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Epidemic Trend of HIV-1 Drug-Resistant Mutations Isolated From HIV-Infected Patients in Hebei, China from 2008 to 2013

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Abstract

Background: Widespread use of anti-HIV therapies has led to the global development of drug-resistant HIV strains. In China, our current knowledge of HIV-1 strain variation, emerging epidemiological trends and viral genetics underlying drug resistance is limited.

Method: Between 2008 and 2013, HIV-1 strains from 569 HIV-seropositive and AIDS patients undergoing antiviral treatment in Hebei province (China) were genotyped. ART-virological failure (viral load ≥ 1000 copies/ml) and HIV-1 mutations for these strains were analyzed, as were variations in mutation trends during this period.

Results: ART-virological failure in HIV-infected patients decreased significantly between 2008 and 2013 (60.9% vs. 35.0%, $p<0.05$), and showed a significant decreasing trend ($p<0.05$). When all HIV-seropositive patients undergoing antiviral treatment were included in this analysis, however, differences or trends observed were not significant. Six mutations were detected in the HIV-1 protease coding region. Only one (A71V/T) showed a significant difference in prevalence during this period ($p<0.05$). Sixty-one mutations were found in the HIV-1 reverse transcriptase coding region, including 34 related to nucleoside reverse transcriptase inhibitor treatment and 27 related to non-nucleoside reverse transcriptase inhibitor treatment. Thirteen mutations (V75I, T215Y, M41L, L210W, T69D, D67DG, V118I, V75I/T, F77L, T215F, Q151M; NNRTI-related: V108I, M230L) exhibited significant decreasing trends between 2010 and 2013, and two mutations (K238T, V90I) showed significant increasing trends ($p<0.05$).

Conclusion: Continuous monitoring of drug resistance is essential for the design of optimal regimens and improvement of therapeutic outcomes.

Keywords: Acquired immunodeficiency syndrome; Protease inhibitor; Genetics

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Introduction

Since 1995, Anti-Retroviral Therapy (ART) has been widely and extensively used to treat HIV infection and slow progression toward Acquired Immunodeficiency Syndrome (AIDS). ART comprises a combination of drugs that target different steps of Human Immunodeficiency Virus (HIV) replication to reduce viral load, minimize opportunistic infections, allow immune reconstitution, and ultimately lower the mortality rate of AIDS and associated diseases [1, 2]. However, HIV-1 evolves rapidly and ART can lead to acquired mutations that confer drug resistance. Importantly, transmission of resistant HIV-1 strains may cause severe clinical and epidemiological problems, while therapeutic failure resulting from drug resistant HIV-1 strains has become a major factor that limits successful antiviral treatments [3, 4]. As such, surveillance of HIV-1 mutations that do not respond to ART may provide additional information that could guide novel drug development and treatment strategies. The present study investigated ART-virological failure prevalence, mutation variations, and genetic trends exhibited by HIV-1 strains isolated

from HIV-seropositive patients in Hebei province, China that underwent antiviral treatment between 2008 and 2013.

Materials and Method

Patient cohort

A total of 569 HIV-seropositive and AIDS patients (551 adults and 11 children) that received antiviral treatment between 2008 and 2013 at a disease prevention and control center in Hebei, China were included in this study. No patients were included for 2009 because of a lack of participation.

An EDTA anti-coagulated whole blood sample (10 ml) was collected from each patient. Fifty microliters of each sample were analyzed for CD4 cell counts (FACSCount, Becton Dickinson, USA). Plasma was separated from the remaining blood sample and analyzed for HIV-1 viral loads (VL; COBAS AMPLICOR, Roche, USA). A VL ≥ 1000 copies/ml was the criterion used for treatment failure.

HIV-1 RNA isolation and genotyping

HIV-1 RNA was isolated from each plasma sample with a QIAamp®Viral RNA Mini isolation kit (QIAGEN, Hilden, Germany). The *pol* gene sequence was amplified twice by Polymerase Chain Reaction (PCR) with primers [5]. PCR products were analyzed by electrophoresis on a 1% (w/v) agarose gel. PCR products were sequenced by Sangon Biotech Co. Ltd. (Shanghai, China). Sequence fragments were assembled with Contig Express (https://www.lifetechnologies.com/ca/en/home/technical-resources/order-support.html), compared with the sequencing chromatogram, and analyzed for drug resistant mutations using the HIV Drug Resistance Database at Stanford University, CA, USA (hivdb.stanford.edu) [6].

