Assessing the Efficacy of Second-Line Antiretroviral Treatment for HIV Patients Failing First-Line Antiretroviral Therapy in Iran: A Cohort Study

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Abstract- There are limited documents about HIV patients switched to second-line antiretroviral therapy (ART) in resource-limited countries. We aimed to assess the efficacy of second-line ART for HIV patients following first-line ART failure. This was a cohort study of HIV/AIDS patients with first-line ART treatment failure switched to second-line ART between January 2004 and March 2014, who followed for at least 12 months after switching. Fifty of studied patients (85%) were treated with regimens containing lopinavir/ritonavir (Kaletra) and nine of them (15%) treated with other regimes. Seven patients were experienced opportunistic infections in accordance with stage III and IV WHO classification. In this way, 11.8% of patients had aclinicalfailure, and 37 of them (62%) had immunological responses. Weight gain was evident in these patients, and there was a significant correlation between theincrease in CD4 and weight gain (P=0.007). Only 13 patients achieved HIV viral load testing that 6 of them had avirological response after 12 months on second-line ART. No significant associations were found between virological or immunological response and gender, age, and lopinavir/ritonavir regimens (P>0.05).With counselling and supporting in those failing first-line ART, inessential switching to more costly second-line ART can be prevented in the majority of patients. However, patients' need to second-line ART drugs has increased, for which national ART programmes and regular follow-up should be organized. The high cost of these drugs and limited access to viral load testing are main barriers to proper management of patients switched to second-line ART regimens.

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Keywords: Antiretroviral therapy; HIV; Cohort studies; Iran

Introduction

The human immunodeficiency virus (HIV) is a pandemic problem (1,2) changed from life threatening to chronic disease because of the global use and availability of antiretroviral treatment (ART) among HIV-infected patients (1). ART acts by suppressing viral load and returning the immune system. It is estimated that over 35.3 million patients are living with HIV around the world, and almost 10.6 million were getting ART at the end of 2012 (3). Iran is home to approximately 68,000-110,000 people living with HIV (average=86,000, less than 0.2%) (4). Because a particular percentage of HIV-infected patients fail their ART regimens every year, and there is the eventuality of resisting HIV drugs (5,6), a quantized rise in the number of patients failing first-line ART regimens can be expected. There has been little study testing theeffect of second-line ART after first-line ART failure, those most often applied in resource-limited countries (7). In addition, the cost of a second-line regimen represents the main issue, because it is almost seven times higher than that of a first-line ART regimen (8). With high-ART intake, the risk of treatment failure and resistance has become more serious, and switching of patients to thesecond-line regimen is a favoured method for early

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diagnosis of treatment failure, thus decreasing drug resistance changes and improving clinical consequences(9). However, viral load measurements are not routinely accessible in many countries due to its high cost and lack of accessibility.To the present, there is limited information demonstrating experiences of routine viral load testing in HIV patients failed first-line ART and the use of second-line ART in resource-limited settings. Despite an increasing number of trials about the impacts of antiretroviral therapy, there is a lack of knowledge about these kinds of regimens in HIV-infected patients especially those switched to second-line ART in Iran. To address this knowledge gap, the present study aimed to assess the efficacy of second-line ART for patients living with HIV following first-line ART failure in Tehran (capital of Iran) within a governmental hospital that provides ART free of charge. The researchers also stated that results of this study could offer proper strategies for continuing ART treatment and thenecessity to use newer drugs in this field.

Materials and Methods

Study population and design

This was a longitudinal cohort study. A convenience sample of 59 HIV-infected patients who met the inclusion criteria was recruited when referred to the counselling clinic of behavioural diseases and HIV care in Imam Khomeini hospital which is also a reference center for HIV/AIDS cases, located in Tehran, Iran. This study protocol is in compliance with the Declaration of Helsinki and Tokyo guidelines and is approved by Ethical Board of Tehran University of Medical Sciences. Study aims were explained to all participants before signing an informed written consent. Data for each patient from 14th January 2004 to 20th March 2014 were extracted routinely from the hospital electronic database. All participants had active file and were visited regularly every month. Particularly, the registry collects demographic and clinical information such as age, gender, weight, HIV infection background, ART information the starting and changing first and second-line antiretroviral regimens, CD4+T-cell counts cells/µl, clinical and immunological factors, and patient's medical information such as history of opportunistic infections, HBV co-infected, HCV co-infected, and history of addiction.

