Original Article

Adherence to Lipid-Lowering Medication in People Living with HIV: An Outpatient Clinic Drug Direct Distribution Experience

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Abstract

Objective: Adherence to lipid-lowering drugs could be challenging in our patients as it is in the general population, which is described as low as 25%. Our aim was to evaluate adherence to statins and to investigate clinical event impact on it. **Methods:** This retrospective study on HIV+ patients attending to Clinic of Modena (Italy) was conducted in order to evaluate characteristics, clinical events, and adherence on lipid-lowering drugs. All drugs for comorbidities are distributed by the hospital pharmacy and recorded in an electronical database. Adherence was also evaluated in patients who were supplied with antilipemics in external pharmacies through phone calls. Patients were considered adherent if the percentage of correct time of drug refill was >80%. **Findings:** Totally 1123 patients were evaluated. Lipid-lowering drugs (statins, fenofibrate, and omega-3 oil) were prescribed in 242 patients (21.5%). Prescription occurred mainly in those who were older, males, and Italians. Two hundred of them (82.6%) used statins alone, 23 (9.5%) only fenofibrate or omega-3 oil, and 19 (7.8%) a combination of both drugs. The median adherence was 90% while patients with adherence >80% resulted 153 (63.2%). Forty-six (19%) had a clinical history of cardiovascular events; 59% of them, placed in secondary prophylaxis, and 76%, already in treatment, continued to adhere. No differences in terms of adherence according to the type of drug distribution (hospital pharmacy or outside pharmacies) were found. **Conclusion:** Linking the supply of these drugs to that of antiretrovirals led to a good level of adherence higher than that described in the general population. The majority of the patients who experienced a cardiovascular event remain adherent to the prescribed therapy.

Keywords: *Adherence, antilipemics, HIV, medication, Statins*

Received: 29-07-2020.
Accepted: 12-01-2021.
Published: 13-05-2021.

Introduction

The introduction of combination antiretroviral therapy (cART) has radically changed the natural history of HIV infection. The number of HIV-positive people over the age of 60, 70, and 80 has increased in recent years, as have deaths from non-AIDS-related diseases.[1] In particular, the number of deaths due to cardiovascular disease (CVD) is expected to increase due to the longer life expectancy of HIV-positive patients, the effects of HIV on the cardiovascular system, and the dysmetabolism associated with antiretroviral therapy.[2]

In the general population, the known risk factors for CVDs are the adopted lifestyle (e.g., smoking addiction and diet) and comorbidities (hypertension, diabetes, and hyperlipidemia).[3] Inflammation, hypercoagulability, and immunoactivation may be supported by the persistence of HIV replication within selected lymphoid organs; this may lead to CVD despite virological plasma suppression obtained with cART. Immunological events in the intestinal mucosa during acute infection and microbial translocation play a recognized role and are still under

Access this article online

Quick Response Code:

Website: www.jrpp.net

DOI: 10.4103/jrpp.JRPP_20_96

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How to cite this article: Cuomo G, Raimondi A, Rivasi M, Guaraldi G, Borghi V, Mussini C. Adherence to lipid-lowering medication in people living with HIV: An outpatient clinic drug direct distribution experience. J Res Pharm Pract 2021;10:10-6.

study. In addition, the suppression of viral replication is not always accompanied by a recovery of CD4 T-lymphocytes, as in the patients with no immunological response.[4] Furthermore, CART is responsible for cardiovascular risk;[5,6] although the new regimens have a more tolerable profile, the intake of protease inhibitors and nonnucleoside reverse transcriptase inhibitors such as efavirenz is associated with dyslipidemia, lipodystrophy, and insulin resistance. All these reasons may partially explain the greater vulnerability of HIV-positive people to cardiovascular events compared to the general population.[7]

The correct management of HIV-positive people also includes the correct assessment of cardiovascular risk and its treatment. A key part of CVD management is based on the prevention and treatment of dyslipidemia. An increase in low-density lipoproteins (LDLs) in the blood leads to a progressive accumulation of liver cholesterol in the arteries. The subsequent formation of atherosclerotic plaques obstructs the vessel lumen and blocks blood flow and oxygen supply, causing myocardial infarction and stroke.[8]

