A Public Sector Antiretroviral Treatment Programme for Treatment-Experienced Children and Adolescents in the Western Cape Province of South Africa Using Darunavir/Ritonavir-, Raltegravir- and Etravirine-Containing Regimens

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Conflict of interest statement

- Member of the national & Western Cape Paediatric 3rd line ARV committees
- Paediatric advisory board member for Mylan, GSK and received honoraria

Background & context

- Increasing need for new cART regimens among HIV-infected children & adolescents with treatment failure on 1st and 2nd line regimens
- SA ART guidelines (since 2010):

Age of child at cART initiation	1st line cART	2nd line cART	'3rd line cART'
<3 yrs	ABC/3TC/LPV/r	Expert opinion	Expert opinion/genotyping
>3 yrs	ABC/3TC/EFV	AZT/3TC/LPV/r	Expert opinion/genotyping

- No standard 2nd line after 1st line PI failure or '3rd line' cART regimen in South Africa
- Very limited data on children receiving Darunavir/ritonavir (DRV/r), Raltegravir (RAL), or Etravirine (ETR)-containing cART as part of routine clinical care in resource-limited settings
- Dolutegravir (DTG) was not available during the study period

Recommendations on 2nd & 3rd line ART regimens for children in SA

1st line regimen		2nd line regimen		3rd line regimen
Pre-2007	Post-2007	Pre-2010	Post-2010	Post-2013
• Children <6 mths & HIV/TB coinfection: 2 NRTIs+RTV	• Children <3 yrs/<10 kg: 2 NRTIs+ LPV/r	• AZT+3TC (ddI)+ EFV (or NVP)	• Expert opinion (genotype result & expert committee consensus)	• Based on genotype result & expert committee consensus
• Children >6 mths of age: 2 NRTIs+ NVP/EFV	• Children >3 yrs/>10 kg: 2 NRTIs+EFV	• AZT+3TC (ddI)+ LPV/r (RTV)	• AZT+3TC+LPV/r	

Eligibility for genotypic resistance testing (W Cape, 2015)

- Patients on a PI regimen with ≥3 viral loads of ≥1000 at least 8-12 weeks apart after adherence has been addressed
  - Children (<15yrs) on PI regimen for ≥1 year
  - Adults on PI regimen for ≥2 yrs

- Requires submission of motivation including adherence assessment to provincial DoH

Objective of the study

- To describe the characteristics and early treatment outcomes of ART-experienced children (<20 years of age) from the Western Cape province of South Africa treated with DRV/r-, RAL- or ETR-containing regimens.

