

Incidence of Early Virological Failure and the evolution of antiretroviral drug (ARV) resistance mutations in Ugandan children

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Background

- HIV-infected individuals in resource limited settings are at increased risk for unrecognized virologic failure and the subsequent development of antiretroviral resistance because of limited access to virologic testing.
- There are limited longitudinal data about the incidence of early virologic failure and the evolution of resistance in non-subtype B HIV+ children.

Aims

- To determine the prevalence of early virologic failure (EVF) in HIV+ African children starting ARV therapy
- To characterize the timing of ARV-mutation accumulation in this population
- To predict the impact of these mutations on second-line therapy options

Methods

Subjects

- Children with HIV and Malaria Project, (CHAMP), an observational cohort in Kampala, Uganda.
- ARV initiated per WHO/Ugandan guidelines. ART switch decisions were based on immunological and clinical criteria
- Early Virologic Failure was defined by having HIV RNA >1000 copies/ml in the 6 to 9 month period after ARV initiation (not attributable to non-adherence to ART)

Laboratory Techniques

- Plasma HIV RNA levels were quantified every 12 weeks with fresh plasma samples by Roche Amplicor (Version 1.5); level of detection was 400 copies/ml.
- Population sequencing of HIV-1 *pol* was performed using banked plasma specimens.

Composite discrete genotypic susceptibility scores (dGSS)

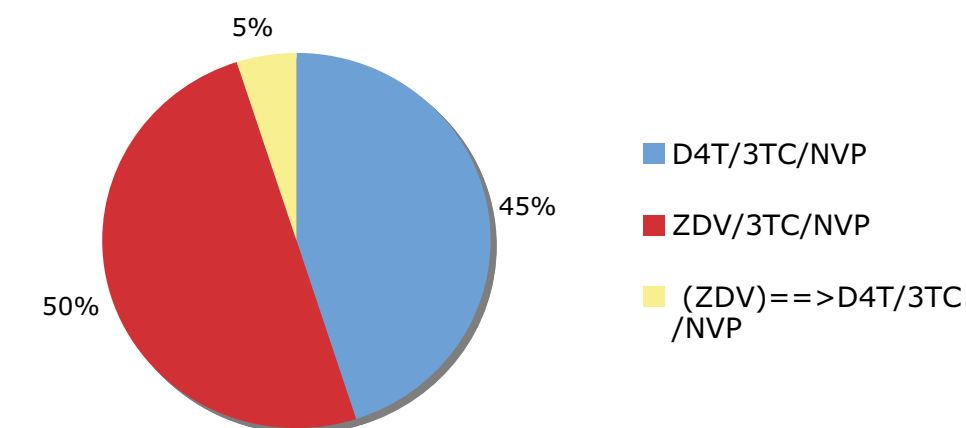
- dGSS scores predict the activity of ARV's for a given strain linking specific mutations to a large database of clinical studies (<http://hivdb.stanford.edu/>)
- dGSS scores were calculated for each subject's 1) current regimen and 2) the standard Ugandan second-line regimen.
- Susceptibility scores were tested for a correlation with increasing time using the Spearman rank correlation test.

Results

Treatment characteristics

- Median duration of ART prior to genotypic testing 24.8 months (IQR 20–30.7)
- Median duration of virologic failure prior to genotypic testing 15.2 months (IQR 11.1–20.4)

Figure 1. Antiretroviral Regimens



Prevalence of Early Virologic Failure

- 126 children had a median 746 follow-up days beyond 6 months of ARV.
- 18 (14%) experienced Early Virologic Failure
 - All had detectable viremia at every point tested during in follow-up.
 - 2 had a history of maternal NVP uses as PMTCT

Timing of ARV-Resistance Mutations

40 samples from 14 children yielded successful genotypic resistance testing.

Notes to Tables 1 and 2 (below):

- * estimated as time from 90 days after ARV initiation (since viremic at 6 months)
- not tested in this time period; "none": tested but none detected
- Thymidine Associated Mutations (TAMs) are underlined
- † All mutations with potential impact on Etravirine (ETV-m) are underlined
- ‡ Exposure to Nevirapine for prevention of mother to child transmission was reported
- ^ Number with 1 or more mutations affecting NVP and EFV

