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Effectiveness of antiretroviral treatment in patients from Pereira and Manizales

Efectividad del tratamiento antirretroviral en pacientes de Pereira y Manizales

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ABSTRACT

Objective Evaluating the effectiveness of antiretroviral therapy in a sample of Colombian patients diagnosed as having HIV/AIDS and being treated by the Colombian Health Social Security System (CHSSS)
Methods A descriptive study was conducted among 134 HIV/AIDS patients of any age or gender who had received antiretroviral therapy in the cities of Pereira and Manizales between July 1st 2008 and June 30th 2009. The following factors were assessed from the clinical history of the patients seen in three health insurance companies: viral load, CD4 count, antiretroviral treatment regimens, prescribed daily doses of medications, length of disease evolution, duration of therapy, history of opportunistic diseases, and drug costs.
Results There was male predominance (91 men *cf* 43 women), mean age beingf 39 years, and an average of 59 months since diagnosis. All treatment regimens were defined by each drug's defined daily dose (DDD). The therapy was effective in 74.5 % of patients. Effectiveness was defined as being viral load < 400 copies/ml. About 79.1 % of patients had had their viral load measured during the last 6 months. Non-adherence to treatment and a history of having acquired 2 other sexually- transmitted infections were associated with an increased risk of uncontrolled HIV infection. The average value of drugs per year per patient was $4,077.2 ± 3,043.8 U.S. dollars/year.
Conclusions Non-adherence to treatment remains one of the most important issues regarding antiretroviral therapy effectiveness, so programmes intended to control HIV/AIDS must address this problem.

Key Words: Antiretroviral agent, HIV, acquired immunodeficiency syndrome, effectiveness, Colombia (*source: MeSH, NLM*).

RESUMEN

Objetivo Evaluar la efectividad del tratamiento antirretroviral en una muestra de pacientes con diagnóstico de VIH/SIDA en dos ciudades colombianas.
Métodos Estudio descriptivo en 134 pacientes en tratamiento para VIH/SIDA de cualquier edad y género en Pereira y Manizales entre 1 de julio de 2008 y 30 de junio de 2009. Se evaluó: carga viral, conteo de linfocitos CD4, esquemas antirretrovirales, dosis diaria prescrita, tiempo evolución de enfermedad, duración de terapia, antecedentes de enfermedades oportunistas, costos de medicamentos.
Resultados Predominio masculino (91 hombres vs 43 mujeres), promedio de edad: 39 años y 59 meses de evolución de la enfermedad. Todos recibían esquemas a Dosis Diarias Definidas recomendadas. La terapia era efectiva en 73,6 % de los pacientes (carga viral <400 copias/ml). Se pudo establecer que la falta de adherencia al tratamiento y el antecedente de haber tenido otras 2 infecciones de transmisión sexual se asociaban con mayor riesgo de no controlar la infección por VIH. El valor promedio de los medicamentos por año por paciente fue de US$ 4 077.2 ± 3 043.8 dólares.
Conclusiones La falta de adherencia al tratamiento sigue siendo uno de los problemas más importantes para garantizar efectividad, por lo cual los programas de control del VIH/SIDA deben asegurarla.

Palabras Clave: VIH, Síndrome de Inmunodeficiencia Adquirida, agentes antirretrovirales, efectividad, Colombia (*fuente DeCS, BIREME*).

HIV/AIDS is a disease which is caused by a human retrovirus, the human immunodeficiency virus (1,2). An estimated 32.2 million people had been infected with HIV or had AIDS worldwide by late 2007 (3). Almost 13.9 million people have died due to HIV infection since the beginning of the HIV/AIDS pandemic; 140,125 cases of HIV/AIDS had been registered in Colombia in 2009 according to the World Health Organisation (4).

In addition to non-pharmacological measures, the use of antiretroviral medicine has become fundamental to HIV/AIDS treatment. These drugs have fundamentally altered the disease's natural history (4,5) by reducing HIV progression and increasing patients' survival (6,7). The current management strategy consists of using highly active antiretroviral therapy (HAART) (6-11).

