

Validation of four AIDS-case definitions in HIV-infected intravenous drug users in Barcelona, Spain

Validação de quatro definições de caso de aids em usuários de drogas injetáveis em Barcelona, Espanha

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Abstract

The objective of the study is to assess the sensitivity and specificity of four epidemiological AIDS-Case Definitions (CDC-87, CDC-93, Europe-93 and Revised Caracas) in HIV-infected intravenous drug users (IDU). The authors carried out a cross-sectional study with 136 IDUs, HIV-infected from a Men Penitentiary Center and from a drug addiction treatment center of Barcelona, Spain, between October/93 and April/94. A protocol, including demographic, clinical and laboratory variables was used by one doctor and the laboratory tests were done in the same institution. After that, the patients were classified in the four Epidemiological AIDS-Case Definitions used by this study. As gold standard we used the CD4 Cell Count (out point 200 or 14% CD4+). The number of AIDS cases varied between 31 and 84 according to the type of AIDS definition. The CDC-93 AIDS definition implied an increase of 170.9% in the number of cases in relation to CDC-87 AIDS-Case Definition. The sensitivities of the CDC-87, CDC-93, Europe-93 and Revised Caracas Epidemiological AIDS – Case Definitions were 34.2, 88.6, 45.6 and 56.9% while the specificities were 93.0, 75.4, 75.4 and 77.2%, respectively. The positive predictive values were between 72.0% (Europe-93) and 87.1% (CDC-87) and the negative predictive values were between 50.0% (Europe-93) and 82.7% (CDC-93). The authors concluded: the sensitivity and specificity of Caracas Revised Epidemiological AIDS-Case Definition was better than Europe-93 AIDS Case Definition. So this Definition can be very useful in countries and situations where the CD4 Cell Count is not available for technical or economical reasons.

Keywords: Acquired Immunodeficiency Syndrome, epidemiology. Substance abuse, intravenous. Epidemiologic research design. Sensitivity and specificity. Spain.

Resumo

O objetivo do estudo é observar a sensibilidade e a especificidade de 4 definições epidemiológicas de Caso de Aids (“CDC-87”, “CDC-93”, “Europa-93” e “Caracas Revisada”) em usuários de drogas (ilícitas) intravenosas, infectados pelo HIV/VIH. Os autores realizaram um estudo com 136 usuários, infectados pelo HIV/VIH, de um centro penitenciário para homens e de um centro de tratamento de usuários de drogas de Barcelona, Espanha, entre Outubro/1993 e Abril 1994. Um protocolo, incluindo variáveis demográficas, clínicas e laboratoriais, foi usado pelo mesmo médico e os testes laboratoriais, necessários à investigação, realizados na mesma instituição. Em seguida, os pacientes da amostra foram classificados nas 4 definições de Caso de Aids usados pelo estudo. Como padrão foi usada a contagem de CD4+. O número de casos de Aids variou entre 31 e 84 segundo a definição de Caso de aids utilizada. O uso de Definição CDC-93 implicou no aumento de 170,9% no número de casos com relação a Definição CDC-87. As sensibilidades das definições de Caso de Aids – CDC-87, CDC-93, Europa-93 e Caracas Revisada foram respectivamente, 34,2, 88,6, 45,6 e 56,9%, enquanto as especificidades foram, respectivamente, 93,0, 75,4, 75,4 e 77,2%. Os valores predictivos positivos estiveram entre 72,0% (Definição Europa-93) e 87,1% (“CDC-87”) e os valores predictivos negativos se apresentaram entre 50,0% (“Europa-93) e 82,7% (“CDC-93”). Os autores concluíram que a Definição Epidemiológica de Caso de Aids “Caracas Revisada” apresentou melhor sensibilidade e especificidade que as apresentadas pela Definição de Caso de Aids “Europa-93”. Por este motivo, a Definição de Caso “Caracas Revisada” pode ser útil em países e situação onde a contagem de células CD4+; por razões técnicas ou econômicas, não é disponível.

Palavras-chave: Síndrome da imunodeficiência adquirida, epidemiologia. Abuso de substâncias por via endovenosa. Desenho de pesquisa epidemiológica. Sensibilidade e especificidade. Espanha.

Introduction

Definition plays a fundamental role in any scientific work, as does the use the definition is put to and its subsequent validation. Despite the fact that the causal agent in AIDS was identified as far back as 1983 and since that time the disease has become much more prevalent, different definitions are still applied, thereby hindering international comparisons.

