The CQUIN Learning Network

Optimizing ART for Adolescents in the Context of Changing Guidelines for Antiretroviral Therapy

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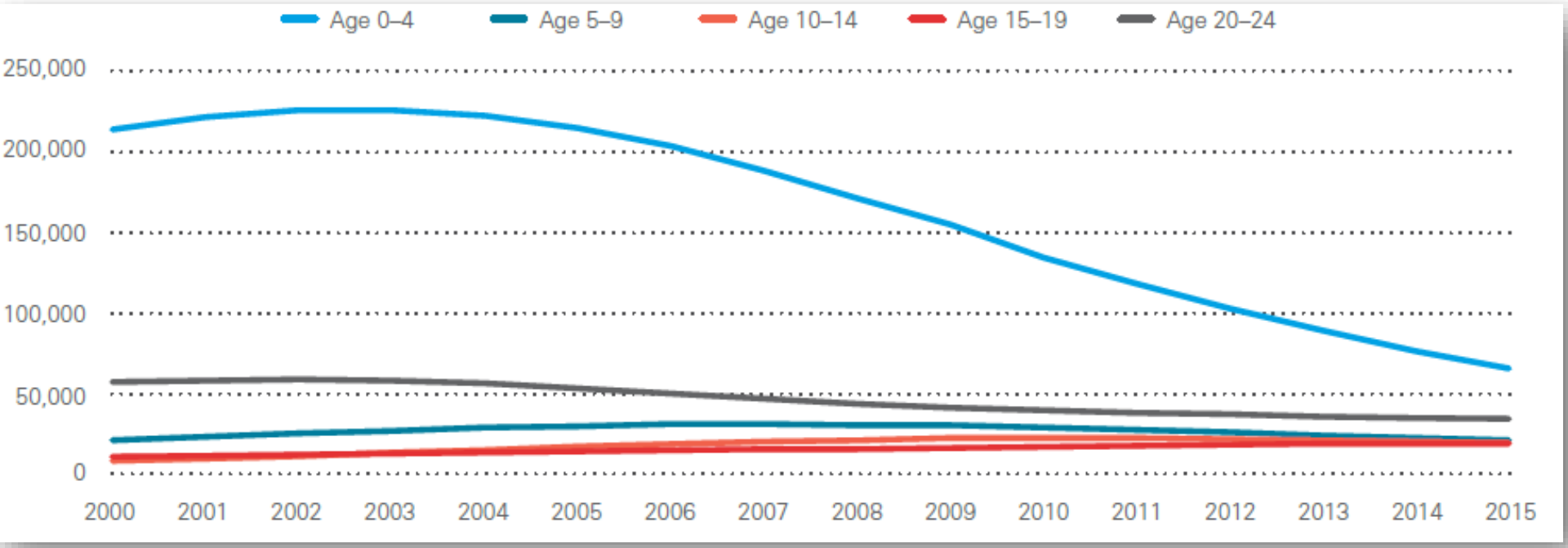
HIV LEARNING NETWORK
The CQUIN Project for Differentiated Care

ICAP
GLOBAL. HEALTH. ACTION.
Columbia University
Mailman School of Public Health

Overview

- What are the challenges that adolescents have with ART?
- Recommendations for adolescents in the WHO guidelines
- What do we mean by optimization?
- What are optimal ART choices for adolescents?
- Conclusion

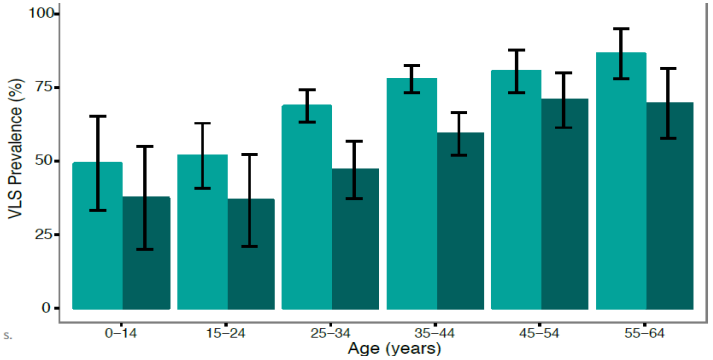
Deaths have declined significantly among all age groups except adolescents 10-19 years



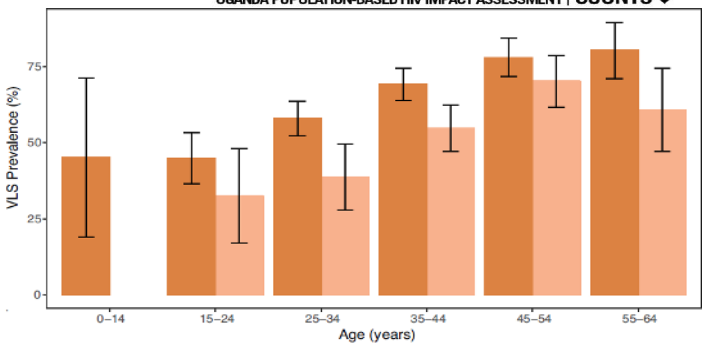
Global Response report and UNAIDS 2016 estimates

Population-level HIV incidence assessments: Viral Suppression is lowest in children, adolescents and young adults

