

Key Obstacles and Issues to provision of ART to Children in Resource-Poor Settings

Diana M Gibb

Medical Research Council Clinical Trials Unit, UK

d.gibb@ctu.mrc.ac.uk

Clinical, Psychosocial, Programmatic Obstacles and Issues for Paediatric ARVs

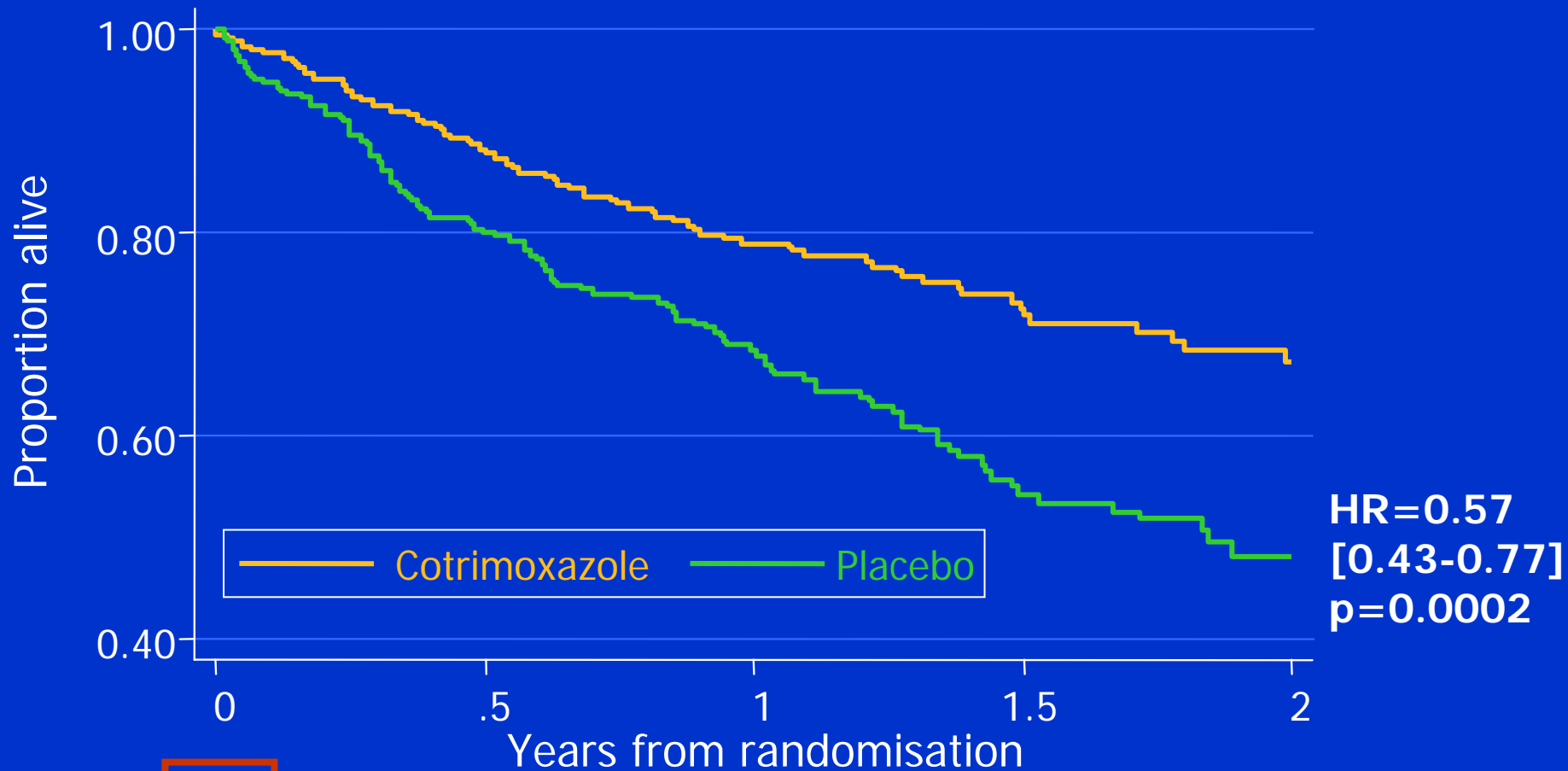
- Obstacles to testing children for HIV
- Lack of expertise on paediatric ARV management, especially 'when to start':
 - Clinical staging non-specific
 - Prognostic tests poor in young children
 - Logistics of family clinic approach
- ART Availability
 - Cost of individual drugs
 - Lack of appropriate paediatric formulations and Fixed Dose Combinations
 - Not a priority for pharmaceutical companies
- Lack of advocates for children

Obstacles to HIV Testing in Children

- By families and care-givers
 - fear, stigma, other priorities
- By health professionals
 - lack expertise to recognise clinical HIV
 - see no benefit in testing
 - lack counselling expertise for families
- Lack of diagnostic tests for young children
- Disclosure issues (older children)

Death by time at risk

(534 children > 1 year in the CHAP Trial, Lancet in press)