The most commonly used definitions are those of the *Centers for Disease Control* (CDC-87¹ and CDC-93²), Europe-93³ and “Revised Caracas”⁴⁻⁶ which have replaced the 1982 CDC definition⁷. The Europe-93 definition, which is a variation of the CDC-93, is the most widely used in Europe. The Revised Caracas definition, also has been referred to as “the Caracas clinical AIDS definition”, the “PAHO”, “OPS”, or “Rio de Janeiro definitions”, as the Pan American Health Organization / Organización Panamericana de Salud sponsored the Caracas workshop which drafted it, and the empirical basis for it was the clinical research in Rio de Janeiro, Brazil, which is considered to be extremely useful in developing countries and may be an efficient tool for the epidemiological monitoring of AIDS since it is based on general signs and low-cost laboratory tests.

Validation is the process that examines the degree to which the results of measurements correspond to the real state and/or presence of the phenomenon being measured⁸. In certain cases it is necessary to find a tool whose validity is inferior but which is more viable in operational terms. This implies the need to investigate its degree of validity against others whose validity is greater, using internationally accepted criteria as a gold standard. In this way the strengths and weaknesses of the tool to be used can be established.

The objective of this study is to validate the definitions of cases of AIDS (CDC-87, CDC-93, Europe-93 and Revised Caracas in a population of HIV-infected injecting drug users (IDU) with a high prevalence of tuberculosis (TB).

Patients, Materials and Methods

The population studied consisted of HIV-infected IDU patients attended by medical services of the "Modelo" Prison or the "Sportdrog" center for drug-addicts in Barcelona, between October 1993 and April 1994.

In each case a standard survey was completed on the basis of a standardized interview and a clinical examination. The details recorded included different kinds of variables: demographic (age and gender), clinical (tuberculous infection/disease and AIDS diagnosis) and laboratory (CD4+ and CD8+ lymphocyte subsets).

Tuberculous infection was investigated using the tuberculin skin test with 2 UT of PPD-RT 23. In line with the criteria used in Spain, induration of 5 mm or more after 72 hours was considered a positive reaction⁹. The lymphocyte subsets were analyzed with monoclonal antibodies using flow cytometry. All the medical examinations were performed by the same doctor.

IDUs were defined as injecting drug users who had habitually (more than once a week) consumed such drugs during the previous year. HIV infection was determined by the ELISA method and confirmed by Western blot test.

Patients were classified according to the following definitions of AIDS: CDC-87, CDC-93, Europe-93 and Revised Caracas. This last definition attributes points on the basis of signs, symptoms and diseases and requires patients to obtain a total score above 9⁵.

The *Gold Standard* was taken as an HIV-infected IDU patient with a total of number of CD4+/l lymphocytes less than $0.2 \times 10^9/l$ or less than its expression as percentage (14%)¹⁰.

The sensitivity of each definition was calculated as the percentage of patients who satisfied its criteria among all HIV+ IDU with CD4+ lymphocytes less than $0.2 \times 10^9/l$ or less than 14% of total lymphocytes.

The specificity of the definitions was calculated as the percentage of IDU and HIV+ presenting a total number of CD4+ lymphocytes equal to or greater than $0.2 \times$

$10^9/l$ or 14% who failed to satisfy the criteria for AIDS of their respective definitions, in relation to the total of those presenting a total number of CD4+ lymphocytes equal to or greater than $0.2 \times 10^9/l$ or 14%.

The positive predictive value (PPV) was the proportion among all patients satisfying the criteria of a definition classifying them to have AIDS who actually had CD4+ cell levels $<0.2 \times 10^9/l$ or $<14\%$ of lymphocytes. The negative predictive value (NPV) was the proportion among all patients **not** satisfying the criteria of an AIDS definition who had CD4+ cell levels $\geq 0.2 \times 10^9/l$ or $\geq 14\%$ of lymphocytes.

The number of persons to be included in the study was calculated on the basis of other studies undertaken to validate definitions of AIDS cases which all involved between 100-150 people¹¹⁻¹³.

The data gathered were fed into computers and treated using the statistical programs SPSS-PC and EPIINFO 5.0. The statistical tests applied were the χ^2 and Mc Nemar.

Results

The study included 136 patients, of whom 115 (84.6%) were from the "Modelo" prison and 21 (15.4%) from the "Sportdrog" center. By gender, 133 (97.8%) were males and 3 (2.2%) females. By age-group, 44% were between 21 and 30, 54% were between 31 and 40 and 2% were over 40. The average number of CD4+ lymphocytes was $0.24 \times 10^9/l$ (SD +/- 0.017). Of the subjects studied, 69 (50.7%) presented a total number of CD4+ lymphocytes less than $0.2 \times 10^9/l$.

The number of AIDS cases was between 31 and 84, depending on the definition used. Applying the CDC-93 definition produced 170.9% more cases than the CDC-87 definition, 68.0% more than Europe-93 and 44.8% more than the Reviewed Caracas (Figure).