MPHIA
MALAWI POPULATION-BASED HIV IMPACT ASSESSMENT
A DROP THAT COUNTS



UPHIA
UGANDA POPULATION-BASED HIV IMPACT ASSESSMENT
A DROP THAT COUNTS



ZAMPHIA
ZAMBIA POPULATION-BASED HIV IMPACT ASSESSMENT
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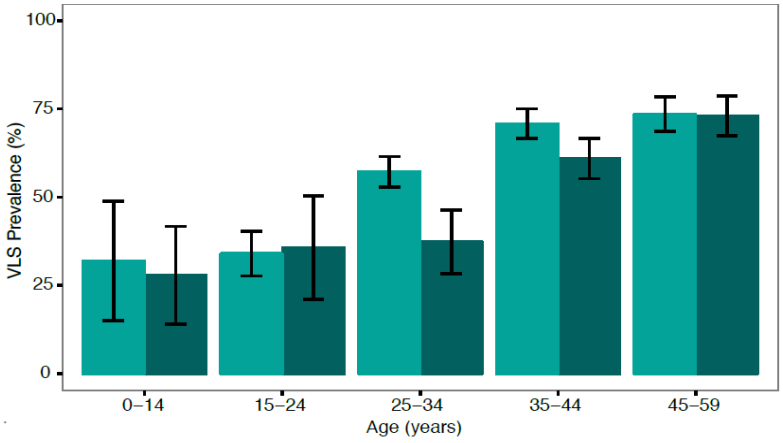
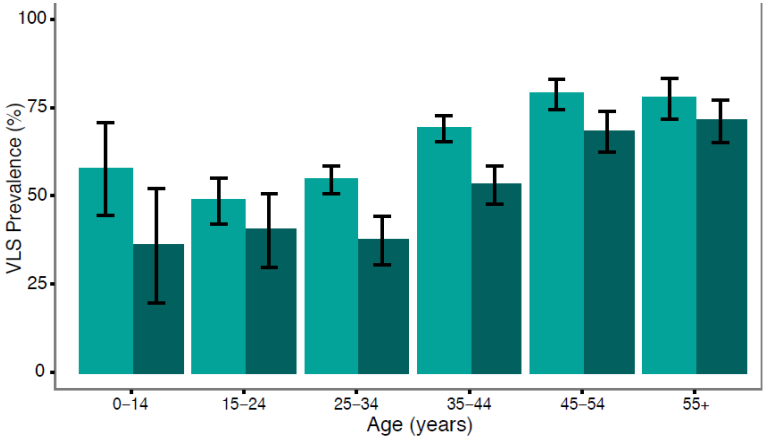
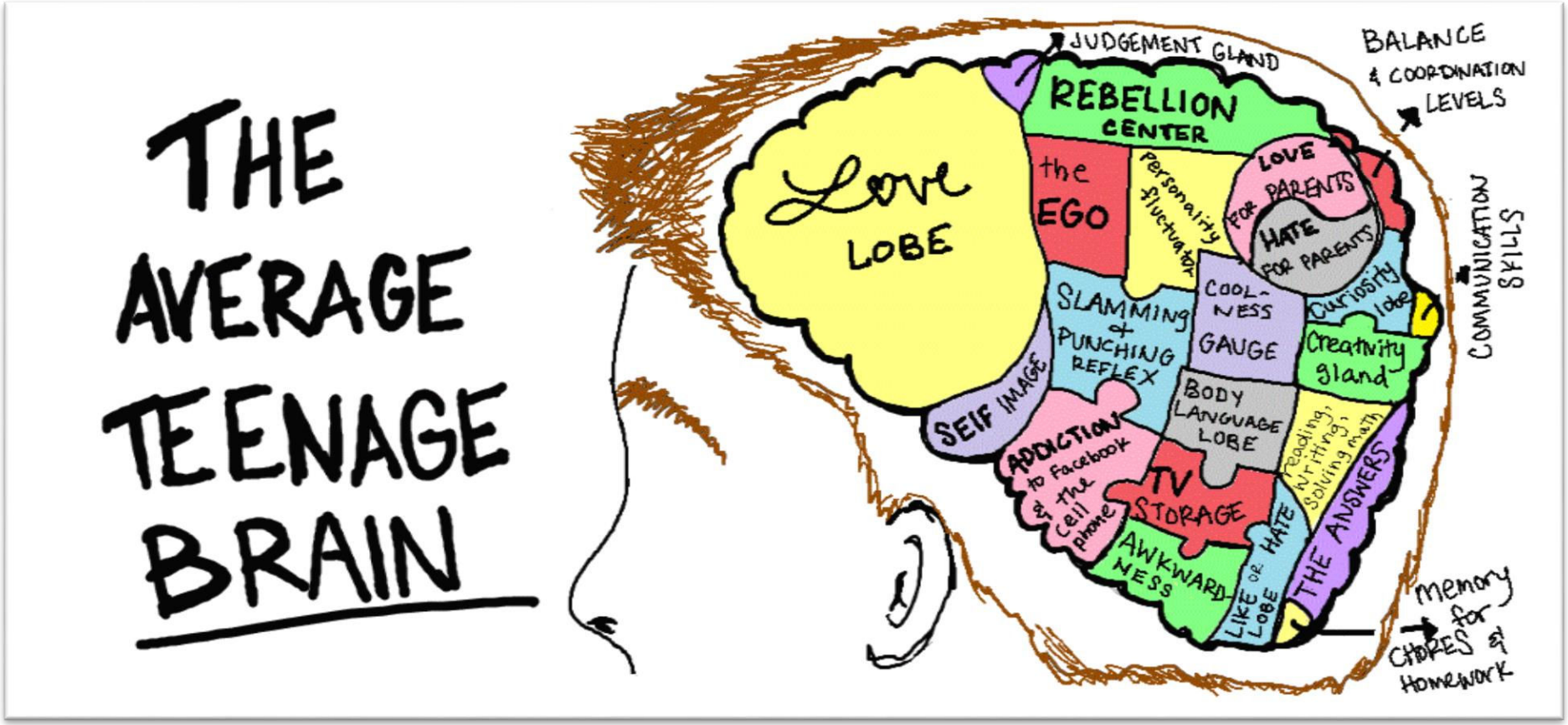


