

Time to First-line ART Failure and Switch to Second-line ART in the leDEA Pediatric Cohort

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HIV Pediatrics Workshop - Melbourne
July 2014

ART in Children

- Initiation: 2013 WHO guidelines recommend all <5 years
- Duration: Once initiated, ART is lifelong
- Viral suppression first-line: 53% at 12 mo (95% CI, 50-55%)¹
- Durability of first-line
 - Cross-sectional survey (2008-2009)²
 - Southern Africa leDEA sites: 3%
 - Asia leDEA sites: 10%
 - Rates of switch at 5 years of ART
 - Europe (EPICC)³ cohort: 16.7%
 - Thailand⁴ cohort: 21%
 - Europe, North and South America (PENPACT)⁵ trial: 29%

¹ Ciaranello, *Clin Infect Dis* 2009; ² TApHOD and leDEA South Africa, *JIAS* 2011; ³ Judd, *AIDS* 2011;

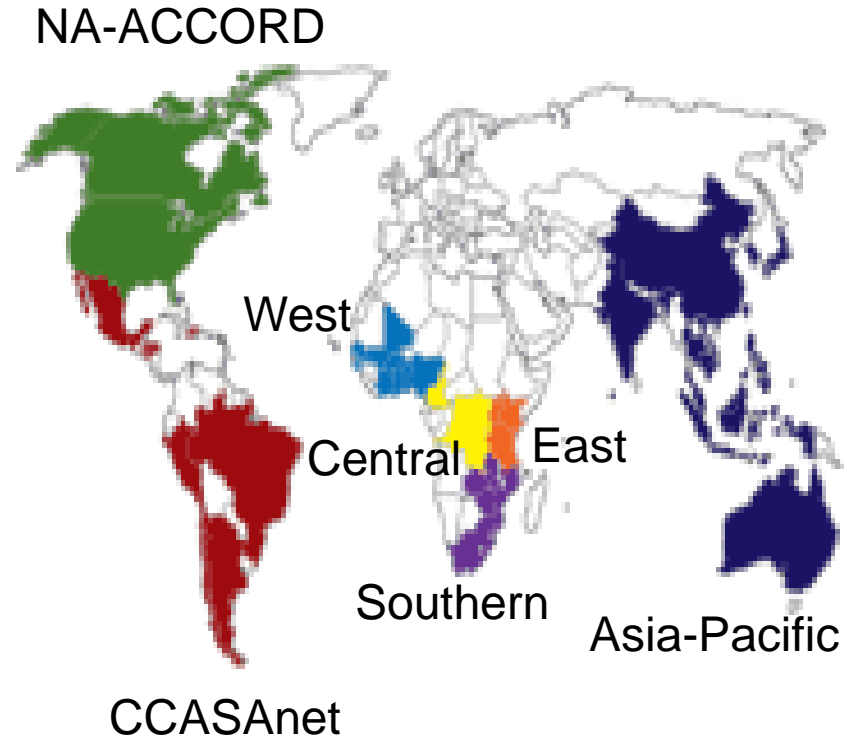
⁴ Collins, *JAIDS* 2013; ⁵ Babiker, *Lancet ID* 2011.

Objectives

- To determine the time from first-line ART initiation to treatment failure in children
- To assess the time from failure to initiation of second-line ART in children

leDEA Global Consortium

- Established in 2005
- Funded by: NIAID, NCI, NICHD
- Seven geographic regions addressing high priority questions about HIV care
- Core functions:
 - Collect/define key variables
 - Harmonize data
 - Apply new analytic methods to HIV epi research



Methods

Population:

- Eligibility: Age 2-13 years at ART initiation

Outcomes:

- Failure after 24 weeks on ART as defined by the site
 - *Clinical*: appearance or reappearance of WHO 3 or 4 disease; increase in WHO stage
 - *Immunologic*: develop/return to thresholds
 - CD4 <200 cells/ μ l or CD4% <10 for a child between 2-5 years
 - CD4 <100 cells/ μ l for a child \geq 5 years
 - *Virologic*: \geq 5000 copies/ μ l
- Change to second-line ART
 - Class change (e.g., NNRTI to PI) + \geq 1 NRTI

