IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Optimizing treatment for children and adolescents: The power of NOW

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World Health Organization

OUTLINE

- **Yesterday**
  - WHO 2016 ARV guidelines (2nd edition)
  - Evidence used and challenges
  - Key treatment recommendations
- **Today**
  - Introduction of better drug options
  - Need for priority formulations
  - Support development of better formulations
- **Tomorrow**
  - The challenges of testing sooner and closer
  - Dealing with the adolescent wave
  - Innovative therapeutic strategies for investigation

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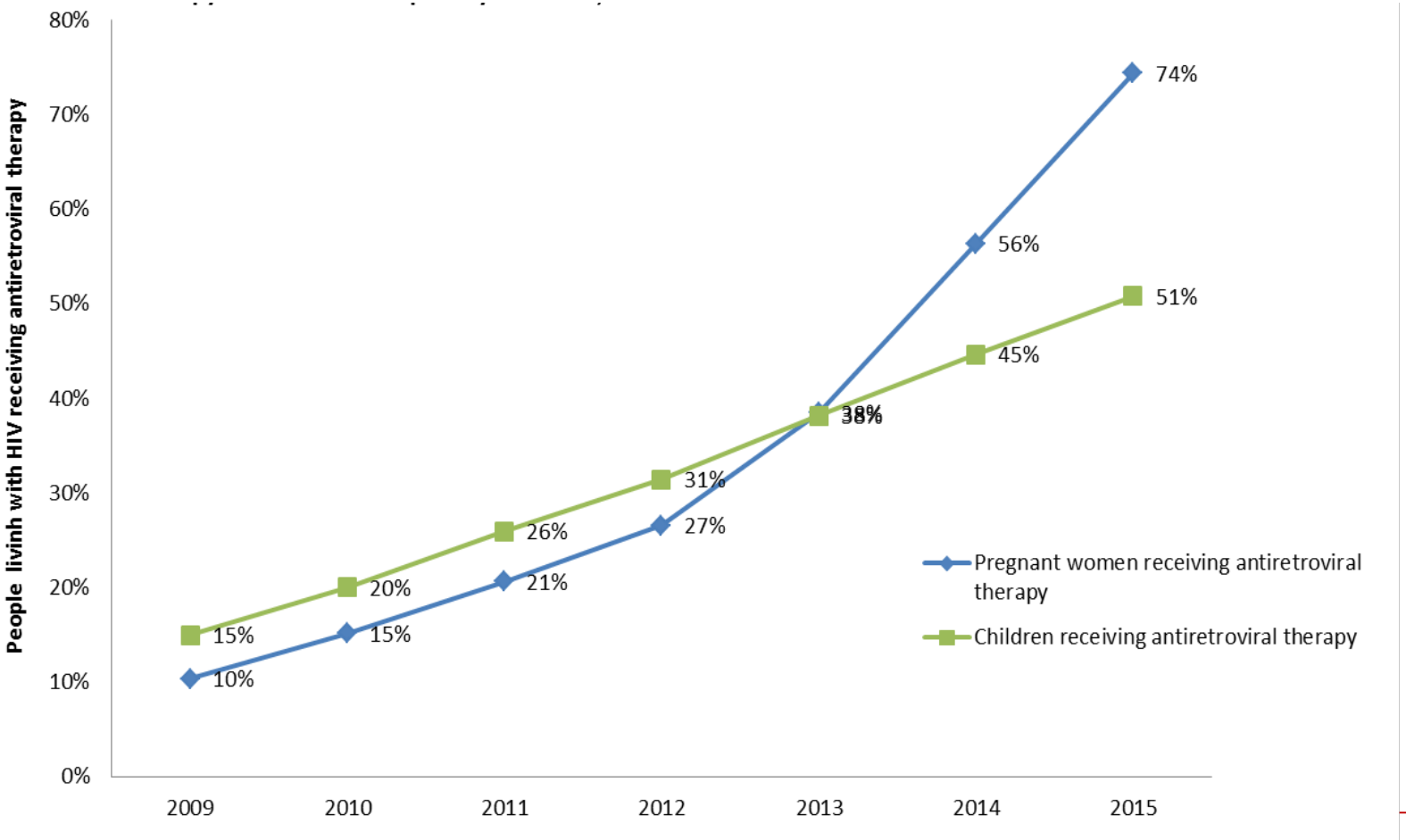
Paediatric coverage still lags behind