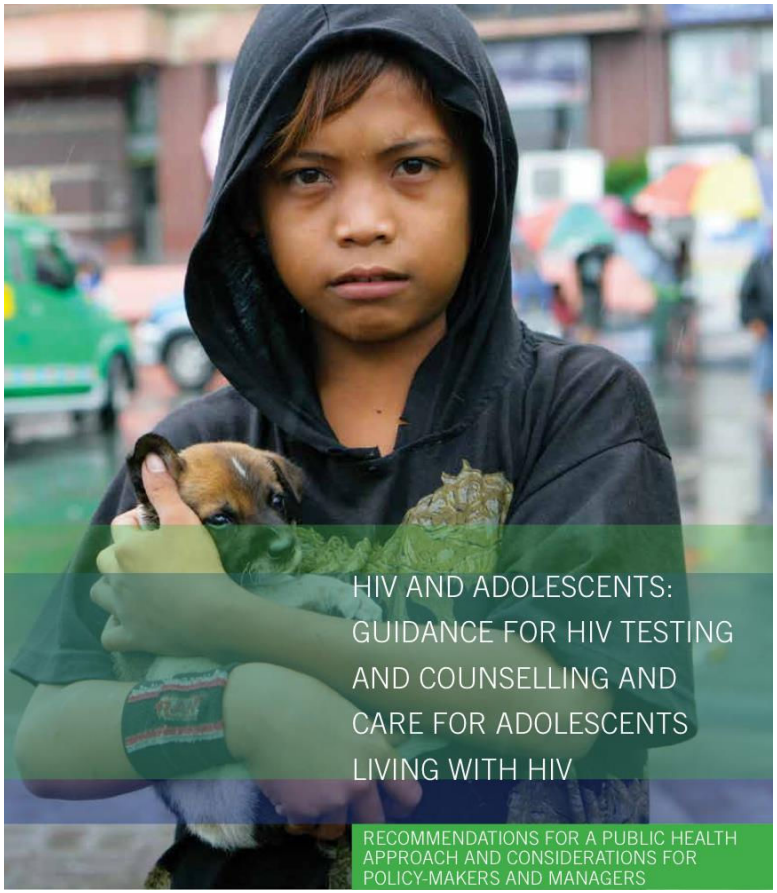
ZIMPHIA
ZIMBABWE POPULATION-BASED HIV IMPACT ASSESSMENT

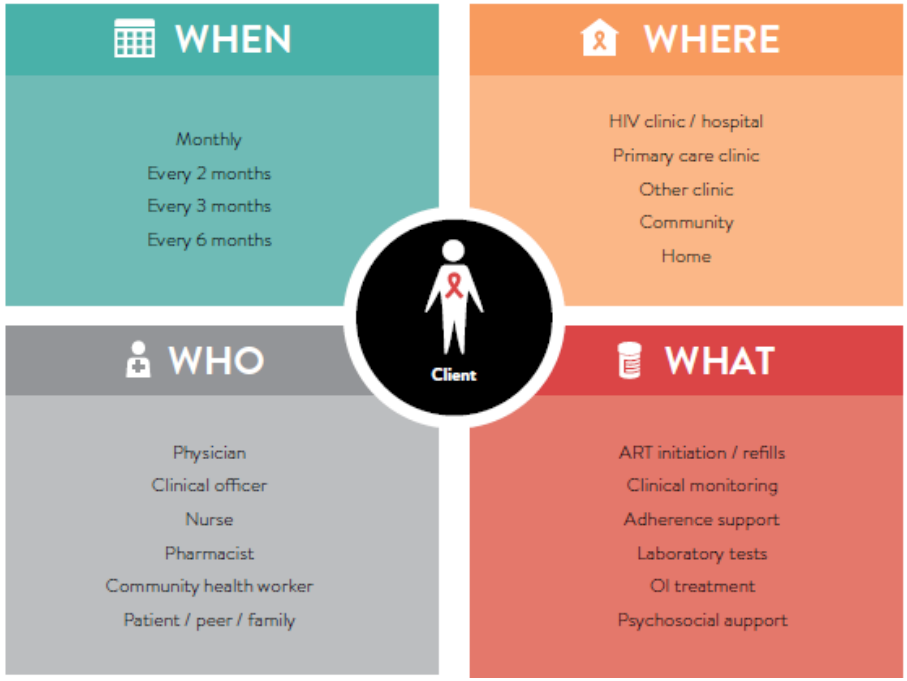


An unfortunate state of mind, or is it?