Statistical analysis

Data were analyzed with the χ^2-test, the χ^2-test for trends, and the Fisher's exact probability test using SPSS 17.0 software (SPSS, Chicago, USA). A p value<0.05 was considered statistically significant.

Ethics statement

All investigations and HIV-1 tests were informed and voluntary, and participants agreed that their samples may be used for the purpose of controlling and preventing HIV. Written informed consent was obtained from all adult patients and parents/guardians of HIV-1 positive children in this study. Our study was approved by the local Ethics Committee at Hebei Province Centers for Disease Control and Prevention (IRB-2012004).

Results

Prevalence of HIV-1 drug resistance

Between 2008 and 2013, the percentage of patients with drug resistance dropped from 60.9% to 35.0% among ART-failure patients, and this decreasing trend was statistically significant (p<0.05). However, when all HIV-positive patients undergoing antiviral treatment (including ART success patients) were included in our analysis, differences in prevalence and trends were not statistically significant (Table 1, p>0.05).

HIV-1 drug resistance among different antiretroviral regimens

As shown Table 2, the first line antiretroviral drugs were included in regimen 1, regimen 2 and other regimens. Regimen 1 and regimen 2 belonged to the first line therapeutic regimens, and other regimens contained LPV/r. The distribution of HIV-1 DR in these three regimens between 2008 and 2013 showed no significant difference (P>0.05) and no significant trend (χ^2=0.088, P=0.766). However, in 2011, the distribution of HIV-1 DR in these three regimens showed a significant difference (P<0.05), and the proportion of HIV-1 DR in regimen 1(86.1%, 31/36) was obviously higher than regimen 2(4.3%, 3/7) and other regimens (4.0%, 2/5). There were no significant different distribution of DR in 2008(P>0.05), 2010(P>0.05), 2012(P>0.05) and 2013(χ^2=2.232, P=0.328), respectively.

HIV-1 drug resistance among different HIV-1 genotypes

As shown in Table 3, HIV-1 genetic diversity was identified in this study, from subtype B and CRF01_AE in 2008 to subtype B, subtype C, CRF01_AE, CRF07_BC, CRF08_BC, CRF02_AG and URF. The distribution of HIV-1 DR in three main subtypes (subtype B, subtype C and CRF01_AE) showed the significant difference (P<0.001). Particularly, the proportion of HIV-1 DR in subtype B indicated the significant decreasing trend (χ^2=98.571, P<0.001), from 2011 to 2013. The above phenomenon suggested that HIV-1 genetic diversity and DR difference has become the barrier of HIV prevention.

HIV-1 RNA mutations

HIV-1 protease gene mutations

Mutations detected in the HIV-1 protease coding region were analyzed (Table 4). Six different mutations were detected in HIV-1strains isolated from patients in 2010 (V32AV, Q58E, M46IM, M46L, L10I, A71V/T), three mutations were detected in HIV-1 strains isolated from patients in both 2012 and 2013 (M46L, L10I, A71V/T), and two mutations were detected in HIV-1 strains isolated from patients in 2011 (L10I, A71V/T). Of these, only three mutations (M46IM, M46L, and Q58E) were related to Protease Inhibitor (PI) treatment failure. Conversely, the most frequently observed mutations in this patient cohort (A71V/T, L10I, 32AV) were not related to PI treatment failure. Only one mutation (A71V/T) rate displayed a significant difference among ART-failure patients between 2010 and 2013 (p<0.05). When tested for trends, however, we did not detect any statistically significant trend for any of the six mutations that were identified (p>0.05).

HIV-1 reverse transcriptase gene mutations related to Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Tables 3 and 4 list detected mutations related to Reverse Transcriptase Inhibitor (RTI) treatment failure in the patient cohort. Between 2010 and 2013, 12 mutations related to Nucleoside Reverse Transcriptase Inhibitor (NRTI) treatment failure were found in the HIV-1 reverse transcriptase coding

Table 1 HIV-1 drug resistance among ART-failure patients between 2008 and 2013.