Antiretroviral therapy effectiveness is determined by assessing virological response by measuring viral load, results having less than 400 copies/ml indicating an adequate response and results under 50 copies/ml indicating an optimal response. Evaluating the immune response through CD4 lymphocyte measurements is also useful, results greater than 250 cells/mm^3 indicating an adequate response (11,12). Different studies have shown that

antiretroviral therapy results can vary, successful control covering 25 % to 84 % of patients (11,13,14).

The effectiveness of antiretroviral therapy and the factors associated with it were assessed in a group of HIV/AIDS patients in two Colombian cities to improve healthcare quality. This study evaluated antiretroviral treatment used on HIV/AIDS patients affiliated to the Colombian Health Social Security System (CHSSS) by determining the percentage of patients in whom such therapy was effective. Viral load, CD4 lymphocyte count, medications used, side effects experienced and the defined daily dose (DDD) were recorded. The study also explored several factors associated with the effectiveness of treatment, including history of sexually transmitted infections (STD), opportunistic diseases, and adherence to treatment, treatment failure, and medication intolerance. Finally, the invoiced cost of the antiretroviral drugs was defined.

MATERIALS AND METHODS

A descriptive observational study on the use of antiretroviral drugs was performed with patients of all ages and sexes who were diagnosed with HIV/AIDS and affiliated to the CHSSS (National Social Security Health System) through three health insurance companies (EPS, Empresa Promotora de Salud) in the cities of Pereira and Manizales (Colombia). A census form was used for collecting data related to July and December 2009 regarding all patients who had previously been diagnosed with HIV/AIDS and who had been receiving antiretroviral therapy from 1st July 2008 to 30th June 2009. Data regarding drug prescription and effectiveness were analysed using these patients' complete medical records which were available from the respective EPSs. The updated information was used, along with the complete patient follow-up forming part of the HIV/AIDS treatment programme.

The information was collected by a physician and a patient information database was constructed from the data obtained from each patient's clinical history. The following variables were recorded:

- Socio-demographic data regarding age, sex, marital status (single or married) and type of CHSSS membership (subscriber or dependent);
- Background concerning having a partner diagnosed as having HIV/AIDS, previous diagnosis of opportunistic diseases or other sexually-transmitted diseases (STDs);

- Initial measurement of viral load (copies/ml) and CD4 count (in cells/mm^3) and that most recently recorded in the medical history during the last 6 months;
- Combinations of antiretroviral drugs with their respective DDD, including those started immediately before the viral load and CD4 count measurements;
- Length of time since diagnosis;
- Start time for antiretroviral treatment; and
- The billed cost of antiretroviral drugs obtained from the EPS's invoicing databases.

Each diagnosis was confirmed by Western blot. The group included patients who had died, left the programme or had continued active treatment. Patients of any age and both genders were included and paraclinical results with viral load and CD4 count measurements were not required. Patients having a less than six month latency period between diagnosis and initiation of treatment and data collection were excluded. The protocol was submitted for scientific review and technical and bioethical evaluation by the appropriate authorities from the Universidad Tecnológica of Pereira's Health Sciences Faculty and the EPSs in the category of safe research.

Excel was used for constructing the database and SPSS 17.0 for Windows (SPSS, Inc., Chicago, IL, USA) was used for data analysis. The chi-square test was used for establishing associations between variables by subgroup (controlled patients having less than 400 copies/ml compared to uncontrolled patients having more than 400 copies/ml of viral load). Mean differences were established by a nonparametric test (i.e. the Wilcoxon test). Binary logistic regression models were applied using infection control as the dependent variable. Statistical significance was predetermined to be $p< 0.05$ (95 % confidence interval).