Cotox
Placebo

265
269

232
211

177
143

106
72

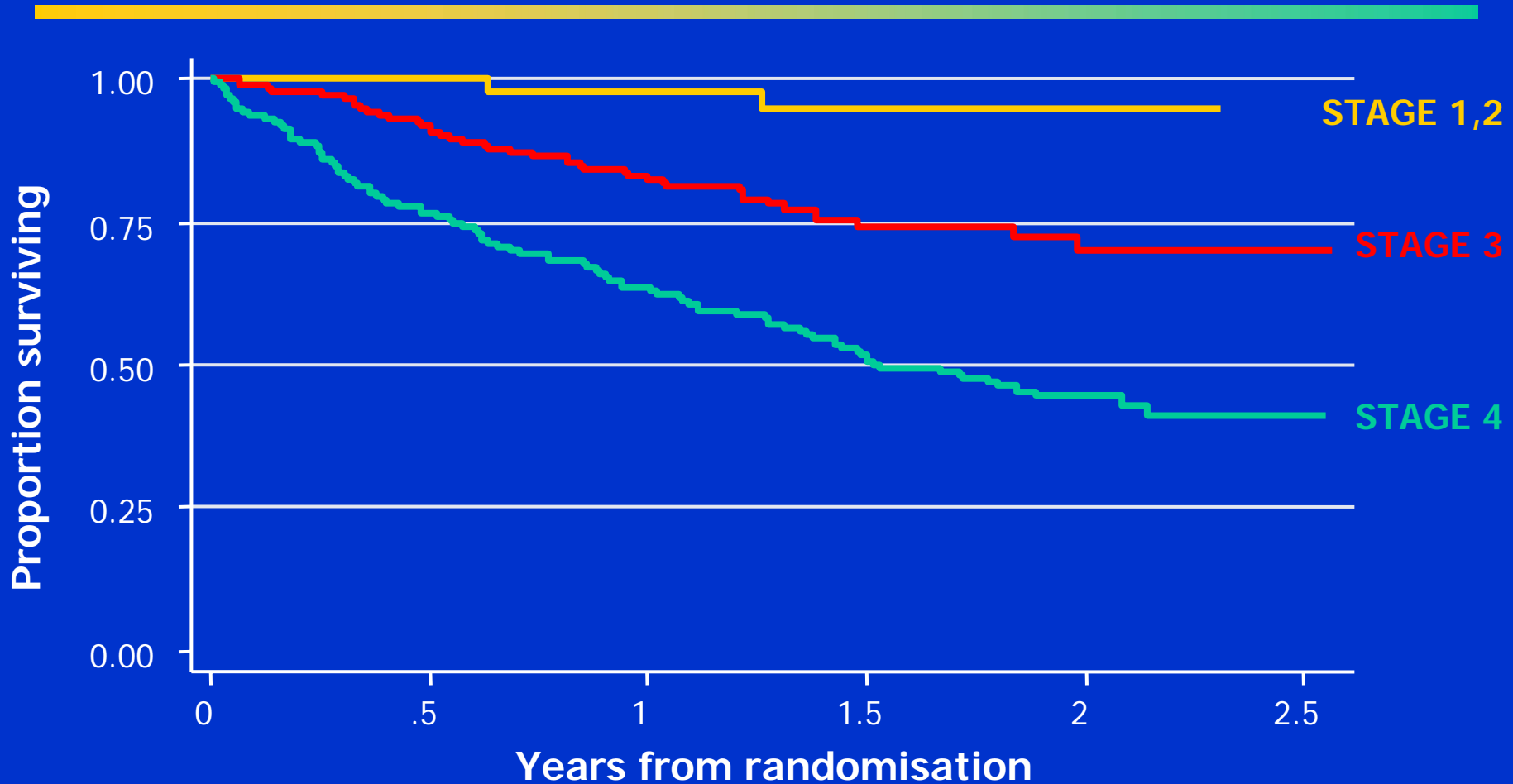
47
29

HR=0.57
[0.43-0.77]
p=0.0002

Clinical Paediatric WHO Staging

- Differences in disease patterns in resource-poor settings
- More overlap with commonly seen infectious diseases
- Major effect of malnutrition
- Recently proposed 4-stage WHO classification

Mortality by New WHO stage at baseline (534 children >1 year in the CHAP trial)



Similar separation in all age groups

New WHO Paediatric Staging

- TB diagnosis was a poor predictor of mortality in CHAP:
 - Nearly all Presumptive (?Correct) diagnoses
- Effects of “malnutrition” and low weight likely to capture HIV and non-HIV related mortality

CD4%, CD4 count and TLC values corresponding to 12-month risk of death of ~5%

(from HIV Paediatric Prognostic Markers Collaborative Study, HPPMCS)

Age	CD4%	CD4 Count	TLC
<= 1 year	25-35%	~1000-1500	~3,900-5700
1-3 years	15-25%	~500-800	~2000-3,900
3-5 years	10-15%	~ 200-350	~1500-2000
5-10 years	7-10%	< 200	~1000-1500
10+ years	<7%	< 200	~1000

Antiretroviral Drugs Obstacles and Issues

Issues for dosing of ART in children

- Large variability in pharmacokinetic (PK) parameters
 - age (and PK data by age-group often sparse)
 - effect of nutritional status, ethnicity
- Methods of dose calculation (per m² or per kg)
- Formulations may not be bioequivalent
 - (liquid versus capsule – eg EFV)
- Ability to give with/without food (ddI, NFV)

Issues for dosing of antiretroviral drugs in children

- PK data by age group are sparse
- Few data on the effect of race, nutritional status
- Young children require higher doses
- unclear when to change to adult doses
- dose according to weight or surface area:
 - somewhat arbitrary
 - where both available, may not correspond (eg NVP)
- Formulations may not be bio-equivalent (eg EFV)