The main pharmacological treatment of hypercholesterolemia is represented by statins,[9] in patients who do not respond to changes in diet and physical exercise, by reducing the risk of vascular events up to 21% and cardiac events of 24%.[10] The effect of statins in seropositive patients is similar to the general population[11] and produces a lowering of LDL cholesterol values from 15% to 35%; moreover, statins delay the process of atherosclerosis and have been shown to have an anti-inflammatory and immunomodulatory effect. Statins are well tolerated, the most known side effect is myopathy, which is infrequent and characterized by an increase in muscle enzyme creatine phosphokinase.[12]

Fibrates represent another class of lipid-reducing drugs; their effect results in a reduction of cardiovascular risk by 16% and coronary events by up to 21%.[13] Among the therapies of hypertriglyceridemia, omega-3 plays a controversial role; it is prescribed in the secondary prevention of cardiovascular events because it is helpful to improve endothelial function and stabilize atheromasic plaques; moreover, it would reduce the level of triglycerides in the blood by increasing oxidation.[14]

Although the regular intake of lipid-reducing therapies decreases the risk of cardiovascular events, long-term adherence to these drugs has proven to be very low in the general population, even in those who had already experienced CVD.[15] Poor adherence to statins has been reported up to 50%, while 25%–50%[16] of the patients stop taking these drugs between 6 months and 1 year after prescription, and within 2 years, the withdrawal rate reaches 75%. The increased risk of adverse outcomes associated with poor statin adherence is well known in the literature.[17] The reasons behind the low compliance are quite various and mainly represented by: the indications for the prescription (primary rather than secondary prevention), being a new consumer of statin, the number of pills to be taken due to comorbidity, side effects, the belief that drugs of a different class can cause the same adverse reactions, and the cost of the drugs themselves.[18,19] We know that in HIV patients, the adherence to hypolipidemic drugs is similar to that of the general population and that the pill burden related to CART can be a challenge.[20] The aim of this study is to evaluate the adherence to hypolipidemic drug therapy in our cohort of patients followed at the Infectious Diseases of Modena, and to investigate how clinical events can impact the adherence itself.

Methods

This is a retrospective observational study conducted on patients followed at the Infectious Diseases Clinic of Modena (Italy). Inclusion criteria were as follows: HIV-1 Ab positivity, any stage of HIV infection according to the Centers for Disease Control and Prevention (CDC) classification (1993), age >18 years old, at least two clinical checks in the period January 1–December 31, 2016, duration of follow-up from the linkage to care of at least 12 months, and residence in the Province of Modena. Refill of HIV antiretroviral and other HIV comorbidities drugs prescribed by the infectious disease specialists was directly distributed in the dedicated pharmacy of the hospital to all patient inhabitants in the Province of Modena, and recorded in an electronically database as like as demographical and clinical data. Patients who, after an electronic check, were found not to have withdrawn their antilipemic medications at the hospital pharmacy were contacted to verify whether they really had not retrieved the medications or had done it at an outside pharmacy. In case of nonhospital, outside dispensation of lipid-lowering medications, external pharmacies were called in order to check the adherence. Demographic and clinical data about the study population were collected (age, gender, race, country of birth, HIV ways of transmission, HIV clinical status, antiretroviral therapy, and HIV viral load). HIV clinical status was defined by the CDC classification (Atlanta, 1993). HIV viral load was determined using Abbott RealTime HIV-1 Viral Load Assay (limit 40 copies/ml). Data about lipid-lowering medication prescription (statins, fenofibrate, and omega-3 oil) were recorded. Blood levels of total cholesterol, high-density lipoprotein (HDL) cholesterol,