RESULTS

Table 1 gives the characteristics of the population studied. There was a predominance of males (91 men and 43 women: 2.1:1 ratio) in the 134 patients diagnosed with HIV and undergoing antiretroviral treatment in both Colombian cities, average age being less than 39 years old. CHSSS affiliations was as follows: EPS subscribers in Pereira (n=42 patients, 31.3 %; 0.93 HIV patients per 1,000 members prevalence), EPS dependent in Pereira (n=49, 36.6 %; 1.22 HIV patients per 1,000 members prevalence rate) and EPS subscribers in Manizales (n=43, 32.1 % of the sample; 1.07 HIV patients per 1,000 members

prevalence rate). The onset of illness was 59.0 ± 42.1 months on average (range 4 to 186 months). Average treatment onset was 47.5 ± 32.6 (range 1 to 161 months). A significant percentage of patients also had a partner who was infected by HIV and many of the patients also had a history of opportunistic infection. Some also had a history of having acquired other sexually-transmitted diseases (STD).

Table 1. Socio-demographic, clinical and pharmacological characteristics for the 134 HIV/AIDS patients who were treated by the Colombia Health Social Security System (CHSSS) in Pereira and Manizales from July 2008 to June 2009

Characteristics	
Age (μ ± years old)	38.61 ± 10.74
Gender (female/male, %)	32.1/67.9
Marital status (single/married, %)	50.0/50.0
Affiliation (subscriber/dependent, %)	63,5/36.5
Diagnosis-onset latency time HAART (μ ± DE, months)	17.0 ± 28.3
Deaths during the study period (%)	3.7
Couple having HIV (yes/no/data lacking, %)	28.4/48.5/23.1
Background opportunistic diseases	
Candidiasis (%)	24.6
Tuberculosis (%)	17.2
Toxoplasmosis (%)	9.7
Pneumocystis (%)	4.5
Cryptococcosis (%)	4.5
Histoplasmosis (%)	3.7
A history of previous STDs	
Condylomatosis (%)	22.4
Herpes (%)	14.9
Gonorrhoea (%)	11.2
Syphilis (%)	9.0
Most frequently used treatment regimens	
Efavirenz+Lamivudine/Zidovudine (%)	32.1
Lamivudine/Zidovudine+Lopinavir/Ritonavir (%)	14.9
Abacavir+Lamivudine+Lopinavir/Ritonavir (%)	5.2
Indinavir+Lamivudine/Zidovudine+Ritonavir (%)	5.2
Abacavir+Didanosine+Lopinavir/Ritonavir (%)	4.5
Efavirenz+Estavudine+Lamivudine (%)	4.5
Lamivudine/Zidovudine+Nevirapine (%)	4.5
Estavudine+Lamivudine+Lopinavir/Ritonavir (%)	3.7
Efavirenz+Abacavir+Lamivudine (%)	3.0
Abacavir+Lamivudine /Zidovudine (%)	2.2
Others (21 more) (%)	20.1

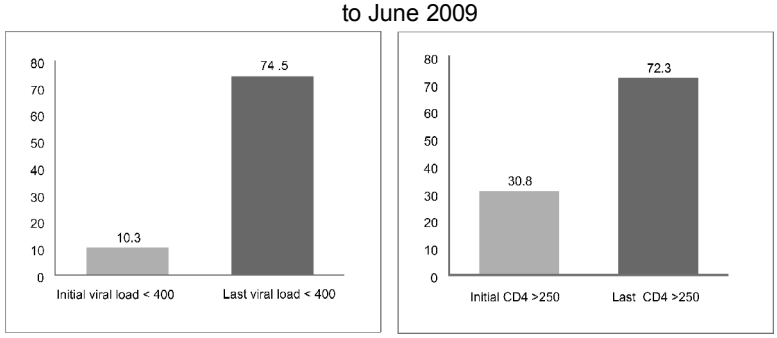
The treatment regimens used are presented in Table 1. All patients received regimens having DDD for each medication. It was striking that 31 different treatment regimens were found in the 134 patients; 18 of these 31 schemes (58.1 %) were registered in the HIV/AIDS Clinical Practice Guidelines and the remaining 13 (42.0 %) were not standard Colombian regimens. It was observed that antiretroviral treatment had been modified from the original regimen in 71 cases (53.0 %), while the other 63 patients had continued with

their original therapy. The most frequently used treatments for comorbidities were gemfibrozil for dyslipidaemia (8.2 % of patients), acyclovir for herpes virus infections (3.0 %) and ferrous sulphate for anaemia (3.0 %). One patient was being treated for active tuberculosis.