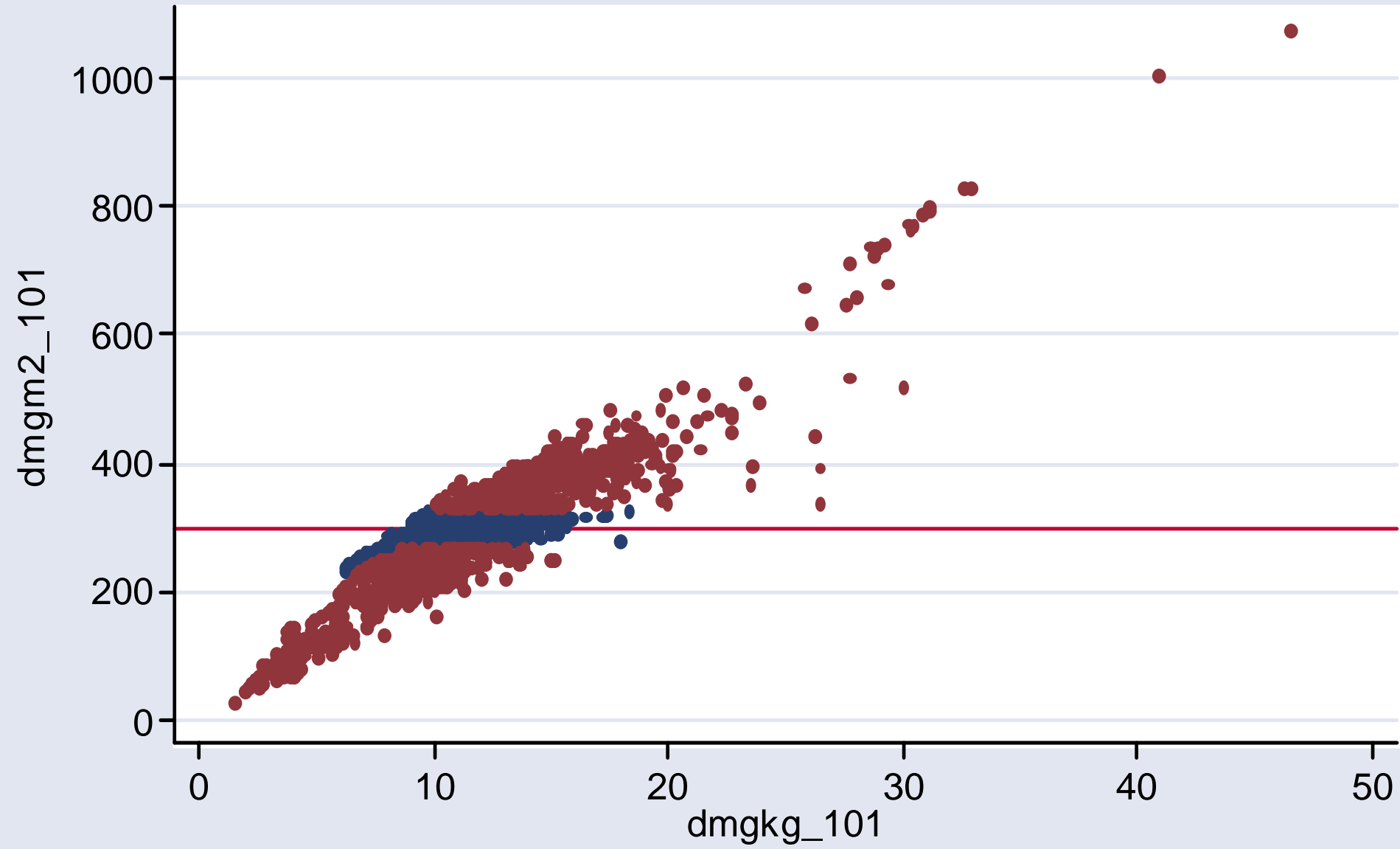
Dose by weight or Body Surface Area (BSA)

- BSA relates to renal clearance:
 - drugs cleared by the kidney should be dosed by BSA
 - PK is not fully explained by variability in BSA
 - Newborns and premature babies need reduced doses
- BSA calculations crude:
 - require measurement of height and weight
 - subject to error (many reports in the literature):
 - Normograms underestimate values in infants
 - Formulae are complex – calculator required:
 - Most equations derived from well-nourished Caucasian children
- In 1998, the UK Children's Cancer Group (UKCCSG) produced tables for estimating BSA based on weight alone