Methods

Data Sources:

- Patient level data pooled from 5 leDEA Regions
- Site-level survey
 - Standard first- and second-line regimens
 - Method(s) for assessing failure

Analysis:

- Cumulative incidence computed:
 - For first-line failure and second-line switch
 - Death and LTFU treated as a competing event
- Cause-specific proportional hazards model
 - To identify factors associated with each outcome

Patient Characteristics

Characteristics N=16,183	N (%)
Region	
Asia-Pacific	1883 (11.6)
Central Africa	49 (0.3)
East Africa	7101 (43.9)
Southern Africa	5823 (36.0)
West Africa	1327 (8.2)
Female	7964 (49.2)
Deceased	775 (4.8)
Lost to follow-up¹	2877 (17.8)
Initial regimen type	
NNRTI-based	15818 (97.7)
NRTI-based	54 (0.3)
PI-based	311 (1.9)
	Median (IQR)
Age at first visit	5.8 (3.5-8.7)
Age at ART start	6.7 (4.4-9.4)
CD4 cells/μl at ART start²	231 (73-423) ³
CD4% at ART start²	13 (8.0-18) ⁴

[1] >6 months without a visit and no documentation of transfer

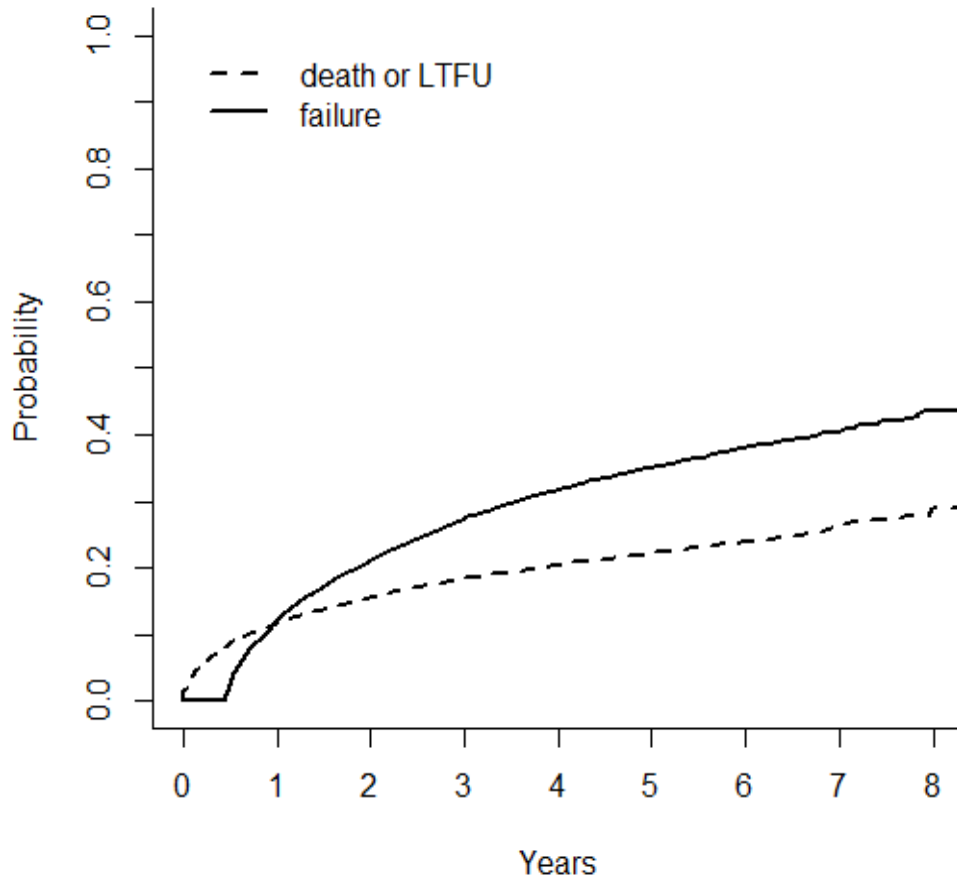
[2] Within 90 days prior and 7 days post ART initiation

