592

Etravirine/Rilpivirine-Specific Mutations Selected by Efavirenz and Nevirapine in Kenyan Patients Failing ART

Keith W. Crawford[1], Dorothy Njeru [2], Jonah Maswai [3], Milton Omondi [4], Jane Kinetto [3], Duncan Apollo [2], Apollonia Aoko [3], Raphael Langat [3], Lawrence Gitano [2], Jemutai Tarus [3], Tiffany E. Hamm[1]

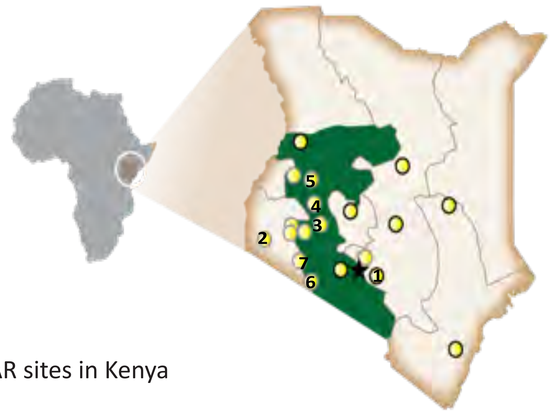
[1]Global Health Programs, US Military HIV Res. Program, Bethesda, MD, [2]US Army Military Res. Unit -Kenya (USAMRU-K), Nairobi, Kenya, [3]US Army Military Res. Unit -Kenya (USAMRU-K), Kericho, Kenya, [4]US Army Military Res. Unit -Kenya (USAMRU-K), Kisumu, Kenya.

BACKGROUND

Antiretroviral drugs may produce different mutation patterns in different HIV-1 subtypes. RV288 is a multi-center PEPFAR Basic Program Evaluation that is being conducted in Kenya, Tanzania, Uganda and Nigeria. This cross-sectional study will estimate the rate of virologic suppression of patients on first-line HAART. We report here on the appearance of drug resistance mutations unique to etravirine and rilpilvirine exposure occurring in Kenyan patients with non-B subtypes failing first line therapy with neviripine or efavirenz.

METHODS

Patients on first-line HAART for at least 6 months were randomly selected from 7 different hospitals for a one-time study visit. Labs performed included a viral load, clinical chemistries and hematology, absolute CD4+ lymphocyte count and CD4+ cell percentage. Subjects with a viral load > 1000 cps/ml were referred for adherence counseling while a sample was submitted for genotypic resistance testing. Viral load (HIV RNA) was quantified from plasma by PCR using Roche Amplicor Version 1.5 with lower detection limit of 400 copies/ml. Genotyping was done on archived plasma samples using the Truegene HIV-1 genotyping kit. The study was approved by the WRAIR and KEMRI IRB's.



MHRP PEPFAR sites in Kenya

Site Map	Hospital	Location	Total # enrolled	# virologic suppressed	% suppressed
1	Defense Forces Memorial Hospital	Nairobi	316	190	60%
2	Kombewa District Hospital	Kombewa	109	58	53.2%
3	Kericho District Hospital	Kericho	136	108	79.4%
4	Nandi Hills District Hospital	Nandi Hills	97	40	41.2%
5	Kapsabet District Hospital	Kapsabet	111	37	33.3%
6	Kapketet District Hospital	Kapkatet	110	86	78.1%
7	Litein Mission Hospital	Litein	87	73	84%

Table 1. Percent of subjects virologically suppressed by site.

RESULTS

Virologic suppression rates by study site are shown in table 1. A total of 215 subjects had VL>1000 and 115 of these had more than one mutation. All subjects were receiving EFV or NVP with two NRTI's and no subject had ever been exposed the etravirine or rilpivirine. There were 14 subjects (13.8%) with a mutation at reverse transcriptase position 138 (A,G, K or Q, Table 2), mutations associated with ETR/RPV.

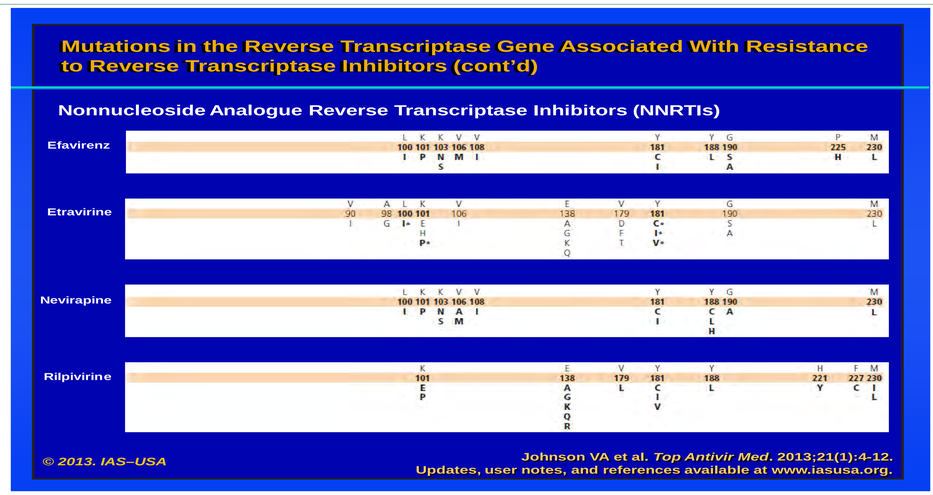


Table 2. Cases of subjects failing EFV/NVP-based regimens with a mutation at position 138.

No.	Regimen[1]	Subtype	Time-on-treatment	HIV RNA (cps/ml)	Mutation
1	EFV + AZT + 3TC	A1	> 24 months	708,134	E138G
2	NVP + AZT +3TC	A1	>24 months	734,322	E138A
3	EFV + AZT + 3TC	A1	>24 months	74,858	E138Q
4	NVP + TDF +3TC	B	13-24 months	1,021	E138K
5	EFV + D4T + 3TC	CRF_01_AE	>24 months	109,987	E138A
6	EFV + D4T + 3TC	A1	>24 months	5,463	E138A
7	NVP + AZT + 3TC	A1	> 24 months	4,242	E138Q
8	EFV + TDF + 3TC	CRF_01_AE	> 24 months	3647	E138A
9	EFV + TDF + 3TC	A1	.>24 months	27,784	E138G
10	EFV + AZT + 3TC	A1	6-12 months	21,114	E138A
11	EFV + AZT + 3TC	A1	>24 months	4,428	E138A
12	NVP + TDF + 3TC	D	13-24 months	313,281	E138G
13	EFV + TDF + 3TC	A1	6-12 months	1,700	E138K
14	NVP + TDF + 3TC	A1	6-12 months	1,902	E138A

CONCLUSIONS

- It appears that EFV and NVP can produce mutations at position 138 (characteristic of Etravirine/Rilpivirine) in HIV-1 non-B subtypes. This phenomenon has not been previously reported.
- The potential of these mutations to occur in patients failing EFV or NVP-based regimens complicates sequencing drugs in the NNRTI-class and emphasizes the importance of resistance testing.

DISCLAIMER

This work was supported by a cooperative agreement (W81XWH-07-2-0067) between the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., and the U.S. Department of Defense (DOD). This research has been supported by the President's Emergency Plan for AIDS Relief (PEPFAR) through the U.S. Department of Defense. The views expressed are those of the authors and should not be construed to represent the positions of the U.S. Army or the Department of Defense.