Years	Resistance in subjects (i.e., patients with failed treatments)			Resistance in all patients studied		
	Subjects (n)	Resistant subjects (n)	Resistant subjects (%)	Patients (n)	Resistance patients (n)	Resistant patients (%)
2008	46	28	60.9	257	28	10.9
2010	60	32	53.3	439	32	7.3
2011	48	36	75.0	624	36	5.8
2012	112	61	54.5	897	61	6.8
2013	303	106	35.0	1274	106	8.3
χ^2-test	χ^2=39.640	p<0.001		χ^2=8.818	p=0.066	
χ^2-test for trend	χ^2=23.455	p<0.001		χ^2=0.019	p=0.891	

Table 2 HIV-1 drug resistance among different antiretroviral regimens used by patients between 2008 and 2013.

Years	Subjects	ART regimens			χ^2-test	P
		Regimen 1	Regimen 2	Others[a]		
2008	46 (28)[b]	31 (19)	12 (6)	3 (2)	F	0.787
2010	60 (32)	45 (24)	11 (5)	4 (3)	F	0.662
2011	48 (36)	36 (31)	7 (3)	5 (2)	F	0.005
2012	112 (61)	94 (55)	11 (4)	7 (2)	F	0.152
2013	303 (106)	233 (78)	32 (15)	38 (13)	2.232	0.328

Regimen 1: 3TC+D4T+NVP/ EFV, 3TC+AZT+NVP/EFV
Regimen 2: DDI+D4T/AZT+EFV/NVP and TDF+3TC+EFV were included
a: ART regimens containing LPV/r
b: number in bracket represent cases with drug resistance
F: Fisher`s exact-test result

Table 3 HIV-1 drug resistance among different HIV-1 genotypes between 2008 and 2013.

Years	Subjects	Genotypes				
		Subtype B	Subtype C	CRF01_AE	CRF07_BC	others[b]
2008	46 (28)	41 (25)	0 (0)	5 (4)	0 (0)	0 (0)
2010	60 (32)	46 (27)	2 (0)	12 (5)	0 (0)	0 (0)
2011	48 (36)	37 (33)	1 (0)	10 (3)	0 (0)	0 (0)
2012	112 (61)	67 (39)	32 (20)	11 (1)	2 (1)	0 (0)
2013	303 (106)	139 (62)	4 (1)	133 (40)	23 (3)	4 (0)
χ^2-test	χ^2=98.571 P<0.001					
χ^2-test for trend	χ^2=18.126 P<0.001					

a: CRF08_BC(2 cases), CRF02_AG(1case) and URF(1 case) were included

region: A62V, M184V, T215Y, M41L, L210W, D67N, K70R, T215F, K219E, K65R, Q151M, and L74V/L (Table 5). Of these, M184V occurred most frequently (68.75% in 2010 and 57.55% in 2013). Nine mutations (V75I, T215Y, M41L, L210W, T69D, D67DG, V118I, V75I/T, and F77L) exhibited statistically significant differences in prevalence during this period (p<0.05). The observed decreasing trend for all nine mutations was statistically significant (p<0.05). Additionally, two mutations (T215F and Q151M) exhibited no statistically significant changes during this time period; however, they both demonstrated decreasing trends that were significant (both p<0.05).

Table 4 Mutations in the HIV-1 protease coding region detected between 2010 and 2013 in Hebei, China.

Mutation	2010			2011			2012			2013			χ^2	p	χ^2 for trend	p
	Patients (n)	Resistant patients (n)	Resistant patients (%)	Patients (n)	Resistant patients (n)	Resistant patients (%)	Patients (n)	Resistant patients (n)	Resistant patients (%)	Patients (n)	Resistant patients (n)	Resistant patients (%)				
L10I	2	32	6.25	1	36	2.78	0	61	0	3	106	2.83	-	0.232	0.688	0.407
A71V/T	**3**	**32**	**9.375**	**14**	**36**	**38.89**	**16**	**61**	**26.23**	**23**	**106**	**21.70**	**8.64**	**0.034**	0.05	0.823
V32AV	1	32	3.125	0	36	0	0	61	0	0	106	0	-	0.136	3.573	0.059
Q58E*	1	32	3.125	0	36	0	0	61	0	0	106	0	-	0.136	3.573	0.059
M46IM*	1	32	3.125	0	36	0	0	61	0	0	106	0	-	0.136	3.573	0.059
M46L*	1	32	3.125	0	36	0	3	61	4.92	3	106	2.83	-	0.646	0.086	0.769

Related to treatment failure; bold font: statistical significance (p<0.05); "-" represents Fisher`s exact-test result.

