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Drug resistance patterns in HIV patients with virologic failure in Iran

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Abstract

We reviewed the medical charts of 1,700 patients diagnosed with HIV who referred to a central HIV clinic in Tehran between 2004 and 2017. Participants who had a viral load of > 200 copies/mL after six months or more on antiretroviral therapy (ART) were grouped as virologic failure (VF). We assessed the demographic characteristics, diagnosis date, first ART regimen, and resistance to various ART drugs. Out of 1,700 patients, 72 (4.2%) had a treatment failure. Among those with treatment failure, 51.3% were on zidovudine + lamivudine + efavirenz, 13.9% were on tenofovir + lamivudine + lopinavir/ritonavir, and 12.5% were on tenofovir + emtricitabine + efavirenz. In patients with treatment failure, the highest resistance was to nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) combination (44.4%). In these patients, resistance to tenofovir (one of the NRTIs) was 29.1%. The highest treatment failure was observed among patients treated with nevirapine (NVP) and efavirenz (EFV)-based regimen. Our findings suggest that protease inhibitors should be considered as first-line drugs in ART regimens in VF patients in Iran.

Authorship Contributions

S.S.: Designed and performed experiments. M.R. : Performed experiments. Z.N: Designed experiments and co-wrote the paper. O.D.: Performed bioinformatic analyses. E.M.: Performed experiments. A.M.: Supervised the research

Disclosure of conflicts of Interest

Authors declare that they have no conflict of interest.

Statement of Ethics

The study was approved by Tehran University of Medical Sciences (TUMS) Ethics Committee (reference number: IR.TUMS.VCR.REC.1397.966). This paper was also supported by the National Institutes of Health (R25 MH064712).

Keywords

HIV/AIDS; Virologic Failure; antiretroviral therapy; Iran

Introduction

In 2017, an estimated of 36.9 million people were living with HIV worldwide. Among them, 21.7 million were receiving antiretroviral therapy (ART) and 940,000 (670,000–1.3 million) died from AIDS-related illnesses [1]. The HIV pandemic is still a public health issue worldwide, especially in developing countries [2, 3]. HIV is growing in also in the East Mediterranean Region countries, including Iran [4, 5]. According to the national HIV registry system, in 2017, the number of people living with HIV (PLWH) in Iran was 34,949, including 84% men and 16% women and the number of AIDS-related deaths was 9,477 by March, 2017 [2, 6].

Since 2008 over eight million people received ART in the developing countries [7]. ART could significantly increase the quality and quantity of life for PLWH. An appropriate treatment, chosen at the right time is crucial to achieve the favorable outcome. With an effective treatment, there could be a substantial reduction in viral load and an increase in the number of CD4 cells; however, about 12% to 32% of patients fail to achieve these desirable outcomes [8, 9].

One emerging problem beside the ART expansion is HIV drug resistance (HIVDR) mutants, which is attributed to HIV mutating and replicating capabilities in presence of ART drugs. HIVDR deactivate the drugs which formerly controlled the viral replication. This led to attempt in introducing more effective medications in ART regimen which carry new side effects and consequently impose more economic burden on both the patient and health system [7, 10].

The treatment failure and further spread of HIV drug resistant mutants could compromise the effectiveness of ART and last 90 target for viral suppression. It also increases the HIV mortality and morbidity [7, 10, 11]. Therefore, appropriate surveillance of HIV patients receiving ART should be implemented in order to improve the adherence which is essential to achieve the desired outcome and prevent the emergence of HIVDR mutants [7].

ART is available and free of charge for all PLWH in Iran. Despite its beneficial therapeutic effects, recently, a growing body of evidences showed the first-line treatment sometime failed; it is not clear which one and how frequent [10, 12]. Early detection of treatment failure could substantially reduce the complications and prevent the new viral mutants to emerge. Therefore, in this study, we aimed to investigate prevalence of the treatment failure, and the patterns of resistance to various ART drugs among the PLWH in a major referral hospital in Iran.

Methods

1. Participants

We reviewed the medical charts of 1700 HIV patients who referred to the Voluntary Counseling and Testing (VCT) center in Imam Khomeini Hospital in Tehran between 2004 and 2017. Those who lost to care, died, transferred out or incarcerated were excluded. We found a total of 72 patients with virological failure (VF).

