

Diagnostic tests in HIV management: a review of clinical and laboratory strategies to monitor HIV-infected individuals in developing countries

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Abstract We conducted a systematic review on the performance of diagnostic tests for clinical and laboratory monitoring of HIV-infected adults in developing countries. Diagnostic test information collected from computerized databases, bibliographies and the Internet were categorized as clinical (non-laboratory patient information), immunologic (information from immunologic laboratory tests), or virologic (information from virologic laboratory tests). Of the 51 studies selected for the review 28 assessed immunologic tests, 12 virologic tests and seven clinical and immunologic tests. Methods of performance evaluation were primarily sensitivity and specificity for the clinical category and correlation coefficients for immunologic and virologic categories. In the clinical category, the majority of test performance measures was reported as >70% sensitive and >65% specific. In the immunologic category, correlation coefficients ranged from $r = 0.54$ to $r = 0.99$ for different CD4 count enumeration techniques, while correlation for CD4 and total lymphocyte counts was between $r = 0.23$ and $r = 0.74$. In the virologic category, correlation coefficients for different human immunodeficiency virus (HIV) ribonucleic acid (RNA) quantification techniques ranged from $r = 0.54$ to $r = 0.90$. Future research requires consensus on designing studies, and collecting and reporting data useful for decision-makers. We recommend classifying information into clinically relevant categories, using a consistent definition of disease across studies and providing measures of both association and accuracy.

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يمكن الاطلاع على الملخص بالعربية في صفحة 587.

Introduction

In developed countries, immunologic and virologic status of human immunodeficiency virus (HIV)-infected patients is monitored using laboratory markers. Cluster designation 4 (CD4) cell count and human immunodeficiency virus (HIV) ribonucleic acid (RNA) level (or viral load) have been shown to predict both clinical outcomes and disease progression.¹⁻³ Past guidelines published by WHO also recommended the use of CD4 cell count and HIV RNA to monitor HIV-infected individuals.^{4,5} As part of its "3-by-5" initiative, WHO proposed a tiered patient monitoring framework with CD4 cell count at the district level and CD4 cell count and HIV RNA quantification at the regional level, but with neither compulsory for patient management (Table 1). However,

these guidelines provide limited guidance on other diagnostic tests to guide therapeutic decision-making in HIV management.^{6,7}

Our objective was to review the literature on the performance of diagnostic tests for clinical and laboratory monitoring of HIV-infected adults. We compiled relevant qualitative and quantitative information to make it accessible to a wide range of users and to identify key challenges regarding the method of HIV-related diagnostic test data collection and reporting in developing countries.

Methods

Overview

We conducted a formal, systematic review of the literature on clinical and laboratory monitoring of HIV-infected individuals in developing countries between

February and April 2004. Literature was confined to published sources and conference abstracts identified through computerized databases, published indices and bibliographic references.

Study Selection

We selected studies according to a priori inclusion and exclusion criteria (Table 2). Inclusion criteria were determined in two stages. Test performance evaluation was defined as sensitivity and/or specificity as well as correlation coefficients. We considered assessment of instruments, equipment, or other technology used to perform the diagnostic tests as secondary criteria for study inclusion.

Exclusion criteria were also identified in two stages. We assumed that the basic biologic and cellular mechanisms of HIV disease progression are similar

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Table 1. WHO-recommended tiered laboratory capabilities for antiretroviral monitoring in limited-resource settings^a

Primary health care centres (level 1)	District hospitals (level 2)	Regional referral centres (level 3)
Rapid HIVab test	Rapid HIVab test	Rapid HIVab test
Haemoglobin (if ZDV ^b is being considered for use) ^c	Capability to resolve indeterminate rapid HIVab test by second serological method	FBC and differential CD4+ cell count ^d
Pregnancy testing ^e	FBC ^f and differential	Full serum chemistries (including but not restricted to electrolytes, renal function, liver enzymes, lipids)
Referral for sputum smear for tuberculosis (if microscopy not available)	CD4+ cell count ^d ALT ^g Pregnancy testing ^e Sputum smear for tuberculosis	Pregnancy testing ^e Sputum smear for tuberculosis Viral load testing ^h

Source: World Health Organization. *Scaling up Antiretroviral Therapy in Resource-Limited Settings: Treatment Guidelines for a Public Health Approach*. 2003 Revision. Geneva: WHO; 2004.

^a This table only considers testing that is desirable for proper monitoring of antiretroviral toxicity, efficacy and two prominent concomitant conditions (pregnancy and tuberculosis). It is not meant to be comprehensive with respect to other diagnostic capabilities that are important in the comprehensive care of HIV-infected persons. Other resources are available for these considerations.

^b ZDV = zidovudine.