LDL cholesterol, and triglycerides (Abcam Cholesterol and Triglyceride Assay kit) tested before and during lipid-lowering drug treatment (at least 3 months after the beginning of therapy) were reported, and a univariate analysis was performed. We investigated the patients' cardiovascular history by taking note from our outpatient clinic archives of the following events, occurred before and after the prescription on lipid-lowering drugs: myocardial infarction, acute coronary syndrome, hospitalizations for newly detected angina pectoris, and newly detected coronary atherosclerosis. Adherence to lipid-lowering drugs was tested by calculation of correct time of drug supply for each patient (based on number of pills per box and medical prescription). Patients were considered adherent if the percentage of correct time of drug refill was >80%. Statistical analysis was done by median and interquartile range for continuous variables, and of frequency for categorical variables. In univariate analysis between different groups, continuous variables were compared using nonparametric analysis (Mann–Whitney) and categorical variables were compared using the Chi-square test. $P < 0.05$ was considered to be statistically significant. Data were obtained using IBM SPSS 23 statistics software, IBM Corporation, Armonk, NY, USA. The study was reviewed and approved by the local Institutional Review Board and was conducted in accordance with the ethical standards of the Institutional and National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. All involved persons gave witnessed informed verbal consent. Data were collected anonymously.

Results

During the year 2016, 1598 patients were observed and 1123 respected the inclusion criteria, so they were enrolled in the study. As shown in Table 1, they were mostly male (744/1123, 66.3%), and the median age was 50 years old (range: 43–56). Patients were non-Italians in 78% of cases (876/1123). Patients on AIDS were 247 (22%). One thousand and eight-five patients (96.6%) were on highly active antiretroviral therapy (HAART) and 1011 (90.4%) had undetectable HIV RNA in the plasma. Patients with a prescription of an antilipemic drug of at least 3 months were 242. Univariate analysis [Table 1] between patients with antilipemic drug prescription and other HIV patients without showed that patients on lipid-lowering treatment were mostly male (73.1% vs. 64.4%, $P = 0.010$) and were significantly older (median age: 55 years [range: 50–61] vs. 49 years [range: 43–56], $P < 0.001$). They were also more frequently Italians (86.8% vs. 75.6%, $P < 0.001$) and consequently Caucasians (90.1% vs. 82.4%, $P = 0.019$). Patients under antilipemic drugs had a significantly higher level of clinical definition of AIDS than the other HIV patients (29.3% vs. 20%, $P = 0.002$) and were most frequently on HAART (99.2% vs. 95.9%, $P = 0.013$). HIV RNA undetectability was significantly more observed in patients under antilipemic treatment (94.2% vs. 89.4%, $P = 0.024$). There were no statistically significant differences in terms of HIV ways of transmission ($P = 0.990$). Table 2 summarizes the type of prescribed antilipemic drug: 200 patients (82.6%) underwent to a monotherapy with statin, while 23 (9.5%) assumed a monotherapy of fenofibrate/omega-3 oil. A combination of both statin and fenofibrate/omega-3 oil was prescribed in 19 patients (7.9%). Statins prescribed were as follows [Table 2]: atorvastatin in 188 patients (86.1%), rosuvastatin in 15 (6.7%), pravastatin in 12 (5.4%), fluvastatin in 3 (1.3%), while 1 patient (0.4%) assumed simvastatin. Among the 242 patients who were prescribed antilipemic drugs: 175 (76.4%) received the drug from the hospital pharmacy, 42 (17.4%) from other external pharmacies, while 15 patients (6.2%) never withdrew nor took the antilipemic drugs. Figure 1 summarizes our assessment of the adherence to lipid-lowering drugs. The median adherence resulted to be 0.9 (90% of correct drug refill, range: 0–1); 15 patients (6.2%) had never taken the

Table 1: General characteristics of the study population and univariate analysis between patients on antilipemic therapy

Characteristics	Prescription of antilipemic drugs (*n*=242; 21.5%)	Not prescribed (*n*=881; 78.5%)	Total (*n*=1123)	*P*
Gender				0.010[#]
Female	65 (26.9)	314 (35.6)	379 (33.7)	
Male	177 (73.1)	567 (64.4)	744 (66.3)	
Age (years)	55 (50-61)	49 (41-54)	50.0 (43.0-56.0)	<0.001[§]
Foreign born	32 (13.2)	215 (24.4)	247 (22.0)	<0.001[#]
AIDS	71 (29.3)	176 (20.0)	247 (22.0)	0.002[#]
On HAART	240 (99.2)	845 (95.9)	1085 (96.6)	0.013[#]
Undetectable HIV RNA	228 (94.2)	783 (89.4)	1011 (90.4)	0.024[#]