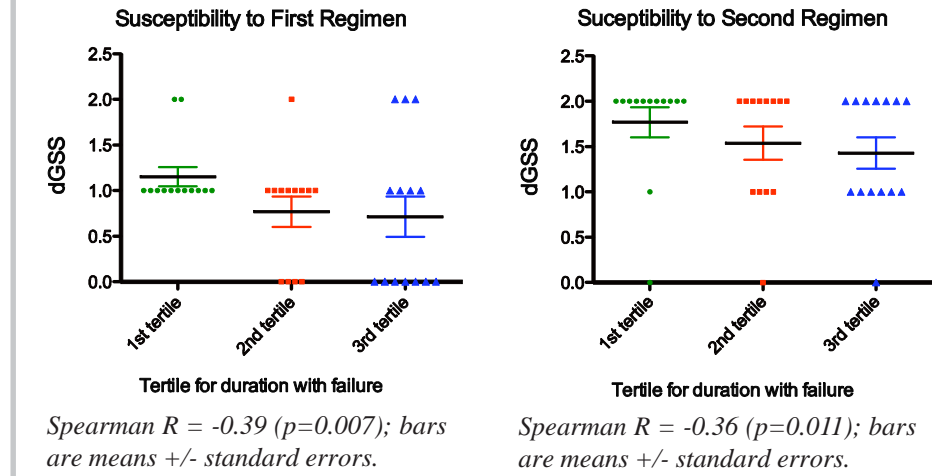
Table 1. Nucleoside Reverse Transcriptase Inhibitor (NRTI)-Associated Mutations*

Subject	Months of Failure*					NRTI Received
	0-5 mo	6-11 mo	12-17 mo	18-23 mo	24-29 mo	
1	-	-	D67N, A62V, M184V	D67N, M184V	D67N, A62V, D67N, M184V	D4T, 3TC
2	M184V	-	T215Y, M184V	-	T215Y, M184V	AZT, 3TC
3	-	-	V75I, M184V	V75I, M184V	-	D4T, 3TC
4†	-	-	-	-	M184V	D4T, 3TC
5†	M184V, K219R	-	-	K70R, M184V	K65R, T69D, K65R, T69D	D4T, 3TC
6	-	-	T215F, M184V	T215F, M184V	M184V	AZT, 3TC
7	-	M184V	M184V	-	M184V	AZT, 3TC
8	M184V	M184V	M184V	T215F, M184V	T215F, M184V	D4T, 3TC
9	M184V	Y115F, M184V	-	M184V	-	AZT, 3TC
10	M184V	-	-	M184V	-	AZT, 3TC
11	K65R	M184V	M184V	-	-	AZT, 3TC
12	M184V	M184V	M184V	-	-	AZT, 3TC
13	M184V	M184V	-	K70R, K219E, M184V	-	D4T, 3TC
14	M184V	M184V	M184V	-	-	AZT, 3TC
M184V	9/9 (100%)	7/7 (100%)	9/9 (100%)	8/8 (100%)	6/7 (86%)	
1 TAM [†]	0/9 (0%)	0/7 (0%)	3/9 (33%)	4/8 (50%)	3/6 (50%)	
≥2 TAM [†]	0/9 (0%)	0/7 (0%)	0/9 (0%)	1/8 (13%)	1/6 (17%)	

Table 2. Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI)-Associated Mutations*

Subject	Months of Failure*					NNRTI Received
	0-5 mo	6-11 mo	12-17 mo	18-23 mo	24-29 mo	
1	-	-	K101E, Y181I	K101E, Y181I	K101E, Y181I	NVP
2	K103N	-	K103N	-	K103N	NVP
3	-	-	none	none	-	NVP
4†	-	-	-	-	Y181C, V179T, K103N	NVP
5†	K103N	-	-	K103N	V90L, Y181C, K103N	NVP
6	-	-	A98G, K103N	K103N	K103N	NVP
7	-	V179D, Y188L	V179D, Y188L	-	V179D, Y188L	NVP
8	Y181C	Y181C	Y181C	Y181C, V108I	Y181C	NVP
9	E138A	E138A, G190A, K103N	-	E138A, G190A	-	NVP
10	none	-	-	none	-	NVP
11	Y181C, V108I	K103N, V108I	K103N, V108I	-	-	NVP
12	G190A	G190A	K101H, G190A	-	-	NVP
13	Y181C, V108I	Y181C, V108I	-	Y181C, V108I	-	NVP
14	none	G190A	G190A	-	-	NVP
Prevalence						
1 ETV-m [†]	5/9 (55%)	5/7 (71%)	4/9 (44%)	2/8 (25%)	2/7 (29%)	
2 ETV-m [†]	0/9 (0%)	1/7 (0%)	3/9 (22%)	2/8 (25%)	3/7 (43%)	
NVP/EFV [^]	6/9 (67%)	7/7 (100%)	7/9 (78%)	6/8 (75%)	7/7 (100%)	

Figure 2. Predicted impact on first- and second-line ARV regimens (dGSS Scores)



Conclusions

- 14% of HIV infected children that started ARV-therapy in this cohort experienced Early Virologic Failure
- Most had M184V and NNRTI-mutations within 6 months, TAMs after 12, and 2 ETR-mutations by 30 months
- With persistent and unrecognized virologic failure, HIV-infected children with Early Virologic Failure could develop significant resistance that compromise the efficacy of second-line options
- These data underscore the need for affordable methods to identify viral failure and drug resistance in this population.

Acknowledgments

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