T172

Greater Persistence of Drug Resistance Mutations in HIV-1 Subtype C than other Subtypes among Women Exposed to Single-Dose Nevirapine (SDNVP) for the Prevention of Mother-to-Child Transmission of HIV-1 (PMTCT)

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Background

Single-dose NVP is widely used for PMTCT in resource-limited settings, but it often selects for viral drug resistance mutations in women soon after exposure.

The selected drug resistance mutations may compromise the efficacy of antiretroviral therapy (ART) when these women are placed on treatment.

As part of a multi-country study of non-nucleoside reverse-transcriptase (NNRTI)-based ART in Kenya, Thailand and Zambia, we conducted the following study to see whether HIV-1 subtypes have any influence on the persistence of NNRTI-related drug resistance mutations in women exposed to single-dose NVP for PMTCT.

Objectives

To investigate the impact of HIV-1 subtypes on the persistence of drug resistance mutations in women exposed to single-dose NVP for PMTCT.

Methods

330 single-dose NVP-exposed women were included in the sub-study and none of the women received an antiretroviral tail following single-dose NVP.

Among the 330 women, 182 women were from Zambia, 86 from Thailand and 62 from Kenya.

A broadly-sensitive in-house sequencing-based genotyping assay was used to genotype the reverse transcriptase gene encompassing codons 1-251.

We also used allele-specific real-time PCR assays to screen for minor levels of NNRTI-associated drug resistance mutations including K103N, V106M/I, Y181C and G190A.

Subtype classification was determined by phylogenetic analysis using MEGA 4 software.

Association of HIV-1 subtypes with the persistence of drug resistance mutations at <3, 4-6, 7-12 and >12 months was analyzed and considered statistically significant when *P* value was ≤0.05.

Results

HIV-1 viral subtype distributions and clinical characteristics of study cohort

Subtype/CRF (No. patients)	C (N=181)	A (N=46)	CRF01_AE (N=80)	Others (N=23)
	C (178) C/U (3)	A1 (37) A2 (2) A1/A2 (1) A1/C (1) A1/U (5)	CRF01_AE (79) CRF01_AE/B (1)	B (4) CRF10_CD (4) D/U (6) U (4) B/A1 (1) B/AE (1) G (1) G/C (1) J/K (1)
Time since exposure (Median months, IQR)	11.8 (5.0, 23.1)	5.2 (2.1, 10.7)	26.4 (13.1,45.9)	4.4 (1.8,10.1)
Baseline VL (Median copies/ml)	73,090	278,124	106,338	127,000
Baseline CD4 (median cells/µL)	163	159	161	145

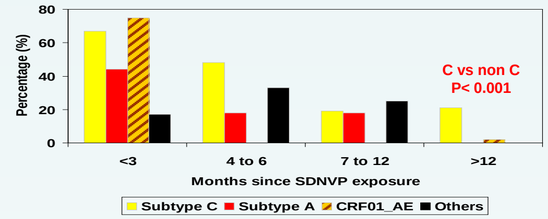
CRF: Circulating Recombinant Form

Persistence of drug resistance mutations by subtypes after single-dose NVP exposure by conventional sequencing assay

	Subtype C		Subtype A		CRF01_AE		Others	
Months since SDNVP exposure	No. with DRM/No. tested	%	No. with DRM/No. tested	%	No. with DRM/No. tested	%	No. with DRM/No. tested	%
<3	17/30	57	4/17	24	6/8	75	3/7	43
4-6	4/23	17	0/11	0	1/4	25	2/6	33
7-12	1/40	3	1/12	8	0/4	0	0/5	0
13-24	**2/46**	**4**	**0/6**	**0**	**0/22**	**0**	**0/1**	**0**
25-65	**2/42**	**5**	**nt***	**nt**	**0/42**	**0**	**0/4**	**0**
Total	**26/181**	**14**	**5/46**	**11**	**7/80**	**9**	**5/23**	**22**

*: Not tested. DRM = drug resistance mutations

Persistence of drug resistance mutations in subtype C-infected women after single-dose NVP exposure by allele-specific real-time PCR



	Subtype C		Subtype A		CRF01_AE		Others	
Months since SDNVP exposure	No. with DRM/No. tested	%	No. with DRM/No. tested	%	No. with DRM/No. tested	%	No. with DRM/No. tested	%
<3	19/28	67	7/16	44	6/8	75	1/6	17
4-6	11/23	48	2/11	18	0/4	0	2/6	33
7-12	6/31	19	2/11	18	0/3	0	1/4	25
13-24	**9/42**	**21^**	**0/6**	**0**	**1/21**	**5**	**0/1**	**0**
25-65	**9/36**	**25^**	**nt***	**nt**	**0/42**	**0**	**0/4**	**0**
Total	**54/160**	**30**	**11/44**	**25**	**7/78**	**9**	**4/21**	**19**

DRM = drug resistance mutations; ^: P<0.001 compared C with non-C; *: Not tested.

Conclusions

NNRTI drug resistance mutations were detected more frequently in subtype C than non-subtype C by allele-specific RT-PCR among women exposed to SDNVP more than one year prior, suggesting that drug resistance mutations associated with NNRTI resistance may persist longer in subtype C.

Although conventional sequencing does underestimate the prevalence of drug resistance mutations among subtype C-infected women exposed to single-dose NVP (compared with real time PCR) , the clinical consequences of long term persisting mutations are uncertain and require further study (See Poster# 916).

Acknowledgements

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