NNRTI dosing

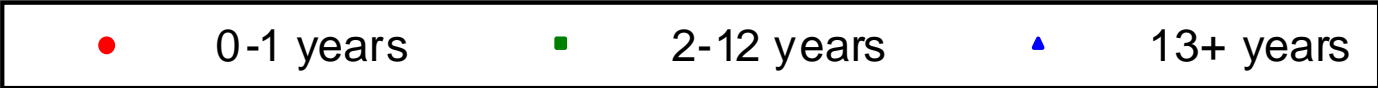
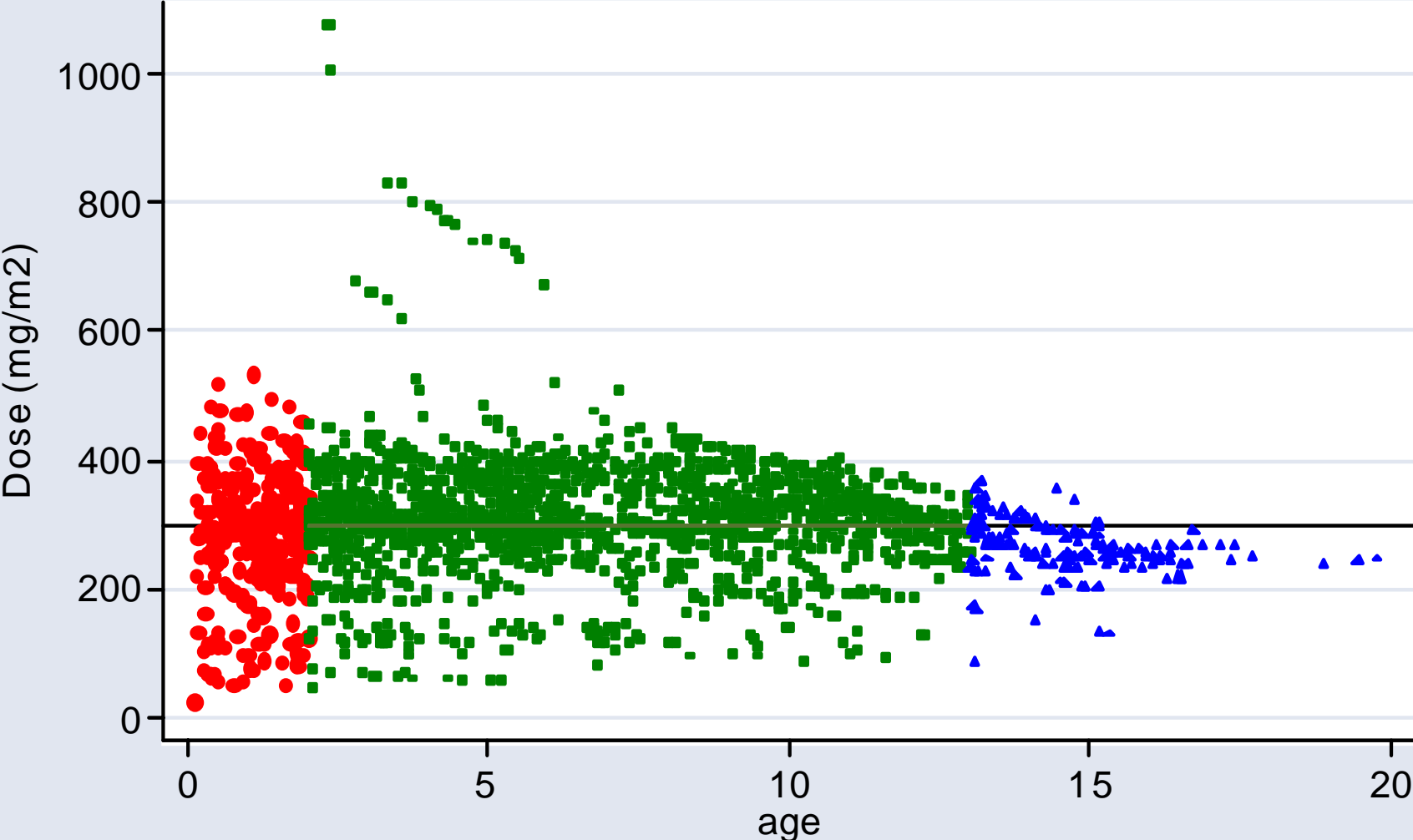
	Recommendation
Nevirapine	300-400mg/m ² to max 400mg 7mg/kg if <8yr 4mg/kg if >8yr
Efavirenz	15mg/kg ^{kg} to max 600mg (dose liquid according to weight bands)