Incomplete treatment was found in 28 cases (20.9 % of the sample); physicians reported several reasons why patients had not taken their prescribed therapy (non-adherence, leaving the CHSSS due to unemployment, ignorance). There were also 19 cases (14.2 %) of therapeutic failure requiring modification of initially prescribed therapy. Changes in treatment regimen occurred in 29 patients (21.6 %) because of them developing adverse drug reactions, the most notable being gastrointestinal intolerance (n=8, 5.9 %), anaemia (n=6, 4.4 %), dyslipidaemia (n=5, 3.7 %), depression (n=5, 3.7 %) and nephrolithiasis (n=3, 2.2 %).

Viral load measurements were taken at the time of diagnosis for 97 out of the 134 cases (72.3 % of patients). Measurements from the last semester before data collection were found for 106 patients (79.1 % of the sample) having different distributions, as follows: 89.8 % in EPS-subsidised Pereira, 81.4 % in EPS-contributing Manizales and 64.3 % in EPS-contributing Pereira. The number of patients having initial and final viral loads having less than 400 copies/ml is shown in Figure 1. Antiretroviral therapy was effective in 73.6 % of patients at the time of data collection. Average baseline viral load was 161,863 ± 497,751 (range: 25-4,600,000 copies/ml) and final load was 28,672 ± 125,105 (range: undetectable-1,077,800 copies/ml). Statistically significant differences were found between average initial and final viral loads when using nonparametric tests for establishing the difference between averages (p=0.017).

Figure 1. Distribution of patients having viral load and CD4 lymphocyte measurements treated by the CHSSS in Pereira and Manizales, from July 2008 to June 2009



CD4 lymphocyte measurements taken at the time of diagnosis were found for 104 of the 134 cases (77.6 % of patients); measurements from the last semester before data collection were obtained in 112 cases (83.6 %). The number of patients having greater than 250 cells/mm3 initial and final CD4 lymphocyte counts is presented in Figure 1. An adequate immunological response to antiretroviral therapy was established in 72.3 % of patients. Average initial CD4 lymphocyte count was 242.3 ± 437.8 (range: 2-4210 cells/mm3) and the final count was 408.9 ± 235.3 (range: 13-1 099 cells/mm3). Statistically significant differences were found between average initial and final CD4 lymphocyte counts ($p<0.001$) when using nonparametric tests to establish the difference between averages. In 78 out of 106 cases (73.6 %) there was a statistically significant correlation between the last viral load in HIV control range and the last CD4 lymphocyte count adequate immune response range ($p<0.001$).

Comparing controlled and uncontrolled patients

Table 2 presents the results of a bivariate analysis comparing the controlled HIV patient subgroup and the uncontrolled HIV patient subgroup. There was a statistically significant association between HIV control rate and specific variables such as a patient's insurance company, the city where a patient had been treated, having a history of two other STDs (condylomata and genital herpes), a history of cryptococcal infection and non-adherence to antiretroviral therapy. After treatment modifications, 61.1 % of patients having had treatment failures had viral load values in the control range and 84.6 % of patients who had reported medication intolerance were controlled.

The dependent variable for multivariate analysis was non-control of HIV (viral load greater than 400 copies/ml); the independent variables were the insurer through whom a patient was being treated, having a history of cryptococcal infection, a history of two other STDs and non-adherence to treatment. The binary logistic regression model revealed that the independent variables associated with the risk of non-control for HIV were non-adherence to therapy (0.133 odds ratio [OR]: 0.046-0.380 95 % confidence interval [95 % CI]: $p<0.001$) and having a history of two other STDs (0.087 OR: 0.017-0.458 95 %CI: $p=0.004$). It was found that the variable associated with an increased likelihood of controlled HIV was to be insured and be handled by the Manizales EPS (5.05 OR: 1.165-21.948 95 %CI: $p=0.03$).