The treatment GAP continues to exist

Source: Global Plan report 2016

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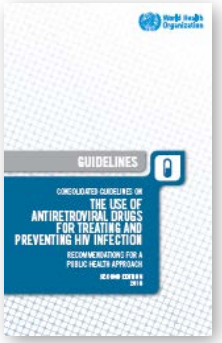
2015 WHO ARV Consolidated Guidelines



Test earlier and closer

Treat earlier and better

Taylor Service delivery

Critical tool to reach the Treatment targets

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Which evidence did we use in 2015?

- IeDea[1] casual modelling added to the body of evidence suggesting that earlier ART is better
- P1060[2] demonstrated that infants and young children need more potent regimens.
- NEVEREST[3] and MONOD[4] supported the substitution of LPVr with EFV to simplify treatment
- PENPACT-1[5], CHAPA-3[6] and ARROW[7] all contributed to inform the current 1st line approach in older children
- Registrative trials[8] and pharmacovigilance studies[9] reassured us on the use of 2nd and 3rd line drugs

1. Shoemaker et at 2016; 2. Palumbo et al 2010 and Violari et 2012; 3. Coovadia et al. 2014; 4.Timité-Konan et al 2016; 5. Babiker et al. 2011; 6. Musiime et al.2014; 7. Kekitinwa et al. 2013; 8. Nachman et al 2013; 9. Baylee et al 2015.

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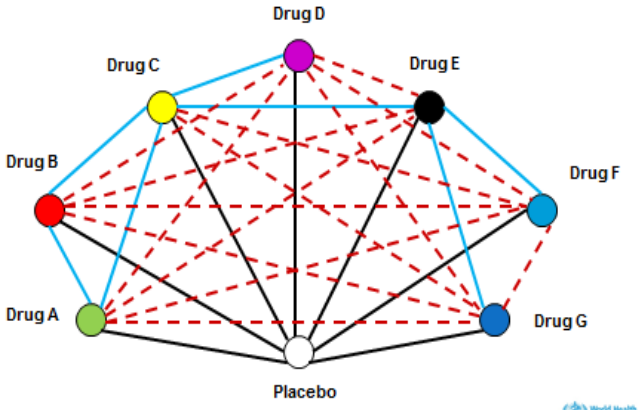
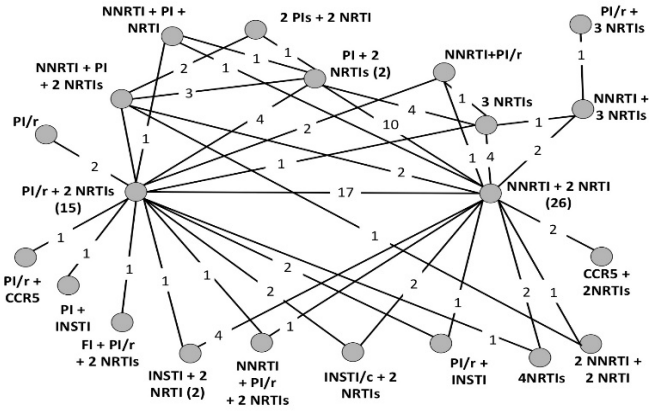
Where did we struggle?



Ioannidis J. CMAJ 2009. Integration of evidence from multiple treatment meta-analyses: a primer on umbrella reviews, treatment networks and multiple treatments meta-analyses.