And we've been trying to address this challenge



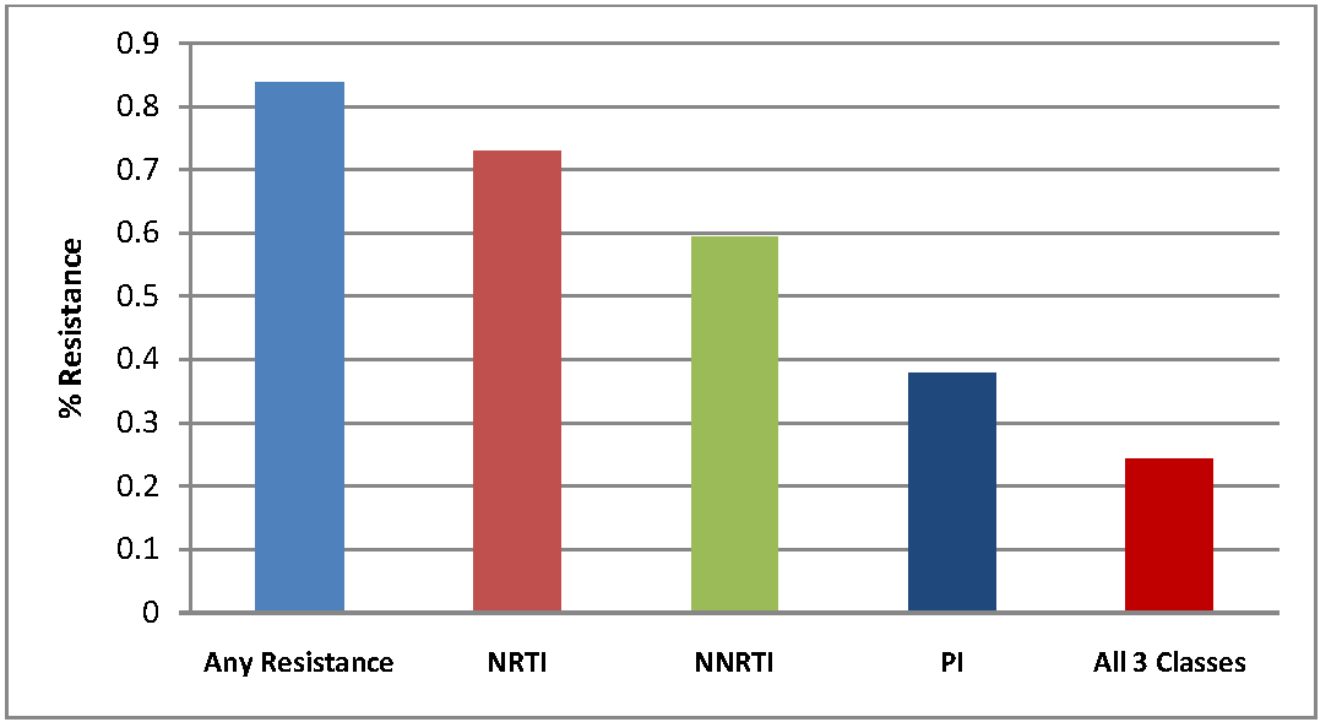


Concerns about increasing levels of HIV Drug Resistance

- A systematic literature review of pretreatment drug resistance in children documented high rates of resistance in children starting ART, particularly those that had been exposed to NNRTI's during PMTCT
- In South Africa, one study showed that 63.7% of infants and children <18 months had HIVDR
  - NNRTI resistance: 62.7%
  - NRTI resistance: 13.9%
- At the end of 2015 only 14% of children 0-15 years across 66 LMIC were on boosted PI-based regimens
- Limited data is available on resistance in adolescents in sub-Saharan Africa

http://apps.who.int/iris/bitstream/10665/255896/1/9789241512831-eng.pdf?ua=1

Viral resistance in sexually active youth with HIV RNA>5000 copies/ml (n=38)



- 42% of 92 sexually active ≥1 VL >5000 copies/ml
- 81 % had resistance to ≥1 ARV class
- 24% had some resistance to drugs in all 3 classes
- 63% with resistance reported unprotected sex

Slide courtesy of Theodore Ruel

Tassiopoulos, CID, 2013.

