Expanded Spectrum of Antiretroviral-Selected Mutations in Human Immunodeficiency Virus Type 2

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BACKGROUND

There has been no systematic review or meta-analysis of published HIV-2 sequence data from ARV-naïve and ARV-treated persons. Here, we reviewed published HIV-2 pol sequences to define HIV-2 PR, RT, and IN natural variability and the spectrum of treatment-selected mutations (TSMs) in PR, RT, and IN.

METHODS

We performed a meta-analysis of HIV-2 pol sequences in GenBank for which ARV histories are available and determined the prevalence of each amino acid (AA) at positions 1-99 in PR, 1-240 in RT, and 1-270 in IN according to ARV status and HIV-2 group. Mutations were defined as AAs that differed from the HIV-2 consensus AA sequence. Mutations in >1 sequence from the same person were counted only once. Nonpolymorphic (NP) mutations were defined as mutations with a prevalence <1.0% in persons naïve to the relevant drug class.

Fisher's exact test was performed to assess the association of each mutation with exposure to ARV treatment regardless of HIV-2 genotype. Multivariable logistic regression was performed to examine the association of each mutation with treatment adjusting for the possible confounding effect of HIV-2 group. TSMs were required to be significantly associated with therapy by both Fisher's exact test and logistic regression. The Holm's method was used to control the family-wise error rate for multiple-hypothesis testing at an adjusted p value ≤0.05. The adjustment for multiple-hypothesis testing was performed separately for PR, RT, and IN mutations meeting the following criteria: (i) occurring in >=3 treated persons receiving an ARV belonging to the relevant drug class and (ii) occurring >=2 times more commonly in ARV-experienced vs. ARV-naïve persons.

RESULTS

PR: Of 983 PR samples from 739 persons, 888 (90.3%) were group A and 75 (7.6%) group B. 523 (53.2%) samples were from 483 PI-naïve persons, 408 (41.5%) were from 232 PI-treated persons, and 52 (5.3%) were from persons with uncertain PI history. Of the 232 PI-treated persons, ~75% received IDV and/or LPV/r.

Among PR sequences from PI-naïve persons, 62 mutations at 38 positions had a prevalence >=1.0%. Compared with the consensus HIV-1 PR sequence, different HIV-2 consensus AAs were present at 5 major HIV-1 PI-resistance positions: (i) at positions 32, 46, and 47, the HIV-1 PI-resistance AAs (V32I, M46I, I47V) were the HIV-2 consensus; (ii) at position 82, the HIV-1 polymorphism V82I, was the HIV-2 consensus; and (iii) at position 76, L76M, a variant not reported in HIV-1 strains, was the HIV-2 consensus.

Sixteen mutations occurring in >=10 PI-treated persons were significantly associated with PI therapy (Table 1). Twelve were nonpolymorphic, including V33I, K45R, V47A, I50V, I54M, T56V, V62A, A73G, I82F, I84V, F85L, and L90M. Four were polymorphic including V10I, I64V, V71I, and L99F. Additional nonpolymorphic mutations at HIV-1 PI-resistance positions included F53Y, I54L, A73T, M76L, N83D, I84L, and I89T in 3 persons and G48V and I82L in 2 persons.

Table 1. Prevalence of Nonpolymorphic and Polymorphic HIV-2 PR Mutations in PI-Naïve and -Treated Persons Significantly Associated with PI Therapy