^c In primary health care centers where laboratory facilities are not available or in the absence of laboratory-based haemoglobinometry, the WHO haemoglobin colour scale can be used together with clinical signs to evaluate anaemia (more information available from: www.who.int/bct/).

^d Scale-up of antiretroviral treatment under the "3 by 5" plan does not require uniform CD4 (cluster designation 4) testing availability but, because of the value of this test in patient monitoring, WHO will work with Member States to make this a reality.

^e EFV = efavirenz. EFV should not be given to women with childbearing potential unless adequate contraception is assured, nor to women in the first trimester of pregnancy.

^f FBC = full blood count.

^g ALT = amino alanine transferase.

^h Because of the cost and technical issues associated with viral load testing, this test is not currently recommended as part of the present treatment guidelines. However, it is hoped that more cost-effective technologies will allow regional referral centers to acquire this capability given its utility in assessing treatment failure.

for all HIV-infected individuals; because the relationship between CD4 cell count and HIV RNA has been shown to reflect disease progression rather than test performance,¹ we excluded studies solely on the association between these two measures.

Neither use nor type of treatment (e.g. antiretroviral therapy or opportunistic infection prophylaxis) was used as inclusion or exclusion criteria.

Data extraction

To integrate available information on diagnostic tests for monitoring HIV patients into a format useful for decision-making, we classified diagnostic test information from each study into three categories: (1) clinical information, defined as non-laboratory-based patient information including physical examination, clinical staging system and/or clinical history; (2) immunologic information, defined as information obtained from diagnostic laboratory tests assessing immunologic function; and (3) virologic information, defined as information obtained from diagnostic laboratory tests assessing virologic status. We chose these categories to reflect current, clinically

and policy relevant approaches to monitoring HIV-infected individuals.

We recorded data from studies that met the inclusion criteria, but did not violate the exclusion criteria. Data included number a of study subjects, mean age, gender distribution, sensitivity and/or specificity of diagnostic tests, correlation measures, demographic information, treatment type, presence of co-infection, HIV-1 or HIV-2 infection, HIV subtype, type of diagnostic test(s) examined, assay used to perform the diagnostic test and performance evaluation method. Geographic locations were classified by region.⁹ For the purpose of this review we defined urbanity as a major city and/or its outlying areas. A second reviewer examined a subsample to ensure internal validity of data extraction.

For studies reporting sensitivity and specificity, we categorized tests as either *reference standard* or *index* test. The reference standard was defined as the best available diagnostic test, which served as the comparison for an alternative test.^{10,11} Sensitivity was defined as $Pr(\text{positive test} \mid \text{disease condition present})$,

or the probability that the specified value or condition as measured by the index test reflected the value or condition as measured by the reference standard. Specificity was defined as $Pr(\text{negative test} \mid \text{disease condition absent})$, or the probability that the absence of the value or condition as measured by the index test reflected the absence of the value or condition as measured by the reference standard. If two methods of flow cytometry (the gold standard in enumerating CD4) were evaluated, single-platform flow cytometry was considered the reference and dual-platform the index. When appropriate, diagnostic test characteristics were derived.

For studies that compared across categories, we listed information in all relevant categories. When studies examined various diagnostic tests *within* a particular category (e.g. comparison of different CD4 cell count assays and different CD8 cell count assays), we presented the diagnostic test results for each type of diagnostic test.¹² However, when multiple results for the same diagnostic test were reported, we showed only a single representative result.

Table 2. Inclusion and exclusion criteria: study selection for the systematic review of diagnostic tests in HIV management

Inclusion criteria	Exclusion criteria
<p>Stage 1 HIV seropositive adults Studies conducted in low- or middle-income settings⁸ Use of clinical staging classification or diagnostic tests with intent to monitor HIV disease progression Journal publication or conference proceeding in English, French, or Spanish</p> <p>Stage 2 All Stage 1 + performance evaluation of immunologic, virologic, and/or clinical diagnostic tests</p>	<p>Stage 1 Studies exclusively on the association between CD4 cell count and HIV RNA Studies conducted in high-income settings⁸ Studies providing only setting-specific immunologic or virologic reference values In vitro studies, reviews or reports</p> <p>Stage 2 Studies not reporting relevant quantitative data on diagnostic test characteristics, including studies referring to results on diagnostic test performance but which presented no data Results not stratified by HIV serostatus Studies solely on prognosis or survival Studies on laboratory methods Results not stratified by relevant gross national income status Studies evaluating HIV RNA <i>gag</i> sequences Studies evaluating tests for HIV diagnosis Studies involving subjects from developing countries but with laboratory diagnostics conducted in developed countries Citation bias (i.e. conference proceeding subsequently published in peer-reviewed journal)</p>

Results

Of the 125 articles or conference proceedings we identified for detailed review, 51 were included. Seventy-two were excluded based on Stage 1 or Stage 2 exclusion criteria, while two were irretrievable due to incomplete or incorrect bibliographic information.

