Predictors of primary non-adherence to concomitant chronic treatment in HIV-infected patients with antiretroviral therapy

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ABSTRACT

Objectives To identify the independent risk factors of primary non-adherence to chronic concomitant treatment in HIV-positive patients, and to measure primary and secondary non-adherence rates to chronic treatments, and secondary non-adherence to antiretroviral therapy and the prevalence of concomitant chronic diseases.

Methods We conducted a retrospective study that included HIV-infected patients with antiretroviral treatmentwho attended the pharmaceutical care office between January and December 2012. The dependent variable was primary non-adherence to concomitant prescription drugs for chronic diseases. To know the predictors of concomitant primary non-adherence, we performed a univariate analysis and a multivariate binary logistic regression model to identify the independent predictors of primary non-adherence to co-medication.

Results Out of 598 patients analysed, 333 patients had a new co-medication prescribed during the studied period. The number of comorbidities per patient was 2.3 and the patients were treated with an average of 3.4 drugs. The rates of primary and secondary non-adherence to co-medication were 8.4% and 44.4%, respectively. The co-occurrence of primary and secondary non-adherence was 24.9%. The number of comorbidities (p=0.001) and co-medications (p=0.001) was significantly higher in patients who had primary non-adherence to co-medication. Furthermore, there was a statistically significant relationship between primary non-adherence and patients treated with psychotropic drugs (p=0.03). The multivariate analysis showed the independent predictor of primary non-adherence to co-medication was the number of co-medications (p<0.001).

Conclusion One-third of new concomitant medications prescribed to HIV-positive patients were never filled from the pharmacy. The number of co-medications was identified as a predictor of primary non-adherence to chronic concomitant treatment in HIV-infected population.

INTRODUCTION

Highly active antiretroviral treatment (HAART) has significantly managed to control HIV which is now considered a chronic disease.[1] Increasing patient's life expectancy has brought about an increase in the incidence of comorbidities such as hypertension, dyslipidaemia or diabetes.[2] Approximately 33% of HIV-infected patients have hypertriglyceridemia, 22% have hypercholesterolaemia, 8% have arterial hypertension and 3% have diabetes mellitus.[3]

The presence of multiple comorbid conditions in HIV patients has led to an increased polypharmacy which may limit adherence and therapeutic success. Adherence to a medication regimen is generally defined as 'the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen'. The rate of adherence for individual patients is usually defined as the percentage of prescribed doses over a specified period.[4] Most studies have focused on 'secondary non-adherence' which occurs when patients do not pick up their prescriptions on time or completely discontinue their medications.

Primary non-adherence is a new concept based on not having filled the initial prescription in a 14-day period after medical prescription. Nowadays, primary non-adherence is infrequently calculated and has recently begun to be examined from a population perspective.[5]

Primary non-adherence rates are broad, ranging from 0.5% to 57.5% depending on the type of study, therapeutic drug group and methodological factors, such as how primary non-adherence is defined. Usually, in health delivery systems, primary non-adherence studies have been limited to the treatment of chronic diseases such as diabetes, hyperlipidaemia and hypertension, with rates of secondary non-adherence from 3.2% to 13% depending on the drug therapeutic group.[6 7]

In Spain, HIV-infected patients purchase antiretroviral medication in specialised hospital pharmacies without any cost. However, comorbidity medication is collected in the community pharmacy and they do have a cost. Primary adherence to HAART is almost 100% because the doctor and the patient agree on the beginning of treatment, and the patient immediately visits the hospital pharmacy to fill his or her medication. So, hospital pharmacists are used to measuring secondary adherence to HAART, but it is important to know what happens with adherence to medication for treatment of comorbidities and if the goals are achieved. Hospital pharmacists should check the treatment goals for both HIV and comorbidities.

Nowadays, the number of studies related to primary non-adherence is limited, and there is not any study that has evaluated the primary non-adherence in patients with HIV. Identifying the risk factors associated with primary non-adherence may help physicians manage these patients.

The aim of this study was to analyse the primary non-adherence rates to chronic concomitant

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treatment in patients with HIV. The secondary objectives were to identify the independent risk factors of primary non-adherence to chronic concomitant treatment, and to evaluate the secondary non-adherence rates to chronic concomitant treatment and to HAART.

METHODS

We conducted a retrospective observational study in a hospital that included HIV-infected patients with active antiretroviral therapy for at least 1 year and with a new co-medication (defined as treatment for at least 3 months for a chronic disease prescribed in the study period) who were attended in the pharmaceutical care of a pharmacy service between January and December 2012. We excluded patients enrolled in clinical trials.