Network Metanalysis -
a paediatric/adolescent dream

- Adults trials do not include subjects below 18 years
- Lack of age-stratified and time-updated analysis
- Head to head comparisons are rare
- New drugs are either not approved or limited evidence exist on their use
- Critical trials became more challenging with the fast-changing policies
- Adult data drives the policy change and extrapolation is not always possible nor appropriate (ie infants)
- Programmatic needs became the biggest driver

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Treat earlier and better

Offering optimal regimens in age-appropriate formulations

	Children including adolescents	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 LPV/r
		TDF + 3TC + EFV (or NVP)	
		AZT + 3TC + EFV (or NVP)	ABC or TDF + 3TC + ATV/r or LPV/r

Complexity is unavoidable but some optimal formulations exist and more are needed to deliver the preferred regimens that maximise efficacy and minimize toxicity

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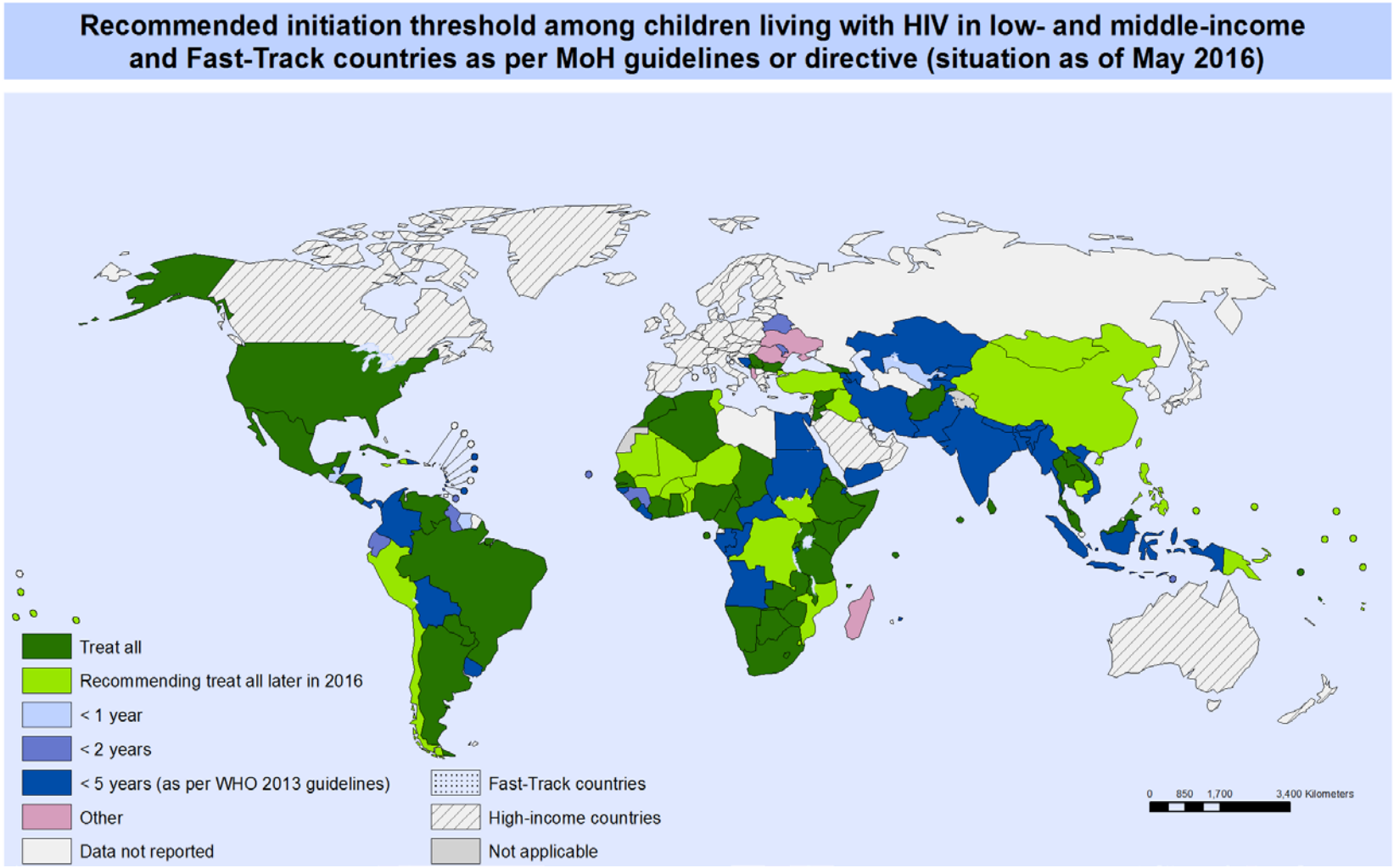
Shift to Treat All children is happening