Absolute number and percentage (%) for all categorical variables. Median and range (minimum-maximum) for age. [#]Chi-square test, [§]Mann-Whitney U-test. HAART= Highly Active Antiretroviral Therapy, HIV: human immunodeficiency virus, AIDS: acquired immunodeficiency syndrome

prescribed drugs (0% of adherence), 17 patients (7%) had an adherence from 0% (>0) to 20% (<0.2), 25 patients (10.4%) from 20% (>0.2) to 40% (<0.4), 16 patients (6.6%) from 40% (>0.4) to 60% (<0.6), and 16 patients (6.6%) had a percentage of adherence from 60% (>0.6) to 80% (<0.8). One hundred and fifty three patients (63.2%) were considered adherent (the percentage of correct time of drug refill was >80%.). Table 3 shows that there were no statistically significant differences in terms of adherence according to the type of drug distribution (hospital pharmacy or outside pharmacies); the median adherence results 0.90 (range: 0.008–1) in patients with a hospital refill and 0.99 in patients with outside pharmacy refill (P = 0.810), while the percentage of adherent patients (>0.8) resulted 67% (124 patients) and 69% (29 patients), respectively (P = 0.818). Table 4 summarizes the total levels of lipid in our population under antilipemic drugs before treatment (at baseline, BL), and during treatment (at least 3 months, OT); in the general population under antilipemic drugs (all 242 patients), total cholesterol and LDL cholesterol levels decreased of a mean (standard deviation) of 95.15 (69.31) mg/dL

Table 2: Frequency and types of the prescribed statins for the study patients

Type	Number of patients (%)
Antilipemic drugs prescribed	
Statin alone	200 (82.6)
Combination of both	19 (7.9)
Fenofibrate/omega-3 oil alone	23 (9.5
Total	242 (100)
Statins (219 patients)	
Atorvastatin	188 (86.1)
Rosuvastatin	15 (6.7)
Pravastatin	12 (5.4)
Fluvastatin	3 (1.3)
Simvastatin	1 (0.4)

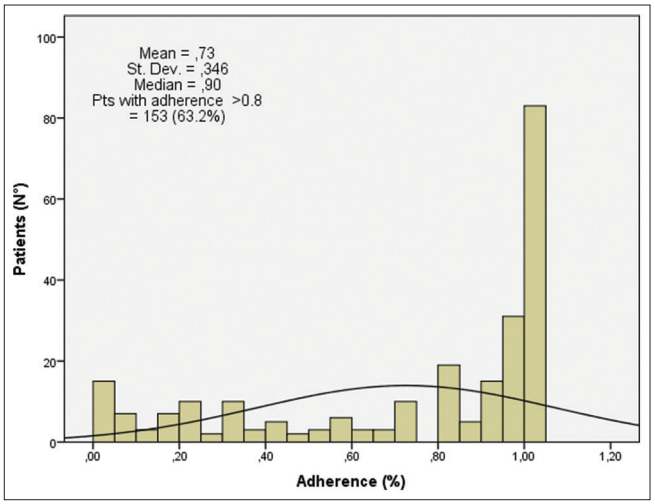

Figure 1: Assessment of the adherence to antilipemic drugs (number of patients and relative percentage on adherence)

Table 3: Differences in terms of adherence due to type of drug dispensation

	Hospital pharmacy distribution (total=185)				Outside pharmacy distribution (total=42)				*P*
	Mean	SD	Median	Range	Mean	SD	Median	Range	
Adherence	0.78	0.29	0.90	0.08-1.00	0.76	0.34	0.99	0.05-1.00	0.818§
Patients with adherence >80%, *n* (%)	124 (67)				29 (69)				0.810§