The dependent variable was primary non-adherence to concomitant prescription drugs for chronic diseases. The independent variables were sex, age, undetectable plasma viral load (HIV RNA <20 copies/mL), secondary non-adherence (HAART and co-medication), number of comorbidities, number and type of co-medication (antacid therapy, psychotropic drugs, lipid-lowering drugs, antihypertensive, cardiovascular therapy, antidiabetics) and the presence of specific diseases (viral liver disease, dyslipidaemia, central nervous system disease, cardiovascular disease or hypertension disease).

Primary non-adherence was defined as the failure to fill prescription within 14 days from the day it was prescribed.[8] Secondary non-adherence was measured by assessing the proportion of days covered by medication (PDC). The patient was considered primary non-adherent if primary adherence failed to, at least, one medication, and secondary non-adherent if there was at least one drug with PDC below 90.0%.

Secondary adherence to antiretroviral treatment in the last 3 months was obtained through dispensing records of the pharmacy program *FarmaTools*. Primary and secondary adherence to co-medication in the last 3 months were obtained through electronic prescriptions in the digital health records *Diraya*.

The remaining variables were obtained by consulting analytics and microbiology reports, and by examining the medical history of each patient.

We carried out a descriptive analysis with the patients enrolled (co-medication). Quantitative variables were expressed as the average value and SD or medians and percentiles (P25 and P75) and qualitative variables as percentages (%).

Subsequently, to identify the independent predictors of primary non-adherence to co-medication, variables that had shown statistical significance in the univariate analysis were included in a multivariate binary logistic regression model. The level of significance was defined at 5.0%. The validity of the model was evaluated by the Hosmer and Lemeshow test. The sample size was estimated according to the Freeman equation ($10\times(\mathbf{k}+1)$, where 'k' expresses the number of covariates). Therefore, it was necessary to include at least 320 patients with non-HIV co-medication (160 patients adherent to co-medication and 160 non-adherent to co-medication). Data analysis was performed using the statistical package SPSS V.20.0 for Windows (SPSS, Chicago, Illinois).

RESULTS

Five hundred and ninety-eight HIV-infected patients with active antiretroviral therapy for at least 1 year were attended in the pharmaceutical care during the study period. Overall, 333 patients (55.7%) had a new co-medication prescribed in the study period and were enrolled in the study. Most of them were men (78.9%). The mean age was 48.8 years. The baseline and clinical characteristics of patients are detailed in table 1. The number of comorbidities per patient was 2.3 and the number of drugs for treatment of these comorbidities was 3.4 per patient.

Table 1 Demographic and clinical characteristics of the patients included in the study

Variable	Frequency
Sex, n (%) Female Male	70 (21.1) 262 (78.9)
Age (years), mean (SD)	48.8 (8.8)
Primary non-adherence to co-medication, n (%)	28 (8.4)
Secondary non-adherence to co-medication, n (%)	83 (24.9)
Primary and secondary non-adherence to co-medication, n (%)	148 (44.4)
Secondary non-adherence to HAART, n (%)	49 (14.71)
Undetectable plasma viral load (HIV RNA <20 copies/mL), n (%)	259 (77.8)
Number of comorbidities, mean (SD)	2.32 (1.28)
Number of co-medications, mean (SD)	3.44 (2.70)
Antacid therapy, n (%)	125 (37.5)
Psychotropic drugs, n (%)	179 (53.8)
Lipid-lowering drugs, n (%)	103 (30.9)
Cardiovascular therapy, n (%)	80 (24.0)
Antidiabetic drugs, n (%)	30 (9.0)
Viral liver disease, n (%)	132 (39.6)
Dyslipidaemia, n (%)	97 (29.1)
Central nervous system disease, n (%)	85 (25.5)
Cardiovascular or hypertension disease, n (%)	77 (23.1)

HAART, highly active antiretroviral treatment.

Overall, the rates of primary and secondary non-adherence to co-medication were 8.4% and 44.4%, respectively. The co-occurrence of primary and secondary non-adherence was 24.9%. On the other hand, the rate of secondary non-adherence to HAART was 14.7%.

The most frequently prescribed drugs were psychotropic drugs (53.8%), antacid therapy (37.5%) and lipid-lowering drugs (30.9%). On comorbid conditions, 39.6% of patients had viral liver disease, 29.1% had dyslipidaemia, 25.5% had central nervous system disease and 24.5% had cardiovascular or hypertensive disease.

Variables that reached statistical significance with primary non-adherence rate to co-medication in the univariate regression analysis were the number of comorbidities (OR=1.34; 95% CI 1.12 to 1.61), number of co-medication (OR=1.16; 95% CI 1.07 to 1.26) and patients treated with psychotropic drugs (OR=1.67; 95% CI 1.05 to 2.66). Other treatments, as well as sex, age, type of comorbidities, plasma viral load or secondary non-adherence to HAART, did not influence primary non-adherence to co-medication. Table 2 shows the relationship between these variables and primary non-adherence to co-medication.