2. Instruments

Patient's demographic characteristics, viral load markers, TCD4+ count and selected ART regimen were extracted from the patients' medical records, using an information datasheet. The history of treatment failure, drug resistance results and alternative regimens were also recorded. The treatment failure was determined based on the virologic features of the patients. The 2018 AIDS Info Instruction (retrieved from https://aidsinfo.nih.gov/guidelines) was applied so as to determine the treatment failure. Based on this instruction, the presence of 200 or more copies per milliliter of viral load after six months of continuous and effective ART is considered as treatment failure. Resistance tests were performed for the viral loads more than 1,000 copies/mL and based on the results, the second line regimen begun. We included all drug resistance mutations that presented low-, intermediate-, or high-level resistance. The RNA genome of HIV has several genes such as Reverse transcriptase (RT), Protease (Pro) and Integrase (INT). These genes may mutate and cause drug resistance in HIV + patients. For this reason, drug resistance was evaluated by amplification of these genes using specific primers by polymerase chain reaction (PCR) and sequencing of products. Then, results in the analysis were extracted based on the Stanford HIV drug resistance website (hivdb.stanford.edu).

3. Ethical considerations

The study protocol was approved by the institutional review board (IRB) of Tehran University of Medical Sciences (TUMS). All the information sheets were secured in a locked shelve where only authorized person had access. The digital data file was secured by a password which was only known to study researchers.

4. Statistical analysis

To analyze the data, we used the SPSS software (Version 22). Descriptive statistic was used in order to describe the study participant and frequency of different drug resistance patterns.

Results and Discussion

1. Study population

The analyzed the data for 72 patients with VF. Majority were male (68.1%), aged 35–50 years old (61.1%), unemployed (36.1%), had high school education (51.4%), had history of drug use (55.6%), and have had acquired infection from high-risk heterosexual contacts (54.2%). Most of the patients were on ART regimen for 37 months or more (86.1%) (Table 1).

2. Virologic Failure

The mean of first-CD4 count (CD4 count right after ART initiation) was 262.4 cells/μl and the mean of last-CD4 count (CD4 count after ART) was 349.6 cells/μl. The mean of first viral load was 191309.7 copies/ml while the mean of last viral load was 32312.2 copies/ml. Following the treatment, the mean of last-CD4 count was significantly higher than the mean of first-CD4 count (P<0.001). In total, 72 (4.2%) out of 1700 HIV patients experienced the treatment failure. The highest numbers of virologic failure were 19 (26.4%) patients receiving NNRTIs and 32 (44.4%) patients receiving NNRTIs + NRTIs.

The most frequent failed regimens were AZT-3TC-EFV (51.3%), TDF-3TC-LPV/r (13.9%) and TDF-FTC-EFV (12.5%) (Table 2). The highest resistance level was related to nevirapine (NVP) (73.6%) and efavirenz (EFV) (70.8%) (Table 3). There was no significant relationship between drug type and resistance level (P-value> 0.05).

We found that in less than 5% of patients the HIV treatment failed. The highest drug resistance belonged to NRTIs and NNRTIs combination. The highest rate of virologic failure was attributed to nevirapine (NVP) and efavirenz (EFV). Resistance to tenofovir (TDF) as the most common prescribed NRTIs, was observed in less than one thirds of patients.

Offering HIV mediations to all at the time of diagnosis or at early as possible after diagnosis worldwide raises concerns about emerging drug resistance, mainly due to lack of compliance in regular and continuous drug intake. Patient’s adherence to therapy is a key component of a successful ART program [13, 14]. Lack of knowledge in patients about ART and the importance of adherence, misconceptions about side effects, and dealing with many other priorities in life [15], feeling sick [16] and other co-infections and concomitant diseases [17] were reported as factors associated with ART nonadherence.

