Originales

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Viral Load in Spanish HIV patients: trends since the introduction of HAART

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The aim of this study is to describe trends in the percentage of samples with undetectable HIV viral load in Spain after the implementation of HAART. A descriptive observational study of HIV-VL measurements carried out in the microbiology department of the Hospital Clínico Universitario de Valladolid (HCUV) was conducted over a 9-year period (1996-2004).

Regarding the trend over the study period, the 30-39 years age group accounted for most of the samples, although the percentage decreased from 65.5% to 59.6% over the study period. In contrast, the 40-49 years group increased from 9.1% to 14.5%. The preponderance of men, with percentages above 70%, was observed during the whole period.

Although the purpose of this treatment is to maintain undetectable viral loads, since 1999 more than 60% of non-first samples had detectable levels.

Based on the results of the VL trend among HIV/AIDS patients observed in this study, a large number of patients maintain elevated detectable VL years after HAART was implemented. Although different factors may be the cause of this and should be delimited in future studies, the phenomenon observed demonstrates the usefulness of monitoring VL and analyzing its time trend to gain further knowledge about the therapeutic results and care of HIV patients as a whole, also serving as the basis for corrective measures.

Key words:
HIV, Viral Load, HAART.

Tendencia en la evolución de la carga Viral de VIH en pacientes españoles: desde la introducción de la terapia antirretroviral de alta eficacia

El objetivo de este trabajo ha sido describir las tendencias en el porcentaje de muestras con carga viral (CV) de VIH indetectable en una serie española, después de la introducción de la terapia antirretroviral de alta eficacia (HAART). Se ha llevado a cabo un estudio descriptivo observacional de las determinaciones de CV de VIH realizadas en el departamento de microbiología del Hospital Clínico Universitario de Valladolid (HCUV) durante un período de 9 años (1996-2004). Las muestras procedentes de individuos cuya categoría de edad se encontraba en el intervalo de 30-39 años fueron las mas numerosas, y la proporción de CV indetectables en este grupo disminuyó del 65,5% al 59,6% durante el período de estudio. Al contrario en el grupo de 40-49 años aumentó del 9,1% al 14,5%. Los varones, con porcentajes encima del 70%, fueron el grupo preponderante durante el período entero.

De acuerdo con nuestros hallazgos un porcentaje importante de pacientes (más del 60%) mantiene niveles de CV detectable en las muestras de seguimiento, a pesar de la introducción de las terapias «HAART» desde 1999.

La presente aportación demuestra la utilidad de monitorizar la CV y su tendencia en el tiempo, como indicador de la eficiencia terapéutica; aunque sean necesarios estudios futuros que pueden matizar los factores involucrados en este hecho de cara a optimizar los cuidados y la terapia de los pacientes con infección VIH.

Palabras clave:
VIH, Carga Viral, Terapia antirretrovial de alta eficacia

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INTRODUCTION

The viral load (VL) measurement has been a key tool for monitoring clinical status and therapy response in HIV pa-

tients[1-3]. Undetectable values have been widely used as a reliable indicator of minimum viral replication[4,5]. In contrast, detectable values in treated patients indicate failure of antiretroviral therapy[6,7] and have been associated with the appearance and selection of resistance viral lineages to this treatment[8-10].

Spain is one of the European countries with the highest rates of HIV infection. Nonetheless, various measures such as free antiretroviral therapy availability, VL monitoring, and tests to detect antiretroviral resistance have achieved a decrease in the figures of AIDS patients in the last years[11]. The diagnosis activity developed by the microbiological laboratory of a tertiary hospital in Castilla y Leon over the last 15 years has provided greater understanding of VL as a tool to monitor and control treatment among HIV/AIDS patients managed in the Spanish Health System[12,13].

The aim of this study is to describe the characteristics of the patients monitored by a tertiary hospital laboratory since the implementation of the highly antiretroviral therapy (HAART) to 2004 and to identify trends in the percentage of samples with an undetectable HIV viral load.

MATERIALS AND METHODS

A descriptive observational study of HIV-VL measurements carried out in the microbiology department of the Hospital Clínico Universitario de Valladolid (HCUV) was conducted over a 9-year period (1996-2004). The patients included came from seven hospitals, the primary care centres in the city of Valladolid, and four penitentiary centres (table 1).

The VL was measured by reverse transcription-polymerase chain reaction (RT-PCR) (Cobas Amplicor HIV-1 Monitor[MT], Roche Diagnostics; Branchburg, NJ, USA) using the standard test, with a detection threshold of 400 copies of RNA/mL, until March 2000 followed thereafter by the ultra-sensitive test, with a detection threshold of 50 copies of RNA/ml.