Subsequently, multivariate analysis showed that the number of co-medication was the only independent predictor of primary non-adherence to co-medication (OR=1.18; 95% CI 1.08 to 1.28). The value of the Hosmer and Lemeshow test confirmed the validity of this model (p=0.28).

DISCUSSION

Our study shows that HIV-infected patients have a high rate of primary non-adherence to co-medication. Also, the number of prescribed drugs for treatment of other chronic diseases was

Table 2 Univariate analysis results

Variable	n (%)	PNA,* n (%)	PA,† n (%)	OR (95% CI)	p Value‡
Sex: Male Female	262 (78.7) 71 (21.3)	91 (82.0) 20 (18.0)	172 (77.4) 50 (22.5)	1.33 (0.75 to 2.37)	0.333
Age in years, mean (SD)	49.0 (9)	48.0 (8.8)	48.8 (8.8)	0.99 (0.96 to 1.02)	0.414
Undetectable plasma viral load (HIV RNA<20 copies/mL)	259 (77.8)	88 (79.3)	171 (77.0)	0.88 (0.5 to 1.53)	0.641
SNA to HAART§	49 (14.7)	21 (18.9)	28 (12.6)	0.62 (0.87 to 3.0)	0.132
Number of comorbidities, mean (SD)	2.3 (1.3)	2.6 (1.5)	2.1 (1.2)	1.34 (1.12 to 1.61)	<0.001
Number of co-medication: mean (SD)	3.4 (2.7)	4.2 (3.4)	3.1 (2.3)	1.16 (1.07 to 1.26)	<0.001
Antacid therapy	125 (37.5)	43 (38.7)	82 (36.9)	1.08 (0.67 to 1.73)	0.749
Psychotropic drugs	179 (53.8)	69 (62.2)	110 (49.5)	1.67 (1.05 to 2.66)	0.030
Lipid-lowering drugs	103 (30.9)	29 (26.1)	74 (33.3)	0.71 (0.43 to 1.17)	0.181
Cardiovascular therapy	80 (24.0)	29 (26.1)	51 (23.0)	1.12 (0.65 to 1.89)	1.186
Antidiabetic drugs	30 (9)	9 (8.1)	21 (9.5)	0.77 (0.34 to 1.75)	0.540
Viral liver diseases	132 (39.6)	52 (46.8)	80 (36)	1.53 (0.97 to 2.44)	0.070
Dyslipidaemias	97 (29.1)	30 (27.0)	67 (30.2)	0.86 (0.52 to 1.42)	0.551
Central nervous system diseases	85 (25.5)	28 (25.2)	57 (25.7)	0.98 (0.58 to 1.89)	0.929
Cardiovascular or hypertension diseases	77 (23.1)	27 (24.5)	50 (22.5)	1.11 (0.65 to 1.89)	0.713

*Patients whose primary adherence failed at least to one concomitant medication.
†Patients with primary adhesion to all concomitant medications.
‡It represents the level of significance between variable and PNA to concomitant treatments.
§Patients whose adhesion percentage to HAART did not exceed 90.0%.
HAART, highly active antiretroviral treatment; PA, primary adherence; PNA, primary non-adherence; SNA, secondary non-adherence.

identified as an independent risk factor for primary non-adherence to these drugs.

Adherence to medication is directly associated with improved clinical outcomes, higher quality of life and lower healthcare cost across many chronic conditions.[4 9] However, most medication adherence researches have focused on secondary adherence, in part because they were based on estimates obtained from pharmacy claims databases where adherence can only be estimated for patients who have purchased the drug. New technologies, including electronic prescribing and the development of electronic medical records, have created the opportunity to know primary non-adherence rates. This allows researchers to design more rigorous adherence studies and to have a more precise understanding of adherence.

To date, primary non-adherence to co-medication has not been measured in HIV-infected patients. However, our findings are consistent with most of the studies developed in non-HIV population. These studies reported a rate of primary non-adherence between 24.0% and 31.0%.[10–12] On the contrary, other studies have found lower rates of primary non-adherence (2.0%–15.0%).[5 6 13 14] This may be due to the differences between the definitions of primary non-adherence, differences in the studied populations and the use of different methodologies. On the other hand, some studies have determined primary non-adherence to the type of drugs, like lipid-lowing therapy, antihypertensive and antidiabetic drugs. However, we evaluated the primary non-adherence to all co-medications. Also, we have been very strict because we defined primary non-adherence as the failure to fill the prescription within 14 days from the day it was prescribed, and we considered a patient non-adherent when one of the prescriptions had not been filled.

In our study, although the rate of secondary non-adherence was higher than primary non-adherence, most of the patients (74.8%) who were primary non-adherent were also secondary non-adherent. Therefore, the measure of primary non-adherence may help identify prematurely patients with poor adherence and contribute to potentially preventable complications over the long term.