[3] Patients \geq 5 years

[4] Patients <5 years

Results

Probability of Failure or Death/LTFU



- **Total: 16,183**
 - Failure: 4,032
 - Death/LTFU: 2,837
- 1 year after ART
 - Failure: 12.0%
(95%CI: 11.5-12.6)
 - Death/LTFU: 11.6%
(95%CI: 11.2-12.2)
- 5 years after ART
 - Failure 35.0%
(95%CI: 34.3-36.2)
 - Death/LTFU: 22.1%
(95%CI: 21.4-23.1)

Results

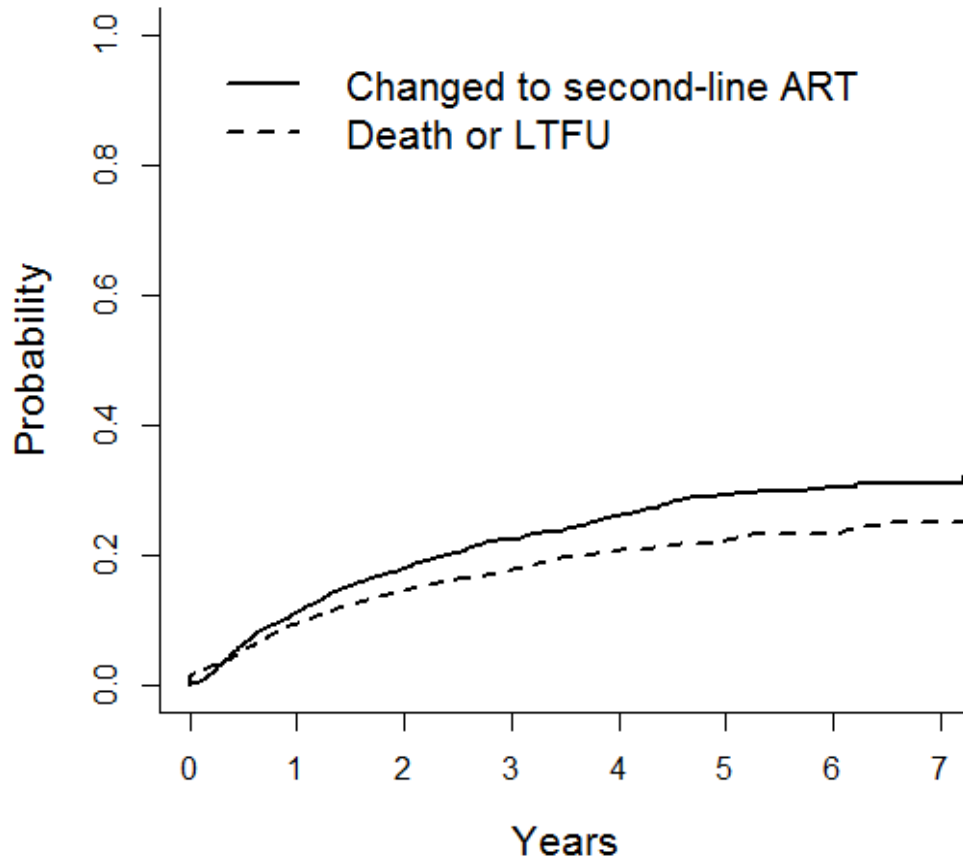
FACTORS ASSOCIATED WITH FAILURE AND DEATH/LTFU