Mutation	PI-Naïve (483)	PI-Treated (232)	Fold	P[1]
Nonpolymorphic				
V33I	4 (0.8%)	24 (10.3%)	12	<0.000001
K45R	0 (0.0%)	26 (11.2%)	>>>	<0.000001
V47A	**0 (0.0%)**	**39 (16.8%)**	**>>>**	**<0.000001**
I50V	**2 (0.4%)**	**16 (6.9%)**	**17**	**0.000001**
I54M	**2 (0.4%)**	**43 (18.5%)**	**45**	**<0.000001**
T56V	1 (0.2%)	29 (12.5%)	60	<0.000001
V62A	1 (0.2%)	19 (8.1%)	40	<0.000001
A73G	2 (0.4%)	11 (4.7%)	11	0.006
I82F	**2 (0.4%)**	**42 (18.1%)**	**44**	**<0.000001**
I84V	**1 (0.2%)**	**20 (8.6%)**	**41**	**<0.000001**
F85L	2 (0.4%)	28 (12.1%)	29	<0.000001
L90M	**1 (0.2%)**	**39 (18.6%)**	**88**	**<0.000001**
Polymorphic				
V10I	12 (2.5%)	39 (17.0%)	6.8	<0.000001
I64V	8 (1.7%)	41 (17.7%)	11	<0.000001
V71I	40 (8.3%)	100 (43.1%)	5.2	<0.000001
L99F	44 (9.4%)	47 (23.0%)	2.5	0.0002

Table 2. Prevalence of Nonpolymorphic and Polymorphic HIV-2 RT Mutations in NRTI-Naïve and -Treated Persons Significantly Associated with NRTI Therapy Between Positions 1 and 240

Mutation	NRTI-Naïve (333)	NRTI-Treated (252)	Fold	P[1]
Nonpolymorphic				
K40R	3 (0.9%)	14 (6.3%)	7	0.03
A62V	**2 (0.6%)**	**19 (7.7%)**	**13**	**0.0003**
K65R	**1 (0.3%)**	**56 (22.5%)**	**74**	**<0.000001**
K70R	**0 (0.0%)**	**18 (7.2%)**	**>>>**	**0.00001**
Y115F	**0 (0.0%)**	**10 (4.0%)**	**>>>**	**0.01**
Q151M	**3 (0.9%)**	**51 (20.2%)**	**22**	**<0.000001**
M184I	**1 (0.3%)**	**17 (6.7%)**	**22**	**0.0003**
M184V	**3 (0.9%)**	**147 (58.33%)**	**65**	**<0.000001**
S215Y	**0 (0.0%)**	**14 (5.6%)**	**>>>**	**0.0003**
Polymorphic				
N69S	9 (2.7%)	24 (9.6%)	3.5	0.03
V111I	31 (9.3%)	80 (31.9%)	3.4	<0.000001
F214L	7 (2.1%)	30 (12.0%)	5.7	0.00008

Table 3. Prevalence of Nonpolymorphic and Polymorphic HIV-2 IN Mutations in INSTI-Naïve and -Treated Persons Significantly Associated with INSTI Therapy

Mutation	INSTI-Naïve (236)	INSTI-Treated (60)	Fold	P[1]
Nonpolymorphic				
Q91R	1 (0.4%)	8 (13.3%)	31	0.0005
E92A	**0 (0.0%)**	**5 (8.3%)**	**>>>**	**0.01**
E92Q	**0 (0%)**	**12 (20.0%)**	**>>>**	**<0.000001**
T97A	**0 (0%)**	**19 (31.7%)**	**>>>**	**<0.000001**
G140S	**0 (0%)**	**7 (11.7%)**	**>>>**	**0.0004**
Y143G	**0(0%)**	**4 (6.7%)**	**>>>**	**0.05**
Q148R	**0 (0%)**	**7 (11.7%)**	**>>>**	**0.0004**
A153G	**1 (0.4%)**	**10 (16.7%)**	**39**	**0.00003**
N155H	**1 (0.4%)**	**17 (28.3%)**	**67**	**<0.000001**
H156R	2 (0.8%)	10 (16.7%)	20	0.0001
R231ins	0 (0%)	7 (12.3%)	>>>	0.0003
Polymorphic				
I84V	15 (6.4%)	19 (31.7%)	5.0	0.00004
A119T	4 (1.7%)	8 (13.3%)	7.9	0.02
V141I	3 (1.3%)	8 (13.3%)	10.5	0.008

Among the nonpolymorphic PI-selected mutations that are not known as HIV-1 resistance mutations, T56V was significantly correlated with I54M and I64V; V33I with V47A, I50V, and I64V; K45R with I47A; and F85L with A73G (Figure 1A).