But suboptimal regimens are still being used

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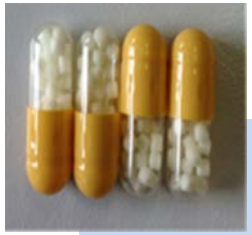
Introduction of better options doesn't happen over night



LPVr pellets

- LPV/r pellet was USFDA tentatively approved in May 2015. Approved for use from 2 weeks but no dosing for <5kg
- Palatability still not optimal
- Acceptability data from CHAPAS2
- Administration in exclusive BF and young infants below 3 months is problematic
- Feasibility data being gathered
- In country registration undergoing but happening slowly

RAL

- Full paediatric programme now almost down to neonates
- Granules formulation is not practical in resource limited settings
- Chewable tablets could be used as dispersible but bioequivalence to be demonstrated
- Limited experience in first line use for infants and young children
- No generic production and price remains relatively high

Research to address these unknowns and support introduction in countries

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Rationale for prioritisation

LPVr 4-in-1: first line for under 3 years to address the lack of optimal formulations

EFV triple: first line 3-10 years to provide an FDC to maximise adherence and simplify procurement

ATVr and DRVr: use in 2nd and 3rd line formulations and overcome issue with separate administration of RTV

NVP

MORE DRUGS and FORMULATIONS ARE URGENTLY NEEDED (PADO PRIORITY)

