Challenges for paediatric ARVs development
What's in the pipeline?

Marc Lallemant

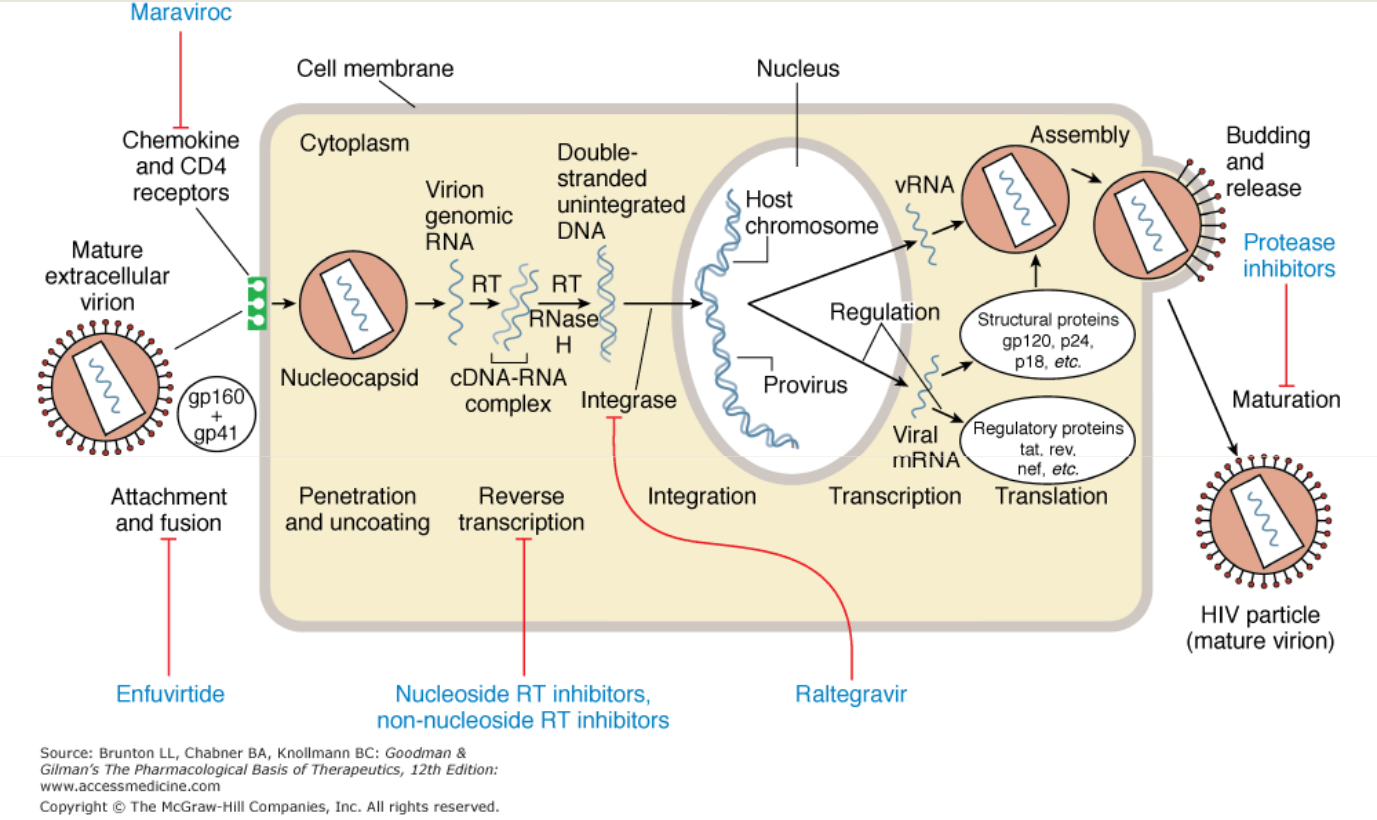
Acknowledgement

TAG i-base

DNDi
Drugs for Neglected Diseases *initiative*

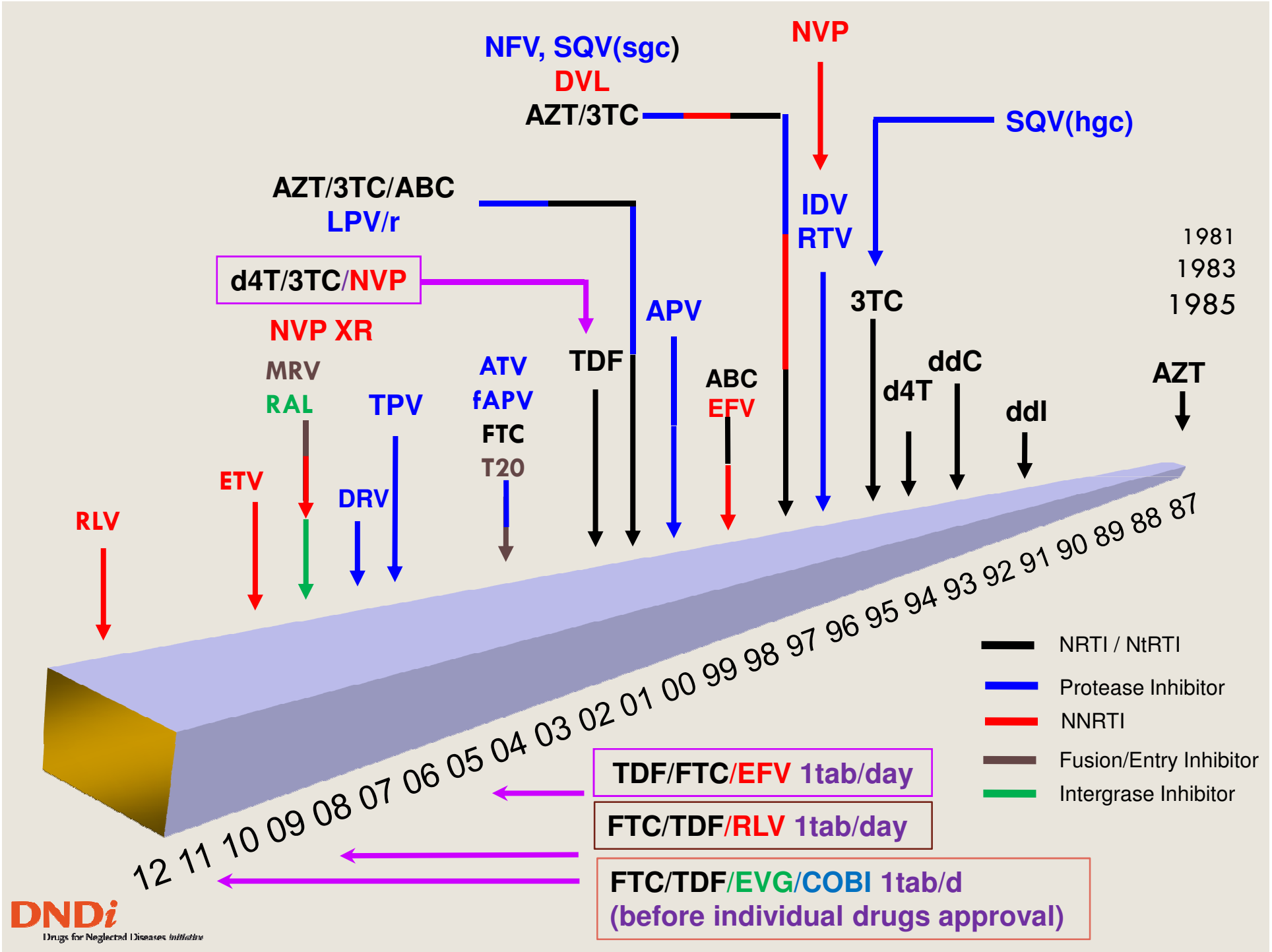
Antiretroviral drug discovery

- 1981: AIDS
- 1983: HIV
- 1985: tests
- Virus
  - Drug targets



- 1987 – today: 25 years of incessant antiretroviral drug discovery

DNDi
Drugs for Neglected Diseases initiative


NFV, SQV(sgc)
DVL
AZT/3TC
NVP
SQV(hgc)
AZT/3TC/ABC
LPV/r
IDV
RTV
d4T/3TC/NVP
NVP XR
APV
3TC
1981
1983
1985
MRV
RAL
ATV
fAPV
FTC
T20
TDF
ABC
EFV
ddC
d4T
AZT
ddI
TPV
ETV
DRV
RLV
12 11 10 09 08 07 06 05 04 03 02 01 00 99 98 97 96 95 94 93 92 91 90 89 88 87
NRTI / NtRTI
Protease Inhibitor
NNRTI
Fusion/Entry Inhibitor
Intergrase Inhibitor
TDF/FTC/EFV 1tab/day
FTC/TDF/RLV 1tab/day
FTC/TDF/EVG/COBI 1tab/d
(before individual drugs approval)
DNDi
Drugs for Neglected Diseases initiative