Inclusion criteria included patients who (a) had been positively diagnosed with HIV-infection, (b) failed first-line antiretroviral therapy regimens, (c) were under second-line antiretroviral treatment regimens for a period of 12 months, (d) had no audio-visual or psychological problems, and (e) subsequently met CD4+T-cell counts cells/µl and/or clinical criteria for second-line antiretroviral treatment regimens failure. All death cases were excluded. Also, we excluded those left their treatment and taken less than 12 months following the treatment regimen.

Definition and procedures

Second-line ART was appointed as the regimen used for thetreatment of HIV patients who failed the first-line ART, and generally it would include of a protease inhibitor (PI) and two or three nucleoside reverse transcriptase inhibitor (NRTI) (10). Longitudinal data on CD4+count for thesame patient at different time were presented.

Analysis of viral load included all present viral load measured in a subset of patients. Routine viral load test was compared at the different time of switching determined by at least one viral load test between 3,6 and 12 months after initialling second-line ART (baseline) in at least 50% of patients cured at that hospital. Last CD4+T cell count followed by theinitiating date of ART was taken as the baseline level. Increasing at least 25 cells/µl in baseline CD4+counts during thefirst year was defined immunological response. Also having no opportunistic infections/disease after 3 months receiving second-line antiretroviral treatment regimens was considered aclinical response. For CD4+counts below 100 cells/µl and HIV viral loads above 100,000 copies/µl,the time window was extended to one year point of clinical/immunological second-line failure.

Statistical analysis

Data were analysed by the statistical packages for social science (SPSS), version 16.0. In order to describe patient characteristics, mean±standard deviation (SD) and frequency as the number or percentage were calculated. First, normality distribution of variables was tested. Differences and relations between variables were assessed by performing independent sample-*t*-test and chi-square test. To measure differences in proportions, we also used Fisher's exact test. *P* less than 0.05 were considered significant.

Results

The socio-demographic and baseline characteristics of 59 HIV-infected patients failing first-line

antiretroviral regimens are summarized in table 1.

Table 1. General characteristics of the HIV-infected patients included in the study

Parameters		PI regimen n=50 (84.7%)	Other regimens n=9(15.3%)	Overall n=59
Age (year)	<37	14 (24)	2 (3)	16 (27)
	≥37	36 (62)	7 (11)	43 (73)
Mean±SD		43.5 ±12.6	43.1 ±1.18	43±9.03
Sex n (%)	Male	40(67.8)	7 (11.9)	47 (79.7)
	female	10 (16.9)	2 (3.4)	12 (20.3)
Drug addiction	IDU	11 (22)	1 (1)	12 (23)
	NIDU	8 (13)	3 (4)	11 (17)
	No	31 (52)	5 (8)	36 (60)
HBV co-infected	Yes	13 (22)	1 (2)	14 (24)
	No	37 (62)	8 (14)	45 (76)
HCV co-infected	Yes	16 (27)	3 (5)	19 (32)
	No	34 (57)	6 (10)	40 (68)
Weight (Mean±SD)	Baseline	66 ± 12	71±21	67±13
	After 12 months	67±12	72±21	68±14
(Mean±SD)		31±15	32±20	32.7±16.9

Clinical assessment

During year follow-up, seven patients (11%) were experienced opportunistic infections which were consistent with stage III or IV of World Health Organization (WHO) classification that indicatesadvanced phase of thedisease and considered as aclinical failure.