Non-adherence had been studied in HIV-infected patients before, but most of the studies have focused on secondary non-adherence to HAART. There is only one study that has determined secondary non-adherence to HAART and specific co-medications to treat cardiovascular diseases such as ACE inhibitor, angiotensin receptor blocker or statin.[15] In this study, the rate of non-adherence ranged from 37.0% to 41.6%, considering a target adherence of a PDC of 80% or greater. In our study, secondary non-adherence to co-medication was slightly higher (69.4%), but we measured the adherence to all medications to treat chronic comorbidity and considered a patient as non-adherent when PDC was below 90%.

About the factors associated with primary non-adherence, we found that HIV patients with more drug prescriptions to treat chronic comorbid conditions have a higher risk of primary non-adherence and therapeutic failure. On the contrary, in other studies of primary non-adherence in the general population, patients using a greater number of medications were more likely to be adherent.[12 16] Perhaps HIV patients give less importance to other comorbidities. However, studies focused on factors associated with secondary non-adherence have shown that the use of multiple medications was associated with non-adherence increases in the general population and in HIV-infected patients.[17–20] Most of these studies were focused on polypharmacy, whose most common definition is the use of six or more medications.[21] In other diseases, there is evidence to support that co-medication negatively impacts secondary adherence. Studies have shown that adherence to concomitant antihypertensive and lipid-lowering medication decreases as the number of co-medication prescribed increases.[22 23] Conversely, Pizzirusso *et al* investigated the impact of hepatitis C treatment initiation on adherence to concomitant medications, and they did not find reduction in adherence, although treatment for HIV is not comparable with treatment for hepatitis C, which has a specific duration.[24]

Others studies have found that primary adherence varies with drug type, and medication class was the strongest predictor of adherence.[6 11 12] In our study, we measure adherence to all drugs for the treatment for comorbid conditions in general, not by medication type. However, we found no statistically significant differences between the type of prescribed medication and primary non-adherence to co-medication.

About the number of comorbidities, in our study the average of comorbid condition per person was 2.3, data similar to those obtained in previous studies (2.0–2.4).[25 26] The most frequent pathologies were viral liver diseases, dyslipidaemia and central nervous system diseases, unlike other studies where the most frequent pathologies were arterial hypertension, chronic obstructive pulmonary disease and diabetes. In our study, we did not find a statistically significant relationship between the different pathologies and the primary non-adherence. However, Rolnick *et al* found a variation in adherence rates in different diseases: more than 75.0% of patients with hypertension, hyperlipidaemia, osteoporosis, multiple sclerosis and cancer were adherent, whereas adherence in patients with diabetes and in those with asthma was 51.0% and 33.0%, respectively.[27] In HIV-positive population, different studies have shown that metabolic complications of HIV infection, neuropsychological dysfunction and bipolar disorder can affect adherence to HAART.[28–30]

Since the introduction of HAART, the average age of HIV-infected individuals had increased, so patients are more often exposed to chronic diseases and need more concomitant medication. Despite this, adherence studies have focused exclusively on HAART. Our study has been focused on adherence to general treatment and not only on antiretroviral therapy. This may be due to several reasons: these patients could give more importance to HIV infection than the rest of their pathologies. Moreover, HAART is dispensed in hospitals, with close monitoring and control by a hospital pharmacist.

A limitation of the study is related to its retrospective design. Because of this, we only used the electronic dispensing record to measure adherence to co-medication. However, in the pharmaceutical care consultation, we control the adherence of HIV patients periodically using Simplified Medication Adherence Questionnaire (SMAQ).[11] Therefore, in the study, we were able to measure adherence to HAART through two methods, as recommended in the Study Group on AIDS (GESIDA) / National AIDS Plan guideline.[31]

Another limitation of the study is that none of the patients were contacted after the investigation to explore why the prescriptions were not filled (some patients might have access to the medication from other sources). On the other hand, we do not have information about prescriptions included in the private health system.

CONCLUSION

One-third of new concomitant medications prescribed to HIV-positive patients are never filled from the pharmacy. The number of co-medication was identified as a predictor of

What this paper adds?

What is already known on this subject?

1. The presence of multiple comorbid conditions in HIV patients has led to an increased likelihood of polypharmacy, which may limit adherence and therapeutic success.
2. Nowadays, research has mainly focused on secondary non-adherence, and there is not any study that had evaluated primary and secondary non-adherence in HIV patients.
3. There are few studies related to primary non-adherence, and there is not any study that had evaluated primary non-adherence in HIV patients. Identifying the risk factors associated with primary non-adherence may help physicians manage these patients.

What this study adds?

1. One-third of new concomitant medications prescribed to HIV-positive patients were never filled from the pharmacy.
2. The number of co-medications was identified as a predictor of primary non-adherence to chronic concomitant treatment in HIV-infected population.

primary non-adherence to chronic concomitant treatment in HIV-infected population.

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