

Antiretroviral drug resistance mutations among patients failing first-line treatment in Hanoi, Vietnam

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Objectives: To study the prevalence of drug resistance and genotype testing for HIV drug resistance on HIV/AIDS patients with first-line antiretroviral treatment failure at Dong Da Hospital, Hanoi, Vietnam.

Patients and methods: Forty-seven patients in Dong Da Hospital, Hanoi, with confirmation of first-line antiretroviral therapy (ART) failure were enrolled in this study from June 2006 to December 2016. Both the protease and reverse transcriptase genes were amplified and sequenced using Trugene[®] HIV-1 Genotyping Kit and OpenGene[®] DNA system at the biomolecular laboratory of the National Institute of Hygiene and Epidemiology, Vietnam. The Stanford HIV database algorithm was used for interpretation of resistance data and genotyping.

Results: Drug resistance mutations were 90.7% in patients with first-line treatment failure. Amongst patients with drug resistance mutation, 97.7% resisted to non-nucleoside reverse transcriptase inhibitors (NNRTIs), followed by nucleoside reverse transcriptase inhibitors (NRTIs, 95.3%) and protease inhibitors (PIs, 11.6%). Amongst the genetic mutations resistant to NNRTIs, G190S mutation was the highest (51.2%), K101HQ mutation was 39.5% and Y181I mutation was 34.9%. In genetic mutations to NRTIs, M184V mutation was 88.4%. In thymidine analogue mutations, K70R mutation was the most common (37.2%), followed by D67N, T215F and T69N mutations (27.9%, 27.9% and 25.6%, respectively). In genetic mutations in PIs, M36I and K20R mutations made up 9.3%. In NNRTIs, the prevalence of nevirapine resistance was 55.8%, and that of efavirenz resistance was 4.7%. In NRTIs, the ratio of lamivudine resistance was 93.0%, and that of zidovudine resistance was 9.3%. No lopinavir/ritonavir resistance was recorded.

Conclusions: Drug resistance mutations in patients with first-line ART failure had a high prevalence of NNRTI and NRTI resistance but still susceptible to PIs.

Keywords: HIV-1 drug resistance, first-line antiretroviral therapy failure, genetic mutation for drug resistance, virological failure

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Introduction

HIV is a public health issue. In 2017, 21.7 million patients were receiving antiretroviral therapy (ART).¹ ART improves the quality of life and survival of HIV patients and controls HIV transmission; however, these benefits can be limited by HIV-1 drug resistance (HIV-DR).² Moreover, this condition can severely limit the treatment options for new patients and shorten the time to treatment failure.³ The

mutation patterns associated with HIV-DR are complex, and the resistance to other drugs develops when the failed regimens continue to be given.⁴

In Vietnam, the public health approach to providing highly active ART was rolled out in 2005, and a free national program was then rapidly expanded. There are growing concerns about the occurrence and spread of HIV-DR in Vietnam. HIV-DR prevalence (6–8%) is reported amongst high-risk populations (such as female sex workers and injecting drug users).^{5,6} This prevalence is persistently low (<5%) in Northern Vietnam⁷ and low to moderate (2.4–5.48%) in Southern Vietnam⁸ despite that it slightly increased from 1.8% in 2007 to 6.6% in 2012 in Haiphong (Northern Vietnam).

The existence of HIV-DR is significantly associated with the early development of virological failure. The initial treatment choice should be based on resistance testing in treatment-naïve patients.⁹ However, in Vietnam, viral load and HIV-DR genotypic test are only recommended for people who are suspected of a clinical or immunological failure of first-line treatment.¹⁰

In Vietnam, data on HIV-DR amongst people with first-line therapeutic failure are limited. Thus, this study investigated the patterns of HIV-DR amongst adults (age >18 years) diagnosed with first-line ART failure according to the WHO guidelines in a northern major city, Hanoi, Vietnam.

Materials and methods

Study population and data collection

In this study, the inclusion criteria of participants were as follows: adults (>18 years old) who received first-line ART regimens according to the National Guideline in 2005¹¹ for more than 6 months and those who had certain WHO criteria for immunological or clinical treatment failure. The participants were enrolled in this study between June 2006 to December 2016 at Dong Da Hospital, Hanoi, Vietnam.

The first-line ART regimens comprised two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) along with a non-nucleoside reverse transcriptase inhibitor (NNRTI) (including ZDV/3TC/NVP regimen: zidovudine [ZDV] + lamivudine [3TC] and nevirapine [NVP] or d4T/3TC/NVP regimen: stavudine [d4T] + lamivudine [3TC] + nevirapine [NVP]). Patients consented to participate in the study and were excluded from the study when they did not follow the protocol. A diagnosis of treatment failure was made according to WHO guidelines.¹²

HIV drug resistance mutation testing was ordered based on the plasma viral load, and 47 patients with virological failure who had a viral load of 1,000 copies/ml or above at the time of analysis were selected for genotyping analysis. Blood samples of 47 patients were collected, and the plasma specimens were stored in standard criteria for analyses. Sample collection was performed at the biomolecular laboratory of the National Institute of Hygiene and Epidemiology.