- The number of approved drugs decreases with children's age

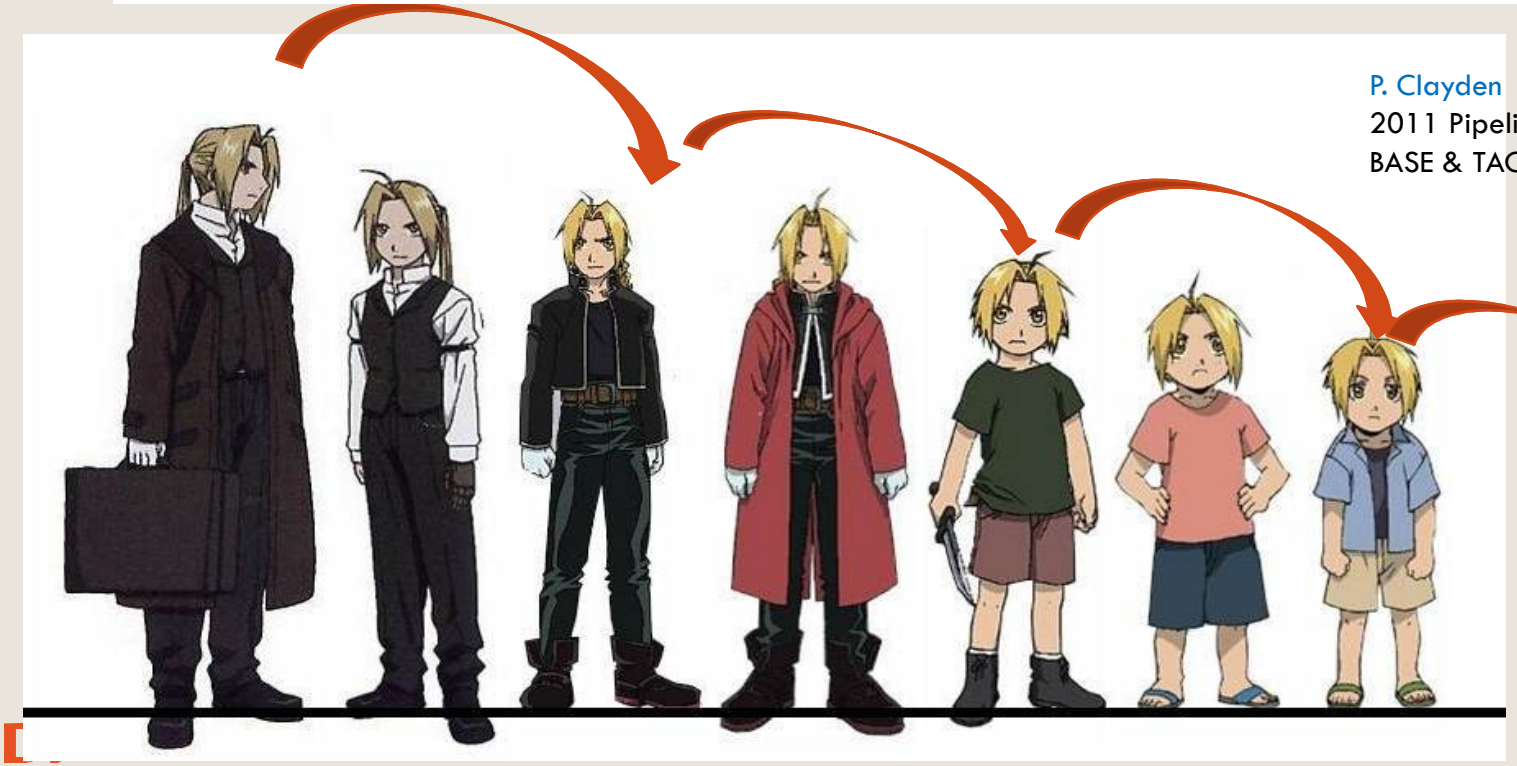
- Polly Clayden

2012 Pipeline report I-BASE & TAG

TABLE 2. Pediatric FDA Antiretroviral Approvals by Age Group (Years)

0–2	2–6	6–12	12–18	Adults
				maraviroc
				enfuvirtide
				raltegravir
				saquinavir
			maraviroc (>16)	indinavir
			enfuvirtide	atazanavir
		enfuvirtide	raltegravir	darunavir
		raltegravir	atazanavir	nelfinavir
	raltegravir	atazanavir	darunavir	fosamprenavir
	darunavir (>3)	darunavir	nelfinavir	ritonavir
	tipranavir	nelfinavir	fosamprenavir	lopinavir
	nelfinavir	fosamprenavir	ritonavir	rilpivirine
	fosamprenavir	ritonavir	lopinavir	delavidine
	ritonavir	lopinavir	delavidine (>16)	etravirine
fosamprenavir	lopinavir	etravirine	etravirine	efavirenz
ritonavir	efavirenz	efavirenz	efavirenz	nevirapine
lopinavir	nevirapine	nevirapine	nevirapine	tenofovir
nevirapine	tenofovir	tenofovir	tenofovir	zalcitabine
zidovudine	zidovudine	zidovudine	zidovudine	zidovudine
stavudine	stavudine	stavudine	stavudine	stavudine
lamivudine	lamivudine	lamivudine	lamivudine	lamivudine
emtricitabine	emtricitabine	emtricitabine	emtricitabine	emtricitabine
didanosine	didanosine	didanosine	didanosine	didanosine
abacavir	abacavir	abacavir	abacavir	abacavir

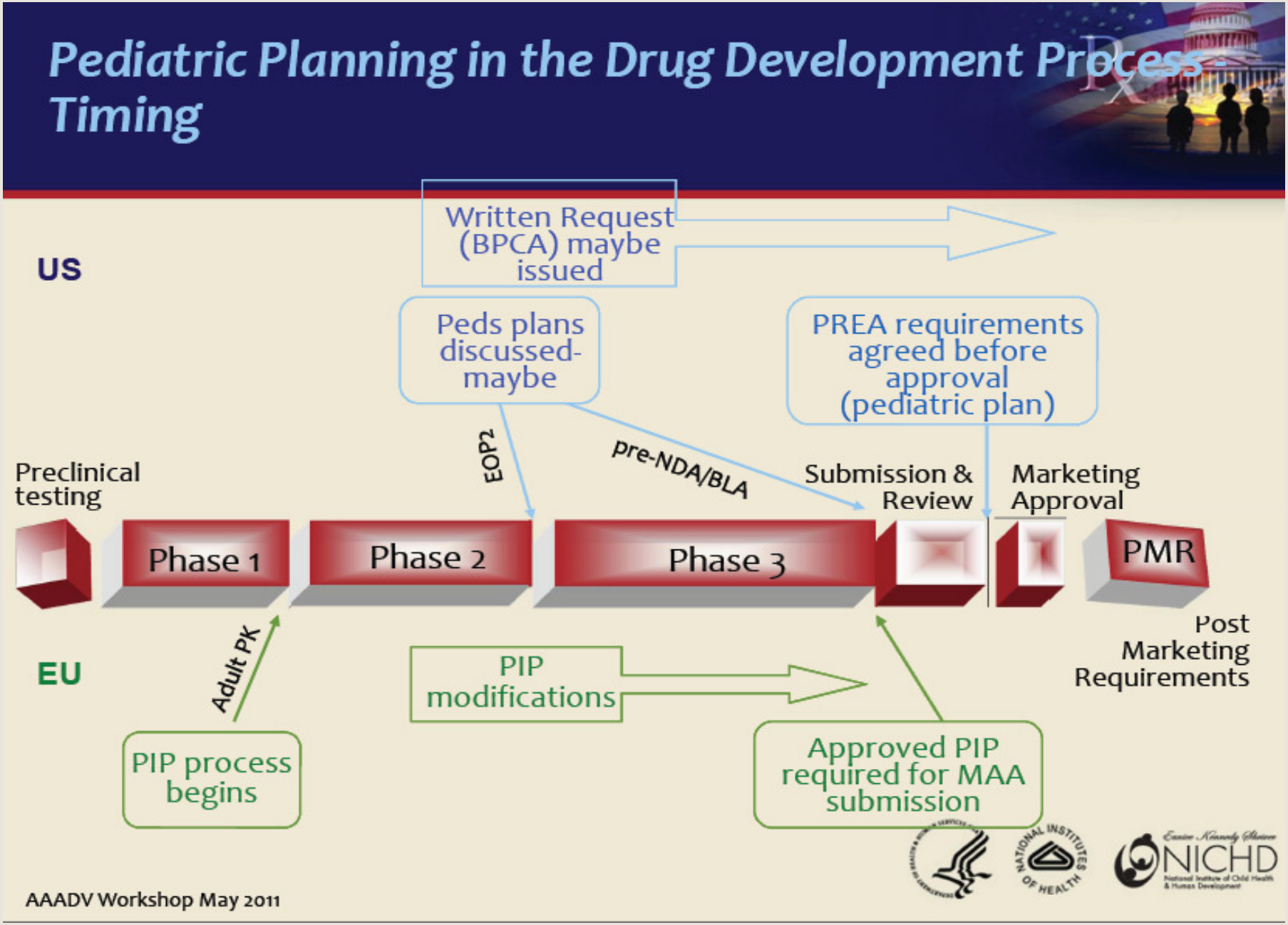
Drug	Calendar years	Time in years between adult approval and PD	Manufacturer
Didanosine	1991–2001	9.9	Bristol-Myers Squibb
Lamivudine	1995–2001	5.7	GlaxoSmithKline
Saquinavir*	1995–2010	14.9	Roche
Stavudine	1995–2001	5.7	Bristol-Myers Squibb
Ritonavir	1996–2005	9.3	Abbott
Nevirapine	1996–2001	5.5	Boehringer Ingelheim
Nelfinavir	1997–2003	6.5	Agouron
Abacavir	1998	<1	GlaxoSmithKline
Lopinavir/ritonavir	2000–2007	7.5	Abbott
Emtricitabine	2003–2005	2.9	Gilead
Tipranavir	2005–2007	2.7	Boehringer Ingelheim



P. Clayden
2011 Pipeline report I-BASE & TAG.

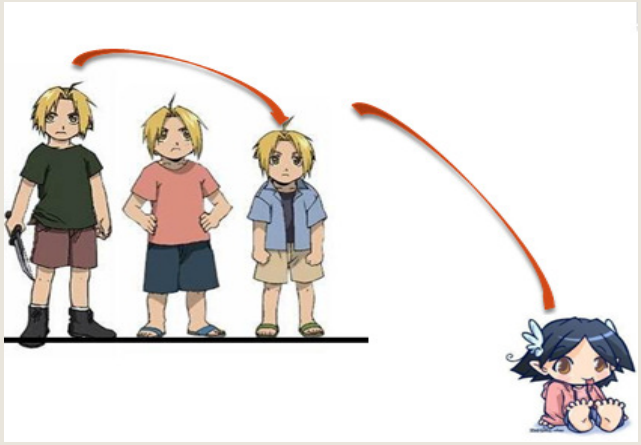
DND
Drugs for Neglected Diseases *initiative*

Pediatric Planning in the Drug Development Process - Timing



Pediatric indications in 2011-2012

- **Darunavir** (DRV) oral suspension formulations for children ages 3–<5 and >6 years unable to swallow tablets
- **Raltegravir** (RAL) chewable tablets for children 2–18 years old;
- **Tenofovir** (TDF) oral powder and tablets of for children 2–<18 years old
- **Etravirine** (ETR) tablets for 6–18 years old;
- **Fosamprenavir** (FOS) oral suspension for children 4 weeks to <6 years old.