The variables collected included age, gender, infection-related risk factors, sexual behavior, and requesting site. For the statistical analysis of continuous variables, the mean and standard deviation (SD) was calculated and for categorical variables, the percentage with respect to the total number of patients.

The primary endpoint was the VL, with each VL measurement classified as undetectable, if the result was below the limits described above, or as detectable, if otherwise. The overall trend of the percentages of patients with undetectable VL by year compared to the number of consultations received was analyzed by linear regression, stratifying according to initial visit or subsequent visit; statistical significance was defined as a = 0.05.

RESULTS

Over the nine-year follow-up period VL was monitored in 2,839 patients, with a total of 16,251 samples analyzed. The average age of patients was 32.9 years (SD, 9.16); and the proportion of men higher than women (77%). Most patients had a history of drug abuse (69.5%) or high-risk sexual contacts (20%), with predominantly heterosexual behaviour (88.8%) (table 1). The median VL was 14,000 copies of RNA/ml.

Regarding the trend over the study period, the 30-39 years age group accounted for most of the samples, although the percentage decreased from 65.5% to 59.6% over the

Table 1	Distribution of the Frequency and Estimators of Central Tendency for the Study Variables in HIV Patients Asked to Undergo Viral Load Testing at the Laboratory of the Hospital Clinico Universitario of Valladolid in 1996–2004

| Variable	N	%
Patients	2,839	100
Sex		
Women	645	22.8
Men	2,174	76.7
Age (years)		
Mean(SD): 32.9 (9.2)		
< 19 y	83	4.5
20-29 y	445	23.9
30-39 y	1050	56.5
40-49 y	204	11
> 50 y	77	4.1
Risk factors for infection		
Intravenous drug users (IDU)	428	69.5
High risk sexual contact	123	20
IDU-high risk sexual contact	27	4.4
Transfusion	14	2.3
Vertical	24	3.9
Sexual behaviour		
Bisexual	11	2.8
Heterosexual	355	88.8
Homosexual	34	8.5
Samples	16,251	100
Viral load (copies of RNA/ml)		
Mean(SD): 70,277.2 (14,000)		
Log of viral load (log copies of RNA/ml)		
Mean(SD): 4.0 (1.0)		
Referral centre:		
Primary care centres	92	0.6
Hospitals	13,563	83.5
Penitentiary centre	894	5.5
Others	1,667	10.3

a)

b)

c)
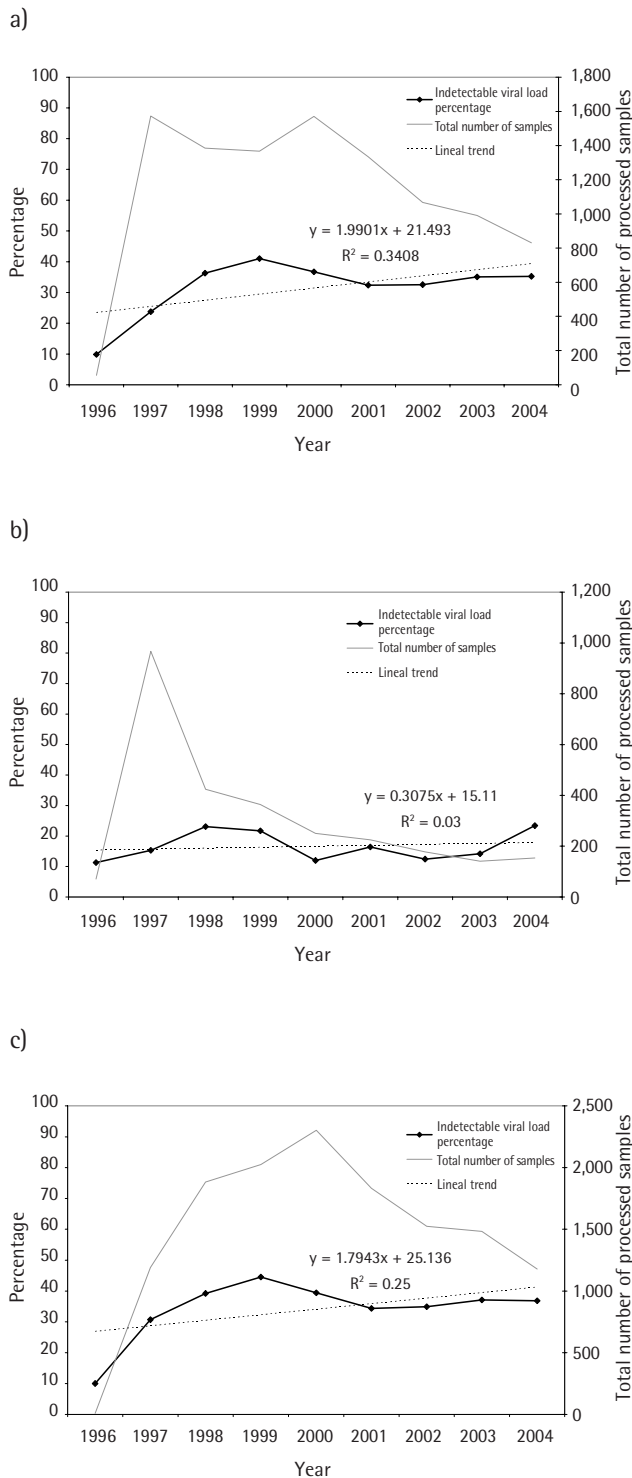
Figure 1   *Trends of the percentage of detectable VL values, number of total samples processed yearly and fit of the trend line for the percentage of detectable VL compared to the total sample analyzed (a), samples from initial visits (b) and samples from second and subsequent visits (c) (1996-2004).*