Drug resistance genotyping and drug resistance analyses

Drug resistance was evaluated by sequencing reverse transcriptase and protease genes that were amplified and sequenced using the Trugene[®] HIV-1 Genotyping Kit and OpenGene[®] DNA system.¹³ We used the Stanford Database to assess and determine the DR mutation profile of all sequences (available at <http://hivdb.stanford.edu/>). The virus is defined as susceptible to an HIV medication if the total score for that drug is 9 or less, whereas low-level, low-level, intermediate-level and high-level resistance to ARV is identified if the total score is 10–14, 15–29, 30–59 or ≥ 60 , respectively.

Ethics statement

The protocol was approved by the Ethics Committee of Hanoi City. The study was in line with the Declaration of Helsinki. Before the collection of blood samples, written informed consent was provided to all participants after a thorough explanation of the purpose of this study. Moreover, patients had the right to discontinue at any time during the study.

Statistical analysis

The statistical analysis was conducted using the SPSS version 20.0 package (IBM Corporation, Armonk, NY, USA). Descriptive analyses were performed by calculating the mean and standard deviation, median and interquartile range and the frequency.

Results

In 47 patients with first-line treatment failure, 43 (90.7%) had drug resistance mutations. The characteristics of patients who failed first-line treatment are shown in Table 1.

According to the drug resistance mutations, 97.7% resisted to NNRTIs, followed by NRTIs (95.3%) and PIs (11.6%). More details are shown in Table 2.

Table 1 Demographics of 47 patients with first-line treatment failure

Demographic variable	Value	Note
Gender: n (%)		
Male	30 (63.8)	
Female	17 (36.2)	
Age: n (%)		Mean \pm SD
< 30 years	3 (6.4)	34.15 \pm 4.03
30-39 years	41 (87.2)	
40-49 years	3 (6.4)	
Duration of first-line ART use (months)		Min-Max (months)
Mean \pm SD		9.07 – 111.30
Male	54.48 \pm 27.99	7.73 – 81.07
Female	36.80 \pm 19.23	7.73 – 111.30
Total	46.81 \pm 26.09	p-value = 0.046
Initial first-line regimen		
d4T/3TC/NVP	31 (66.0)	
ZDV/3TC/NVP	16 (34.0)	
Risk factor		
Injecting drug user	18 (38.3)	
Sexual exposure	18 (38.3)	
Injecting drug user and Sexual exposure	11 (23.4)	
CD4 cell count		
< 50	16 (34.0)	
50-99	16 (34.0)	
100-199	7 (14.9)	
200-349	8 (17.1)	
\geq 350	0 (0)	

Abbreviation: ART, antiretroviral therapy.

Amongst the genetic mutations resistant to NNRTIs, G190S mutation was the highest (51.2%), K101HQ mutation was 39.5%, and Y181I mutation was 34.9% (Table 3).

In genetic mutations to NRTIs, M184V was the most common ARV-resistant pattern (88.4%). In thymidine analogue mutations (TAMs), K70R mutation was the most common (37.2%). The proportions of D67N and T215F mutations were 27.9% and 27.9%, respectively (Table 4).

In genetic mutations to PIs, M36I and K20R mutations made up 9.3% (Table 5).

In NNRTIs, the prevalence of nevirapine resistance was 55.8%, and that of efavirenz resistance was 4.7%. In NRTIs, the ratio of lamivudine resistance was 93.0%, and that of zidovudine resistance was 9.3%. No lopinavir/ritonavir resistance was recorded (Table 6).

Table 2 Frequency of drug resistance mutations by drug class

Gene resistance mutations	Number of patients (Total: n=43)	Percentage (%)
NNRTI resistance	42	97.7
NRTI resistance	41	95.3
PI resistance	5	11.6
NNRTI + NRTI resistance, Non-resistance with PI	35	81.4
NNRTI + NRTI + PI resistance	5	11.6
NNRTI resistance, Non-resistance with NRTI and PI	2	4.7
NRTI resistance, Non-resistance with NNRTI and PI	1	2.3

Abbreviations: NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Table 3 Frequency of NNRTI resistance