HIV-1 reverse transcriptase gene mutations related to non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Of all NNRTI-related mutations (Table 6), K103N occurred most frequently each year between 2010 and 2013 (40.62%–25.47%). This was followed by Y181C (40.625–32.08%), and V108I (21.87%–7.55%). During this period, V108I and M230L displayed statistically significant decreasing trends, whereas K238T and V90I exhibited significant increasing trends (p<0.05). Furthermore, only V106I, M230L, and V179D exhibited statistically significant differences (p<0.04) in prevalence during this period.

Discussion

Since the appearance of the first anti-HIV agent, zidovudine, extensive and widespread use of antiviral therapies has induced adaptive gene mutations in HIV RNA. Li et al. reported that drug-resistant HIV strains account for 43.14% of all investigated strains [6], while Boden et al. found that 5–16% of newly HIV-infected individuals in Europe and the USA are infected with HIV-1 drug-resistant strains [7]. Epidemiological data have clearly linked drug resistance resulting from HIV-1 mutations to failed antiviral treatment and accelerated patient death [8, 9].

Since the first HIV infection reported in Hebei Province in 1989, the cumulative 4148 HIV-1-infected individuals and 1860 AIDS patients have been reported in the province by the end of 2013,. The recorded mortality rate for these AIDS patients to date is approximately 31%. In 2003, the Chinese government issued a set of "free care and financial aid" policies regarding treatment of HIV-infected individuals and AIDS patients. These policies have substantially reduced morbidity and mortality in these groups, as well as improved quality of life.

It has been reported that during antiretroviral treatment, approximately 50% of HIV-infected patients develop at least one major drug-resistant viral mutation that greatly affects treatment outcome [10-15]. In 2007, Chen et al. studied drug resistance in AIDS patients undergoing antiviral treatment in Hebei, China [16]. They found that only 2.6% of AIDS patients in this Chinese province developed drug resistance, and this was significantly lower than comparable data recorded in other regions of the country [6, 11, 17, 18]. In the present study, we report that 60.9% of patients with undergoing antiviral treatment failed to respond to treatment in 2008. We analyzed the change in drug-resistant mutations between 2008 and 2013, and found that the proportion of patients with treatment failure decreased significantly during this period. However, when all HIV-infected individuals were included in our analysis, no statistically significant trend was observed. Furthermore, the distribution of HIV-1 DR in these three regimens between 2008 and 2013 showed no significant difference and no significant trend. This study result suggested that drugs used for antiretroviral therapy with a long time were the main cause of HIV-1 DR, including poor drug-adherence and no change of regimens. Our study also revealed HIV-1 genetic diversity and DR difference among these subtypes, which has become the barrier of HIV prevention.

Taken together, these findings support a growing body of evidence demonstrating that drug resistance should be monitored frequently and treatment regimens be updated appropriately [19]. Both can potentially improve the therapeutic effects of antiviral treatments for people living with HIV and AIDS.

Author's Contribution

HZ and XL implemented the study, analyzed results and drafted the manuscript. XL contributed to the acquisition of the data and revising it critically. YZ and GB carried out the epidemiological investigation. WW performed the statistical analysis. CZ, YL and YW participated in the experiment of HIV-1 molecular biology.

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Table 5 NRTI-related mutations in the HIV-1 reverse transcriptase coding region detected between 2010 and 2013 in Hebei, China.