RT: Of 852 RT samples from 611 persons, 780 (91.5%) were group A and 59 (6.9%) were group B. 336 (39.4%) samples were from 333 NRTI-naive persons, 466 (54.7%) were from 252 NRTI-treated persons, and 50 (5.9%) were from persons with uncertain NRTI history.

Among RT sequences from NRTI-naïve persons, 134 mutations at 83 positions had a prevalence >=1.0%. Compared with the consensus HIV-1 RT sequence, different HIV-2 consensus AAs were present at 3 HIV-1 TAM positions: N210 (rather than L210), S215 (rather than T215), and E219 (rather than K219).

Twelve mutations occurring in >=10 NRTI-treated persons were significantly associated with NRTIs (Table 2). Nine were nonpolymorphic including K40R, A62V, K65R, K70R, Y115F, Q151M, M184V/I, and S215Y. Three were polymorphic including N69S, V111I, and F214L. Six additional nonpolymorphic mutations at NRTI-resistance positions (M41I, D67N, N69T, K70N, I75V, and T215F) occurred in 6 to 9 NRTI-treated persons but were not significantly associated with NRTIs after correction for multiple comparisons.

Among the NRTI-selected mutations that are not known as HIV-1 resistance mutations, K40R was significantly correlated with S215Y and V111I was significantly correlated with A62V, K65R, N69S, Q151M, and F214L (Figure 1B).

IN: Of the 385 IN samples from 321 persons, 320 (83.1%) of the samples were group A and 51 (13.2%) were group B. 252 (65.5%) were from 236 INSTI-naïve persons, 88 (22.9%) were from 60 INSTI-treated persons, and 45 (11.7%) were from persons with uncertain INSTI histories. Of the 60 INSTI-treated persons, 52 received raltegravir and 6 received raltegravir followed by dolutegravir.

Among the IN sequences from INSTI-naïve persons, 145 mutations at 93 positions had a prevalence >=1.0%.

Fourteen mutations occurring in >=4 INSTI-treated persons were significantly associated with therapy (Table 3). Eleven were nonpolymorphic including Q91R, E92A/Q, T97A, G140S, Y143G, Q148R, A153G, N155H, H156R, and an R231 5-amino acid insertion. Three were polymorphic, including I84V, A119T, and V141I. Additional nonpolymorphic mutations included Y143C/R and Q148K, each in 3 INSTI-treated persons, and H51Y, E92G, G118R, G140A, Y143H, S147G, Q148H, and R263K each in 1-2 INSTI-treated persons.

Among the nonpolymorphic INSTI-selected mutations that are not known as HIV-1 resistance mutations, Q91R was significantly correlated with A119T; A153G with I84V, E92A, and N155H; and H156R with E92Q (Figure 1C).

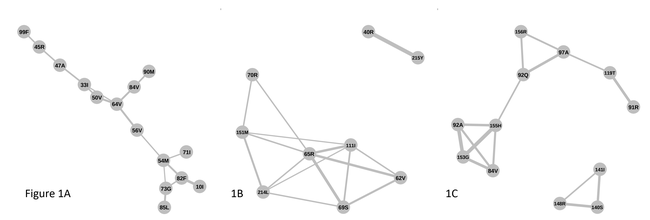


Figure 1A 1B 1C

CONCLUSIONS

In this first meta-analysis of published PR, RT, and IN sequences from ARV-naïve and -experienced persons, we confirmed the association with therapy of many previously reported HIV-2 drug-resistance mutations and identified novel HIV-2-associated nonpolymorphic TSMs. Several of the novel TSMs, particularly those that occurred commonly and that were nonpolymorphic, should be studied for their effects on *in vitro* susceptibility. Further genotypic and phenotypic studies of HIV-2-associated TSMs will improve approaches to predicting HIV-2 ARV susceptibility and providing ARV treatment to HIV-2-infected persons.

ADDITIONAL KEY INFORMATION

The work described here has just been published:

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