Infants, children and adolescents don't have the same ART experience

Infants and children 0-9 years	Adolescents 10-19 years	Young Adult 20-25 years	Old people >25 years

d4T
ddI
ABC
TDF
3TC
AZT
SQV
FTC
NVP
LPV/r
EFV
NFV

Population-level HIV incidence assessments: Viral Suppression is lowest in children, adolescents and young adults

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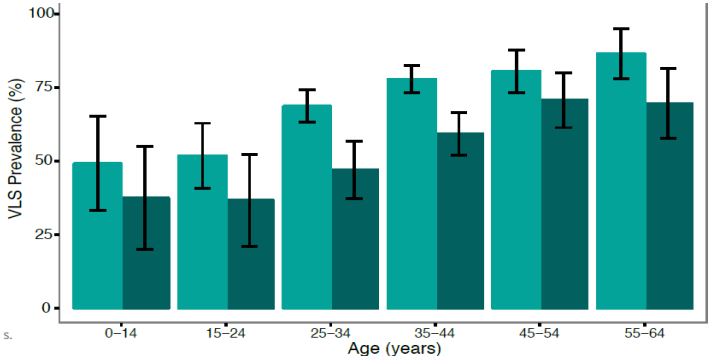

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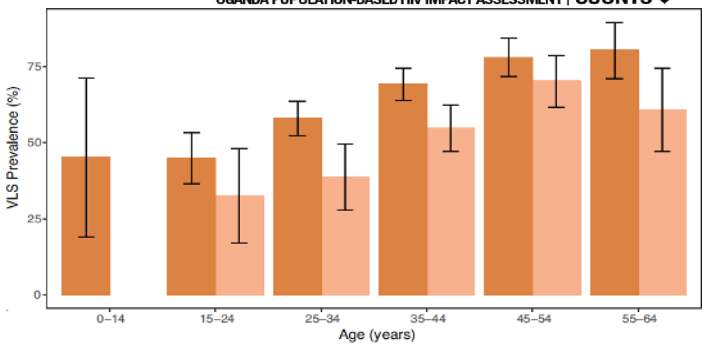

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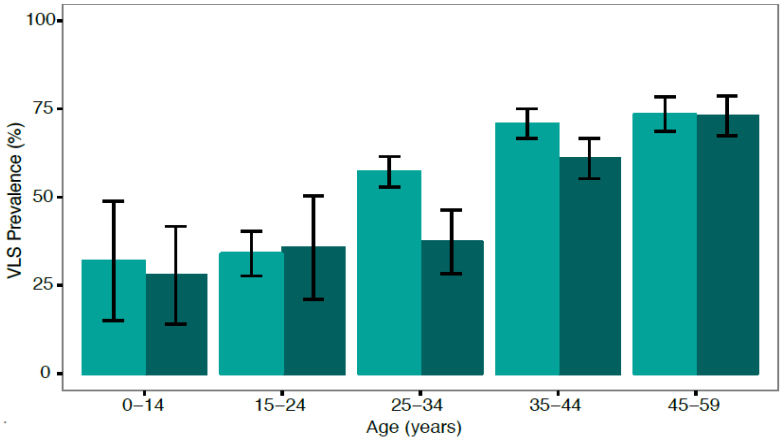

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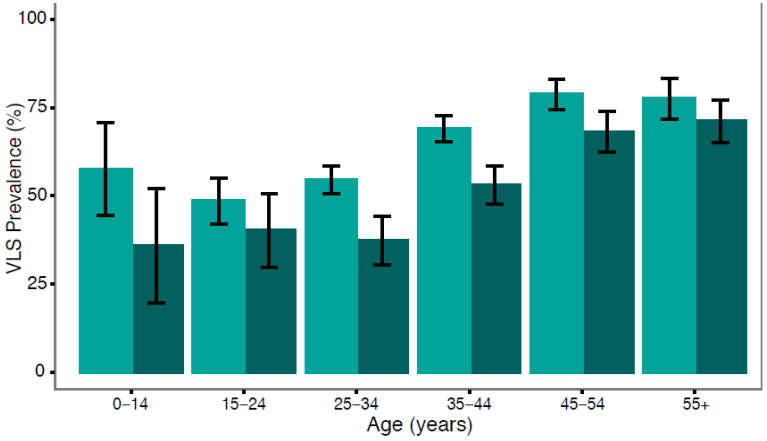


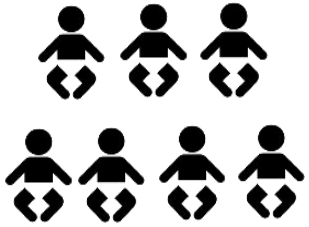
We spend a lot of time thinking about pediatric options

93 adult and adolescent patients

All ages & weight bands

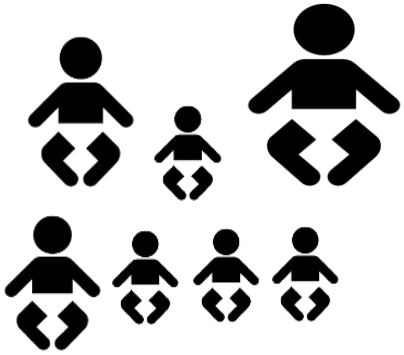
One pill, once-a-day

7 paediatric patients



IATT
THE INTERAGENCY TASK TEAM
The Interagency Task Team on the Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children

Multiple ages and weight bands



Multiple formulations

Adolescents and Adults: Same clinical treatment guidelines

13.1. Recommendations

1. It is recommended to treat all patients with CD4 counts of ≤350 cells/mm^3 irrespective of the WHO clinical stage.
   (Strong recommendation, moderate quality of evidence)
2. It is recommended that all patients with WHO clinical stage 1 and 2 should have access to CD4 testing to decide when to initiate treatment.
   (Strong recommendation, low quality of evidence)
3. It is recommended to treat all patients with WHO clinical stage 3 and 4 irrespective of CD4 count.
   (Strong recommendation, low quality of evidence)