Staggered age de-escalation studies

- **ATV** powder & capsules +/- RTV 3 months to 6 years of age (PRINCE1 and 2 and IMPAACT P1020A)
- **EVG/COBI** reduced-strength tablets and suspension in all age groups (PIP)
- **EVG/COBI/TDF/FTC** reduced strength tabs 6–18 years (PIP)
- **ETR** dispersible tablets 2 months to 6 years (P1090)
- **MVC** CCR5 antagonist oral suspension 2–8y (A4001031)
- **RAL** granules for suspension 6 mg/kg for less than 2 (P1066 & P1097)
- **RIL** 25 mg once daily 12 to18 y, more than 32 kg (PAINT), and granules 0–12 years (TMC278-C220)

ARV & TB Pipeline highlights (PIPs)

- **tenofovir prodrug (**GS-7340) improved PK and cellular penetration, low doses (10-24 mg/d vs 300 mg/d TDF)
  - GS-7340/FTC/EVG/COB studied
  - GS-7340/FTC/DRV/COB, first PI-based single-tablet FDC

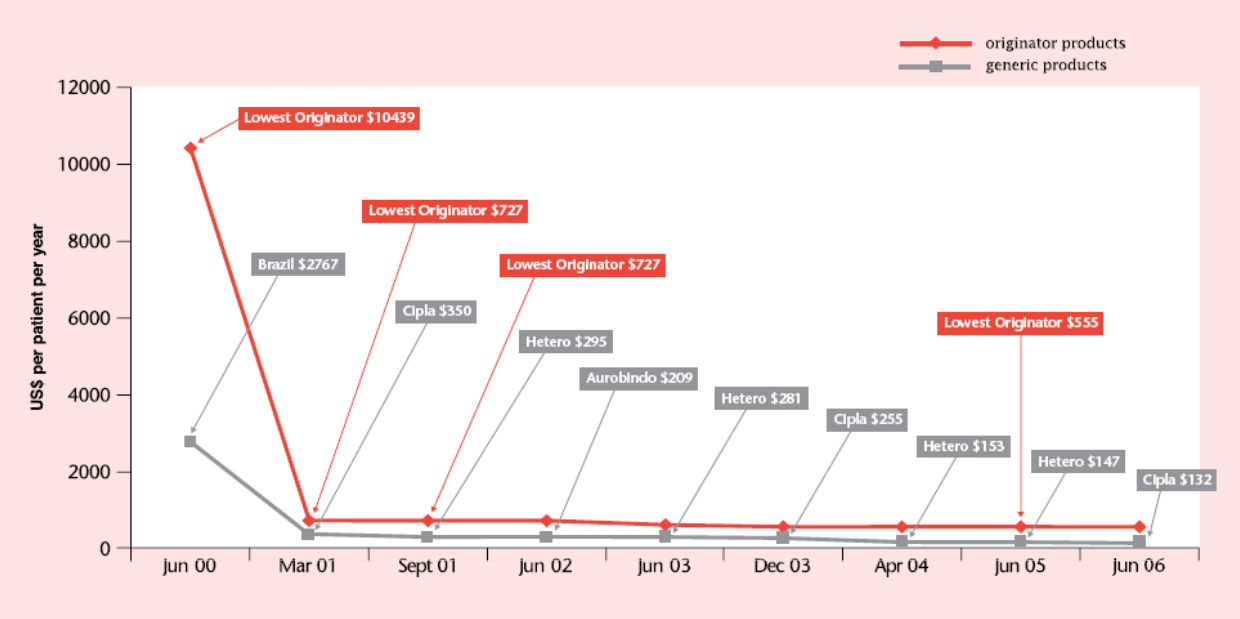
- **Dolutegravir** (DTG), OD in naïve, no boosting, resistance profile distinct from raltegravir? low dose, UGT1A1 (CYP3A minor route) i.e. manageable interactions; pediatric granule formulation (p1093)
  - DTG/ABC/3TC (572-Trii) studied

- **Bedaquiline** (TMC 207) evaluated in DR-TB and DR-TB/HIV co-infected children (p1108)

Caveat 1: Registration ≠ Access

- For 95% of HIV infected children worldwide who live in Africa, Asia and Latin America access , beyond FDA tentative approval, requires:
  - In country regulatory approval
  - Country program adoption (national guidelines)
  - Affordability
  - Efficient supply chain
  - (in addition to timely HIV diagnosis and appropriate monitoring)

Caveat 2: Generic competition, IP & prices



- 100 fold price decrease of 1st line therapy in 6 years
- Will this repeat itself with newer drugs?
  - Widespread patenting in Developing Countries
  - Basic patent expiry date for ETR: 2019; RAL: 2022
- Licenses negotiated from a public health perspective through the Medicine Patent Pool may be a key mechanism

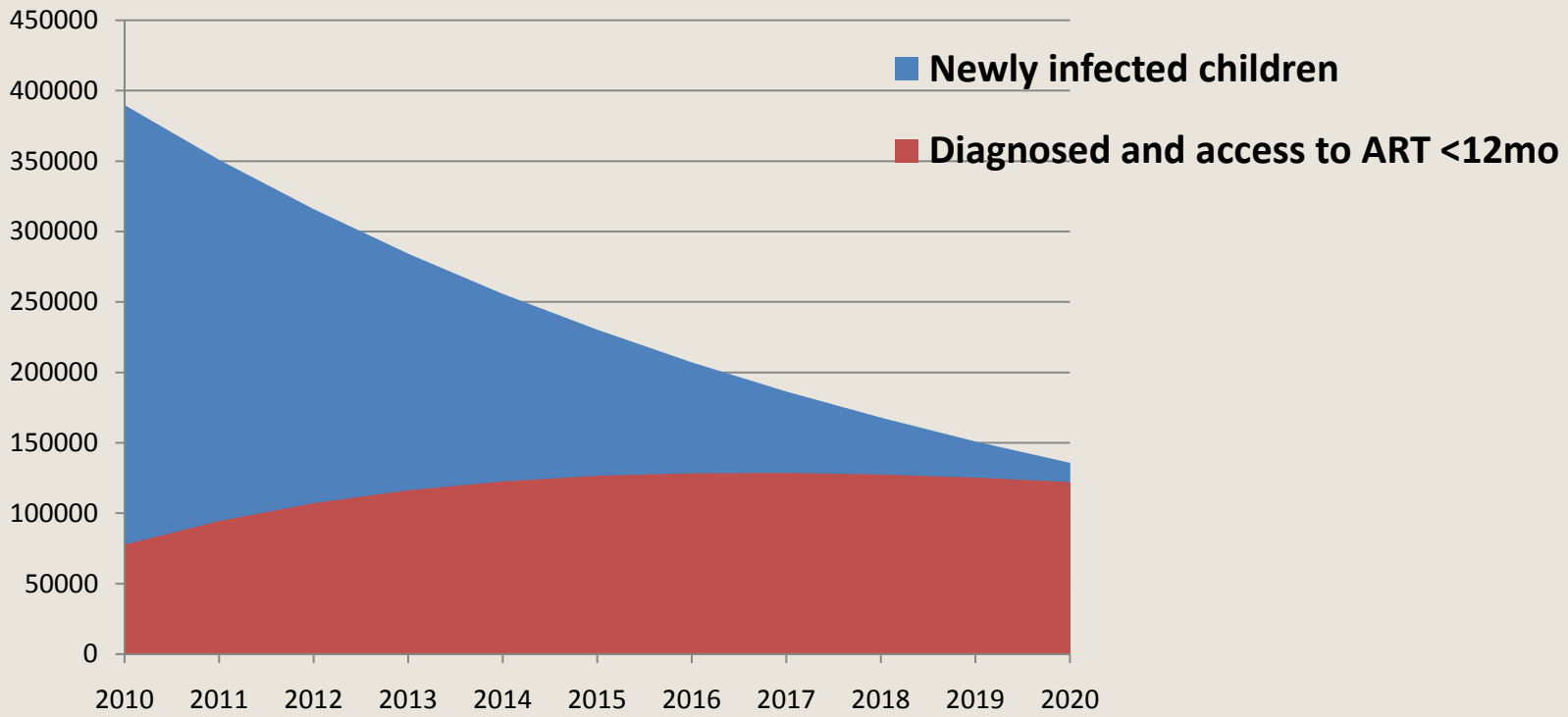
DNDi
Drugs for Neglected Diseases *initiative*

Caveat 3: Generic market fragmentation

- Advocacy to manufacturers has resulted in many formulations of the same drugs
  - Many products (45!) but few options (2 lines!) and still no adapted PI formulation
  - Top 4 (of 45) represent more than 50% of the total market value (UNITAID/CHAI)
- No demand for the WHO prequalified combination (ABC+3TC+ZDV 60/30/60mg tablet)
- Need for consolidated orders to reach manufacturer batch size
  - Up to 9 months delays before order are fulfilled

