Project Brief: Virologic failure in South African Children

Full Title of Study/Programme	A description and comparison of four treatment modalities in children failing highly active antiretroviral therapy (HAART) in South Africa
Technical Focus Area/Key Words	Children and adolescents failing ART, options for management
Rationale	In practice it is difficult for the clinician to know what the optimal treatment is for children who are failing their HAART regimen, particularly if there are ongoing adherence problems, toxicity concerns, or limited future HAART options available. Recent data from the US compared clinical, virological and immunological outcomes at 12 months in children with virological failure managed using 1 of 4 treatment options: 1) continued with their most recent failing HAART regimen; 2) switched to a new HAART regimen; 3) switched to a non HAART regimen (1, 2 or 3 NRTI's or any other ARV's not defined as HAART); or 4) stopped all ARVs. Findings showed that immunological and virological outcomes were worse at 12 months follow-up for those who completely stopped ARVs compared to the other groups. Data from the IeDEA Southern Africa cohort would contribute to this body of evidence.
Primary Objectives	***Objective 1:*** To describe and compare the clinical, immunological, virological and adverse event outcomes in children failing HAART (defined as at least 3 ARV's from at least 2 classes) after at least 6 months of treatment, who continue with one of four following treatment options: 1) Continuing with their current HAART regimen, including those in which 1 ARV drug was added/substituted. 2) Switching to a new HAART regimen, defined by the use of at least 2 new ARVs from at least 2 different classes. 3) Switching to a non-HAART regimen for example containing one (eg. 3TC/FTC monotherapy) two (partial treatment interruption) or 3 NRTI's; PI monotherapy; or any other ARV's not defined as HAART. 4) Discontinuing all ARV's (treatment interruption).
Secondary Objectives	• Describe genotypic resistance results in each group if available. • In children who were restarted on a new therapeutic regimen after treatment options 1-4, describe and compare outcomes after switch in each group.
Primary Endpoint/Outcome	***Outcome measures of Interest:*** • **Clinical** - Change in weight-for-age and height-for-age z-scores. New WHO stage 3 or 4 events (ie. opportunistic infections). - Switch to new therapeutic regimen. - Death. - Loss to follow up.

	• **Immunological** - Change in absolute CD4 count and percentage. • **Virological** - Change in VL.
Secondary Endpoint/Outcome	**Resistance testing** • New genotypic resistance mutations if available.
Study Design	Retrospective observational descriptive and comparative study
Study arms	Children with virologic failure managed with the following strategies: 1) Continuing with their current HAART regimen, including those in which 1 ARV drug was added/substituted. 2) Switching to a new HAART regimen, defined by the use of at least 2 new ARVs from at least 2 different classes. 3) Switching to a non-HAART regimen for example containing one (eg. 3TC/FTC monotherapy) two (partial treatment interruption) or 3 NRTI's; PI monotherapy; or any other ARV's not defined as HAART. 4) Discontinuing all ARV's (treatment interruption).
Study population	Children and adolescents included in the South Africa IeDEA database
Study sample size	Depends on number of children included
Follow up/duration	Data base closure July 31 2014
Study/Programme sites	South African sites contributing data to IeDEA
Study/Programme duration	January 2004-June 2021
Investigators	Lee Fairlie (Lead) Rohan Hazra (Supervisor) (Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institutes of Health, USA) • Nosisa Sipambo (Department of Paediatrics, Chris Hani Baragwanath Academic Hospital) • Harry Moultrie (Wits Reproductive Health and HIV Institute) • Helena Rabie (Department of Pediatrics and Child Health University of Stellenbosch and Tygerberg Hospital; Children's Infectious Diseases Clinical Research Unit) • Mark Cotton (Department of Pediatrics and Child Health University of Stellenbosch and Tygerberg Hospital; Children's Infectious Diseases Clinical Research Unit) • Gadidja Essack (Department of Pediatrics and Child Health Tygerberg Hospital) • James Nuttall (Paediatric Infectious Diseases Unit, Red Cross War Memorial Children's Hospital and the Department of Paediatrics and Child Health, University of Cape Town) • Brian Eley (Paediatric Infectious Diseases Unit, Red Cross War Memorial Children's Hospital and the Department of Paediatrics and Child Health, University of Cape Town) • Karl Technau (Rahima Moosa Mother and Child Hospital) • Ashraf Coovadia (Rahima Moosa Mother and Child Hospital)

	• Gert Van Zyl (Division of Medical Virology, Department Pathology, • National Health Laboratory Service, Tygerberg, and Stellenbosch University) • Russell Van Dyke (Tulane University Health Sciences Center, New Orleans, USA) • Kunjal Patel (Harvard School of Public Health, Boston, USA) • Brad Karalius (Harvard School of Public Health, Boston, USA) • George Seage (Harvard School of Public Health, Boston, USA) • Andrew Wiznia (Jacobi Medical Center/Family Based Services, Bronx, New York, USA)
Other Partners & Collaborators	NIH, PHACS, IMPAACT
Sponsors/Donors	IeDEA
Linked Sub Studies and post grad projects	Nil
Publications/key presentations to date	IAS 2016 – poster presentation ***Virological failure in South African children and adolescents: baseline characteristics and management strategies.*** *L. Fairlie[1], G. Patten[2], H. Rabie[3], R. Hazra[4], K. Technau[5], B. Eley[6], S Sawry [1], F. Tanser[7], A. Boulle[2], R. Wood[8], J. Giddy[9], N. Sipambo[10], M. Cotton[11], J. Nuttall[6], A. Coovadia[5], G. van Zyl[12], G. Essack[3], R. Van Dyke[13], K. Patel[14], B. Karalius[14], G. Seage III[14], M. Schomaker[2], M. Egger[15], M-A Davies[2]*
Progress Update as at	November 2016
Frequency of donor narrative report	Annual
Overall Study/Project Contact	Lee Fairlie (lfairlie@wrhi.ac.za)
Briefing owner and date	Lee Fairlie 22/11/2016