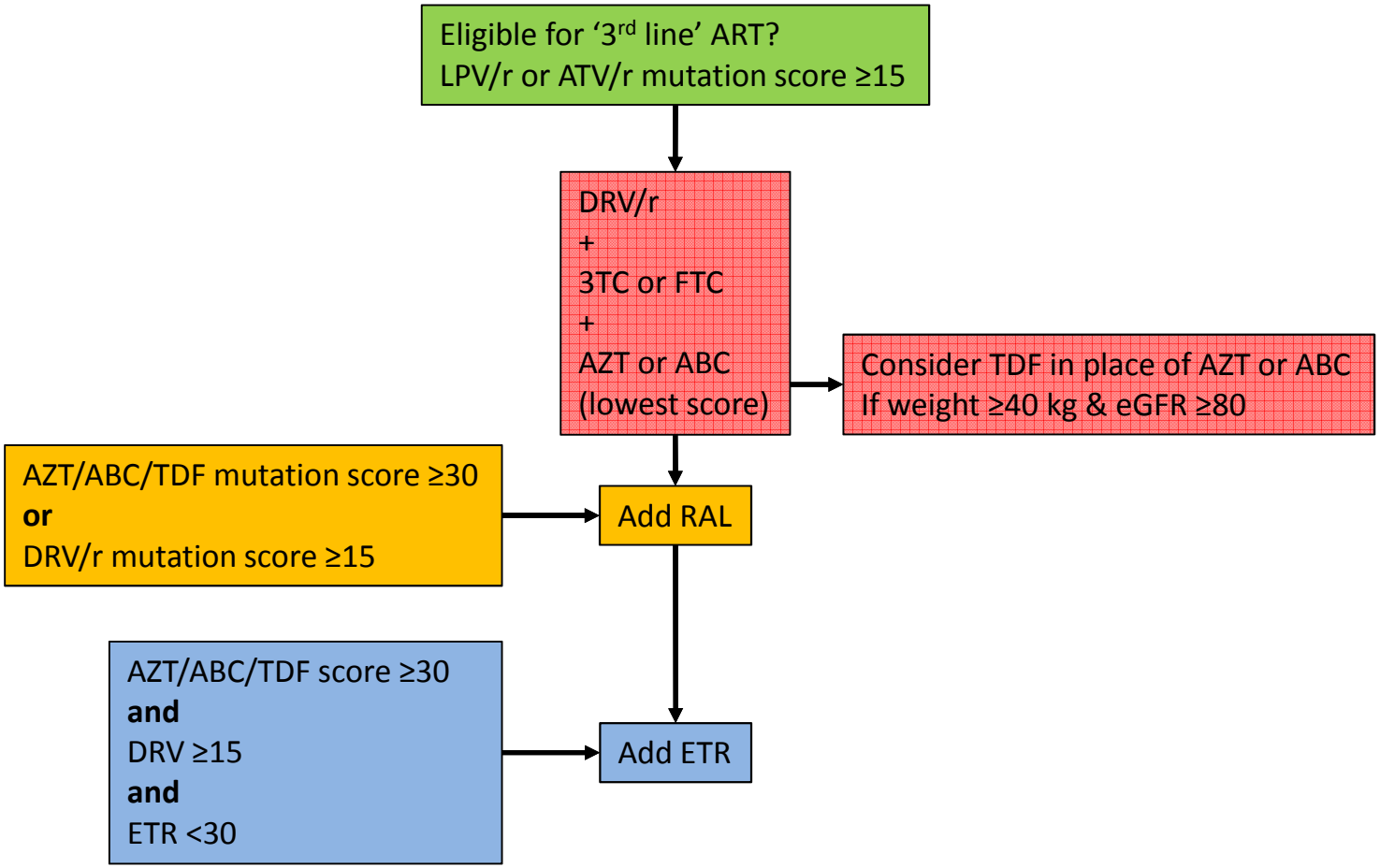
Methods - 1

- Retrospective review
- ART-experienced children
- Receiving a DRV/r-, RAL- or ETR-containing regimen ('3rd line')
- As recommended by a Paediatric Expert Review Committee (ERC)
- Based on HIV genotypic resistance testing (GRT)
  - Variable access to GRT

- Eligiblity for '3rd line' ART (ERC)
  - Protease Inhibitor (PI) resistance on GRT defined as a Lopinavir/ritonavir (LPV/r) or Atazanavir/ritonavir (ATV/r) mutation score (MS) ≥ 15 on the Stanford University HIV GRT interpretation algorithm

- Applications for '3rd line' ART received by the ERC from October 2013 - October 2016

Methods - 2


Eligible for '3rd line' ART?
LPV/r or ATV/r mutation score ≥15
DRV/r
+
3TC or FTC
+
AZT or ABC
(lowest score)
Consider TDF in place of AZT or ABC
If weight ≥40 kg & eGFR ≥80
AZT/ABC/TDF mutation score ≥30
or
DRV/r mutation score ≥15
Add RAL
AZT/ABC/TDF score ≥30
and
DRV ≥15
and
ETR <30
Add ETR

Results - 1

Characteristics of 35 study participants prior to receiving a DRV/r-, RAL- or ETR-containing cART

Characteristic	Value
Age (years)	8.8 (5.5 - 11)
Female	15 (43%)
Year of 1st line ART initiation:	
• Before 2004	2 (5.7%)
• 2004 – 2007	23 (65.7%)
• 2008 - 2011	7 (20%)
• 2012 - 2014	3 (8.6%)
Years on ARVs prior to starting a DRV/r-, RAL- or ETR-containing cART	6.9 (5 - 9.9)
No. of ARVs exposed to prior to start of DRV/r-, RAL- or ETR-containing cART:	
• NRTIs	4 (2 - 4)
• NNRTIs	1 (0 - 1)
• PIs	1 (1 - 2)
Previous exposure to unboosted PI (full-dose Ritonavir)-containing 1st line cART	13 (37%)
Received only 1 prior cART regimen before starting on the '3rd line' regimen (all RTV or LPV/r-based 1st line cART including single drug substitutions from RTV to LPV/r or a single NRTI switch or temporary 3TC monotherapy	12 (34%)

Values are medians (interquartile range) or number (percentage).
ARV, antiretroviral; DRV/r, darunavir/ritonavir; RAL, raltegravir; ETR, etravirine; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; ART, antiretroviral therapy; RNA, ribonucleic acid, ERC, Expert Review Committee.