Caveat 4: Shrinking pediatric HIV population

Projected annual no. of newly infected children and no. receiving early HIV diagnosis and ART during infancy



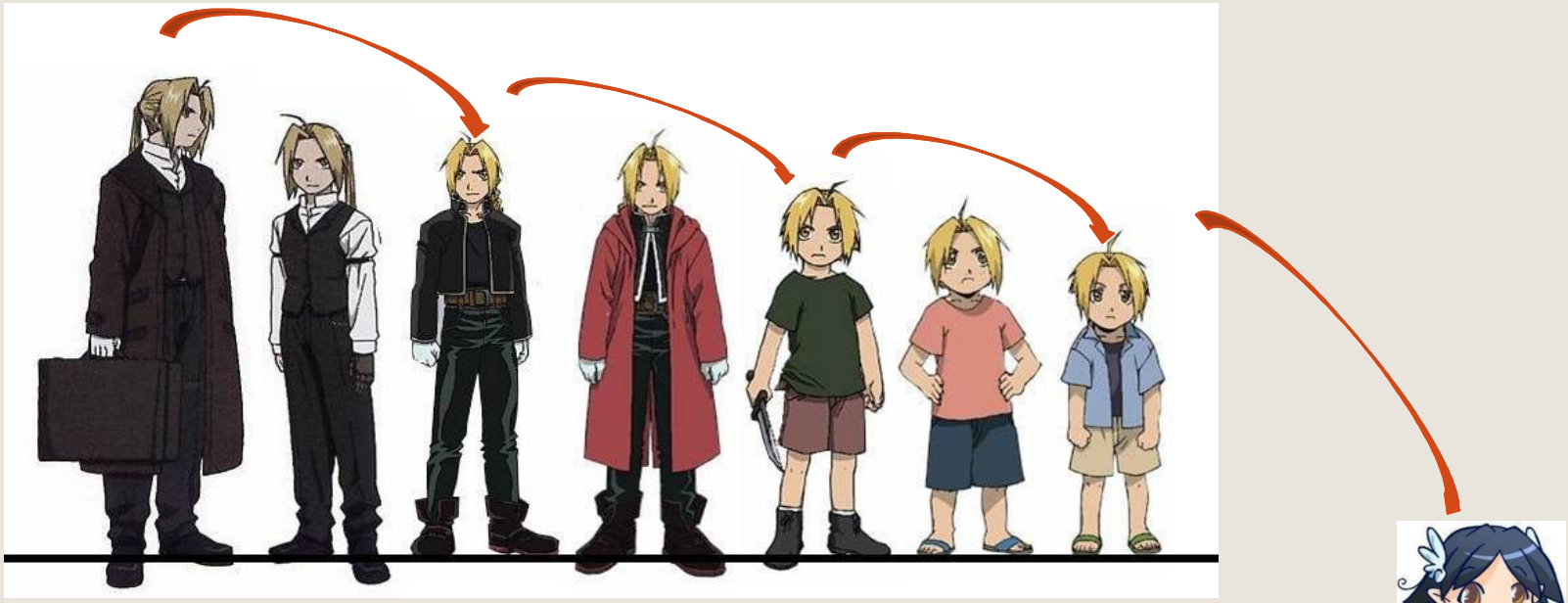
Beyond new drugs

Treatment optimisation: WHO Treatment 2.0

- ✓**Re-formulation** (improve drug bioavailability; stability; acceptability; extended release formulations)
- ✓**Co-formulation** (FDCs or co-blister pack)
- ✓**Dose adjustment/reduction** (reduce toxicity & pill burden/size)
- ✓**Sequencing strategies,** induction-maintenance; intensification
  - ✓NEVEREST (LPV->EFV);
  - ✓ARROW (NNRTI+2 or 3 NRTIs-> NNRTI+2NRTIs or 3NRTIs)
- ✓**Drug manufacturing process** (improve synthesis/reduce cost)
- ✓**Management of TB/HIV co-infection** (RIF PI & NNRTI interactions)
  - ✓Additional RTV to reach a 1:1 superboostin LPV/RTV ratio
  - ✓Evaluation of alternative options: Rifabutin, RAL
  - ✓Appropriately dosed pediatric FDCs (TB Alliance)

DNDi
Drugs for Neglected Diseases initiative

Adapting doses and formulations to children



- Smaller size = Smaller absolute dose
  - Growth requires a wide range of doses (difficult with solid dosage forms)
  - Dose relative to size (mg/kg, mg/m2, $mg/kg^{3/4}$) is not proportional and very difficult to predict
  - Developmental changes in drug absorption, distribution, metabolism, excretion, pharmacogenetics

Requirements for pediatric drug dosage forms

- ensure sufficient bioavailability taking into account children's particularities
  - Reach efficacy target (may undergo a maturation process; for antiretrovirals is assumed to be the same as adults)
  - Remain below toxicity target (not necessarily well known)
- contain nontoxic excipients for the age group
  - Limit of inactive ingredients per the dosing regimen
- acceptable and palatable
  - Taste/Sweetness preference differ around the world
- acceptable dose uniformity

Breitkreutz, J. Boos, Exp. Opin. Drug Deliv. 4: 37-45 (2007)

DNDi
Drugs for Neglected Diseases *initiative*

Requirements for pediatric drug dosage forms

- easy and safe to administer
  - Flexible dosage: dispersible or chewable tablets, sprinkles, granules
  - Minimum dosing frequency
- socio-culturally acceptable (stigmatization)
- have precise and clear product information
- appropriate for caregivers / setting
  - Stability in Zone IV climatic conditions (30°C, 65 or 70% RH)
  - No clean water required for dispensing medication
  - Heat stable – no refrigeration required

Breitkreutz, J. Boos, Exp. Opin. Drug Deliv. 4: 37-45 (2007)

DNDi
Drugs for Neglected Diseases *initiative*

Solid formulations

J. BreitkreutzJ. Breitkreutz, T. Wessel, J. Boos, Paed. Perin. Drug Ther. (1999)

Advantages

- Nontoxic excipients
- Lower price
  - switch from liquids to solid FDCs

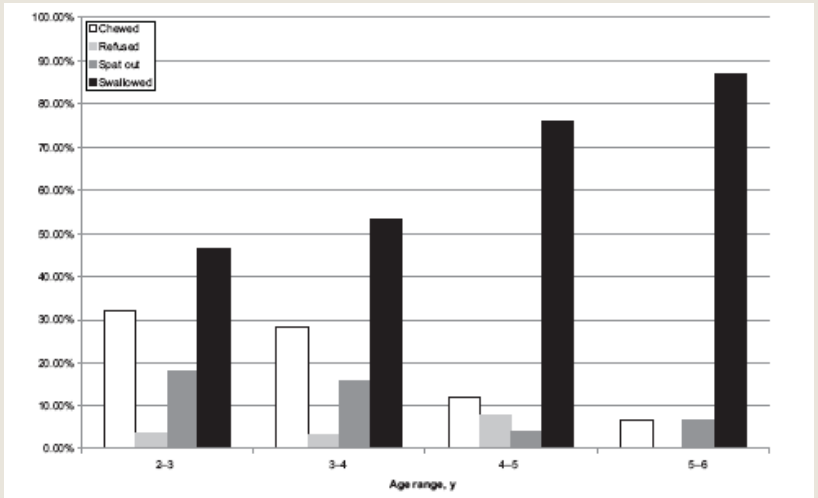
    = US$100 shipment/storage
- Various options for taste masking
- Modified release options
- Stability (storage & in-use & different climates)
- Reduces storage space
- High content uniformity
- Easy administration

Disadvantages

- Dimensions: swallowing
- Requires liquid for swallowing
- Aspiration (safety)
- Difficult dose adaption
- Varying bioavailability
- Dissolution rate impact

Acceptability of 3 mm minitabs in young children

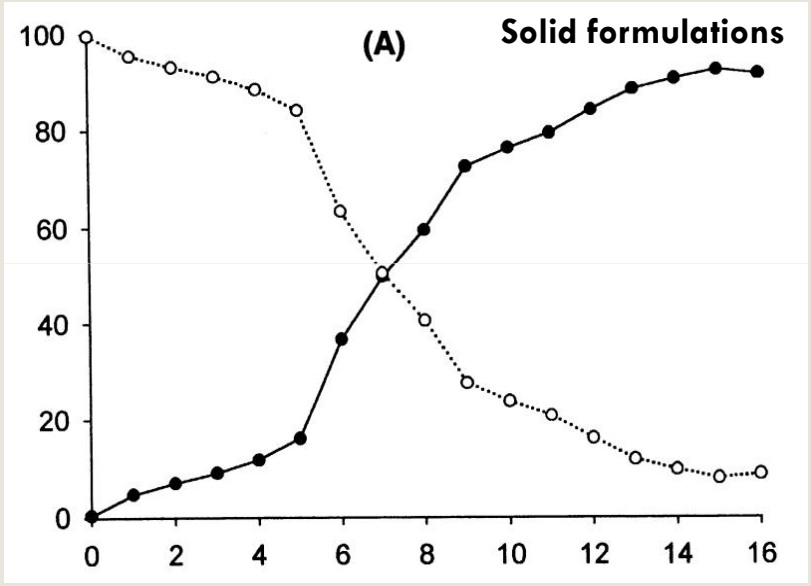
S. Thomson , C. Tuleu, I.C.K. Wong et al., Pediatrics 123: e235-238 (2009)