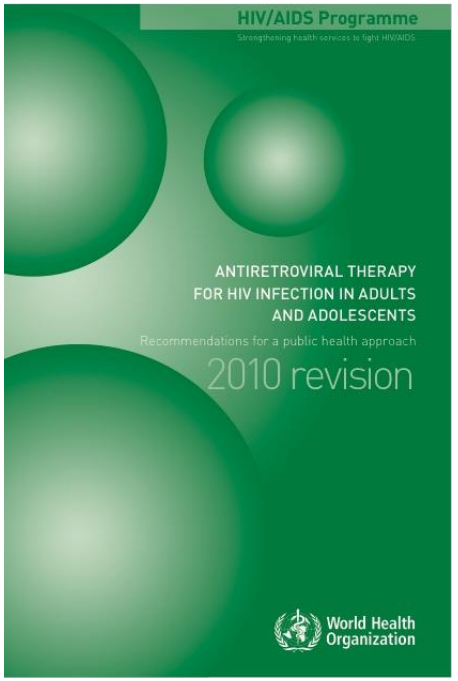


Table 10. Preferred first-line ART in treatment-naive adults and adolescents

Target population	Preferred options	Comments
Adults and adolescents	AZT or TDF + 3TC or FTC + EFV or NVP	Select the preferred regimens applicable to the majority of PLHIV Use fixed-dose combinations

Adolescents and Adults: Same clinical treatment guidelines

Adults and adolescents (≥10 years)	**Initiate ART if CD4 cell count ≤500 cells/mm³** • **As a priority**, initiate ART in all individuals with severe/advanced HIV disease (WHO clinical stage 3 or 4) or CD4 count ≤350 cells/mm³
	Initiate ART regardless of WHO clinical stage and CD4 cell count • Active TB disease • HBV coinfection with severe chronic liver disease • Pregnant and breastfeeding women with HIV • HIV-positive individual in a serodiscordant partnership (to reduce HIV transmission risk)

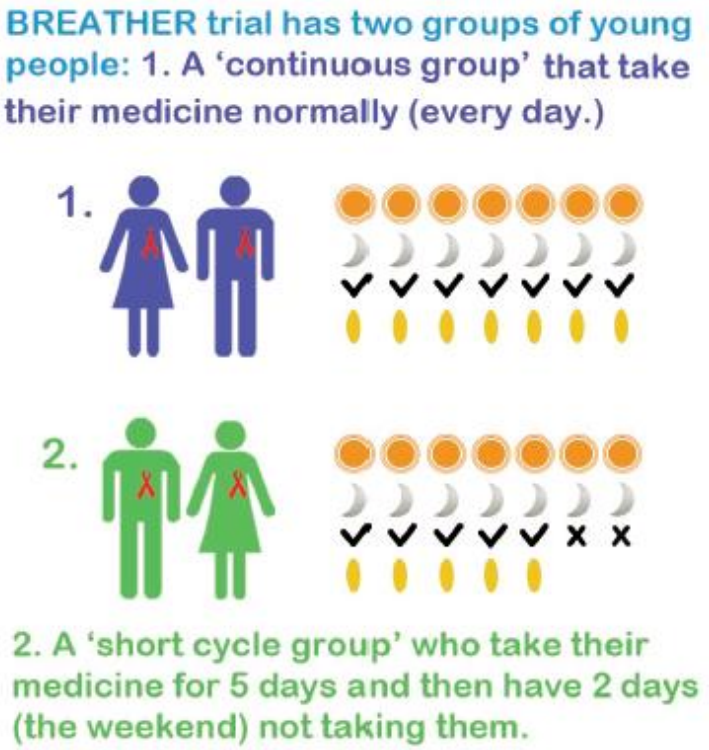
First-line ART	Preferred first-line regimens	Alternative first-line regimens[a b]
Adults **(including pregnant and breastfeeding women and adults with TB and HBV coinfection)**	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP
Adolescents (10 to 19 years) ≥35 kg		AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP ABC + 3TC + EFV (or NVP)

BREATHER (PENTA 16)

• Non-inferiority randomized trial of 199 children aged 8-24 years who were suppressed (viral load < 50 c/ml for > 12 months) and receiving EFV plus two NRTIs.

•RESULTS at 48 weeks:

- 6 (short cycle) vs 7 (continuous) had a confirmed VL > 50 copies/ml [difference -1.2%, 90% confidence interval (CI) -7.3% to 4.9%].
- “no evidence of increased inflammation in the SCT arm.”
- Participants expressed a strong preference for SCT in a qualitative substudy and pre/post-trial questionnaires



Slide courtesy of Theodore Ruel

Butler, et al. Health Technol Assess, 2016.

2016: ART for Adolescents: Still harmonized with Adults

First-line ART	Preferred first-line regimens	Alternative first-line regimens
Adults	**TDF + XTC + EFV**	AZT + 3TC + EFV (or NVP) TDF + XTC + DTG TDF + XTC + EFV_{400} TDF + XTC + NVP
Adolescents	**TDF + XTC + EFV**	AZT + 3TC + EFV (or NVP) TDF (or ABC) + XTC + DTG TDF (or ABC) + XTC + EFV_{400} TDF (or ABC) + XTC + NVP

World Health Organization

Is this the best we can do?