In Table 2, we summarized the mean changes of $CD4^+$ T-cell counts cells/µl from baseline to three, six, and twelve months after second-line antiretroviral regimens. The median baseline $CD4^+$ T-cell count at the time of switching was 169 cells/µl (IQR: 126-204.63), but it increased to 221 cells/µl (IQR: 179.29-263.05) three months after switching and 255 cells/µl (IQR: 210.723-299.77) 6 months after follow-up. The median $CD4^+$ T-cell counts increased steadily throughout 12 months, rising from 169 cells/µl at baseline to 308 cells/µl at months. When we considered the last 12 months of follow-up, we found a significant increase in $CD4^+$ T-cell counts at baseline and 12 months of follow-up (P=0.001).

Table 2. Median $CD4^+$ cell count from baseline to one year later

Variable	Baseline	After 3 months	After 6 months	After 12 months	*P*
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	
$CD4^+$ cell count (cells/ µl)	169 (126-204.63)	221 (179.29-263.05)	255 (210.72-299.77)	308 (262.16-354.76)	0.001

Receiving second-line ART regimen, patients' weight was associated with $CD4^+$ T-cell count (r=0.38; P=0.007). The mean baseline $CD4^+$ T-cell counts were 153 cells/µl in those who were affected by opportunistic infections, and 173 cells/µl in those who did not suffer from opportunistic infections. No significant association was detected between baseline $CD4^+$ T-cell counts and opportunistic infections (P=0.2). Sex, addiction, HCV, HBV, and opportunistic infections were not associated with clinical failure (P>0.05).

Immunological outcomes

We classified all the patients by immunologic outcomes into two groups including response and failure based on $CD4^+$ cell count 12 months after switching ART. Totally, thirty-sevenof patients (62%) had immunological responses, and twenty-twoof them (38%) experienced immunological failure. The mean of baseline CD4 T-cell countbefore changing regimen in those who had animmunological response to the second line ART regimen was 163.6±131 cells/µl. In addition to, the mean baseline CD4 T-cell countof those who had immunological failure before changing treatment was 156.1±98cells/µl.

Twenty-seven of men (67%) and 10 (91%) of women had immunological responses. A significant relationship was not found between sex and immunological responses in this study (*P*>0.05).

The immunological response was found in 78% of addicted patients and observed in 68% of non-addicted. There was no significant correlation between immunological response and addiction (*P*>0.05). The increasing level of haemoglobin and duration of first-line ART regimens were not associated with immunological response (*P*>0.05).

The relationship between HCV co-infected and theimmunological response was not significant, although mean of $CD4^+$ cells/µl increased slightly in those who had co-infected with HCV. The immunological response was found in 74% of HCV co-infected patients and in 68% of those who did not have HCV.

Results related toimmunological outcomes are shown in Table 3.

Table 3. Immunological outcome and baseline characteristics of comprehensive care center study cohort

Parameters		Immunological outcome		*P*
		Response	Failure	
Age (year)	<37	11 (79)	3 (21)	>0.05
	≥37	26 (70)	11 (30)	
	Mean ± SD	42±8	45±11	
Sex n (%)	Male	27 (67)	13 (33)	>0.05
	Female	10 (91)	1 (9)	
Drug addiction n (%)	Yes	15 (78)	4 (22)	>0.05
	No	22 (68)	10 (32)	
Opportunistic infections n (%)	Yes	4 (57)	3 (43)	>0.05
	No	33 (75)	11 (25)	
HBV co-infected n (%)	Yes	6 (75)	2 (25)	>0.05
	No	31 (73)	12 (27)	
HCV co-infected n (%)	Yes	26 (74)	9 (26)	>0.05
	No	11 (68)	5 (32)	
Weight after 12 months	Mean ± SD	69±14	70±15	>0.05
CD4 T-cell count n (%)	Mean ± SD	37 (62)	22 (38)	>0.05
Duration of first-line ART (months)	Mean ± SD	33.4±12	30.9 ± 8	>0.05

Virological assessment

A viral load value before and 12 months after switching second-line ART was available. In general, only 13 patients were able to afford testing HIV viral load before switching and 6 to 12 months after receiving a second-line regimenwhom six of them had avirologic response. After 12 months on ART, the relationship between virologic response and regimes containing PI was not significant (*P*>0.05) (Table 4).