Mutation	2010			2011			2012			2013			χ2	P	χ2 for trend	p
	patients (n)	Resistant patients (n)	Resistant patients (%)	patients (n)	Resistant patients (n)	Resistant patients (%)	patients (n)	Resistant patients (n)	Resistant patients (%)	patients (n)	Resistant patients (n)	Resistant patients (%)				
A62V	3	32	9.375	1	36	2.78	3	61	4.92	5	106	4.72	-	0.688	0.405	0.524
M184V	22	32	68.75	26	36	72.22	41	61	67.21	61	106	57.55	3.548	0.315	2.631	0.105
T69N/T	2	32	6.25	1	36	2.78	0	61	0	5	106	4.72	-	0.213	0.005	0.945
V75I[a]	**3**	**32**	**9.375**	**2**	**36**	**5.56**	**0**	**61**	**0**	**1**	**106**	**0.94**	**-**	**0.019**	**7.589**	**0.006**
T215IT	0	32	0	0	36	0	0	61	0	0	106	0				
T215Y[a]	**8**	**32**	**25**	**9**	**36**	**25**	**4**	**61**	**6.56**	**10**	**106**	**9.43**	**11.932**	**0.008**	**8.036**	**0.005**
M41L[a]	**8**	**32**	**25**	**11**	**36**	**30.56**	**6**	**61**	**9.84**	**11**	**106**	**10.38**	**12.163**	**0.007**	**8.143**	**0.004**
T69S	1	32	3.125	0	36	0	0	61	0	0	106	0	-	0.136	3.573	0.059
V75M	1	32	3.125	1	36	2.78	0	61	0	2	106	1.89	-	0.464	0.268	0.605
L210W[a]	**6**	**32**	**18.75**	**5**	**36**	**13.89**	**2**	**61**	**3.28**	**2**	**106**	**1.89**	**-**	**0.001**	**14.613**	**0.000**
D67N	4	32	12.5	5	36	13.89	6	61	9.84	12	106	11.32	0.403	0.94	0.104	0.748
K70R	1	32	3.125	5	36	13.89	8	61	13.11	18	106	16.98	4.03	0.258	3.253	0.071
T215F[a]	**5**	**32**	**15.625**	**7**	**36**	**19.44**	**6**	**61**	**9.84**	**6**	**106**	**5.66**	**6.773**	**0.079**	**5.427**	**0.02**
K219E	2	32	6.25	1	36	2.78	3	61	4.92	7	106	6.60	-	0.886	0.196	0.658
K219Q	1	32	3.125	2	36	5.56	0	61	0	5	106	4.72	-	0.251	0.071	0.79
K65R	2	32	6.25	1	36	2.78	2	61	3.28	5	106	4.72	-	0.870	0.006	0.939
T69D[a]	**2**	**32**	**6.25**	**2**	**36**	**5.56**	**0**	**61**	**0**	**0**	**106**	**0**	**-**	**0.009**	**8.212**	**0.004**
Q151M[a]	**3**	**32**	**9.375**	**1**	**36**	**2.78**	**2**	**61**	**3.28**	**1**	**106**	**0.94**	**-**	**0.091**	**4.875**	**0.027**
F116Y	1	32	3.125	2	36	5.56	0	61	0	1	106	0.94	-	0.132	2.122	0.145
K70E	0	32	0	0	36	0	0	61	0	1	106	0.94	-	1.000	0.827	0.363
V75A	0	32	0	0	36	0	0	61	0	0	106	0				
V75L	1	32	3.125	0	36	0	1	61	1.64	6	106	5.66	-	0.399	1.617	0.204
M184I	0	32	0	0	36	0	0	61	0	4	106	3.77	-	0.312	3.351	0.067
K219AEGV	1	32	3.125	0	36	0	0	61	0	0	106	0	-	0.136	3.573	0.059
D67DG[a]	**2**	**32**	**6.25**	**2**	**36**	**5.56**	**0**	**61**	**0**	**0**	**106**	**0**	**-**	**0.009**	**8.212**	**0.004**
V118I[a]	**2**	**32**	**6.25**	**0**	**36**	**0**	**0**	**61**	**0**	**0**	**106**	**0**	**-**	**0.018**	**7.177**	**0.007**
K219R	1	32	3.125	0	36	0	0	61	0	1	106	0.94	-	0.424	0.483	0.487
L74V/L	3	32	9.375	1	36	2.78	2	61	3.28	2	106	1.89	-	0.222	3.039	0.081
V75I/T[a]	**3**	**32**	**9.375**	**3**	**36**	**8.33**	**0**	**61**	**0**	**0**	**106**	**0**	**-**	**0.001**	**12.426**	**0.000**
N348I/T	0	32	0	0	36	0	3	61	4.92	0	106	0	-	0.054	0.002	0.967
F77La	**2**	**32**	**6.25**	**1**	**36**	**2.78**	**1**	**61**	**1.64**	**0**	**106**	**0**		**0.043**	**5.741**	**0.017**
E44D	0	32	0	0	36	0	1	61	1.64	0	106	0	-	0.549	0.001	0.981
T69IT	0	32	0	0	36	0	1	61	1.64	0	106	0	-	0.549	0.001	0.981
L74I	0	32	0	0	36	0	1	61	1.64	3	106	2.83	-	0.901	1.852	0.174

a: mutation showing statistically significant trends of variation ($p<0.05$);
"-" represents Fisher`s exact-test result.