NVP

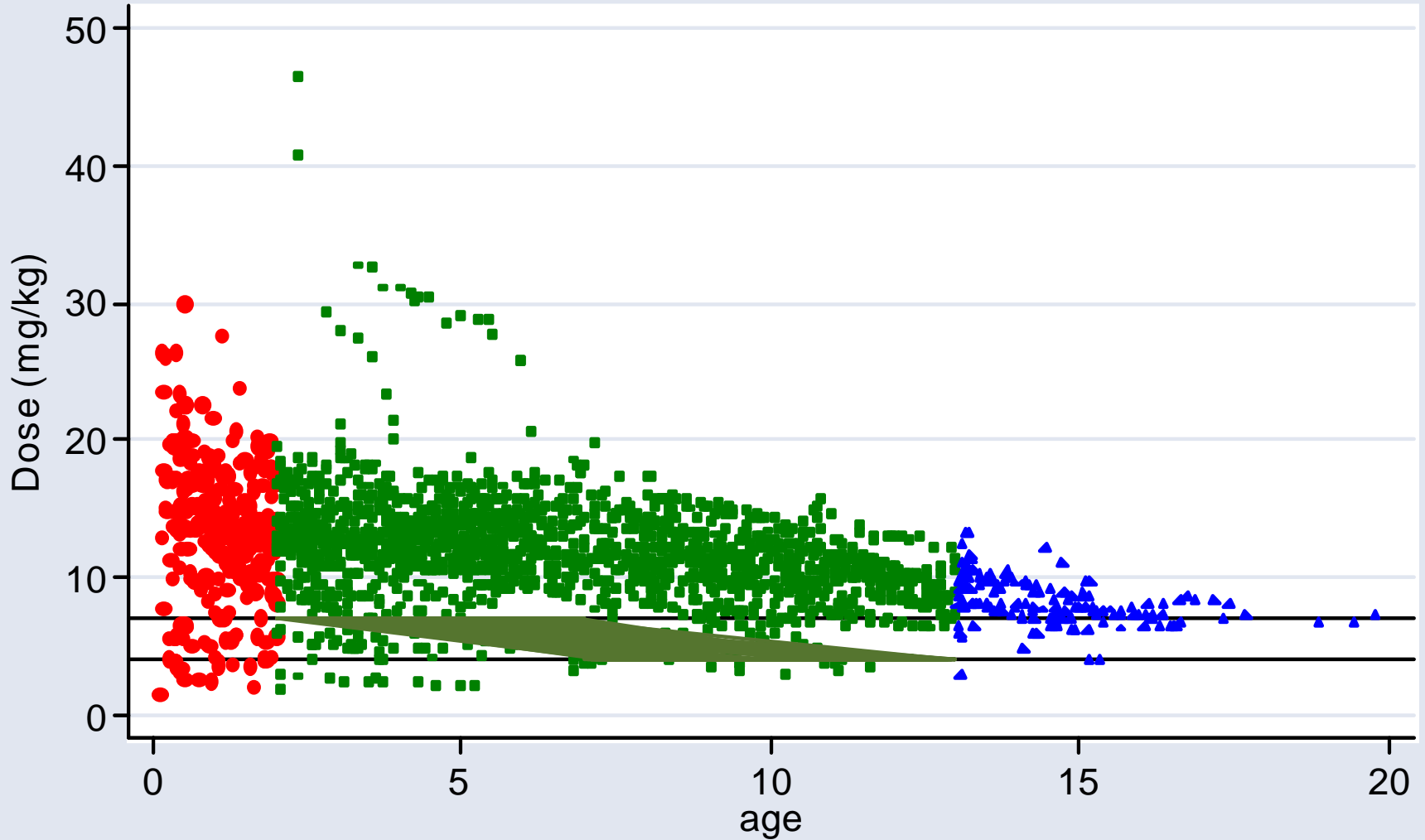


● 90-110% recommended ● <90% or >110% recommended

NVP: DOSE per m2 by AGE



NVP: DOSE per ***KG*** by AGE



Obstacles for Pharmaceutical Companies

- Big Pharma:
 - Formulation difficulties (especially for PI's)
 - 'no business case', especially to make several formulations
 - Extension of patent (FDA); Big stick (being proposed by EU)
- Generic Companies:
 - Also need a business case
 - Lack of expertise and research 'know-how'
 - **Pre-qualification issues**
- Demand Forecasting

Antiretroviral drugs for children in resource-poor settings

- Scored tablets versus liquid formulations:
 - cost
 - storage and transport problems
 - shelf-life
- Fixed-dose combinations – simplification and compatibility with adult treatment
 - Many advantages
 - Need to vary doses of drugs with age and weight

eg: Generic (3TC+d4T+NVP) combination tablets in quarters will underdose for NVP if <15kg as well as being difficult to cut accurately

ART IN FIXED DOSE COMBINATIONS:

d4T + 3TC + NVP



Adult Tablet

Children Tablets

FORMULATIONS

Adult: d4T (30 mg or 40mg), 3TC 150mg, NVP 200 mg)

Children

"Junior" (10 - 30 Kg): d4T 12mg, 3TC 60mg, NVP 100 mg

"Baby" (3 - 10 Kg): d4T 6mg, 3TC 30mg, NVP 50mg



Adult Tablet

Children Tablets

FDCs	Advantages	Disadvantages
Efficacy/ Toxicity	<ul style="list-style-type: none"> • Reduced risk of wrong dose (over or under): <ul style="list-style-type: none"> To prescribe To dispense To take or miss doses by care-giver/child • Less risk of prescribing wrong regimens 	<ul style="list-style-type: none"> • More difficult to alter doses: <ul style="list-style-type: none"> Dose escalation Child growth Toxicity Drug interactions • Less flexibility in regimens • Need to combine drugs with similar half-lives. • Shelf-life determined by least stable
tolerability	<ul style="list-style-type: none"> • Low pill/powder burden 	<ul style="list-style-type: none"> • Limited formulation choices
Simplified treatment	<ul style="list-style-type: none"> • Easier to manage supply, distribution, transportation 	<ul style="list-style-type: none"> • ? Greater risks of drug sharing tablets by adults
Cost / availability	<ul style="list-style-type: none"> • Decrease pharmacy and health professionals time • Should be cheaper to produce 	<ul style="list-style-type: none"> • Incentives to produce • Pre-qualification requirements

Dosing Tables of ARVs for children

- Simple
- Based on weight bands
- Could be linked to Road to Health Chart

Weight Range	Recommended daily dose (min-max)			Total daily tablet	Schedule	D4T	3TC	NVP
	D4T	3TC	NVP					
3-5kg	6-10	24-40	42-70	1	1/2 BD	6	30	50
5-7kg	10-14	40-56	70-98	2	1 BD	12	60	100
8-9kg	16-18	64-72	160-174	3	1.5 BD*	18	90	150
10-14kg	20-28	80-112	180-252	2	1 BD	24	120	200
15-19kg	30-36	120-152	240-320	5	2.5 BD*	30	150	250
20-24kg	40-48	160-192	304-376	3	1.5 BD*	36	180	300
25-29kg	50-58	200-232	400	4	2 BD	48	240	400
30-39kg	60	300	400	2	1 BID	60	300	400
40-49kg	60	300	400	2	1 BID	60	300	400
50-59kg	60	300	400	2	1 BID	60	300	400

Daily dose of **Baby Pedimune** (d4T 6mg, 3TC 30mg, NVP 50mg)

Daily dose of **Junior Pedimune** (d4t 12mg, 3TC 60mg, NVP 100 mg)

