



Antiretroviral Drug Resistance Mutations in HIV-1 Infected Ugandan Children Perinatally Exposed to Single Dose Nevirapine Following Virologic Failure to an NNRTI Based Regimen

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Poster # 850
CROI 2010

ABSTRACT

Background: HIV-1 infected children with perinatal exposure to Single Dose Nevirapine (SDN) have been observed to have virologic failure when initiated on Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI) based Highly Active Antiretroviral Therapy (HAART), probably because the exposure predisposes them to developing NNRTI resistance mutations. We investigated the Drug Resistance Mutations (DRM) in HIV-1 infected SDN exposed children with virologic failure following initiation on NNRTI based HAART.

Methods: 116 HIV infected children aged below 5years at HAART initiation were recruited into a cohort at JCRC in Uganda. 41 of them (63.4% girls, median age at HAART initiation 6months) had prior exposure to SDN. We studied the NNRTI and Nucleoside Reverse Transcriptase Inhibitor (NRTI) genotypic resistance profiles of 20 children (15 exposed and 5 unexposed to SDN) that had virologic failure at week24 and/or at week48 following initiation of NNRTI based HAART. The resistance sequencing was done using in house primers and edited using BioEdit Sequence Alignment Editor and analysed using the HIV drug resistance database of Stanford University.

Results: Virologic failure was in 17/26 (65.4%) SDN exposed compared to 19/52 (36.5%) unexposed ($p=0.0127$); and 18/29 (62.1%) SDN exposed compared to 17/53 (32.1%) unexposed children ($p=0.0086$) at weeks 24 and 48 respectively. In the exposed the commonest NNRTI DRM were: Y181C (4), G190AG (4), K103N (3), V108IV (3), K103R (2); others were: Y181V, M230L, V106A, P225ST, F227FL, A98G and K101E. The commonest NRTI DRM in the SDN exposed were: M184V (10), D67N (4), K70R (4), T219E (2), K219Q (2), E44D (2), T215F (2), T215IT (2); others were: K65R, K219R, T215FY, T215Y, A62V, T69N, V75I, M41L and V118I. Less diversity was observed in the 5 unexposed children with the commonest NNRTI DRM being K103N (4); the others were: K103RS, K238N, G190AG and M230L, and the commonest NRTI DRM was M184V (5), others being: K70R, D67N and L74V. 12 and 8 children had HIV-1 subtypes D and A respectively.

Conclusion: HIV infected children with virologic failure on NNRTI based HAART and prior perinatal exposure to SDN have multiple NNRTI drug resistance mutations commonly Y181C, G190AG, K103N, V108IV as well as multiple NRTI drug resistance mutations commonly M184V, D67N and K70R. Fewer mutations were observed in the children with no prior SDN exposure, making the exposed with virologic failure more likely to have multiple drug resistance.

BACKGROUND

A Single Dose of Nevirapine (SDN) given to prevent mother to child transmission (PMTCT) of HIV leads to development of resistance mutations to NNRTIs when the prophylaxis fails¹

When these HIV infected children have been initiated on NNRTI based HAART regimens, there have been reports of high rates of virologic failure^{2, 3}

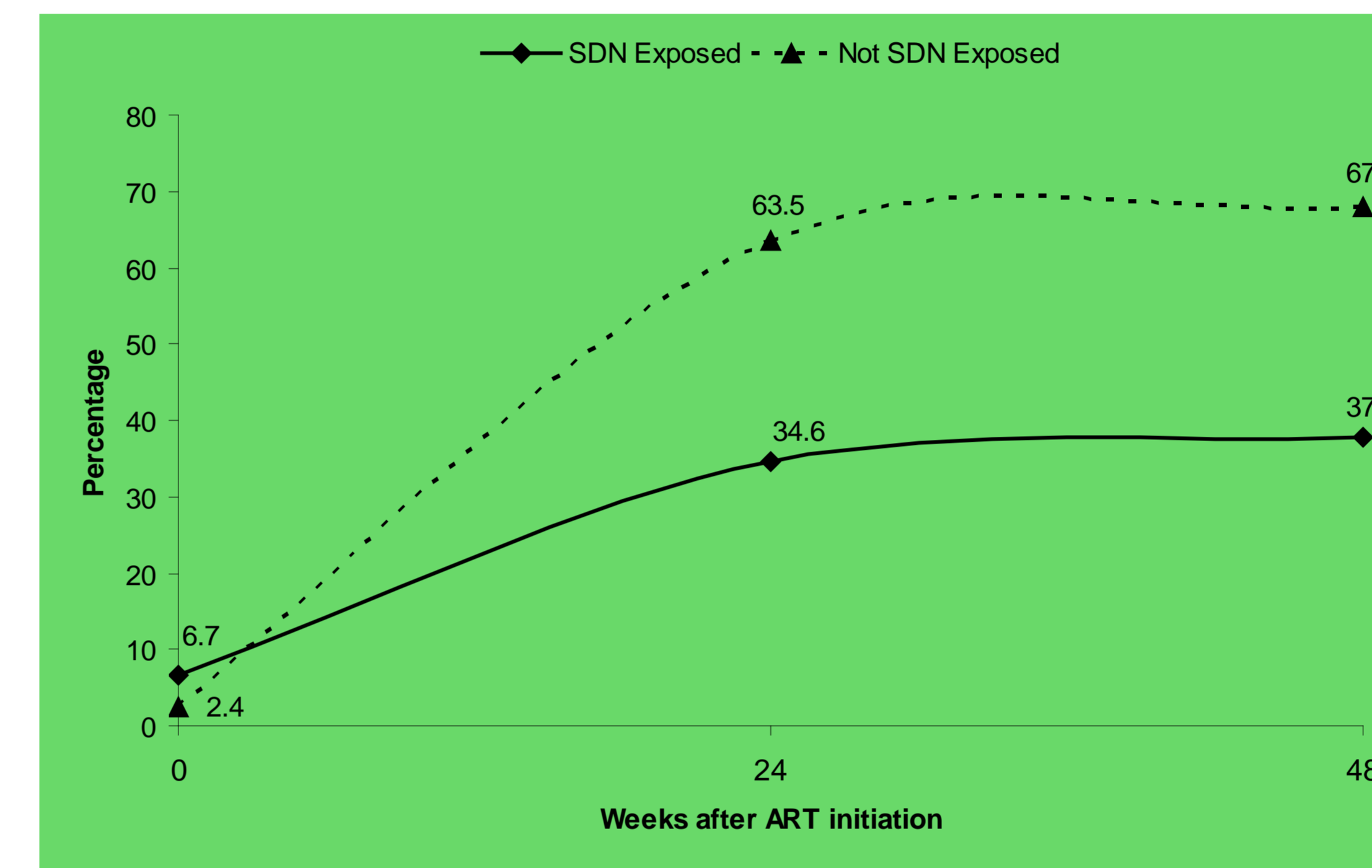
We investigated the Drug Resistance Mutations (DRM) in HIV -1 infected children with perinatal exposure to SDN that developed virologic failure following initiation on NNRTI based HAART

