenofovir /FTC, which are backbone components of first line ART, do we set up the scene for functional monotherapies or de facto suboptimal first line regimen?
- Can we develop other Prep components issued from other classes to preserve the NRTIs efficacy?
- Children will need more treatment options than adults, especially if the get infected with MDRHIV, this needs to be anticipated now.

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merci

- To all the patients and their families, the Cipla and DNDi staff.
- Contact: iandrieux-meyer@dndi.org

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