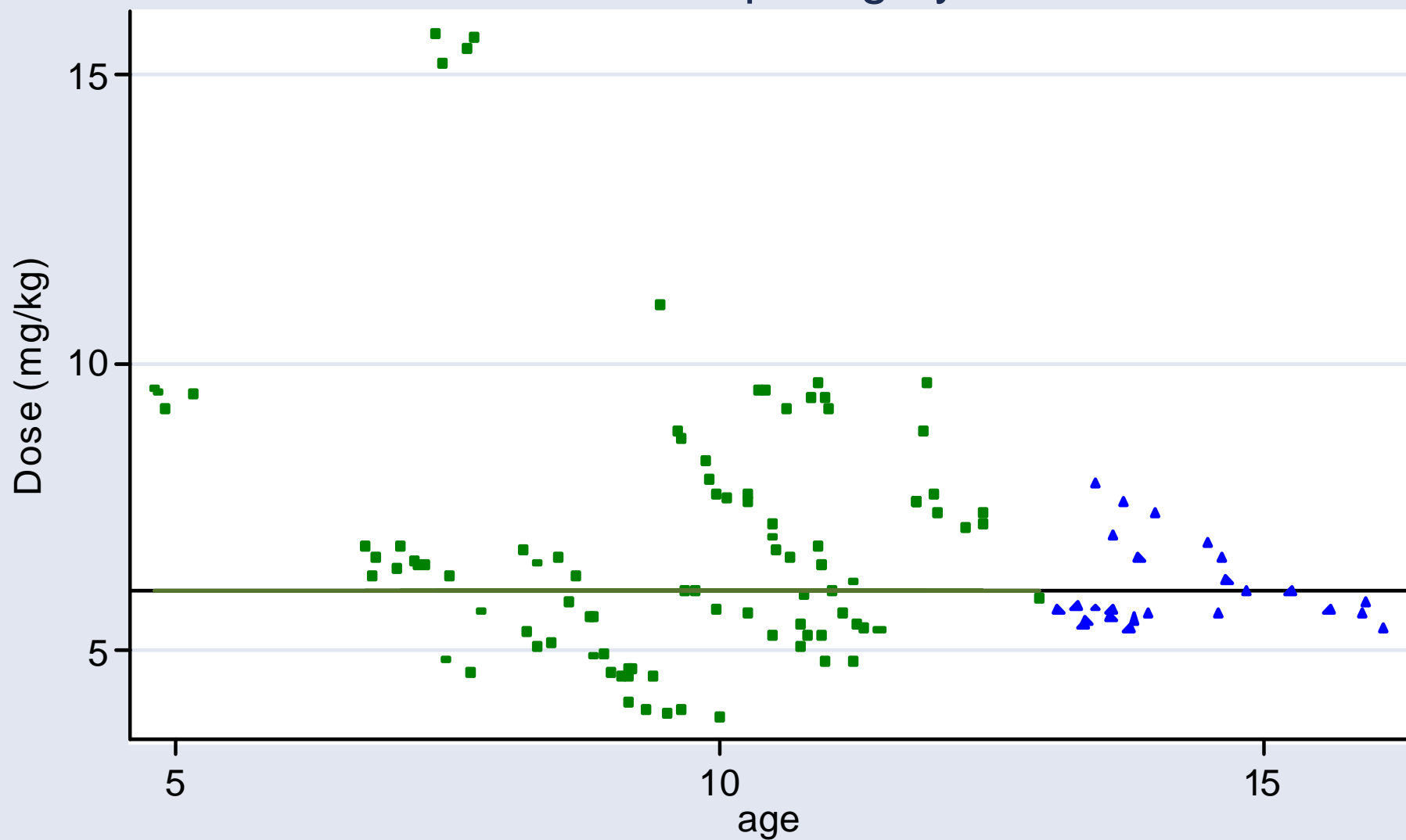
Daily dose of **Triomune 30**

Challenges

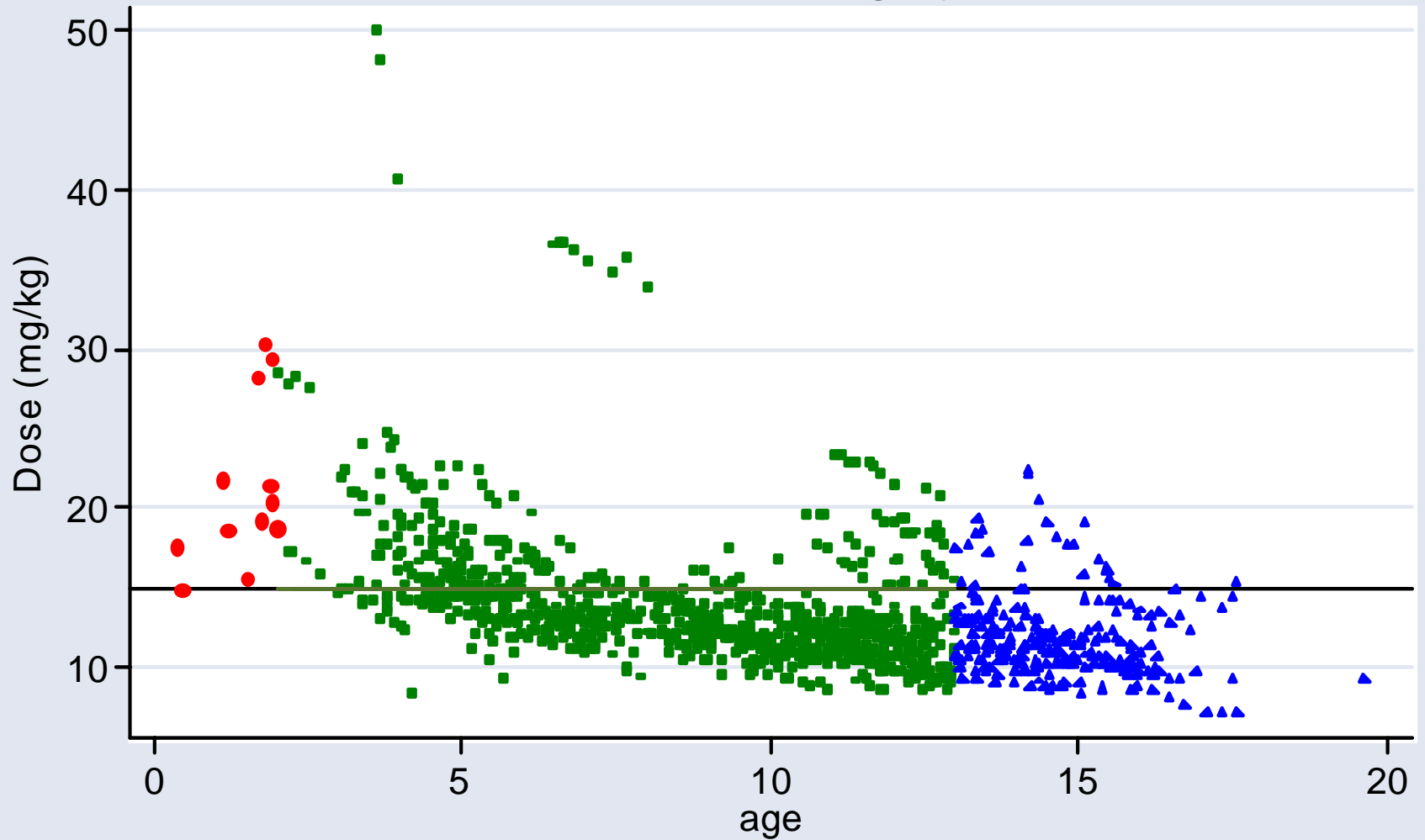
- **Appropriate simple ART formulations and combinations relevant to resource-poor settings urgently needed**
 - **Industry interest and accelerated PK research**
- Integration of adult and paediatric treatment and care:
FAMILY APPROACH
- Applying and Scaling-up what we already know:
 - Cotrimoxazole prophylaxis
 - Nutritional support
- Training in paediatric and family-based care for HIV
- Strengthen links between access to treatment and operational research to answer important questions about natural history and response to ART