Table 4. The relationship between virologic response and ART regimes

ART regimes	Virologic response			*P*
	Positive response n (%)	Unresponsive n (%)	Total n (%)	
PI	5 (42)	7 (58)	12 (100)	> 0.05
Other regimes	1(0)	0 (0)	1 (0)	

So, only forty-six percent of patients with the PIregime had avirologic response. However, the percentage of IDU achieving viral suppression ranged from 47% to 63%, a significant relationship was not found between IDU and viral suppression. Moreover, asignificant relationship was not found between virologic suppressorsand age, gender, duration of first-line ART regimens, baseline $CD4^+$ T-cell count, and addiction (*P*>0.05).

Discussion

The aim of this study was to evaluate the second-line antiretroviral treatment for HIV-infected patients failing first-line antiretroviral therapy. In thepresent study, due to lack of routine HIV viral load monitoring, the detection of treatment failure was mostly done based on clinical and immunological criteria. Thus patients received thefirst-line regimen for a long time that leads to treatment failure. Nowadays, there are instructions based on the evaluation of treatment response and virologicalcriteria; a few similar studies found that addressed only to review immunological and clinical responses on the majority of patients. As our analysis considered characteristics of those patients switched to second-line, we cannot estimate the overall accuracy of clinical criteria for recognizing aviral failure in all patients undergoing treatment. However, our findings expressly corroborate that clinical failure monitoring alone over identifies immunological failure, in consequence early switching to more expensive second-line ART (11,12).

Overall, fifty-nineHIV-infected patients were recruited that most were young. Gender differentials were also observed with males having higher risks (79.6%) of falling first-line ART than females. The proportion of males in thepresent study sample was approximately three-fold that of females which are similar to the proportion of HIV/AIDS patients informed in Nepal (13). Sex and marital status did not significantly affect ART adherence. This result is almost in accord with other studies (14-16), but in contrast to a previous study, the proration of females was more than males (17,18). This gender distribution in our registry is consistent with the statistics published by the diseases management center of Iran's health ministry reported 88.4 % of cases are men in Iran (4).

Consistent with previous studies (19,20), we found that patients with hepatitis C co-infected were more likely to failed first-line ART. Although co-infected with HCV and HBV negatively affected ART outcome, but it was not significant. Immunological failure (49.1%) was the main reason for changing, followed by virological failure (50.8%) in of the patients in the present study. Similarly, the study conducted by Kumarasamy in 2011 in India to investigate tolerance and efficacy of second-line ART regimen showed that immunological failure was the most common reason for switching second-line ART regimen (21). Some studies (22-25) reported treatment failure as the reason for regimen change. According to the study in Uganda, (24) immunological failure just reported virological failure in 56% of the cases. In the study in Coited'IVoure, in 12.4% of the participants was detected treatment failure (25) and based on the study in India, treatment failure predicted for 14% of the cause for changing treatment (23). This may be due to several factors, including lack of the viral load level measuring system, on the incidence of opportunistic infection in the study setting of this study, lack of sequential monitoring of patients with a CD4 count. Most patients had higher CD4 counts at baseline of 169 cells/mm3 which was higher than other studies' report. In a Thai study, the researchers reported that baseline CD4 was 159 (cell/mm^3) (26). Baseline CD4 counts in Patal' study was 123.7 (cell/mm^3) (27).

Amazingly, duration on ART was associated with anincrease in CD4 count cells/µl in this study population. Notably, the improvement in CD4 count cells/µl was kept at first six months among patients in whom ART was started early. The mean increase of $CD4^+$ cells/µl in the first six months was (cell/mm^3) 86 that was lower than Patal and colleagues' study (27). They reported the rate of increasing CD4 count was 163.5 (cell/mm^3) in the first six months and 82 (cell/mm^3) in the second six months While, in thepresent study, the rate of increase CD4 in the second six months was 53(cell/mm^3). The mean increase of $CD4^+$ cells/µl in the first six months was more than the second six months similar another study. Recently, Kumarasamy *et al*., have demonstrated $CD4^+$ T-cell counts cells/µl of patients who sustained of PI suppression regimen increased in first 3 months, but our results showed that the mean $CD4^+$ T-cell count in patients who received PI regimen did not increase after 3 months of follow-up, and significant relationship was not found (21).