According to our *Gold Standard* (a total of number of CD4+/l lymphocytes less than $0.2 \times 10^9/l$ or less than its expression as percentage 14%) the sensitivity ranged from 34.2% (CDC-87) to 88.6% (CDC-93). The specificity ranged from 75.4% (CDC-

93 and Europe-93) to 93.0% (CDC-87) (Table 1). The positive predictive values (PPV) varied from 72.0% (Europe-93) to 87.1% (CDC-87) and the negative predictive values (NPV) between 50.0% (Europe-93) to 82.7% (CDC-93).

The effect of using the CD4+ lymphocyte figure as criterion for diagnosing AIDS can be seen by comparing the CDC-93 and Europe-93 definitions in Table 2. Both definitions identify an equal number of clinical cases, but there is an increase of 68.0% in the absolute number of diagnoses due to the influence of the cases without AIDS-defining diseases but with a number of CD4+ lymphocytes less than $0.2 \times 10^9/l$ or a percentage less than 14% (Table 2).

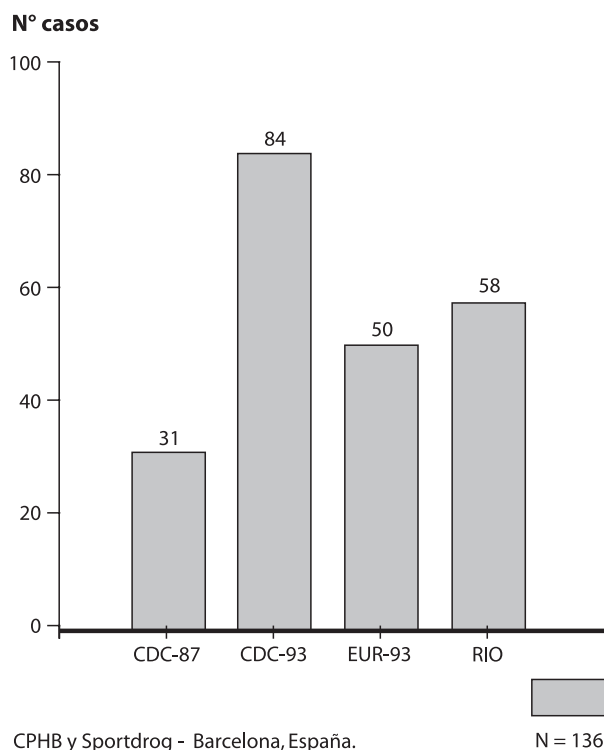
Disseminated or extrapulmonary TB was the criterion for diagnosing AIDS in 65% (20 out of 31) cases with the CDC-87 definition. The inclusion of pulmonary TB produced an increase of 26% (13 out of 50) cases of AIDS with the Europe-93 definition (Table 2).

Discussion

Several AIDS studies have investigated the variation in the number of cases due to changes in definition¹⁴⁻¹⁶, but there have been very few validation studies. Such studies are usually carried out when laboratory tests are unavailable to check HIV¹⁰ infection and they generally involve hospitalized patients in an advanced state of the illness¹³⁻¹⁵.

Such studies suffer from two main drawbacks: a) without determining the existence of HIV infection, specificity and sensitivity are seriously limited, and b) the use of hospitalized patients produces a greater sensitivity which is in fact only apparent, since stages showing a lesser degree of the disease are not validated.

A major difficulty in defining AIDS is the choice of Gold Standard¹⁷. Unfortunately the criteria for AIDS diagnosis have not so far been unified and what is more, the number of definitions has increased as time has gone by. This has effects on epidemiology and public health in so far as it makes interna-



CPHB y Sportdrog - Barcelona, España.

N = 136

Figure 1 - Number of AIDS cases according to AIDS - Case definition utilized. Barcelona. Oct/93-April/94

Table 1 - Sensitivity and specificity of AIDS-case definitions according to Gold Standard criterion (CD4+ $0.2 \times 10^9/l$ lymphocytes or CD4+ <math><14\%</math>).

Definitions	Sensitivity	Specificity
CDC-87	34.2	93.0
CDC-93	88.6	75.4
EUR-93	45.6	75.4
REV.CAR	56.9	77.2

Source: CPHB and Sportdrog - Barcelona, Spain, 1994.

Table 2 - Comparison of AIDS criteria according to Europe-93 and CDC-93 AIDS-case definitions.