DNDi
Drugs for Neglected Diseases initiative

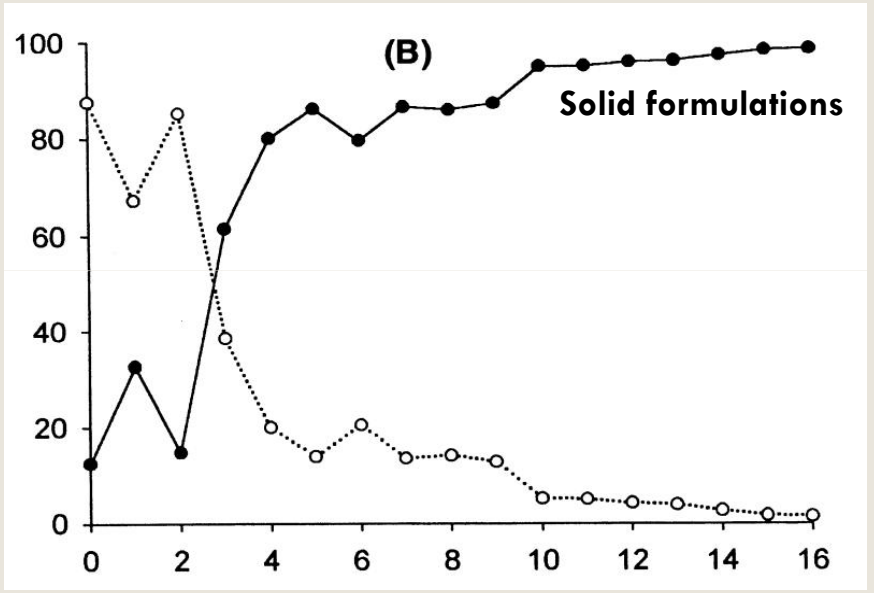
Solid formulations vs. liquid formulations

- Licensed



Age (years)

- Off label use



Age (years)

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

DNDi
Drugs for Neglected Diseases initiative

From off-label use of Adult formulations to Pediatric FDCs

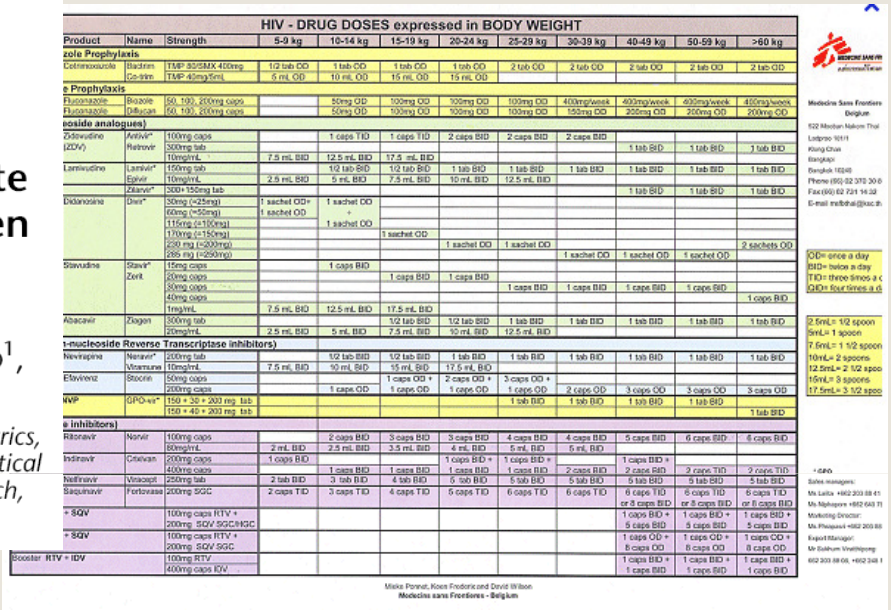
International Journal of STD & AIDS 2005; 16: 420–426

ORIGINAL RESEARCH ARTICLE

A drug dosage table is a useful tool to facilitate prescriptions of antiretroviral drugs for children in Thailand

M Ponnet MD[1], **K Frederix** MD[1], **W Petdachai** MD[2], **D Wilson** MD[1], **A Eksaengsri** MD[3] and **R Zachariah** MBBS PhD[4]

[1]*Médecins Sans Frontières, Bangkok;* [2]*Prachomklao Hospital, Department of Paediatrics, Petchburi;* [3]*Technical and Information Unit, R&D Institute, Government Pharmaceutical Organization, Bangkok, Thailand;* [4]*Médecins Sans Frontières, Operational Research, Medical Department, Brussels, Belgium*



HIV - DRUG DOSES expressed in BODY WEIGHT

Product	Name	Strength	5-9 kg	10-14 kg	15-19 kg	20-24 kg	25-29 kg	30-39 kg	40-49 kg	50-59 kg	>60 kg
zole Prophylaxis											
Cotrimoxazole	Bactrim	TMP 80/SMX 400mg	1/2 tab OD	1 tab OD	1 tab OD	1 tab OD	2 tab OD	2 tab OD	2 tab OD	2 tab OD	2 tab OD
	Co-trim	TMP 40mg/5mL	5 mL OD	10 mL OD	15 mL OD	15 mL OD					
e Prophylaxis											
Fluconazole	Biozole	50, 100, 200mg caps		50mg OD	100mg OD	100mg OD	100mg OD	400mg/week	400mg/week	400mg/week	400mg/week
Fluconazole	Diflucan	50, 100, 200mg caps		50mg OD	100mg OD	100mg OD	100mg OD	150mg OD	200mg OD	200mg OD	200mg OD
oside analogues)											
Zidovudine (ZDV)	Antivir*	100mg caps		1 caps TID	1 caps TID	2 caps BID	2 caps BID	2 caps BID			
	Retrovir	300mg tab							1 tab BID	1 tab BID	1 tab BID
		10mg/mL	7.5 mL BID	12.5 mL BID	17.5 mL BID						
Lamivudine	Lamivir*	150mg tab		1/2 tab BID	1/2 tab BID	1 tab BID	1 tab BID	1 tab BID	1 tab BID	1 tab BID	1 tab BID
	Epivir	10mg/mL	2.5 mL BID	5 mL BID	7.5 mL BID	10 mL BID	12.5 mL BID				
	Zilamivir*	300+ 150mg tab							1 tab BID	1 tab BID	1 tab BID
Didanosine	Videx*	30mg (=25mg)	1 sachet OD+	1 sachet OD							
		60mg (=50mg)	1 sachet OD	+							
		115mg (=100mg)		1 sachet OD							
		170mg (=150mg)			1 sachet OD						
		230 mg (=200mg)				1 sachet OD	1 sachet OD				2 sachets OD
		285 mg (=250mg)						1 sachet OD	1 sachet OD	1 sachet OD	
Stavudine	Stavir*	15mg caps		1 caps BID							
	Zerit	20mg caps			1 caps BID	1 caps BID					
		30mg caps					1 caps BID	1 caps BID	1 caps BID	1 caps BID	
		40mg caps									1 caps BID
		1mg/mL	7.5 mL BID	12.5 mL BID	17.5 mL BID						
Abacavir	Ziagen	300mg tab			1/2 tab BID	1/2 tab BID	1 tab BID	1 tab BID	1 tab BID	1 tab BID	1 tab BID
		20mg/mL	2.5 mL BID	5 mL BID	7.5 mL BID	10 mL BID	12.5 mL BID				
-nucleoside Reverse Transcriptase inhibitors)											
Nevirapine	Nenavir*	200mg tab		1/2 tab BID	1/2 tab BID	1 tab BID	1 tab BID	1 tab BID	1 tab BID	1 tab BID	1 tab BID
	Viramune	10mg/mL	7.5 mL BID	10 mL BID	15 mL BID	17.5 mL BID					
Efavirenz	Stocrin	50mg caps			1 caps OD +	2 caps OD +	3 caps OD +				
		200mg caps		1 caps OD	1 caps OD	1 caps OD	1 caps OD	2 caps OD	3 caps OD	3 caps OD	3 caps OD
NVP	GPO-vir*	150 + 30 + 200 mg tab					1 tab BID	1 tab BID	1 tab BID	1 tab BID	
		150 + 45 + 200 mg tab									1 tab BID
e inhibitors)											
Ritonavir	Norvir	100mg caps		2 caps BID	3 caps BID	3 caps BID	4 caps BID	4 caps BID	5 caps BID	6 caps BID	6 caps BID
		80mg/mL	2 mL BID	2.5 mL BID	3.5 mL BID	4 mL BID	5 mL BID	5 mL BID			
Indinavir	Crixivan	200mg caps	1 caps BID			1 caps BID +	1 caps BID +		1 caps BID +		
		400mg caps		1 caps BID	1 caps BID	1 caps BID	1 caps BID	2 caps BID	2 caps BID	2 caps TID	2 caps TID
Nelfinavir	Viracept	250mg tab	2 tab BID	3 tab BID	4 tab BID	5 tab BID	5 tab BID	5 tab BID	5 tab BID	5 tab BID	5 tab BID
Saquinavir	Fortovase	200mg SGC	2 caps TID	3 caps TID	4 caps TID	5 caps TID	6 caps TID	6 caps TID	6 caps TID or 5 caps BID	6 caps TID or 5 caps BID	6 caps TID or 6 caps BID
+ SQV		100mg caps RTV + 200mg SQV SGC/HGC							1 caps BID + 5 caps BID	1 caps BID + 5 caps BID	1 caps BID + 5 caps BID
+ SQV		100mg caps RTV + 200mg SQV SGC							1 caps OD + 6 caps OD	1 caps OD + 6 caps OD	1 caps OD + 8 caps OD
Booster: RTV + IDV		100mg RTV							1 caps BID + 1 caps BID	1 caps BID + 1 caps BID	1 caps BID + 1 caps BID
		400mg caps IDV									

Mieke Ponnet, Koen Frederix and David Wilson
Medecins sans Frontieres - Belgium

- MSF pediatric drug dosage table (splitting tablets, adding NVP)
- Weight band dosing table created by WHO experts to enable generic production of paediatric FDC
- First paediatric FDC WHO prequalified in 2008, 4 years after adult FDC.