2016: ART for Adolescents: Still harmonized with Adults

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World Health Organization

What is ART Optimization?

- ✓Potent
- ✓Low toxicity
- ✓Well tolerated and easy to take/administer
- ✓High genetic barrier to resistance/durable
- ✓Improve sequencing/switching options
- ✓Can be harmonized across special populations
- ✓Reduce cost

“Yummy or Crummy?”

Discretion

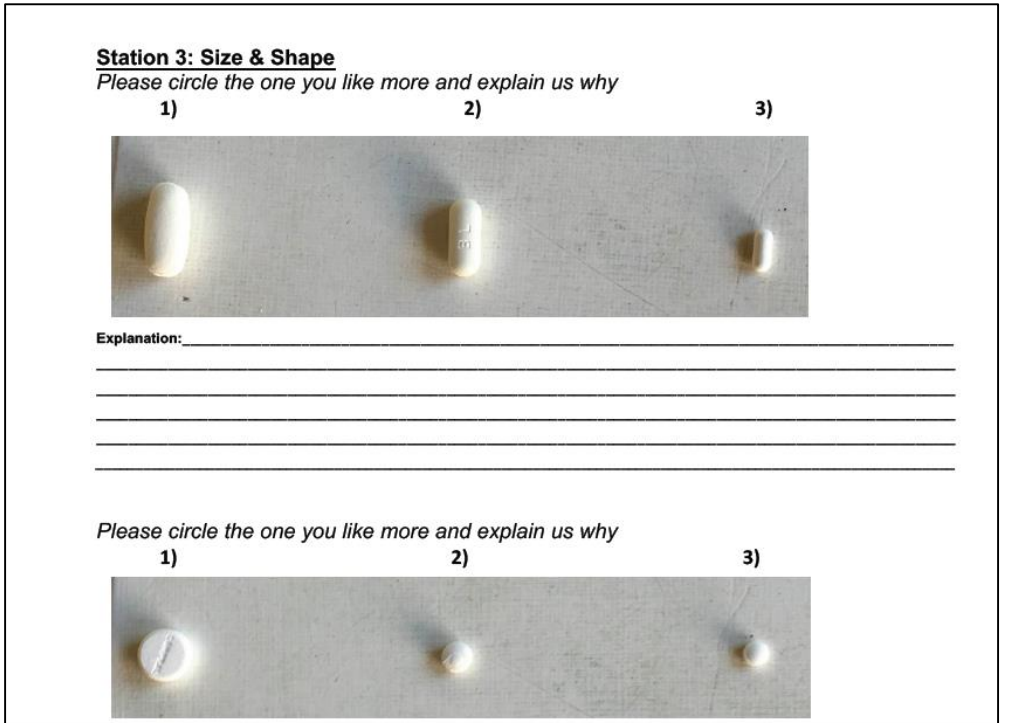
Medicines that conferred confidentiality, were easy to swallow, transport and conceal, were the most highly valued.

Gendered significance

colours, tastes, consistencies and delivery mechanisms

Generational identities

Children and young people had particular needs for the smell, taste and delivery mechanism of medicines.



Station 3: Size & Shape

Please circle the one you like more and explain us why

1) 2) 3)

Explanation:_____

Please circle the one you like more and explain us why

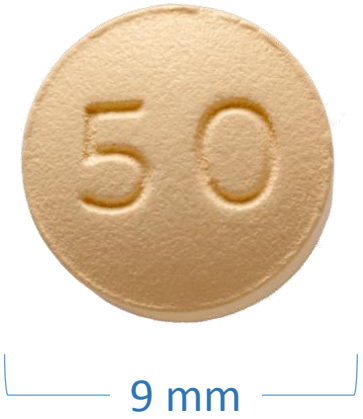
1) 2) 3)

What is ART Optimization for adolescents?

- ✓Potent
- ✓Low toxicity
- ✓Well tolerated and easy to take/administer
- ✓High genetic barrier to resistance/durable
- ✓Improve sequencing/switching options
- ✓Can be harmonized across special populations
- ✓Reduce cost
- ✓Small tablet size
- ✓No interaction with hormonal contraceptives

Dolutegravir (DTG)

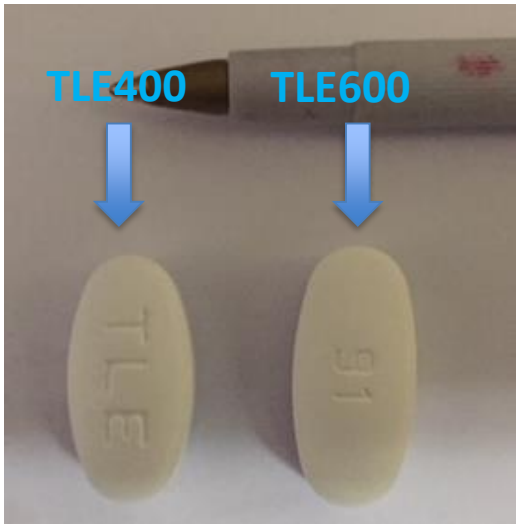
- A “best in class” integrase inhibitor
- Well tolerated
- Low toxicity
- High genetic barrier to resistance
- Once daily dosing
- Small tablet size