§Mann-Whitney U-test. SD=Standard deviation

Table 4: Mean lipid levels at baseline and on treatment with antilipemic drugs and univariate analysis between adherent and nonadherent patients

	Nonadherent patients		Adherent patients		Total		*P*
	Mean	SD	Mean	SD	Mean	SD	
Total cholesterol at BL (mg/dl)	273.47	59.89	276.93	74.18	275.63	69.48	0.713§
Cholesterol HDL at BL (mg/dl)	60.50	22.78	60.04	20.06	60.22	21.12	0.875§
Cholesterol LDL at BL (mg/dl)	165.78	45.54	161.93	37.84	162.83	40.99	0.387§
Triglycerides at BL (mg/dl)	453.32	333.49	593.25	556.95	540.85	489.10	0.033§
Total cholesterol OT (mg/dl)	192.87	52.07	171.09	38.25	178.94*	44.87	<0.001§
Cholesterol HDL OT (mg/dl)	49.25	20.42	49.555	16.07	49.43*	17.77	0.931§
Cholesterol LDL OT (mg/dl)	115.70	41.25	92.13	31.40	100.52*	36.81	<0.001§
Triglycerides OT (mg/dl)	166.77	156.79	177.38	153.10	173.57*	154.17	0.619§
Total cholesterol delta (mg/dl)	78.28	46.37	104.94	78.15	95.15	69.31	0.005§
Cholesterol HDL delta (mg/dl)	8.73	14.08	10.50	15.23	9.78	14.73	0.541§
Cholesterol LDL delta (mg/dl)	47.84	34.76	71.31	40.97	62.45	40.22	0.005§
Triglycerides delta (mg/dl)	287.98	327.23	430.63	528.26	378.58	469.34	0.029§

*P<0.001 versus mean values at BL. §Mann-Whitney U-test. SD=Standard deviation, LDL=Low-density lipoprotein, HDL=High-density lipoprotein, BL=Baseline, OT=On treatment

and 62.45 (40.22) mg/dL ($P < 0.001$), respectively. HDL cholesterol decreased of a mean (standard deviation) of 9.78 (14.73) mg/dL ($P < 0.001$). Triglycerides decreased of a mean (standard deviation) of 378.58 (469.34) mg/dL ($P < 0.001$). Univariate analysis between adherent and nonadherent patients showed significant differences in total cholesterol delta levels (104.94 ± 78.15 mg/dl vs. 78.28 ± 46.37 mg/dl, $P = 0.005$), LDL cholesterol delta (71.31 ± 40.97 mg/dl vs. 47.84 ± 34.76 mg/dl, $P = 0.005$), and triglyceride delta (430.63 ± 528.26 mg/dl vs. 287.98 ± 327.23 mg/dl, $P = 0.029$). We found furthermore significant differences in terms of triglyceride levels at BL (593.25 ± 556.95 mg/dl vs. 453.32 ± 333.49 mg/dl, $P = 0.033$), total cholesterol OT (171.09 ± 38.25 mg/dl vs. 192.87 ± 52.07 mg/dl, $P < 0.001$), and LDL cholesterol OT (92.13 ± 31.40 mg/dl vs. 115.7 ± 41.25 mg/dl, $P < 0.001$). Of the 242 patients on lipid-lowering therapy, 46 (19%) had a clinical history of cardiovascular events distributed as follows: 28 had acute or subacute coronary syndrome, 3 had first episode of angina pectoris, and 15 had newly detected coronary atherosclerosis. Of them, 29 (63%) were not in therapy at the time of the clinical event. Of the remaining 17, who had already been offered therapy to reduce blood cholesterol levels, only 13 had sufficient adherence. After the cardiovascular event, all 29 patients not previously taking antilipemics were placed on secondary prophylaxis with statins, and of these 17 (59%) were subsequently found to be adherent to the prescribed therapy.