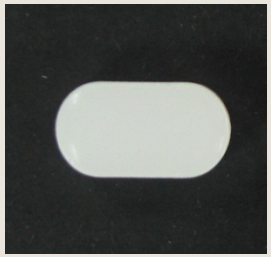
DNDi
Drugs for Neglected Diseases *initiative*

Pediatric Fixed Dose Combinations

- Current pediatric FDCs are NVP based and have been mostly used in older children
- CHER trial
  - HIV diagnosis in the first months of life
  - treatment initiated immediately
- Change in the pediatric HIV treated population
  - Higher viral load & ARV exposed viral population
- P1060 trial
  - regardless of exposure to NVP for PMTCT LPV/r superior to NVP based therapies

Switching from NVP to LPV/r first-line?

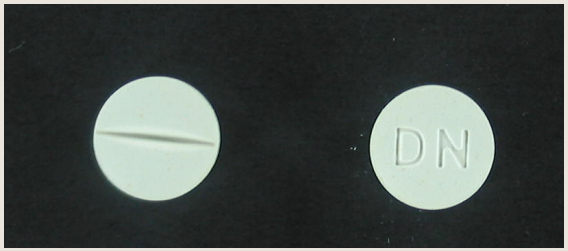
LPV/r + 2 NRTIs



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-infected children

NVP based ART



FDCs available
Baby and junior dosing
Scored tablets
Can be crushed
Easy dosing

DNDi
Drugs for Neglected Diseases initiative

Lopinavir-Ritonavir challenges

- According to the Biopharmaceutics Classification System (BCS) absorption of oral drugs predictable knowing:
  - its intrinsic permeability across the intestinal mucosa
  - its concentration at absorption site
  - and assuming dose form rapid dissolution
    - ≥85% API dissolution from formulated product in 30 minutes

highest dose soluble in 250 mL at pH 1 to 7.5

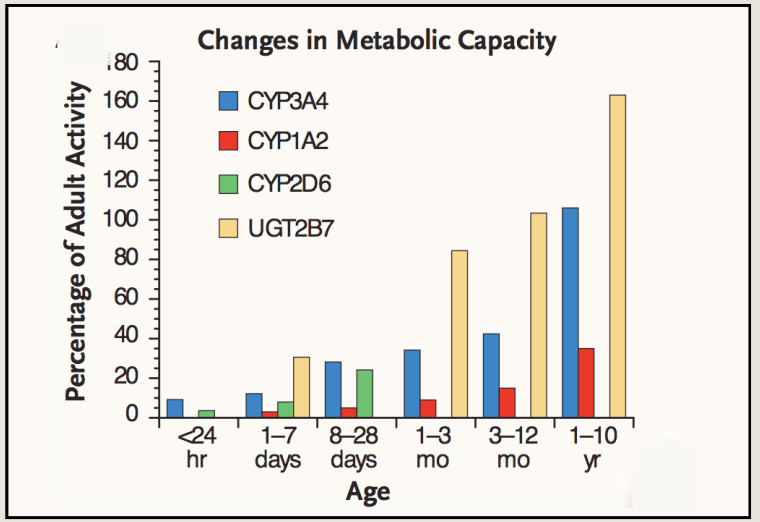
more permeable than co-dosed drug at least 85% absorbed (WHO).

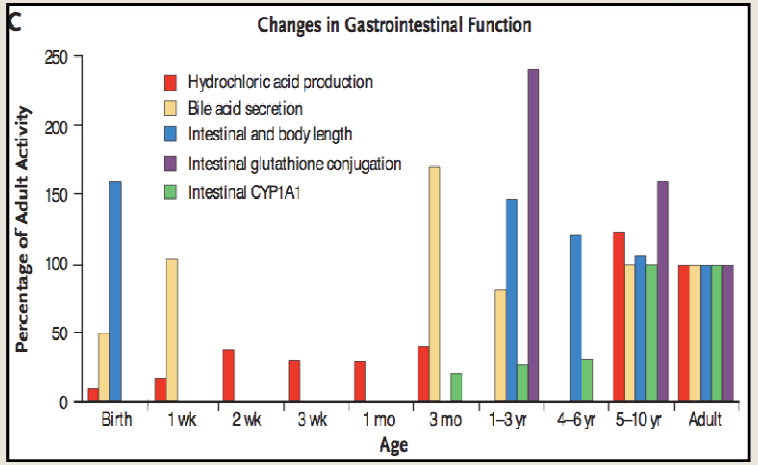
	High solubility	**Low solubility** Particle size, polymorphic forms, solubility enhancers
High permeability	ZDV, FTC	
Low permeability transit time, GI transporters and metabolic enzymes	3TC, ABC	**RTV, LPV**

DNDi
Drugs for Neglected Diseases initiative

Lopinavir-Ritonavir challenges

- LPV requires RTV boosting
  - RTV is a CYP3A4 substrate and inhibitor.
  - Inhibits GI metabolism by enterocytes CYP3A4 and Pgp efflux transporters (Cmax)
  - Inhibits liver CYP3A4 and Pgp thus maintaining LPV half-life
  - Boosting effect may be affected by GI and liver enzyme maturation
- Lopinavir absorbed in the beginning portion of the GI tract
  - Effect of gastric Ph, GI development on absorption



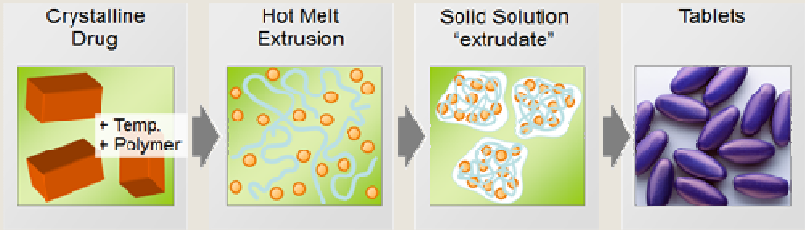


From: Kearns GL et al. N Engl J Med 2003;349(12):1157-67.

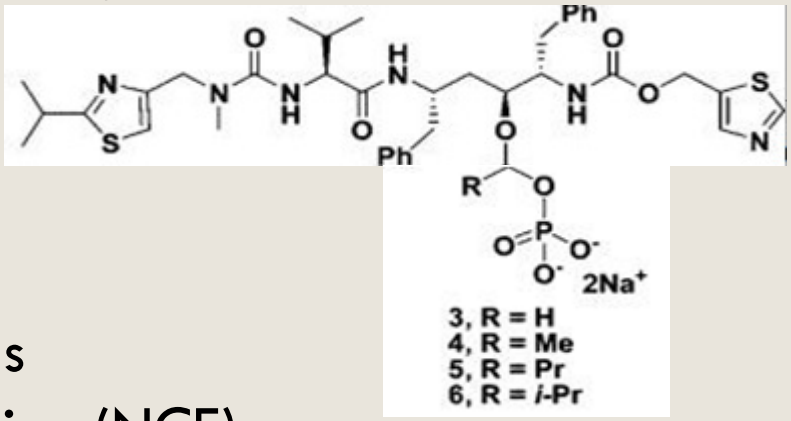
DNDi
Drugs for Neglected Diseases initiative

Initial explorations

- Original LPV and RTV formulations were alcohol based (LVP/r and RTV liquid and soft gel capsules; Abbott)
- Replaced for adults and older children with LPV/r tablets (Abbott)



  - Tablets cannot be used in young children as crushed they loose up to 50% bioavailability
- Alternative options explored by DNDi
  - Prodrugs (eg. RTV)
    - Nano particles
    - Nano dispersions



Encouraging PK in animals

Poor taste; 5 years time line (NCE)

DNDi
Drugs for Neglected Diseases initiative

Cipla meltrex sprinkles lopimune

- Results of adult bioequivalence study presented at CROI 2012

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	

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

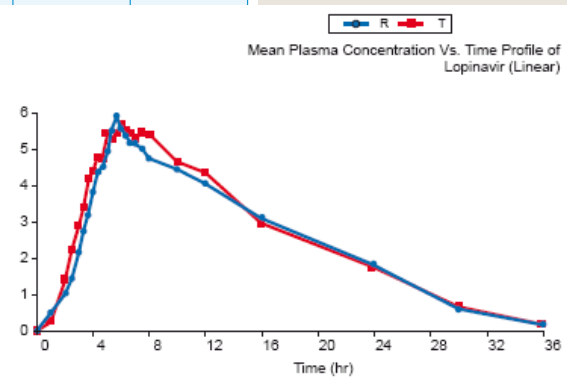


Fig.1a. Mean_Concentration (µg/mL)