- Can be dosed twice daily in patients on TB treatment
- Does not interact with hormonal contraception
- Emerging safety data on use in pregnancy
- Available as
  - 50mg tab
  - TDF/3TC/DTG 300mg/300mg/50mg (aka TLD)
  - ABC/3TC/DTG 600mg/300mg/50mg
- Lower cost than currently preferred 1st line of TDF/XTC/EFV

Reduced-dose Efavirenz

- In treatment-naïve patients, 400mg of EFV was non-inferior to 600mg in **ENCORE1**
- A lower dose of EFV has the potential to
  - Lower cost for the programme
  - Decrease side effects
- Not enough evidence for use in pregnant women
- Not enough evidence for use in patients undergoing TB treatment
- Still has significant interaction with hormonal contraception



Multiple countries are planning to phase in the use of DTG singles and TDF/3TC/DTG

Included or planned to include DTG in national guidelines	Botswana, Cambodia, Cote d'Ivoire, DR Congo, Lesotho, Kenya, Nigeria, Uganda, South Africa, Tanzania, Zimbabwe
Initiated procurement plan for DTG singles	Armenia**, Belarus**, Botswana*, Burkina Faso**, Cambodia*, Cameroon**, Cote d'Ivoire*, DR Congo*, Egypt**, Georgia**, Jamaica**, Kenya*, Nigeria*, Syria**, Uganda* Ukraine**, Zimbabwe

*indicates APWG country
**indicates APWG country with initiated procurement plan but guidelines may not be updated

DTG/TLD Adoption	
	DTG not included in guidelines or no data
	DTG/TLD included in national guidelines (or confirmed plans)
	DTG included in national guidelines and procurement initiated

Who can take DTG?: Newly initiating patients

- 2016 WHO Consolidated guidelines include DTG as an alternative "WHAT to start"

- Evidence of superiority of DTG-containing regimens for <u>treatment-naïve</u> patients

  - **SINGLE**: DTG with ABC/3TC superior to TDF/FTC/EFV over 144 weeks with faster virologic suppression and no drug resistance
  - **FLAMINGO**: DTG with 2 NRTI's superior to DRV/r with 2 NRTI's over 48 weeks
  - **SPRING 2**: DTG non-inferior to RAL over a 96 week period regardless of baseline VL and NRTI back bone

First-line ART	Preferred first-line regimens	Alternative first-line regimens[a,b]
Adults and Adolescents	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + DTG[c] TDF + 3TC (or FTC) + EFV_{400}[c,e] TDF + 3TC (or FTC) + NVP

Who can take DTG?: Patients already on ART

- Stable First-line patients
  - **STRIIVING**: non-inferiority of switch to ABC/3TC/DTG v. continuing current regimen in adults with stable viral suppression

- Second-line patients
  - **DAWNING:** New evidence suggesting DTG superior to LPV/r when combined with ≥ 1 fully active NRTI

- Third-line patients
  - **SAILING**: In patients with viral failure and resistance to ≥2 drug classes DTG superior to RAL when combined with 1-2 other fully active drugs

  - **VIIKING**: In patients with viral failure and INSTI resistance, DTG BD effective when combined with ≥1 fully active drug.

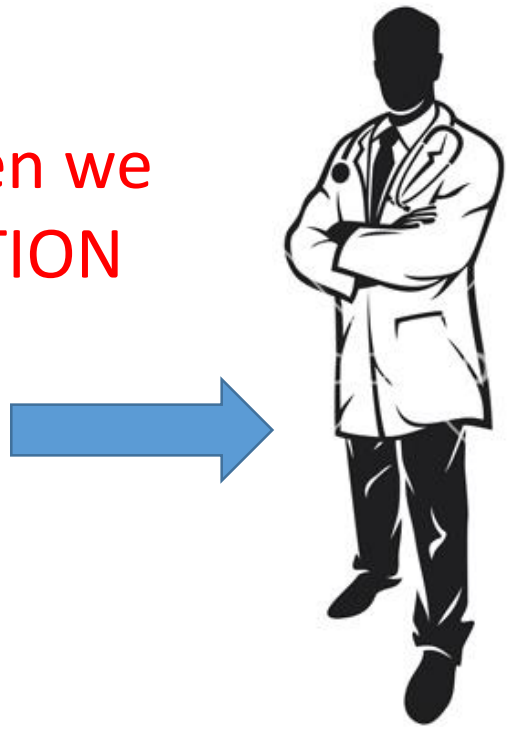
DTG is still active even in heavily treatment experienced patients

- High suppression rates in **STRIIVING** regardless to genotypic susceptibility score after switching to dolutegravir-based regimen in patients with VL suppression

- **DOLULAM**: DTG+ 3TC maintains virological suppression even in heavily treatment experienced patients

This is important when we think about TRANSITION

HCW in Adult clinic



Conclusion

- We need to move beyond the idea that adolescents are just poorly adherent adults
- New adolescent friendly health service delivery models do NOT solve all our problems
- Optimized ART options are now available and being introduced in LMIC
- Dolutegravir-containing regimens give us an opportunity to support our adolescents to get to the last 90 (and beyond!)

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