METHODS

- 116 HIV -1 infected children who initiated HAART aged below 5years were recruited into a cohort at JCRC in Kampala, Uganda.
- 41 of these children (63.4% girls, median age 6months at HAART initiation) had perinatal exposure to Single dose Nevirapine
- For 20 of these children (15 exposed and 5 unexposed) that had virologic failure (Viral load <400 copies/ml) at week 24 and/ or week 48 following initiation of NNRTI based HAART, we studied the NNRTI and the NRTI associated mutations by genotypic resistance testing
- Genotypic resistance sequencing was done using in house primers
- The sequences were edited using BioEdit Sequence Alignment Editor (Version 7.0.5) and analysed using the HIV drug resistance database of Stanford University.

RESULTS

Fig: Proportion of children with Viral Load < 400 copies/ml at zero and at weeks 24, 48 after initiating HAART by SDN exposure status



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ACKNOWLEDGEMENTS

We thank all the patients and their carers for agreeing to participate in this study, as well as the following staff of Joint Clinical Research Centre, Kampala, Uganda: Peter Mugenyi, Cissy Kityo, Francis Ssali, Victor Musiime, Hilda Kizito, Joshua Kayiwa, Winnie Namala, Pauline Katundu, James Nkalubo, Sitefano Tugume, John Okiror, Godfrey Pimundu, Lydia Nakiire, Christine Namulindwa, Peter Awio, Lincoln Mugarura, Dennis Akakimpa, Martin Katuramu, Immaculate Nankya, Fred Kyeyune, Stanley Bulime, Hannah Nanyonjo, Leonard Bagenda, Peter Segonga, Lawrence Tsongo, Deborah Masiira, Annet Nandudu, Ruth Sendi, Wilfred Opilo, Erina Turyaiguriwa, Winnie Kiyimba, Enock Kizito, Florence Odongo, Ruth Nandugwa, Lilian Bagaya, Wilfred Ojumbo, Matthew Odera, Geoffrey Anguyo, Rose Byaruhanga, Priscilla Kyobutungi, Asia Namusoke, Margaret Mugisha, Ruth Enabu, Peter Erimu, Eleanor Nanyingi, Scarlet Mubokyi and Eva Natukunda

RESULTS

Table: NRTI and NNRTI resistance associated mutations identified in each patient by single-dose nevirapine exposure status

	HIV sub type	NRTI Mutations	NNRTI mutations
Exposed	D	D67N, K70R, T215IT, K219Q	V108IV, Y181C, P225ST
	D	K65R, K219R	K103R, Y181C
	D	E44D, M184V, T215F	K103N, V108IV, M230L
	D	E44D, M184V	V106A, G190AG, F227FL
	D	D67N, K70R, M184V, K219Q	G190A
	D		Y181C
	D	M184V	K103N
	D	None	None
	A	M184V, T215FY	Y181V
	A	A62V, M184V, T215F	Y181C
	A	M184V	K103R, G190A
	A	D67N, T69N, K70R, V75I, V118I, M184V, K219E	A98G, K103N, V108I
A	M41L, M184V, T215Y	K101E, G190A	
A	M184V	K103N	
A	D67N, K70R, M184V, T215IT, K219E	Y181C	
Unexposed	D	M184V	K103N, M230L
	D	K70R, M184V	K103N
	D	M184V	K103N
	D	M41I, D67N, K70R, V75M, M184V, L210W, T215Y, K219E	K101E, G190A
A	M184V	G190AG	

SUMMARY

HIV infected children perinatally exposed to SDN with virologic failure on NNRTI based HAART have multiple NNRTI and NRTI drug resistance mutations

Fewer mutations were observed in the children with no prior SDN exposure, making the SDN exposed children with virologic failure more likely to have multiple drug resistance