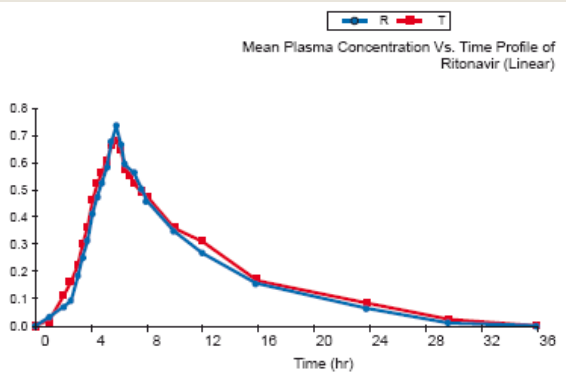
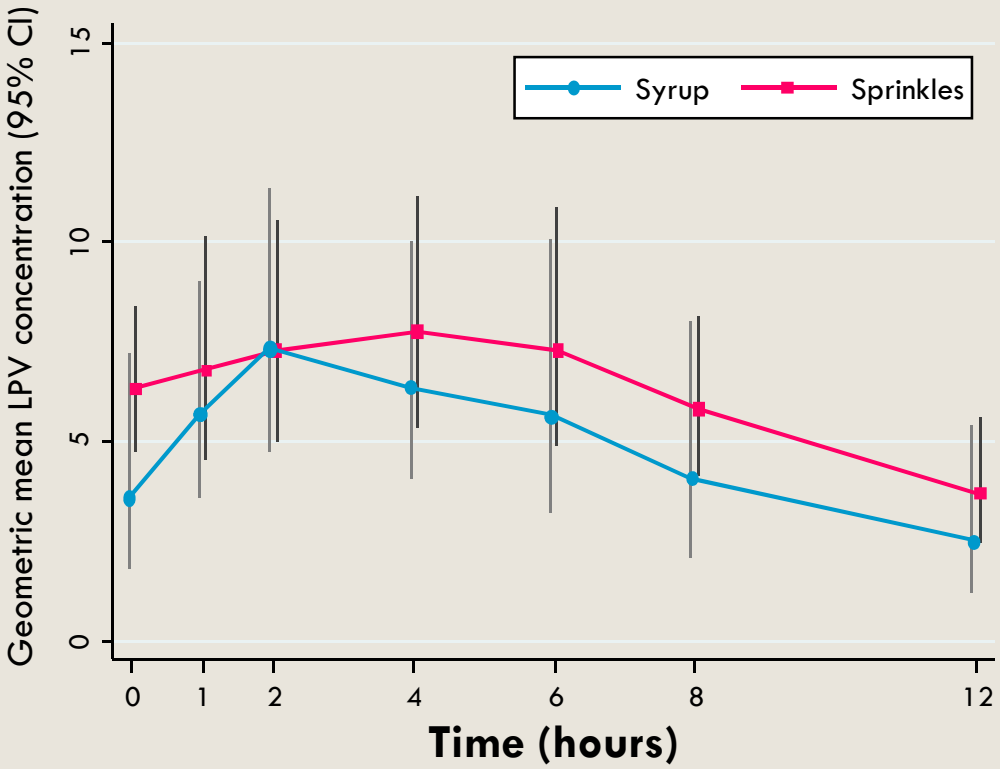


Fig.1b. Mean_Concentration (µg/mL)

DNDi
Drugs for Neglected Diseases initiative

Chapas-2/MRC study
within-infants PK of LPV/r Syrup vs Sprinkles (n=14)

- Exposure LPV in sprinkles comparable to the Abbott oral solution and historical data
- High variability
  - CV%: 62-66%

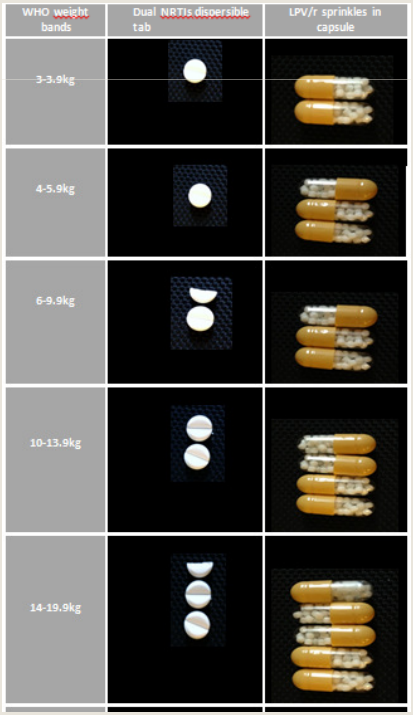


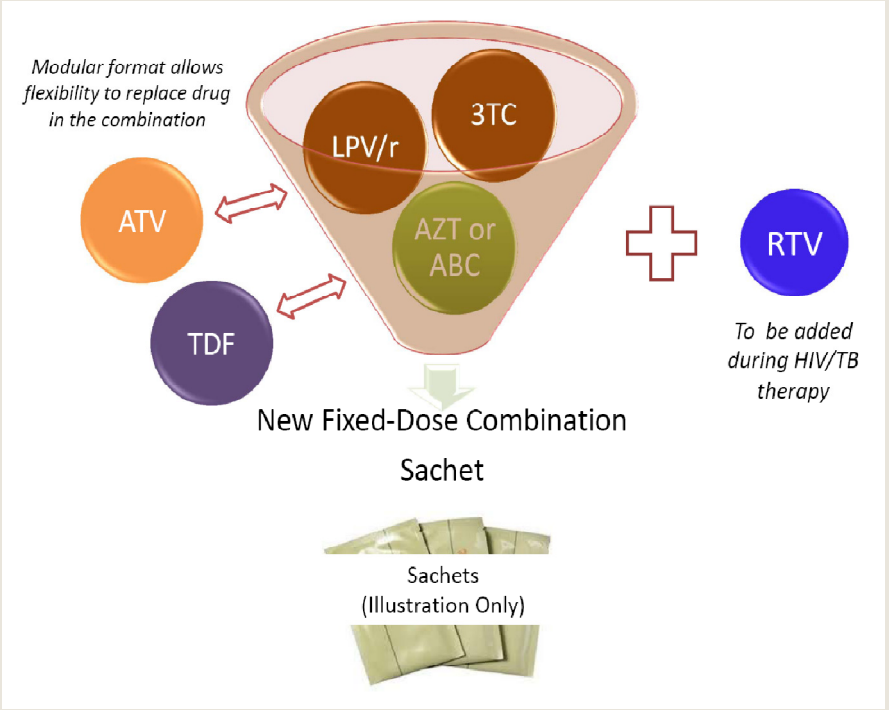
Pharmacokinetics and acceptability of a new generic lopinavir/ritonavir sprinkle formulation compared with syrup/tablets in African, HIV-infected infants and children according to WHO weight-band dose recommendations.
R Keishanyu, Q Fillekes, P Kasirye, et al., on behalf of the CHAPAS 2 trial team; 4th Pediatric workshop 2012

DNDi
Drugs for Neglected Diseases initiative

Cipla – DNDi – MRC partnership

- DNDi has joined MRC to add to Chapas-2 the key cohort of 1 to 4 years of age
- Further develops with Cipla two LPV/r fixed dose combinations





DNDi
Drugs for Neglected Diseases initiative

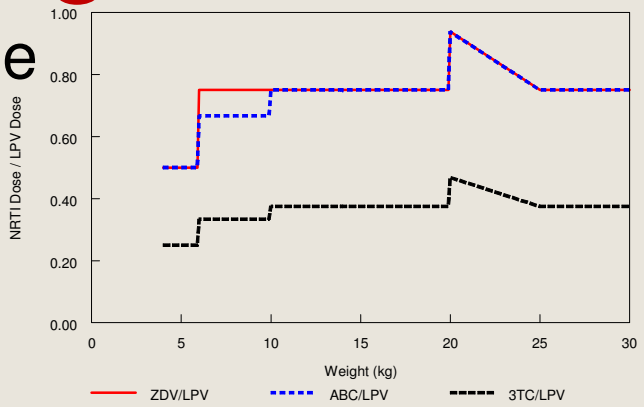
4-in-1 LPVr FDCs basic questions

- Twin sachets or LPVr + NRTIs granules of the same size in a single sachet/capsule?
  - Are all components compatible? At all ratios?
- Can all components be adequately taste masked?
- Given less than 20% loading for LPV/r and 50% for NRTIs, will the amount of excipients remain within acceptable limits?
- Will bioequivalence of all components be confirmed?
  - Consequences on the clinical development?
- What LPV/r : NRTIs ratio? What dosage strengths? For what weight bands?

Ratios, strengths, weight bands

WHO weight bands dosing is a compromise utilizing existing formulations

FDCs must assemble drugs with different metabolic pathways of different maturation kinetics

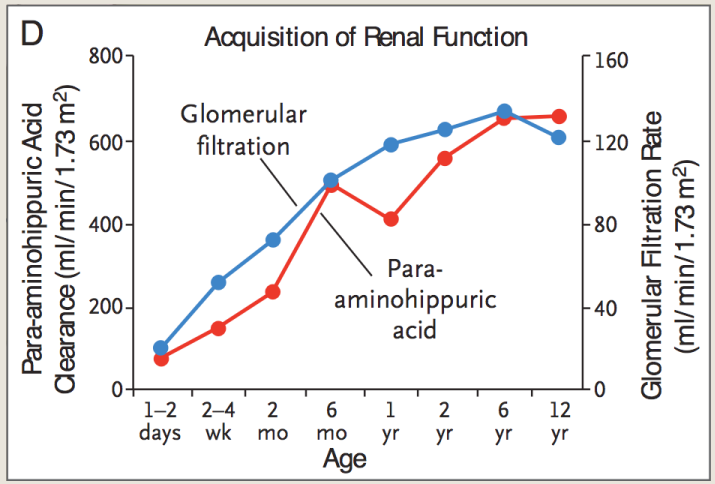


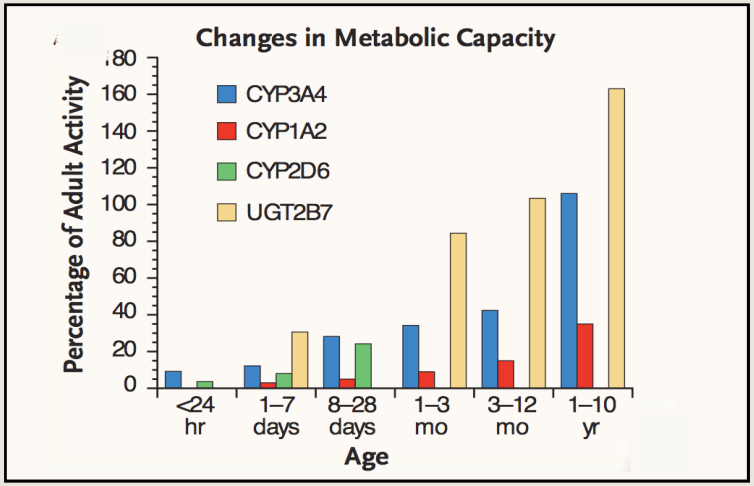
ZDV: glucuronyl transferase + renal excretion