TDF: DOSE per kg by AGE



EFV: DOSE per kg by AGE



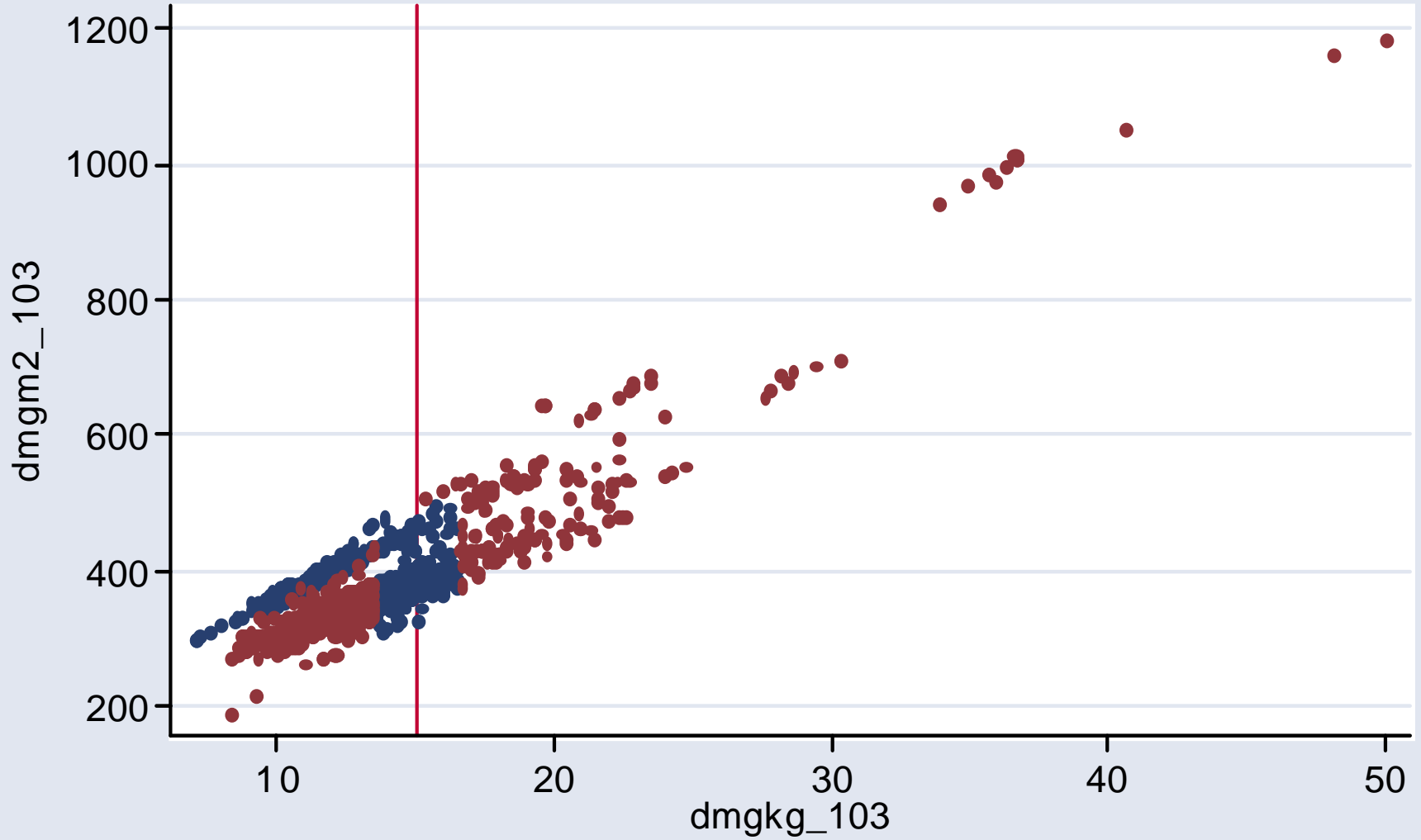
Obstacles - Pre-Qualification

- ‘National and or international regulatory and prequalification procedures may discourage the production of specific paediatric ART formulations’
- WHO requirements
 - Shelf-life studies
 - Dissolution studies
 - Bio-equivalence Studies
 - *PK studies in children*