Factor	Failure			Death/LTFU		
	HR	95% CI	P-value	HR	95% CI	P-value
Male (Ref: female)	1.06	1.0 - 1.13	0.054	1.01	0.94 - 1.09	0.720
Age ART initiation (per year increase)	1.03	1.02 - 1.04	<0.001	0.98	0.97 - 0.99	0.004
Regimen (Ref: NNRTI)						
• NRTI	1.18	0.70 - 2.0	0.543	2.19	1.38 - 3.48	0.001
• PI	0.54	0.40 - 0.72	<0.001	1.12	0.88 - 1.43	0.342
Confirmatory VL (Ref: routine VL)	1.36	1.28 - 1.45	<0.001	1.03	0.95 - 1.12	0.466
No access to VL* (Ref: routine VL)	0.73	0.62 - 0.87	<0.001	2.51	2.23 - 2.82	<0.001

*final 2 rows reflect corrected text following the presentation.

Results

Probability of Change after Failure



- **Total: 4032**

1 year after failure

- Death/LTFU: 9.6%
(95%CI: 8.7 – 10.7)
- Second-line: 11.3%
(95%CI: 10.4 – 12.5)

5 years after failure

- Death/LTFU: 22.3%
(95%CI: 21.0 – 24.6)
- Second-line: 29.3%
(95%CI: 27.9 – 32.0)

Results

FACTORS ASSOCIATED WITH CHANGE TO SECOND-LINE AND DEATH/LTFU						
Factor	Change to Second-Line			Death/LTFU		
	HR	95% CI	P-value	HR	95% CI	P-value
Male (Ref: female)	1.33	1.15 - 1.53	<0.001	1.13	0.96 - 1.32	0.136
Age ART initiation (per year increase)	1.09	1.07 - 1.12	<0.001	1.02	1.0 - 1.05	0.057
Regimen (Ref: NNRTI)						
• NRTI	0.44	0.06 - 3.11	0.409	1.42	0.45 - 4.42	0.548
• PI	0.85	0.38 - 1.90	0.686	0.96	0.43 - 2.16	0.925
Confirmatory VL (Ref: routine VL)	0.54	0.46 - 0.62	<0.001	0.74	0.63 - 0.87	<0.001
No access to VL (Ref: routine VL)	0.52	0.31 - 0.85	0.001	1.31	0.89 - 1.95	0.175

Conclusions

- High rates of death/LTFU and first-line failure were identified in children within 5 years after ART initiation.
- Children in facilities without routine VL were less likely to be identified as failing but more likely to be LTFU or dead.
- Children without access to any VL were less likely to switch.
- Associations with VL access may be related to other site-level factors, including background mortality.
- Of children meeting failure criteria, only a third were changed to second-line ART by 5 years while about a quarter had died.
- Efforts need to be made to determine the reasons for delays in switching of antiretroviral regimens in children who have been identified as failing first-line.

Acknowledgements

To all patients, caregivers, site investigators, and:

Asia-Pacific leDEA

Azar Kariminia
Chuenkamol Sethaputra
Nicolas Durier
Matthew Law

CCASAnet

Catherine McGowan
Pedro Cahn
Jorge Pinto
Carina Cesar

Central Africa leDEA -1

Nelly Kamgaing
Pierre Kariyo
Marcel Mbaya
Wilfred Akam
Jennifer Hemingway-Foday

Central Africa leDEA -2

Don Hoover
Kathy Anastos
Andrew Edmonds
Lydia Feinstein

East Africa leDEA

Rachel Vreeman
Paula Braitstein
Harriet Nuwagaba-
Biribonwoha

Southern Africa leDEA

Matthias Egger
Nicky Maxwell
Fritz Kaeser
Harvard/CEPAC
Andrea Ciaranello

West Africa leDEA

Francois Dabis
Fatoumata Dicko
Fla Kouéta
Karen Malateste
Lorna Renner

INCC

William Wester
Mary Lou Lindergren
Toni Hill
Dana Walker
Firas Wehbe

NIH

Carlie Williams
Rohan Hazra
Melanie Bacon
Rosemary Mckaig
Gerald Sharp
Robin Huebner