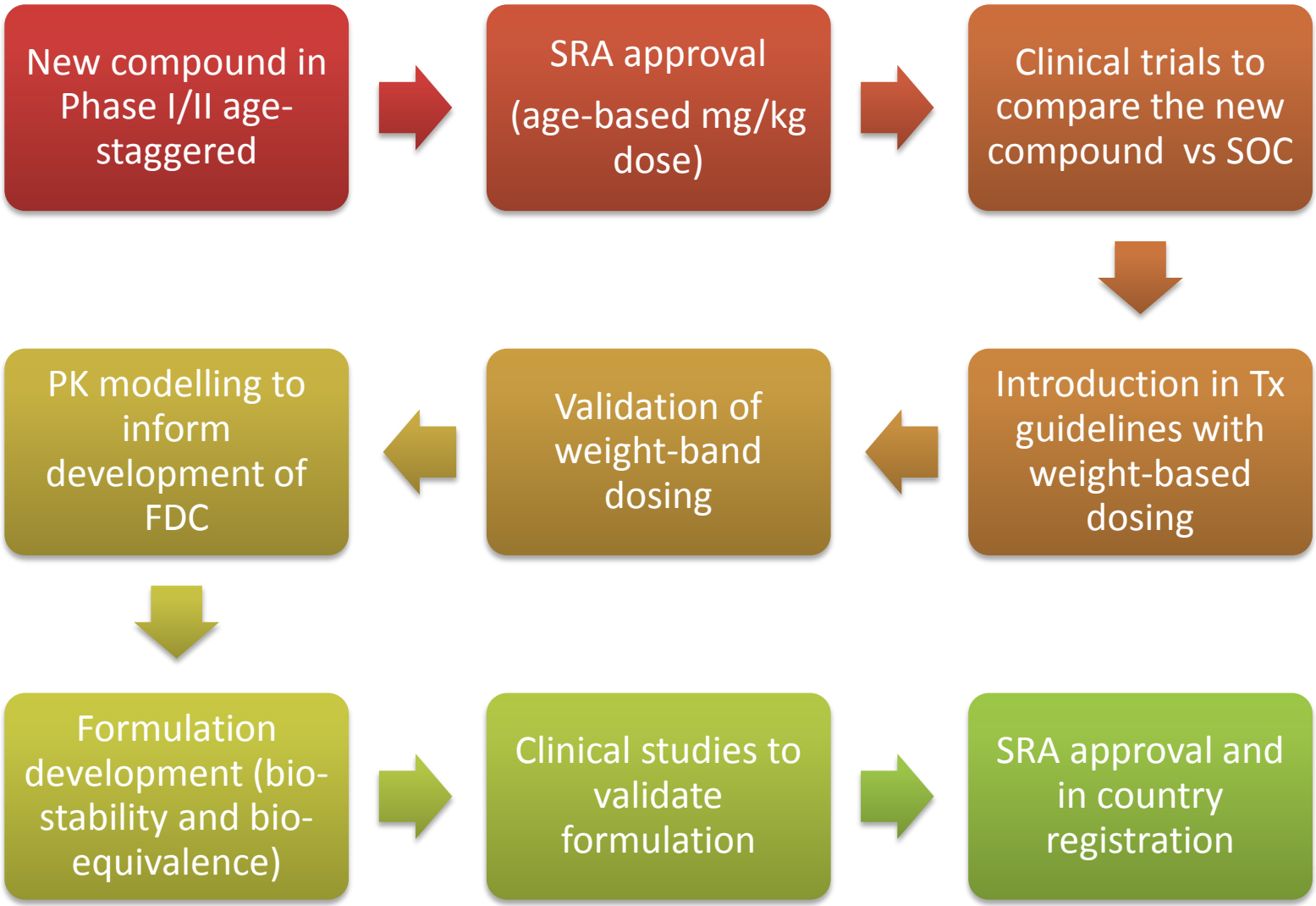
RAL d

introduction of INI for use in 1st line regimen

DTG single or FDCs: identified as key drug to introduce INI in first line with potential for harmonisation across the full age spectrum

TAF: key drug for future use in 1st line to minimise toxicity with potential for harmonization across the full age spectrum

HOW do we GET THEM?



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What can we do NOW?

- Innovate trial design
- Move away from age-cohort approach
- Investigate directly weight band dosing
- Optimize the generation and use of PK data
- Include TB/Hep infected children
- Address acceptability/feasibility
- Simplify regulatory requirements
- Focus efforts on priority formulations

Integration and better coordination can be our key to success

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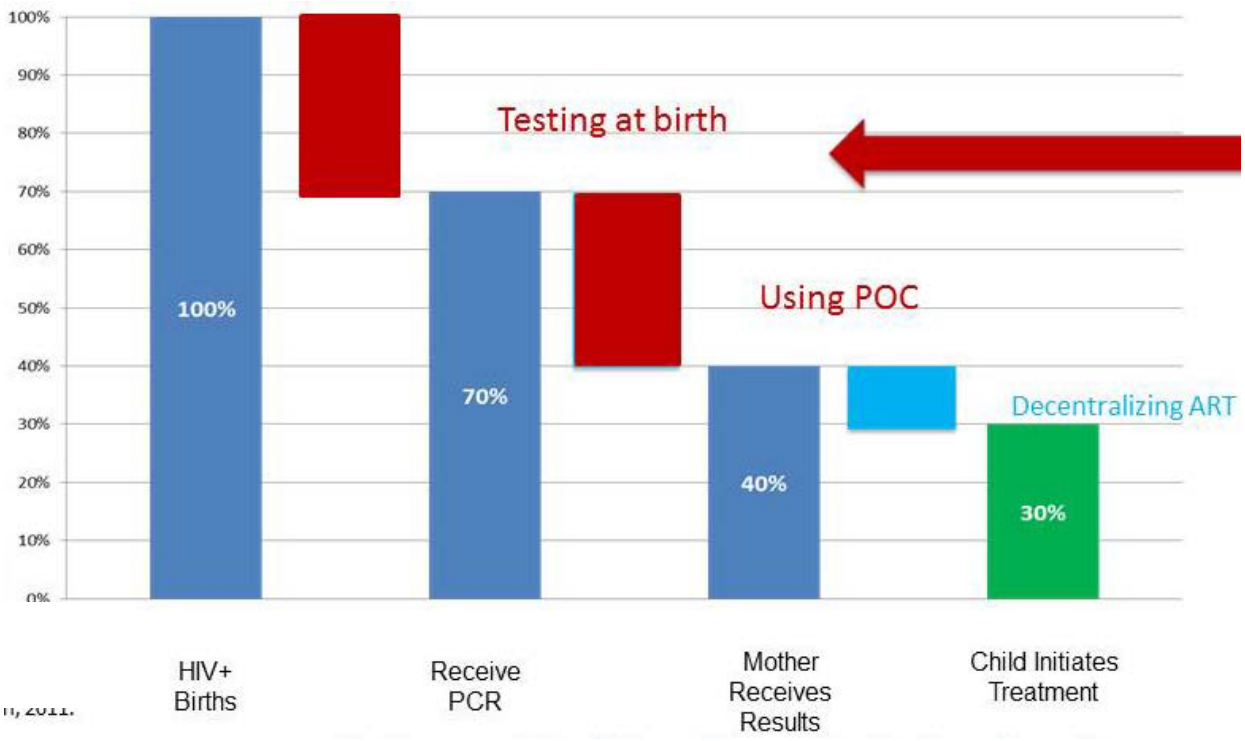
Testing infants earlier and closer



