Poster #: 847

Persistence of HIV Drug Resistance in Children Exposed to Nevirapine Prophylaxis

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Introduction

- Strategies to prevent mother to child transmission (**pMTCT**) of HIV have evolved over the past 15 years in resource-limited settings
  - Single dose nevirapine (**sdNVP**) was simple, inexpensive, and relatively effective intervention [1], but associated with
    - Selection or transmission of resistance
    - Treatment failure when subsequently given antiretroviral therapy (**ART**) containing non-nucleoside reverse transcriptase inhibitors (**NNRTIs**)
- To prevent MTCT World Health Organization (**WHO**) currently recommends,
  - Lifelong ART (option B+) for HIV-infected mothers
  - 6 weeks of once daily NVP for breastfeeding infants
- To treat HIV-infected infants WHO currently recommends,
  - Protease inhibitor (**PI**)-ART for children <3 years of age
  - NNRTI-ART in children ≥ 3 years of age
- PIs are costly and have an unpleasant taste [2]
- A better understanding of the persistence of NVP resistance would help determine when NNRTI-based ART is an option for children with a history of NVP exposure
- We **hypothesized** NVP resistance would persist for a longer time among HIV-infected individuals exposed to a greater number of NVP doses

Methods

- A prospective observational study enrolled HIV-infected children, initiating ART, with previous NVP exposure in Pretoria, South Africa.

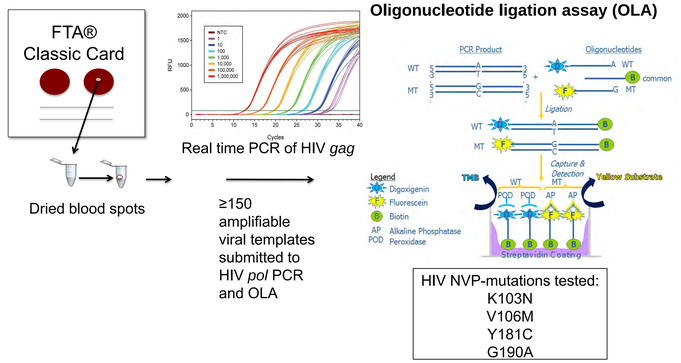

Figure 1. Study schema. Dried blood spots were collected at enrollment and during monthly follow-up visits. Amplifiable HIV subtype C templates were quantified by polymerase chain reaction (**PCR**) of *gag*, and ~150 amplifiable templates were submitted to nested HIV *pol* PCR. NNRTI-resistance was assessed by OLA that quantified the proportion of mutant and wild-type viral templates at 4 codons in reverse transcriptase with a sensitivity of ≥2% mutant.

Results

Table 1. Antiretroviral therapy given for pMTCT and ART regimen initiated at enrollment. Median age at enrollment was 7.5 mo (IQR 4-15) and median age at ART initiation was 9 mo (IQR 5-16). The majority of children had a history of extended NVP (vs. sdNVP) prophylaxis and initiated LPV/r, 55% and 82% respectively.

PMTCT	Children n=88 (%)
sdNVP	40 (45.5)
Extended NVP prophylaxis, median 6 weeks (range 1-24)	48 (54.5)
ART at enrollment	**Children n=88 (%)**
3TC+ABC+LPV/r	73 (82.9)
3TC+ABC(AZT)+EFV/NVP	5 (5.7)
Not initiated	10 (11.4)

Abbreviations. 3TC, lamivudine; ABC, abacavir; LPV/r, lopinavir/ritonovir; AZT, zidovudine; EFV, efavirenz

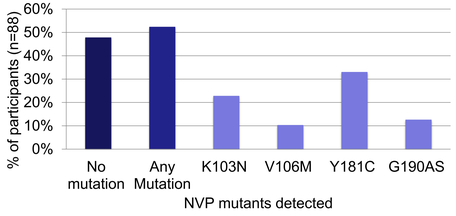

Figure 2. NNRTI-associated mutations detected at enrollment.

- NNRTI-resistance was detected in 52% of children (Y181C (33%), K103N (23%), G190AS (13%), V106M (10%)).
- K103N and Y181C were detected most frequently
- 39/46 (85%) had a mutation at K103N and/or Y181C.
- Children with resistance had a mutant load of 96% (IQR 82-100%), and had a younger median age of 4.5 (IQR 2-9) months vs. 13.5 (IQR 7-24) months, P<0.0001.
- A greater proportion of children with resistance detected at enrollment had received NVP prophylaxis vs. sdNVP (60% (29/48) vs. 43% (17/40); P=0.133)