Discussion

The treatment of CVDs, which, to date, are one of the emerging causes of morbidity and death in increasingly elderly HIV-positive patients on active CART,[21,22] plays a key role in good outpatient management.[23,24] In the specific case of our clinic, this is supported by the large number of hypolipidemic drugs that were provided during the control checkups; in the study period, one-fifth of the patients (21.5%) were provided with statins, fibrates, or omega-3.

The population treated was mostly male and had an average age of 55 years, reflecting data from other studies on HIV-positive patients on hypolipidemic therapy.[3] Patients on antilipemic therapy, as already demonstrated in publications by other authors,[25] had a better immunovirological situation in the period examined, even if in their medical history, they had a greater clinical history of AIDS. As recommended by the guidelines,[26] statins were the first-choice drugs prescribed for the treatment of hypercholesterolemia. Among these, the most widespread statins were the safest in terms of possible drug interactions with antiretroviral therapy: atorvastatin, rosuvastatin, and pravastatin. As expected, according to the literature,[27,28] these drugs proved useful to lower total cholesterol and triglyceride levels, with a difference in the median delta of 92 mg/dL and 260 mg/dL, respectively. These results, combined with data on increased virological suppression in hypolipidemic patients, may support the hypothesis that the anti-inflammatory and immunomodulatory effect of statins may somehow help greater control of HIV infection. In accordance with other authors,[29] adherence to therapy has been shown to be an important factor in achieving acceptable blood cholesterol values in our patients. Compared to the latest data on adherence to statin therapy in the literature, we found that in our patients, compliance was unexpectedly higher than described in the general population; in particular, it was 63.4% compared to 25% as the lowest reported value, with an interruption rate in other studies between 40% and 75%.[30,31]

Investigating the possible reasons for this good and unexpected result, we found that the median percentage of drug supply from our clinic was up to 80%. Most of our patients withdrew their hypolipidemic therapy together with cART from the hospital pharmacy, which is easily accessible from our clinic. It was suggested that prescribing statins as an integral part of the overall treatment of HIV-related disease linked to the delivery of cART, rather than to be obtained in external pharmacies, could be an important and effective factor for adherence. However, we must underline that no significant differences emerged in our study in terms of adherence in patients who withdrew their antilipemic drugs in external pharmacies.

Overall, one-fifth of people with prescription antilipemic drugs had a cardiological history. Interestingly, most of the patients who experienced a cardiovascular event tend to remain adherent to the prescribed therapy. On the other hand, it was also observed that a small percentage of people (4 patients) who did not take the drug before the cardiological event continued not to take it.

In addition to general data on adherence, it will be mandatory to understand the causes of nonprescription to people who have had cardiovascular events with a proper review of the latest guidelines on the use of lipid reduction drugs. Anyway, it will be necessary to complete the study with a longer observation period; one of the main limitations of this work is the short follow-up period; a longer period would be useful for a more adequate evaluation of the correct and accurate adherence to statin therapy. In addition, the method for analyzing adherence could be improved by

creating a shared data system with external pharmacies to better evaluate the number of supplies. Clearly, the measurement of blood cholesterol can reassure the data collected on adhesion. Finally, it would be interesting to explore the reasons for low adherence in people not taking the therapy, even after a higher risk event, and investigate the causes of the failure to reach target cholesterol levels in the adhering population.

In summary, with this study, we show that a careful management of the distribution of non-cART therapies leads to an improved adherence and to an overall more effective treatment of the patients.

Authors' contribution

Cuomo G and Raimondi A participated in the collection of the data, performed the statistical analysis, and wrote the manuscript, equally. Rivasi M and Borghi V participated in the design of the study and in the database application and helped to draft the manuscript. Guaraldi G and Mussini C were substantial contributors to conception and design the study, interpretation of data, revising the manuscript critically, and have given final approval of the version to be published. All authors read and approved the final manuscript.

Acknowledgments

We would like to thank Federica Carli and Marianna Menozzi from Clinic of Infectious Diseases, Azienda Ospedaliero-Universitaria di Modena, Modena, Italy, and Erica Bacca, Carlotta Rogati, Giacomo Ciusa, Marco Tutone, Giovanni Dolci, and Aurora Bonazza from University of Modena and Reggio Emilia.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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