- Birth testing and POC introduction will lead to more neonates initiating ART
- ARV dosing in neonates still largely unknown
- Complex ART to prescribe and administer in neonates
- The right treatment is delivered where children are identified

Fewer new infections will make it harder to conduct efficacy trials and PK studies will become increasingly important

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An adolescent wave to deal with

- Children started on treatment are surviving into adolescence with complex treatment histories and limited ARV options
- Adolescents have poor access to services and are at higher risk for lost to follow-up, poor adherence and rapid selection of HIVDR with limited treatment options
- Implementation of Adolescents Friendly Health Services (AFHS) is critical but probably not enough
- Injectable and implants can be attractive delivery systems to overcome inadequate adherence
- Increasing numbers of adolescents are at risk of acquiring HIV: important to consider the role new ARVs for PreP

Innovations to adolescents first and not "second" - this requires early inclusion of adolescents in drug development studies

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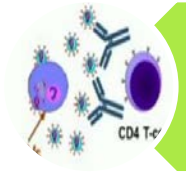
Innovative strategies are needed

Simplification strategies

- Dual therapy (ie. DTG+3TC)
- NRTI sparing (ie. DTG/DRV)

Long-acting and injectable

- Cabotegravir
- Rilpivirin LA



Immunotherapy

- Neutralizing antibodies
- Therapeutic vaccine

Remission

- Early treatment
- Combination strategies

Life-long triple antiretroviral cannot be our long-term goal (particularly in children)

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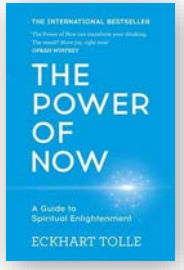
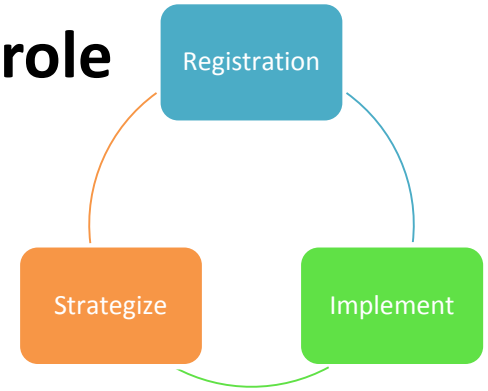
The power of NOW



- **New efforts** are urgently needed: drug optimization is unfinished business
- Research networks continue to play a **critical role**
- **Strategic study design** to address multiple questions and respond to the needs of HIV-infected children where they live
- **Joining forces** can help us reach our goals faster
- **Focus and innovative** thinking about tomorrow and the strategic response required by the shifting landscape of the HIV epidemic



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Thank you

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