Duration NVP	Study ID	K103N			V106M			Y181C			G190A		
		Enr.	6mo	12mo	Enr.	6mo	12mo	Enr.	6mo	12mo	Enr.	6mo	12mo
sdNVP	84	wt	wt	wt	98%	98%	98%	24%	28%	44%	wt	wt	wt
	9	7%	wt	12%	20%	15%	11%	wt	wt	wt	wt	wt	wt
	59	100%	100%	100%	6%	wt	wt	84%	84%	100%	wt	wt	wt
	83	2%	wt	6%	wt	7%	2%	86%	82%	75%	3%	5%	13%
	2	wt	wt	wt	wt	wt	4%	wt	wt	wt	wt	wt	wt
	10	wt	wt	8%	wt	wt	wt	wt	wt	wt	wt	wt	wt
	33	7%	8%	15%	wt	wt	wt	86%	73%	80%	wt	wt	wt
	4	wt	wt	wt	wt	wt	wt	98%	88%	88%	wt	wt	wt
	6	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt
	102	wt	wt	wt	wt	wt	wt	14%	30%	72%	wt	wt	wt
	45	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt
	36	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt
	67	wt	wt	wt	wt	wt	wt	90%	100%	98%	wt	wt	wt
	23	wt	wt	wt	3%	wt	wt	wt	wt	wt	wt	wt	wt
	86	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt
	32	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt
	58	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt
	57	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt
b. Extended NVP Prophylaxis	28	wt	wt	wt	wt	wt	wt	91%	75%	100%	wt	wt	wt
	68	wt	wt	wt	wt	wt	wt	wt	wt	wt	ind#	ind#	ind#
	69	100%	100%	100%	wt	wt	wt	wt	wt	wt	wt	wt	wt
	73	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt
	11	36%	38%	22%	wt	wt	wt	88%	44%	89%	wt	wt	wt
	39	6%	12%	8%	wt	wt	wt	82%	42%	77%	wt	2%	wt
	43	100%	100%	100%	wt	wt	wt	57%	99%	60%	wt	wt	wt
	71	wt	wt	wt	wt	wt	wt	80%	50%	82%	wt	6%	6%
	90	wt	wt	wt	wt	wt	wt	7%	4%	wt	20%	15%	12%
	30	wt	wt	wt	100%	100%	91%	wt	wt	wt	100%	100%	91%
	77	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt
	87	11%	14%	20%	wt	wt	wt	92%	90%	88%	wt	wt	wt
	22	wt	wt	wt	wt	wt	wt	100%	100%	80%	wt	wt	wt
	18	100%	100%	100%	45%	6%	wt	wt	wt	wt	wt	wt	wt
	24	100%	nt	100%	wt	nt	wt	wt	nt	wt	wt	nt	wt
	98	wt	wt	wt	wt	wt	wt	99%	98%	91%	8%	3%	5%
	66	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt
	38	wt	wt	wt	wt	wt	wt	73%	83%	44%	100%	100%	100%
	48	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt
	7	wt	wt	wt	wt	wt	wt	wt	16%	wt	wt	wt	wt
	34	100%	100%	27%	wt	wt	wt	wt	wt	wt	wt	wt	wt
	41	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt
	15	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt
	40	100%	100%	100%	wt	wt	wt	wt	wt	wt	wt	wt	wt
	99	100%	100%	100%	wt	wt	wt	86%	98%	98%	wt	wt	wt
	47	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt
	52	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt
	54	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt
	31	14%	40%	60%	wt	wt	wt	wt	wt	wt	wt	wt	wt
	95	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt	wt
	61	wt	wt	wt	wt	90%	68%	wt	wt	wt	wt	16%	14%

Abbreviations, Enr, enrollment; ind, indeterminate; Mo, months; nt, specimen not tested; wt, wild-type.
G190S, a NVP-resistance mutation not detected by OLA found by consensus sequencing.

Key: 75-100% | 50-74% | 25-49% | 15-24% | 5-14% | 2-4% | 0% (wt)

Figure 3. Heat map shows % of the HIV population composed of mutant in 49/88 children with longitudinal follow-up.

- Children grouped by duration of NVP exposure
- Within groups, children listed by descending age
- 59% (29/49) had mutations detected at enrollment
- % mutant usually "high" (median 98%, IQR 77-100%) and persisted without decay over a median of 13 months (IQR 12-16) to a median of 21 months of age (IQR 17-32)
- One participant, # 61 initiated NNRTI-ART 1 month after enrollment

Summary/Conclusion

Summary:

- Median age at enrollment was 7.5 months
- 52% with NNRTI mutations; "high", median 96% of their HIV population at enrollment
- Prevalence of mutants: Y181C > K103N > G190A > V106M
  - 85% (39/46) with NVP-mutations at Y181C and/or K103N
- The lack of NVP-resistance in the remaining infants suggests that
  - Infants infected at time when NVP not exerting selective pressure
  - Rapid decay of NVP-resistance
  - Non-adherence to NVP
- Persistence of NVP-mutations at "high", median 98% was universal with long term follow-up, suggesting
  - These infants had transmitted-NNRTI-resistance, or
  - NVP-selection during acute infection
  - Their long-lived reservoir is populated with NNRTI-resistant HIV
- Mutants were more prevalent in younger children, suggesting
  - Rapid decay of NVP-resistance in a subset of infants
  - Older children may have been infected with wild-type virus after NVP exposure

Conclusion:

- The persistence of high mutant loads well beyond infancy suggests that drug resistance testing of NVP-exposed children ≥3 years of age prior to NNRTI-ART would likely detect mutants in a substantial % of children, who will likely require PI-ART for suppression of HIV replication.
- Furthermore, given that ART is lifelong, this study shows that ~50% of children <3 years of age could have initiated NNRTI-ART, thus sparing PI-ART for future use.
  - Finally, OLA is a simple, inexpensive assay that can be transferred to resource limited settings. Targeting codons K103N and Y181C to identify NNRTI-associated mutations could further reduce cost of the assay.

References

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