Type of mutation	Frequency	In ARV drug resistance (n=43)	In first-line ARV failure (n=47)
A98G	3	7.0	6.4
M230L	1	2.3	2.1
K101H	6	14.0	12.8
K101E	10	23.3	21.3
K101PQ	1	2.3	2.1
K101EQ	1	2.3	2.1
K101HQ	17	39.5	36.2
K103N	1	2.3	2.1
G190S	22	51.2	46.8
G190A	1	2.3	2.1
Y181I/C/V	15	34.9	31.9
Y181C	1	2.3	2.1
Y181V	3	7.0	6.4
Y188L	3	7.0	6.4
V106I	1	2.3	2.1
V108I	1	2.3	2.1
V179T	3	7.0	6.4
Y179D	1	2.3	2.1
V179E	1	2.3	2.1
P225H	2	4.7	4.3

Abbreviations: ARV, antiretroviral; NNRTI, non-nucleoside reverse transcriptase inhibitor.

Discussion

In previous studies using specimens from voluntary counseling and testing, the prevalence of HIV-DR was persistently low (<5%) in the north,¹⁴ but this level appears to increase rapidly from <5% in 2006¹⁵ to 5%–15% in 2007–2008 in the southern areas.¹⁶ The prevalence of circulating ART-resistant

Table 4 Frequency of NRTI resistance

Type of mutation	Frequency	In ARV drug resistance (n=43)	In first-line ARV failure (n=47)
D67N*	12	27.9	25.5
V75M	16	37.2	34.0
V75IM	1	2.3	2.1
V106I	2	4.7	4.3
V108I	5	11.6	10.6
V118I	4	9.3	8.5
K65R	5	11.6	10.6
K70R*	16	37.2	34.0
K101Q	2	4.7	4.3
K101H	2	4.7	4.3
K210R	1	2.3	2.1
K219E*	4	9.3	8.5
K219E/Q*	2	4.7	4.3
K219Q*	7	16.3	14.9
T69D	2	4.7	4.3
T69N	11	25.6	23.4
T215Y	2	4.7	4.3
T215F*	12	27.9	25.5
T215FS	1	2.3	2.1
T215F/Y	1	2.3	2.1
M41L*	6	14.0	12.8
M184I/V	2	4.7	4.3
M184V	38	88.4	80.9
A62V	2	4.7	4.3
A98G	1	2.3	2.1
L74V	3	7.0	6.4
L210W*	5	11.6	10.6
F77L	2	4.7	4.3
F116Y	2	4.7	4.3
Q151M	3	7.0	6.4
E44D	2	4.7	4.3
H208Y	1	2.3	2.1

Note: *TAMs.

Abbreviations: ARV, antiretroviral; NRTI, nucleoside reverse transcriptase inhibitor.

Table 5 Frequency of PI resistance

Type of mutation	Frequency	In ARV drug resistance (n=43)	In first-line ARV failure (n=47)
L33F	1	2.3	2.1
M36I	4	9.3	8.5
K20R	4	9.3	8.5
L10I	1	2.3	2.1
A71V	1	2.3	2.1

Abbreviations: PI, protease inhibitor; ARV, antiretroviral.

HIV-1 in Northern Vietnam did not increase from 2007 to 2009 although the rate of ART coverage was increased.⁷ In

Table 6 The level of resistance to first-line antiretroviral drugs for individuals

Variables	High-level n (%)	Intermediate level n (%)	Low-level n (%)
NRTIs			
3TC	40 (93.0)	1 (2.3)	2 (4.7)
ABC	13 (30.2)	5 (11.6)	25 (58.2)
AZT	4 (9.3)	21 (48.8)	18 (41.9)
d4T	18 (41.9)	15 (34.9)	10 (23.2)
FTC	40 (93.0)	1 (2.3)	2 (4.7)
ddl	15 (34.9)	3 (7.0)	25 (58.1)
TDF	11 (25.6)	2 (4.7)	30 (69.7)
NNRTIs			
EFV	24 (55.8)	16 (37.2)	3 (7.0)
ETR	2 (4.7)	18 (41.8)	23 (53.5)
NVP	41 (95.3)	0 (0.0)	2 (4.7)
PIs			
ATV	0 (0.0)	0 (0.0)	43 (100.0)
DRV	0 (0.0)	0 (0.0)	43 (100.0)
FPV	0 (0.0)	0 (0.0)	43 (100.0)
IDV	0 (0.0)	0 (0.0)	43 (100.0)
LPV	0 (0.0)	0 (0.0)	43 (100.0)
NFV	0 (0.0)	0 (0.0)	43 (100.0)
SQV	0 (0.0)	1 (2.3)	42 (97.7)
TPV	0 (0.0)	0 (0.0)	43 (100.0)