Cost evaluation

The average value of drugs per year per patient was US$ 4,077.2 ± 3,043.8 (range: $1,198.2 ± 13,187.3 US dollars/year). The cost per 1,000 inhabitants per day was $ 7.02 US dollars (exchange rate representative of the market on August 28th 2009: 2,043 pesos to 1 dollar).

Table 2. Bivariate analysis of socio-demographic, clinical and pharmacological characteristics of 134 HIV/AIDS patients treated by the CHSSS in Pereira and Manizales, from July 2008 to June 2009

Variable	Controlled HIV/AIDS[1] n	(%)	Not controlled HIV/AIDS[1]	(%)	p-value[2]
Insurance company					
Contributing Ins. Pereira	18	(58.1)	13	(41.9)	
Contributing Ins. Manizales	30	(85.7)	5	(14.3)	
Subsidised insurance	34	(77.3)	10	(22.7)	0.009
City					
Manizales	30	(85.7)	5	(14.3)	
Pereira	48	(67.6)	23	(32.4)	0 .047
Gender					
Female	28	(80.0)	7	(20.0)	
Male	50	(70.4)	21	(29.6)	0.293
Age					
> 15 years old	1	(50.0)	1	(50.0)	
16 to 59 years old	74	(73.3)	27	(26.7)	
< 60 years old	3	(100.0)	0	(0.0)	0 .437
Marital status					
Single	43	(79.6)	11	(20.4)	
Married	35	(68.6)	16	(31.4)	0 .108
Partner suffering HIV					
Yes	19	(73.1)	7	(26.9)	
No	46	(80.7)	11	(19.3)	
No data available	13	(56.5)	10	(43.5)	0 .085
History of tuberculosis					
Yes	11	(61.1)	7	(38.9)	
No	67	(76.1)	21	(23.9)	0 .188
History of STD					
With STD	74	(77.1)	22	(22.9)	
With 2 STDs	4	(40.0)	6	(60.0)	0 .011
Treatment following national guidelines					
Yes	65	(77.4)	19	(22.6)	
No	13	(59.1)	9	(40.9)	0.083
Cost range (US dollar/month)					
<$ 244	19	(67.9)	9	(32.1)	
$ 245 to 489	11	(91.7)	1	(8.3)	
> $ 490	14	(63.6)	8	(34.4)	0.202
Reported non-adherence					
Adherent	70	(83.3)	14	(16.7)	
Non-adherent	8	(36.4)	14	(63.6)	0 .000
Reported treatment failure					
Reported	11	(61.1)	7	(38.9)	
Not reported	67	(76.1)	21	(23.9)	0.188

[1] Level of viral load < 400 copies/ml; [2] Based on the chi-square test

DISCUSSION

One limitation of this study was that the patients came from a CHSSS-affiliated population; this did not allow conclusions to be drawn regarding groups having different epidemiological characteristics. Sample size was limited because all cases of affiliated patients who were receiving antiretroviral treatment during the time period stipulated in the study were included, so the study should be extended to include patients from around the rest of Colombia. Moreover, data was obtained from medical records so there has been under-reporting of adverse drug reactions and other variables. A final limitation was that measuring viral load and CD4 count in a cross-sectional study did not lead to observing behaviour over a period of time, thereby only allowing some statistical associations to be inferred.

HIV control is a global problem. The percentages of patients treated in both developed and developing countries having controlled viral load counts vary from 25 to 84 % (11, 13-16). Compared to similar reports in other countries, the finding that 73.6 % of patients in this study had controlled viral load values was a relatively high control rate (11,13,14). The statistically significant difference between average initial and final viral loads supported such control's effectiveness. The correlation between adequate immune response, as indicated by the CD4 count greater than 250 cells/mm^3, and low viral load suggested that the treatment regimens used in these patients were working effectively (11,13,14).