Table 6 NNRTI-related mutations in the HIV-1 reverse transcriptase coding region detected between 2010 and 2013 in Hebei, China.

Mutation	2010			2011			2012			2013			χ^2	p	χ^2 for trend	p
	Patients (n)	Resistant patients (n)	Resistant patients (%)	Patients (n)	Resistant patients (n)	Resistant patients (%)	Patients (n)	Resistant patients (n)	Resistant patients (%)	Patients (n)	Resistant patients (n)	Resistant patients (%)				
K101P	1	32	3.125	0	36	0	0	61	0	0	106	0	-	0.136	3.573	0.059
V106M	1	32	3.125	2	36	5.56	0	61	0	3	106	2.83	-	0.282	0.197	0.657
Y181C	13	32	40.625	14	36	38.89	17	61	27.87	27	106	25.47	4.22	0.239	3.84	0.05
V108Ic	7	32	21.875	4	36	11.11	9	61	14.75	8	106	7.55	5.442	0.142	4.037	0.045
H221Y	0	32	0	6	36	16.67	7	61	11.48	14	106	13.21	5.41	0.144	1.939	0.164
K101E	2	32	6.25	4	36	11.11	10	61	16.39	7	106	6.60	4.757	0.191	0.105	0.746
G190A	2	32	6.25	2	36	5.56	11	61	18.03	11	106	10.38	4.925	0.177	0.705	0.401
K103N	13	32	40.625	16	36	44.44	17	61	27.87	34	106	32.08	3.57	0.312	1.657	0.198
V106A	3	32	9.375	3	36	8.33	2	61	3.28	3	106	2.83	-	0.237	3.263	0.071
V106I[a]	**1**	**32**	**3.125**	**5**	**36**	**13.89**	**0**	**61**	**0**	**11**	**106**	**10.38**	**-**	**0.008**	**0.699**	**0.403**
F227L	2	32	6.25	1	36	2.78	1	61	1.64	3	106	2.83	-	0.616	0.606	0.436
M230L[ac]	**2**	**32**	**6.25**	**3**	**36**	**8.33**	**0**	**61**	**0**	**1**	**106**	**0.94**	**-**	**0.021**	**5.615**	**0.018**
K103IKRT	0	32	0	0	36	0	0	61	0	0	106	0				
V179E	2	32	6.25	3	36	8.33	3	61	4.92	6	106	5.66	-	0.896	0.121	0.728
V179D[a]	**3**	**32**	**9.375**	**0**	**36**	**0**	**3**	**61**	**4.92**	**1**	**106**	**0.94**	**-**	**0.035**	3.424	0.064
Y188C	0	32	0	0	36	0	0	61	0	1	106	0.94	-	1	0.827	0.363
K238T[b]	**0**	**32**	**0**	**0**	**36**	**0**	**0**	**61**	**0**	**5**	**106**	**4.72**	**-**	**0.167**	**4.207**	**0.04**
F227CS	0	32	0	0	36	0	0	61	0	0	106	0				
Y188L	2	32	6.25	3	36	8.33	3	61	4.92	4	106	3.77	-	0.659	0.833	0.362
Y318F	0	32	0	0	36	0	2	61	3.28	0	106	0	-	0.149	0.001	0.973
G190S	1	32	3.125	3	36	8.33	5	61	8.20	8	106	7.55	-	0.861	0.362	0.547
E138Q	0	32	0	0	36	0	1	61	1.64	4	106	3.77	-	0.609	2.657	0.103
K238T	**1**	**32**	**3.125**	**3**	**36**	**8.33**	**4**	**61**	**6.56**	**0**	**106**	**0**	**-**	**0.009**	3.039	0.081
P225H	0	32	0	2	36	5.56	2	61	3.28	4	106	3.77	-	0.686	0.362	0.547
V90I[b]	**0**	**32**	**0**	**2**	**36**	**5.56**	**1**	**61**	**1.64**	**11**	**106**	**10.38**	**-**	**0.056**	**4.92**	**0.027**
K103S	0	32	0	1	36	2.78	2	61	3.28	3	106	2.83	-	0.938	0.506	0.477
A98G	0	32	0	1	36	2.78	2	61	3.28	3	106	2.83	-	0.938	0.506	0.477

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