study period. In contrast, the 40-49 years group increased from 9.1% to 14.5%. The preponderance of men, with percentages above 70%, was observed during the whole period.

The overall percentage of patients with undetectable VL showed a gradual rise until 1999 (41.0%). Figure 1 shows a yearly increase of 10.6% in the percentage of undetectable samples until 1999 that was statistically significant (p=0.02), with values remaining constant thereafter until 2004 (ß=-0.01%, p=0.98). Figure 1b shows that the percentage of undetectable VL in initial measurements remained stable throughout the study period, with no significant trend (ß=0.3%, p=0.66). Likewise, the number of samples analyzed among new patients gradually decreased to 154 samples in 2004. The percentage of undetectable VL in second and subsequent measurements also experienced an increase until 1999 (ß=14.2%, p=0.047), then stabilized in the following years (ß=-0.23%, p=0.76). The total number of samples analyzed in second and subsequent measurements peaked in year 2000, but later decreased (figure 1c).

DISCUSSION

This study presents a descriptive analysis of the VL results obtained among HIV patients by a microbiology laboratory in Spain with longstanding experience in the diagnosis of HIV/AIDS patients over a nine-year period that included the time when HAART was implemented in Spain. The results show no trend in the percentage of patients with detectable VL from 1999 on. These findings indicate that, although the purpose of HAART is to maintain patients with undetectable VL, in clinical practice more than 60% of patients who undergo testing at the second or subsequent visits have observable levels, which means this goal has not been achieved. This is relevant when considering that the prognosis of HIV patients with detectable VL is poorer and that the probability of resistances is higher[14,15].

The general descriptive nature of this study does not allow the specific impact of proper follow-up of patients' particular treatment to be assessed because relevant variables such as follow-up time, therapy administered, number of visits for each patient, and measurement frequency have not been considered. Additionally, other parameters more closely related to clinical stage, such as CD4 lymphocyte levels, would have to be considered for this assessment to be performed[16,17]. Despite the limitations mentioned, the high percentage of detectable VL among patients who have begun follow-up represents a good opportunity to evaluate factors associated with virological failure. In this sense, another metacentre study conducted to assess the prevalence of antiretroviral resistance in patients with recent infection found a resistance prevalence of 14% and a direct relationship with the existence of detectable VL in Spain[18,19].

Another relevant aspect of this study is the profile of patients for whom VL measurements were requested. In terms

of age, the results show an increase in the patient age at which VL is determined, a finding that could be explained by greater patient survival and a lower incidence of the disease[11]. In addition this study shows that the highest number of samples received were from men, intravenous drug users, and heterosexuals, although a history of high-risk sexual contact and homosexuality is also common, accounting for 20% and 8.5% of patients monitored, respectively.

The need to conduct studies on the validity and usefulness of VL was already suggested a decade ago[20]. The value of these studies lies in a large number of contributions, which included the optimization of detection levels[21], the description of response patterns[22], the predictive value of intermittent viraemia[23], and the undeniable usefulness as a marker of antiretroviral response in long-term cohort studies[24,25]. Similar to recent suggestions by Stöhr et al[17], who presented the findings of seven British sites, the present study will help encourage the performance of more powerful observational studies and health care follow-up to determine the behaviour and evolution of VL in clinical practice overall and define, to the extent possible, uniform guidelines for the control of viraemia and the use of antiretroviral therapies that would improve the results.

In conclusion, based on the results of the VL trend among HIV/AIDS patients observed in this study, a large number of patients maintain elevated detectable VL years after HAART was implemented. Although different factors may be the cause of this and should be delimited in future studies, the phenomenon observed demonstrates the usefulness of monitoring VL and analyzing its time trend to gain further knowledge about the therapeutic results and care of HIV patients as a whole, also serving as the basis for corrective measures.

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