3TC: 5% transsulfoxide; unchanged renal elimination

ABC: alcohol dehydrogenase and glucuronyl transferase

LPV: CYP3A enzymes oxidation



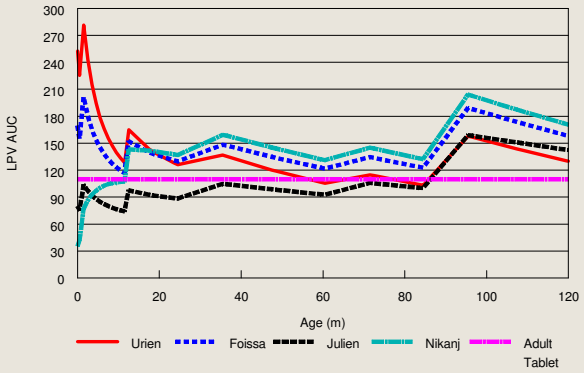


DNDi
Drugs for Neglected Diseases initiative

Which targets? Modeling exposures

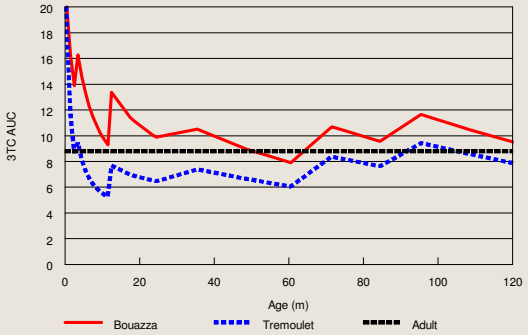
- LPV-AZT-3TC combination
  - LPV: **Cmin** 1 – 8 mg/L (efficacy-toxicity)
  - 3TC: reported **AUCs** in adults (8.9 to 16.6 mg.h/L)
  - AZT: reported **AUC** in adults (3 to 5 mg.h/L)

LPV Exposure by Study



ABC Exposure

3TC Exposure by Study

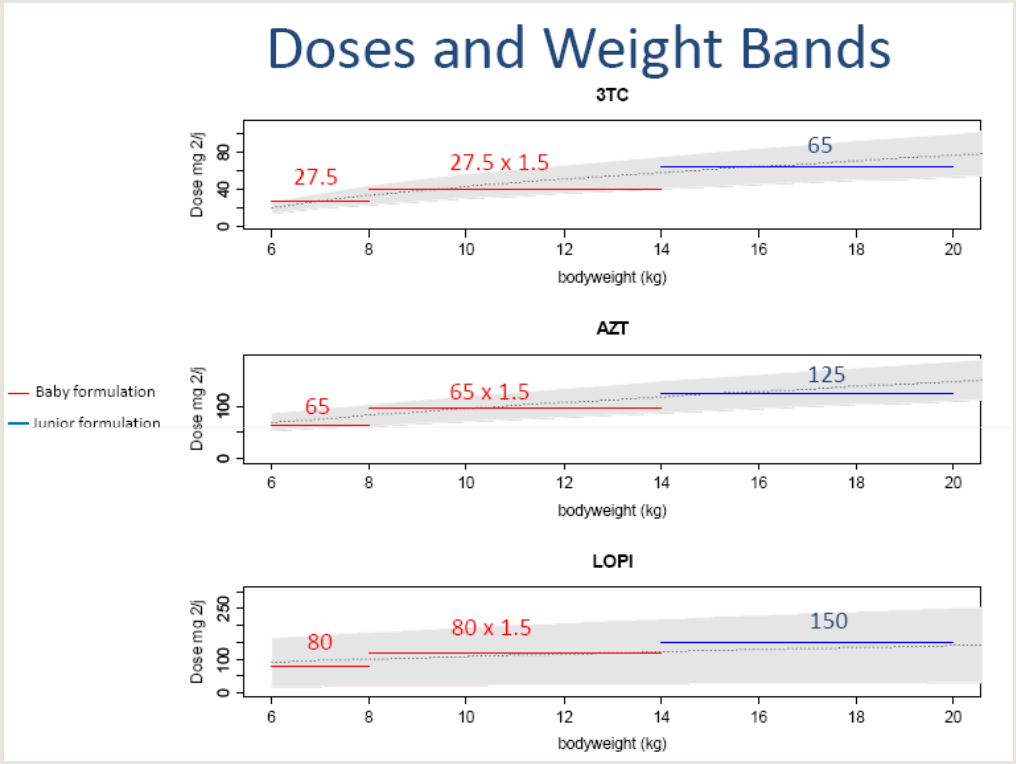


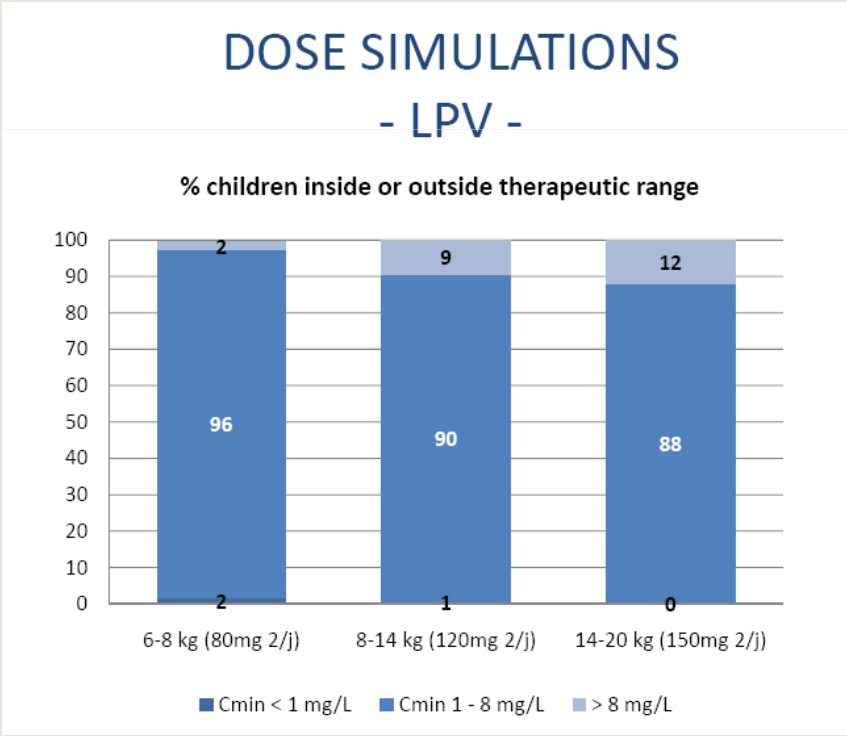
- AUC = Fraction of dose absorbed / clearance fonction of age and weight
- Weight band dosing

Pooling existing PK data and modeling drug exposure according to age and weight bands

DNDi
Drugs for Neglected Diseases initiative

Preliminary results in 6 to 20 Kg





DNDi
Drugs for Neglected Diseases initiative

In summary

- Pediatric drug development is challenging, generally
- The context in which new drugs, new formulations, new combinations will be introduced cannot be ignored:
  - Shrinking pediatric population
  - Fragmented market
  - Intellectual property rights obstacles
- We need to think strategically to give HIV infected infants the best chances to reach adulthood safely while keep all their treatment options

Thank you for your attention

Acknowledgments

Janice Lee

Jean René Kiechel

Stephen Robinson

Ed Capparelli

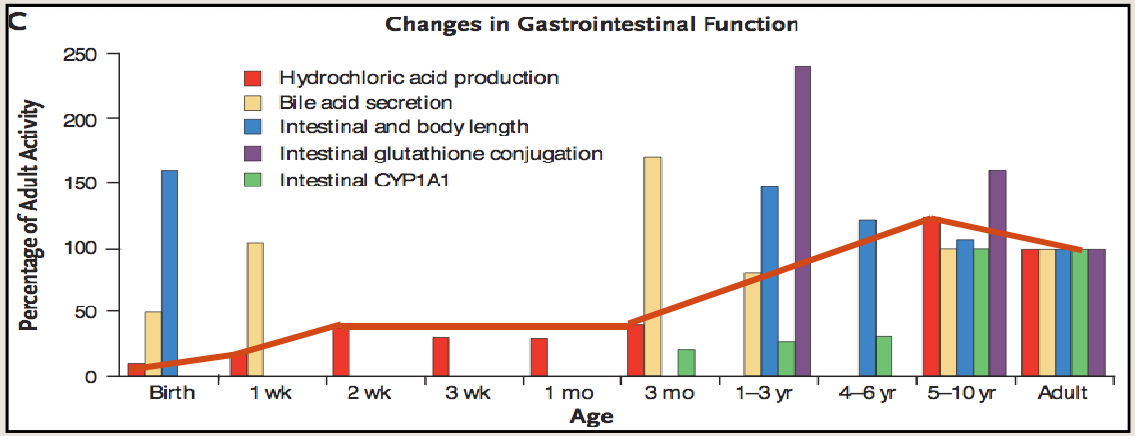
Jean Marc Treluyer

Saik Urien

Drugs for Neglected Diseases *initiative*

Formulation, gastro-intestinal maturation and absorption

- Acceptability of the pediatric formulation is key
- Early gastro-intestinal maturation further modulates absorption
  - Gastric Ph (ionisation, solubility, stability, coating)
  - Gastric emptying time
  - Gastro-intestinal motility
  - Intestinal integrity



DNDi
Drugs for Neglected Diseases initiative