An increasing concern beside the ART extension, is the emerging of HIVDR mutants, which is attributed to HIV mutating and replicating capabilities in presence of ART drugs [8]. In the current study, the highest resistance was observed in NRTIs + NNRTIs regimens (44%). In fact, the NNRTIs regimens sustained the most frequent drug resistance and amongst them, NVP (74%) and EFV (71%) demonstrated the highest resistance rate. A similar study in Iran found the resistance to NVP (21.3%) and EFV (19.7%) as the most frequents drug resistances among HIV patients [18]. They also found that 36.1% of the HIV patients had at least one mutation related to RT inhibitors. The RT inhibitors mutations also reported to reduce the susceptibility to NRTI and NNRTI [18, 19]. The G190A mutation is another common mutation which occurs in 36% of cases [20, 21] and it could reduce the virus response to NVP and EFV more than 50 and 5–10 times, respectively [22, 23]. There are other mutations [24, 25] that cause the HIVDR.

Our study had three major limitations. First, we could not locate the data for all patients particularly children which limit the study external validity. Second, we used the medical record data and so the completeness and quality if data were not perfect and varied over time. Lastly, we only assessed the drug resistance patterns among in those whom treatment failed.

Despite the limitations, our study characterized the ART resistance patterns among HIV patients for whom HIV treatment failed. Our findings suggest to use the protease inhibitors as the first-line drugs in ART regimen in those with VF.

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Table 1.

Baseline characteristics of 72 patients with virologic failure, Tehran, Iran, 2004–2017.

Characteristics	N (%)*
Male	49 (68.1)
Age group (years)	
16–25	1 (1.4)
26–34	17 (23.6)
35–50	45 (61.1)
>50	8 (11.1)
Unemployed	26 (36.1)
Education level	
Illiterate	3 (4.2)
Elementary school	17 (23.6)
High school	37 (51.4)
Academic	9 (12.5)
Marital status	
Single	29 (40.3)
Married	29 (40.3)
Divorced	6 (8.3)
Widow	3 (4.2)
Smoking status	
Ex-smoker	11 (15.3)
Current smoker	35 (48.6)
Past history of drug use	40 (55.6)
Transmission route	
Heterosexual	39 (54.2)
homosexual	3 (4.2)
Drug injection	22 (30.6)
Others (Mother to child, blood/blood product transfusion)	4 (5.6)
ART duration (month)	
0–12	4 (5.6)
13–24	3 (4.2)
25–36	2 (2.8)
37<	62 (86.1)

*Subgroups do not always add up to total due to missing data

Table 2.

ART regimens for people living with HIV that experienced the treatment failure, Tehran, Iran, 2004–2017

Regimen	N (%)
TDF-FTC-EFV	9 (12.5)
AZT-3TC-EFV	37 (51.3)
TDF-3TC-LPV/r	10 (13.9)
TDF-3TC-EFV	7 (9.7)
TDF-FTC-LPV/r	7 (10)
TDF-3TC-ATV/r	6 (8.4)
AZT-3TC-NVP	6 (8.4)
AZT-3TC-LPV/r	5 (7)
TDF-FTC-ATV/r	4 (5.6)
TDF-3TC-LPV/r	3 (4.2)

Table 3.

HIV resistance levels based on medication class, people living with HIV, Tehran, Iran, 2004–2017

Medication	High Level Resistance N (%)	Intermediate Level Resistance N (%)	Low Level Resistance N (%)	Total resistance N (%)
Stavudine	9 (50)	4 (22.2)	5 (27.8)	18 (25)
Didanosine	12 (44.4)	6 (22.2)	9 (33.3)	27 (37.5)
Zidovudine	12 (57.1)	6 (28.6)	3 (14.3)	21 (29.2)
Abacavir	12 (38.7)	9 (29)	10 (32.2)	31 (43)
Lamivudine	41 (93.2)	-	3 (6.8)	44 (61.1)
Emtricitabine	35 (92)	1 (2.6)	2 (5.3)	38 (52.8)
Tenofovir	6 (28.6)	5 (24)	10 (48)	21 (29.1)
Nevirapine	47 (88.7)	3 (5.7)	3 (5.7)	53 (73.6)
Efavirenz	43 (84.3)	5 (9.8)	3 (5.9)	51 (70.8)
Etravirine	3 (9.4)	12 (37.5)	17 (53.1)	32 (44.4)
Riplivirine	10 (27)	12 (32.4)	15 (40.5)	37 (51.3)
Lopinavir	5 (83.3)	-	1 (16.7)	6 (8.3)
Atazanavir	2 (33.3)	-	4 (66.7)	6 (8.3)
Darunavir	1 (50)	1 (50)	-	2 (2.8)