A previous study has reported the same frequency regarding the use of different antiretroviral agents and treatment regimens (17). The most frequent combination (used in 32.0 % of the sample) was Efavirenz + Lamivudine + Zidovudine which the Guidelines of Clinical Practice for HIV/AIDS in Colombia and the SMART study have recommended as being the first choice for treatment at adequate DDD (11,18-20). Using this combination has suggested that physicians are following national and international recommendations when initiating therapy.

Different risk factors were found in the patients being evaluated such as having a history of opportunistic diseases (most importantly, candidiasis and tuberculosis); Kumarasamy and others have reported similar findings (21, 22). A significant number of patients had a history of other STDs (particularly *Condylomata acuminata* and genital herpes) and was likely related to sexual behaviour and inappropriate use of protection (or lack of it) by pa-

tients. A statistically significant association was found between poor viral load control and non-adherence to treatment, which has been established in other studies (23,24). Treatment by the Manizales EPS was associated with a greater likelihood of control than treatment by the Pereira EPS, suggesting that doctors in Manizales were stricter in meeting goals. The finding that not all patients had viral loads (27.7 % initial and 20.9 % in the last 6 months) and CD4 counts showed that doctors were still failing to use these tests to guide their decisions about treatment effectiveness, even though patients should be able to count on this help every 6 months (11).

Non-adherence to treatment remains one of the most important obstacles to ensuring its effectiveness and this study found that one-fifth of patients had problems continuing therapy for some period of time. The different variables which can influence this have to be taken into account, including a lack of patient education regarding the importance of drug therapy and certain behaviour and habits (such as alcohol consumption) which lead patients to occasionally stopping therapy, the social stigma and desire to conceal one's HIV status, an insurer's ability to deliver drugs, loss of employment and, in turn, loss of CHSSS membership. Given the importance of treatment from a public health standpoint, health authorities should design alternatives to ensure that all HIV patients are provided with continuous treatment regardless of their affiliation to a particular system (23,24).

The finding that more than one-fifth of patients had to change their treatment regimens because of intolerance was similar to that reported by other studies (11,15); the undesirable side-effects reported in our study were also similar (15,25). The high percentage of females (27.9 %) who had been diagnosed during pregnancy tests was an indicator of programme effectiveness during early detection of infection and offered the possibility of prophylaxis to reduce the risk of vertical transmission (11).

Therapeutic failure in 14.2 % of cases has also been found in other reports (11,15). However, these results were incomplete because viral load had not been measured in more than one-quarter of the patients, so this finding could have been undervalued. It was notable that an adequate level of control was attained when treatment regimen was modified in patients who had reported therapeutic failure. A matter of concern was the number of patients lacking viral load measurements who were receiving inadequate monitoring, particularly in the contributing Pereira EPS which had the lowest percentage of patients having reported viral load measurements.

It should be noted that the direct cost of antiretroviral therapy was less than that reported by high-income countries (US $19,400 to US$ 23,100 per patient per year) but was in the range of low-income countries (US $350 to $10,000) The CHSSS must evaluate how much it is willing to invest to maintain HIV-infected patients' health and how much should be invested in programmes focused on HIV prevention (26). This supports the notion that the most expensive therapy is not always the best.

According to this study's results, one can describe patients having uncontrolled HIV as being individuals having a history of non-adherence to therapy and having suffered two other STDs during their lifetime. The above findings supported the recommendation that programmes caring for HIV patients should take measures to promote greater adherence, use various resources to facilitate continued access to drugs for all patients, even when they have lost their membership in the CHSSS, actively search for patients who are not obtaining lab tests and attending doctors' visits and ensure that patients are educated about compliance. In addition, clinicians should ensure that all patients periodically participate in paraclinical tests helping to establish the effectiveness of therapy and the immune response. Providers should adhere to the HIV/AIDS clinical practice guidelines adopted in Colombia, promptly detect any lack of HIV control and take measures to ensure the effectiveness of therapy, which may include using genotyping tests to guide therapy modification following treatment failure (11) ♦

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