Adherence to and tolerability of ARVs

- Tolerability of formulations varies with age
- Ability to give with/without food (ddI, NFV)
- Adherence depends on caregivers

EFV

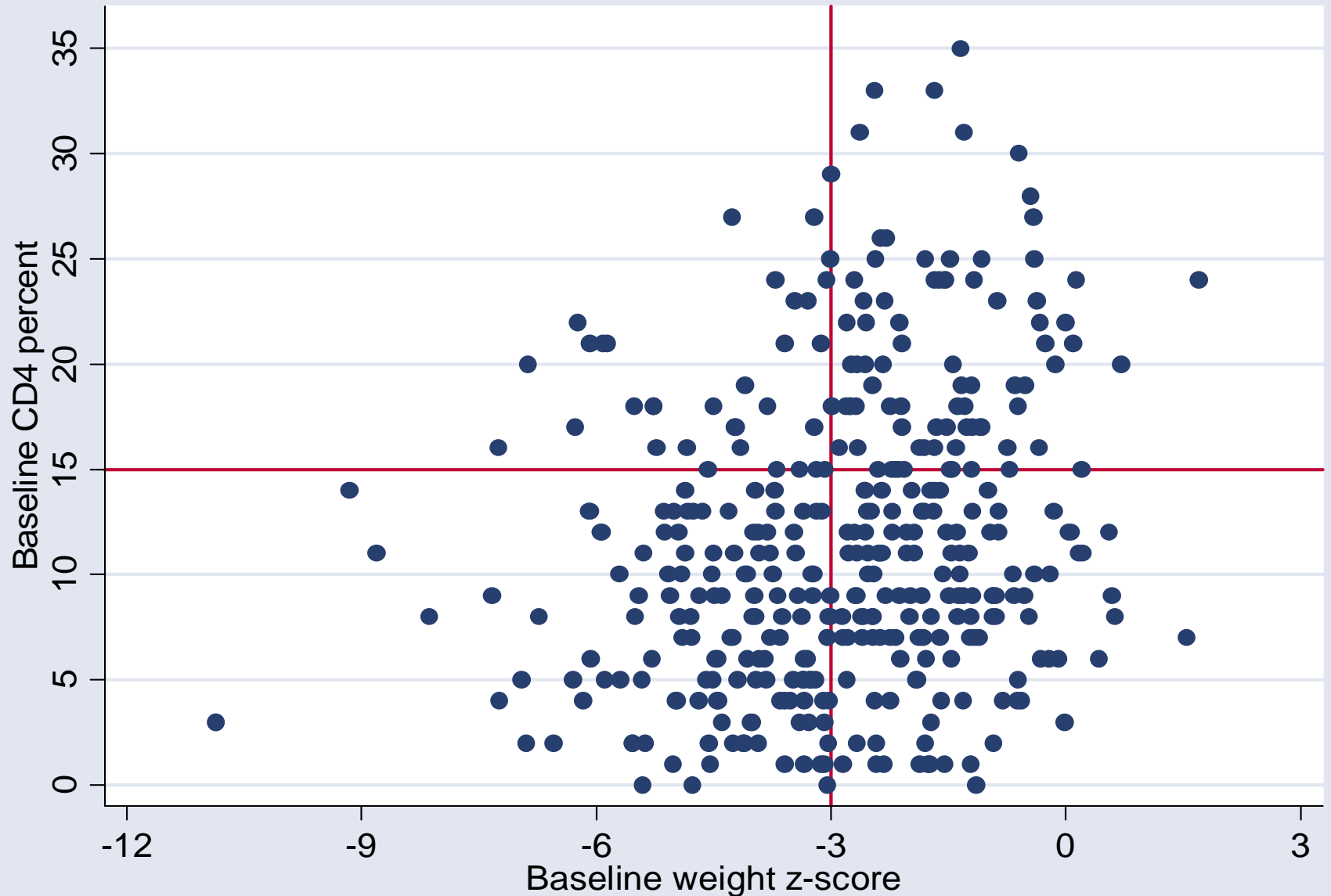


● 90-110% recommended ● <90% or >110% recommended

The Way Forward

- HIV-infected children need advocates
- Partnerships in care, research and training:
 - Between adult, paediatric and obstetric services
 - Between and across countries
- Fast-tracking provision of appropriate ARV formulations and fixed dose drug combinations for children
 - Clinical/industry/research collaborations
- Operational research (requires partnerships and networks):
 - Cohort collaborations
 - Operational research questions on using ART in children
 - Psychosocial issues
 - Linked to capacity strengthening
- Linking prevention and treatment/care

Weight for age by CD4%



Single Antiretroviral Drugs for children

NRTI		NNRTI		PI	
Recommendation		Recommendation		Recommendation	
ZDV	360mg/m ² to max 600mg	NVP	300-400mg/m ² to max 400mg	NFV	110-150mg/kg to max 2500mg
3TC	8mg/kg to max 300mg	EFV	15mg/kg to max 600mg	LPVr	460/115mg/m ² to max 800/200mg
ABC	16mg/kg to max 600mg				
ddI	180mg/m ² to max 400mg				
d4T	2mg/kg to max 80mg				$m^2 = (hgt * wgt / 3600)^{1/2}$

Review dose at EVERY clinic visit – 3-monthly