Abbreviations: NRTI, nucleoside reverse transcriptase inhibitor; 3TC, lamivudine; ABC, abacavir; AZT, zidovudine; d4T, stavudine; ddl, didanosine; TDF, tenofovir disoproxil fumarate; NNRTI, non-nucleoside reverse transcriptase inhibitor; EFV, efavirenz; ETR, etravirine; NVP, nevirapine; PI, protease inhibitor; ATV, atazanavir; DRV, darunavir; FPV, fosamprenavir; IDV, indinavir; LPV, lopinavir; NFV, nelfinavir; SQV, saquinavir; TPV, tipranavir.

our study, 10.95% had drug resistance mutation (43 patients in total; 392 patients received treatment in Dong Da Hospital, Hanoi, from June 2006 to December 2016). The reason behind this high level was that all patients were in-patients and had been followed up continuously.

Drug resistance is an important consideration when choosing ART regimen. We noticed that four patients (~8.51%) did not show resistance-conferring mutations, and the therapeutic failure may have been due to other factors.^{17,18} The mutation pattern in our study was similar to the results of an ADR survey at three clinics in Ho Chi Minh City in 2009.¹⁹ In a previous pre-treatment HIV-DR study, NNRTI resistance was K103N, Y181C, Y188C and G190A, and NRTI resistance was V75M and M184V.²⁰

TAMs occur in different patterns: type 1 includes M41L, L210W and T215Y (14%, 11.6% and 4.7% prevalence, respectively, in our study), and type 2 includes K70R, D67N T215F and K219Q/E (37.2%, 27.9%, 27.9% and 14% prevalence, respectively, in our study). In our study, type 2 TAMs

were more prevalent than type 1 TAMs. This finding indicates that type 2 TAMs had a slight negative impact on abacavir (ABC), didanosine (ddI) or TDF virological response. The accumulation of other mutations observed included TAMs (including M41L, L210W, T215Y, K70R, D67N, T215F and K219Q), resulting in increased resistance to AZT, TDF, D4T, ABC and ddI.^{21,22} The T215Y mutation was observed in 4.7% of the sequences, whereas T215F was detected in 27.9%. This result was in line with that of Yahi N et al, who found that T215F mutation was preferentially associated with K70R (>71%), D67N (>73%) and K219Q/E/N (>76%), whereas T215Y mutation was associated with M41L (>84%) and L210W (>58%).²³

Regarding, 88.4% of patients had HIV-DR in first-line ART failures was the M184V mutation. It was selected by lamivudine (3TC), emtricitabine (FTC) or ABC use and 3TC resistance with high level.²⁴ This result was more highly observed than other mutations similar to the findings of other studies: Winand et al (M184V: 44.0%, n=3,554)²⁵ and El Annaz et al (M184V: 44.0%, n=45).²⁶ This finding can be explained by the M184V mutation in line with lamivudine (3TC) resistance.²⁷ This drug has been proven effective in patients with chronic hepatitis B and is routinely used in treatment in Vietnam.²⁸ Moreover, the prevalence of hepatitis B surface antigen (HBsAg) in the general Vietnam population ranged from 5.7%–24.7%.²⁹ In addition, co-infection with HIV was seen in 28% of HBV-infected IDUs (n=49/174) and 15.2% of commercial sex workers.³⁰ Patients receiving incomplete suppressive 3TC regimens usually develop M184V as their first mutation.^{31,32} This mutation is related to the development of resistance to lamivudine that is part of the major concern in the standard of care provided in Vietnam.

In this study, a considerably low level of resistance to PIs was found in adults (11.6%). The reason why PI resistance was low in patients who failed first-line treatment was probably due to the appropriate switching from first-line regimen to second-line regimen guided by the national guideline. The principle for switching is based on ART history, drug resistance test and monitoring during the first 3 months after switch in.¹⁰ Vietnam's standard second-line PI-based therapies included TDF/3TC or ddI/ABC plus lopinavir/ritonavir.¹⁰ The high efficacy of lopinavir/ritonavir monotherapy in second-line regimens was able to achieve full viral suppression for individuals failing first-line treatment.³³ In Vietnam, the prevalence of PI resistance was high in patients failing second-line ART.³⁴ In our study, the emergence of

PI resistance at the time of first-line virological failure was uncommon (only one patient resisted to saquinavir in intermediate level. No lopinavir/ritonavir resistance was recorded).

Conclusion

Drug resistance mutations in patients with first-line ART failures had a high prevalence of NNRTIs and NRTI resistance but are still susceptible to PIs.

Abbreviations

ART, antiretroviral therapy; RT, Reverse Transcriptase; ARV, antiretroviral; HIV-DR, HIV-1 drug resistance.

Disclosure

The authors report no conflicts of interest in this work.

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