In this study found no significant association between age, sex, baseline $CD4^+$ T-cell counts and viral suppression. In contrast to these findings, Levison and colleagues (28) in a cohort study indicated females and those who delayed switching from failed first-line ART to second-line ART, were at increased risks for lack of viral suppression on second -line ART. Age, sex, ART regimen, and baseline CD4 cell count were as confounding variables. There has been conflicting information on the association between CD4 cell count and viral suppression. As data from their study did not recommend that age and CD4 count at starting second-line ART significantly predicted lack of viral suppression.

Although 78% of addicted patients had animmunological response, the current study showed

that a history of addiction was not associated with an increased outcome of treatment. However, this finding contrasts with a study by Chkhartshvil *et al*., which showed that second-line antiretroviral PI regimen was not associated with virologic failure (29). Percentage of IDU achieving viral suppression ranged from 47% and 63% after first treatment change. Also, history of IDU was not related to virologicresponse. Our study clearly shows that IDUs did not achieve optimal treatment outcomes. It might be because patients with a history of addiction are significantly less involved with their health care worker, and are likely to show a greater rate of treatment rejection. In addition, psychosocial problems can be additional factors related to drug addicts.Factors that might have facilitated to desirable outcomes among patients with ahistory of IDU contain free HIV-related health care, availability of support services in HIV care and methadone substation treatment.

Similar results reported by Levisonand colleagues (28), in our study, appropriate immunological response obtained especially in the first six months of treatment, but unfortunately due to small sample size, the impossibility of measuring viral load testing in all patients, and delay in switch to second-line ART after first-line ART failure appropriate virologic outcomes did not achieve. The national ART procedures suggested routine viral load monitoring to detect thevirological failure. Routine viral load monitoring is an essential tool to identify ART failure at a primary step, and with appropriate management, this will prevent the cumulating of further conflict changes and preserve treatment options (30). Routine HIV viral load monitoring is not currently presented in the public sector in Iran; instead, CD4 count monitoring continues to be applied as the most important means to find treatment failure. When ART expert committee approve treatment failure, viral load monitoring present in the public medical departments on only a by case basis.

Of note, most patients in thepresent study had been exposed to PI regimens from all viral suppression drugs. Although ART with PI in our cohort study was associated with continued increases in CD4 counts and improve immunological response even in patients with lowest %CD4 at baseline, it was not significantly associated with virologic outcome. Soh *et al*. found that better immunological responses were detected between younger children with agreater level of CD4 in patients treated with PI regimen (31). While our study could not proveanyeffect of types of ART on thevirologic outcome, more studies are required to examine such association in alarger cohort of patients.

Limitations of the study

The present study had several limitations. The small sample size in the study is one of the limitations, and so thegeneralizability of findings may limit. Most patients included in this analysis were younger and had not varied access to healthcare. Also, we applied longitudinal analysis using routinely existing data; therefore there might have been unmeasured factors that affected the outcomes. Data on key socio-demographic characteristics which influence outcomes such as neighbourhood effects, income, themain route of HIV transmission, occupational status, family structure, family support and health care systems were not available for this analysis. However, this study is one of the few reports from Iran in relation to themanagement of patients living with HIV, who have failed first-line ART and switched to second-line ART.

This study was designed as to evaluate the second-line antiretroviral treatment for HIV-infected patients failing first-line antiretroviral therapy, in Iranian patients. The results showed the initial response to second-line antiretroviral drugs was successful in 62.8% of treating patients, but unfortunately, thevirologic response was not fully investigated because of resource constraints. Early diagnosis of ART failure through routine viral load monitoring should be noted in situations where ART have been successfully conducted. Sufficient support and comprehensive counselling should be prepared to all patients suspected first-line ART failure. Viral load test should be done three months following raised support in all patients failing ART based on single viral load testing. Using greater sample size and a perfect data from different situations would be required to consolidate the findings in thepresent study.

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