Results - 2

Characteristics of 35 study participants receiving a DRV/r-, RAL- or ETR-containing ART

ART treatment site at time of referral to ERC:	
• **Primary care clinic**	13 (37.1%)
• **District hospital**	3 (8.6%)
• **Regional hospital / tertiary referral hospital**	19 (54.3%)
Provincial distribution at time of referral to ERC:	
• **Within Cape Town metropolitan area**	28 (80%)
• **Outside Cape Town metropolitan area**	7 (20%)
Prior to starting a DRV/r -, RAL- or ETR-containing ART regimen:	
• **CD4+ lymphocyte number (cells/µL)**	405.5 (251.5-541) (n=24)
• **CD4+ lymphocyte percentage**	14.9 (8.3-20.3) (n=13)
• **HIV-1 RNA, log (copies/mL)**	4.45 (3.7-5) (n= 24)

Values are medians (interquartile range) or number (percentage).
ARV, antiretroviral; DRV/r, darunavir/ritonavir; RAL, raltegravir; ETR, etravirine; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; ART, antiretroviral therapy; RNA, ribonucleic acid, ERC, Expert Review Committee.

Results - 3

- Genotypic resistance profiles of 35 children prior to starting '3rd line' cART
- Stanford University genotypic interpretation algorithm
  - Mutation scores ≥ 15 (≥ low level resistance)
- Protease Inhibitor resistance
  - Lopinavir/ritonavir: 32/35 (91.4%)
  - Darunavir/ritonavir: 18/35 (51.4%)
    - 17 low level, 1 intermediate
    - L76V > L33F > I84V > I50V > V11I & T74P
- Non Nucleoside Reverse Transcriptase Inhibitor resistance
  - Etravirine: 16/35 (45.7%) – 6 low, 8 intermediate, 2 high
  - Underestimate of ETR resistance due to timing of genotyping
- Integrase inhibitors not included in genotyping
  - no participants were exposed to this class of drugs at the time of genotyping

Results - 4

DRV/r, RAL- or ETR-containing ART regimens started in 35 study participants with overall immunologic and virologic outcomes on treatment

ART regimens:	Number of children:	
• **DRV/r + 2 NRTIs**	9 (25.7%)	
• **DRV/r + RAL + 1 NRTI**	8 (22.8%)	
• **DRV/r + RAL + 2 NRTIs**	14 (40%)	
• **DRV/r + RAL + ETR + 1 NRTI**	3 (8.6%)	
• **ETR + LPV/r + 1 NRTI**	1 (2.9%)	
Duration on DRV/r-, RAL- or ETR-containing ART at time of analysis (yrs)	2 (1.3-4)	
Outcomes:	Within 12 months (N=23)	At time of analysis (N=21)
• **CD4+ lymphocytes (cells / µL)**	649 (506 - 900)	717 (513 - 980)
• **CD4+ lymphocyte percentage**	27.1 (20.8 - 36.4)	27.2 (20.8 - 35.6)
• **HIV-1 RNA copies/mL**	Within 12 months (N=32)	At time of analysis (N=30)
<50	24 (75%)	23 (77%)
<400	31 (97%)	29 (97%)
≥400	1 (3%)	1 (3%)

Values are medians (interquartile range) or number (percentage).
ART, antiretroviral therapy; DRV/r, darunavir/ritonavir; RAL, raltegravir; ETR, etravirine; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RNA, ribonucleic acid.

Discussion

- Largest description of children and young adolescents treated with DRV/r-, RAL-, or ETR-containing cART in a public sector programme in South Africa
- Impressive early treatment outcomes among ART-experienced children and early adolescents with multidrug-resistant HIV
- No reports of drug-related adverse events or deaths
- Further research required to evaluate standardised 2nd & 3rd line cART regimens for children

Table 4.19. Summary of sequencing options for first-, second- and third-line ART regimens in adults, adolescents, pregnant women and children

Population	First-line regimens	Second-line regimens	Third-line regimens
Adults and adolescents (>10 years)	2 NRTIs + EFV	2 NRTIs + ATV/r or LPV/r[a]	DRV/r[b] + DTG[c] (or RAL) ± 1–2 NRTIs
		2 NRTI + DRV/r[b]	
	2 NRTIs + DTG	2 NRTIs + ATV/r or LPV/r	DRV/r[b] + 2 NRTIs ± NNRTI
		2 NRTI + DRV/r	Optimize regimen using genotype profile
Pregnant or breastfeeding women	2 NRTIs + EFV	2 NRTIs + ATV/r or LPV/r[a]	DRV/r[b] + DTG[c] (or RAL) ± 1–2 NRTIs
		2 NRTIs + DRV/r[b]	
Children (0–10 years	2 NRTI + LPV/r	If less than 3 years: 2 NRTIs + RAL[d]	RAL (or DTG)[f] + 2 NRTIs DRV/r[g] + 2 NRTIs DRV/r[g] + RAL (or DTG)[f] ± 1–2 NRTIs
		If older than 3 years: 2 NRTIs + EFV or RAL	
	2 NRTI + EFV	2 NRTIs + ATV/r[e] or LPV/r	

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