AIDS criteria	Europe-93		CDC-93	
	Nº	%	Nº	%
Candidiasis esophageal	7	14.0	7	8.3
Pneumonia by P.carinii	2	4.0	2	2.4
Toxoplasmosis	2	4.0	2	2.4
Dissemin/Ext.Pul.TB	20	40.0	20	23.8
Rec./Multi Infecc. Bacterial	1	2.0	1	1.2
Kaposi's Sarcoma	3	6.0	3	3.6
Wasting Syndrome	1	2.0	1	1.2
Pulmonary TB	13	26.0	13	15.5
Recurrent Pneumonia	1	2.0	1	1.2
CD4+ <math><200</math> or CD4+ <math><14\%</math>	-	-	34	40.4
Total of cases	50	100	84	100

Source: CPHB and Sportdrog - Barcelona, Spain, 1994

tional comparisons difficult and hinders the management and planning of resources.

In our study, the CDC-93 definition proved to be the most sensitive, followed by Revised Caracas, Europe-93 and CDC-87. These results may be explained by the fact that the first definition includes, as a criterion of AIDS, the reference standard used in this research ($CD4+ < 0.2 \times 10^9/l$ or $CD4+ < 14\%$). It should, however, be pointed out that the Revised Caracas definition showed greater sensitivity than the Europe-93, although the differences obtained were not statistically significant. The CDC-93, Europe-93 and Revised Caracas definitions had similar specificities whereas the CDC-87 showed the most. The paradox of this study is that a "simplified" definition as Revised Caracas is seemed to perform as well as some of the regular ones.

The use of $CD4+$ lymphocytes as a standard is quite recent. The CDC began using them in 1990 to identify the HIV infection stage¹⁸, as this virus was thought to be responsible for the depletion of $CD4+$ lymphocytes¹⁹. However, it was with the CDC-93 definition that the use of these cells in epidemiological monitoring of AIDS was firmly established. Although several authors have suggested the suitability of employing $CD4+$ lymphocyte counts as the *Gold Standard*, there is still a considerable amount of controversy surrounding their use. It has been contended that the number of $CD4+$ lymphocytes can be modified by illness²⁰, medicines, ethnic origin, age, psychological or physical stress and even by the use of drugs.

At all events, in our investigation, where definitions were compared in relation to a particular $CD4+$ limit, all the definitions validated would presumably have been equally affected by these factors and comparison between the definitions would thus not have been affected.

It has been suggested that the decision whether or not to use $CD4+$ lymphocytes also depends on economic, technological and even psycho-social and ideological grounds. The determination of the number of $CD4+$ lymphocytes costs \$150 in the U.S.A.²¹, but the access to this procedure is

not the same for patients from different ethnic groups or those exhibiting different risk behaviors²², not to mention the fact that it is beyond the means of many developing countries. Moreover, classifying patients without symptoms as having AIDS could entail serious psychological and social consequences such as loss of job, restrictions on the use of private medical insurance or reduced income^{23,24}. The ideological question is also closely bound up with the economic aspect. The cost of using preventive drugs to guard against opportunistic infections can run to as much as \$9.367 per patient per year^{25,26}. These medicines may delay the development of the disease and patient hospitalization, which represents the main direct economic cost of the epidemic²⁷. It has been estimated that in the countries of the European Union such costs vary between \$ 13.000 and \$ 70.000 per person per year²⁸. In countries where responsibility for health care is restricted to ill patients, acceptance of definitions of AIDS which include asymptomatic patients entails important economic and political consequences. Nevertheless, it has also been argued that new definitions of AIDS do not in practice alter patients' state of health or health care needs²⁹.

An important aspect of our study that should be taken into account is that it was carried out exclusively with IDU patients with a high prevalence of TB, which might have had a bearing on the large number of AIDS cases detected. Other studies have observed similar symptoms in IDU and homosexuals when the $CD4+$ lymphocyte count was below $0.2 \times 10^9/l$. However, when the count was $0.2-0.5 \times 10^9/l$, the former presented signs and symptoms more frequently³⁰. Selwin et al.³¹ have shown that IDUs display specific features in the development of AIDS, although they attribute these differences to the state of the immune system, tuberculosis infection or the use of preventive drugs, among other factors, rather than to the fact of being an IDU or not.

These findings would suggest the advisability of using the Caracas Revised and Europe-93 definitions in countries where TB

is the largest AIDS-defining disease, especially if determination of lymphocyte subpopulations is difficult or unavailable.

In conclusion, the defining criterion has a considerable influence on the number of AIDS cases recorded in an HIV-infected population. The validated definitions exhibit a degree of sensitivity and specificity compatible with their application in the

epidemiological monitoring of AIDS. However, the use of the Revised Caracas definition – a “clinical” case definition intentionally designed to minimize laboratory or pathologic criteria that might not be available in developing countries – is recommended when it is not possible to analyze lymphocyte subsets, as often happens in the majority of developing countries.

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