Description of included studies

The number of HIV-infected subjects reported in each study ranged from 12 to 2777 (mean = 229.4, standard deviation (SD) 413.0). Mean age ranged from 27.0 to 38.0 years. Weighting mean age by number of study subjects resulted in a weighted mean age of 32.9 years (SD 2.2 years); 35 studies did not report mean age. The percentage of males enrolled in each study ranged from 28.9% to 77.2%. In a weighted analysis, we determined that 51.4% (SD 2.4%) of study subjects were male; gender distribution was not reported in 31 studies.

A description of included studies is shown in Table 3. The majority of studies included in our review assessed immunologic diagnostic tests only (28/51 or 55%). Twelve of 51 (24%) studies assessed virologic tests only while seven (14%) evaluated both clinical and immunologic diagnostic tests. Nine of 51

(18%) measured diagnostic test performance using sensitivity/specificity only, 28 (55%) via correlation coefficient only and 14 (28%) via both sensitivity/specificity and correlation.

Clinical information

We classified nine of 51 studies in this category, with two reporting multiple results for a total of 12 entries (Table 4 (measures of accuracy); Fig. 1 and Fig. 2 (measures of association); all web version only, available from <http://www.who.int/bulletin>). Ten of the 12 entries examined the relationship between clinical and immunologic tests; five of the ten evaluated CD4 or total lymphocyte counts only and a clinical staging or classification system only, and three of the ten compared the performance of various permutations of clinical and immunologic tests. Sensitivity of these 10 entries ranged from 29% when using oral candidiasis to predict CD4 cell counts <200 cells/mm³ to 96% when using clinical staging, total lymphocyte count and white blood cell count to predict CD4 cell count; specificity for these studies was 96% and 83%, respectively.^{17,18} Four entries compared clinical staging to CD4 cell count as measured by flow cytometry and one examined clinical staging and total lymphocyte count as

measured by haematology analyser. Two of 12 entries compared clinical information and virologic information¹⁹ as well as clinical and immunologic information and virologic information.²⁰ Two of 12 entries evaluated performance using measures of association.²⁰

Immunologic information

We classified 39 of 51 studies in this category, with 14 of 39 reporting multiple results for a total of 81 entries (Table 5 (measures of accuracy); Fig. 1 (measures of association); web version only, available from <http://www.who.int/bulletin>). Forty-three of 81 entries assessed only lymphocyte subsets, including CD4, CD8 or CD3 cell counts, or CD4%, CD8% or CD3%. Seventeen entries evaluated different techniques for measuring CD4 cell count, including single- and dual-platform flow cytometry, enzyme immunoassay, bead-based manual counting, immunoalkaline phosphatase and microchip assay. Five assessed different assays for CD4%, while four entries and one entry assessed different assays for CD8% and CD3%, respectively. Four entries examined the association between CD4 cell count and CD4%. Sixteen of 81 entries evaluated the relationship between lymphocyte

subsets and total lymphocyte count, with 14 of 16 entries examining CD4 cell count and total lymphocyte count. Four of 81 entries compared lymphocyte subsets with immune activation markers (e.g. lymphocyte proliferation, tumour necrosis factor- α (TNF- α)) and four with white blood cell counts or associated differentials. Four compared immune function and virologic markers while 10 investigated the relationship between immune function and clinical markers. Fifty-one of 81 entries reported only correlation coefficients, 17 reported only sensitivity/specificity, and 13 reported correlation coefficients and sensitivity/specificity.

We found that studies assessing different techniques for measuring CD4 cell count reported correlation coefficients ranging from $r = 0.54$ to $r = 0.99$.^{21,22} In the four studies examining enzyme immunoassay, correlations between CD4 cell count as measured by dual-platform flow cytometry and enzyme immunoassay were all $r < 0.70$.^{12,21,23,24} When a blood fixative was employed using dual-platform flow cytometry with pan-leucogating, correlations were $r = 0.97$ at day 0, $r = 0.98$ between days 0 and 3, and $r = 0.92$ between days 0 and 7.²⁵ In our review, correlation between total lymphocyte and CD4 cell counts ranged from $r = 0.23$ to $r = 0.74$.^{26,27} Sensitivity when assessing CD4 cell count and total lymphocyte count ranged from 43% for a total lymphocyte count < 1200 cells/mm³ to predict a CD4 cell count < 200 cells/mm³ to 78% for a total lymphocyte count < 1500 cells/mm³ to predict a CD4 cell count < 200 cells/mm³; specificity for these studies was 98% and 80%, respectively.^{28,29} For the 22 entries in which CD4 cell count served as the reference standard and for which sensitivity/specificity were reported, 18 and 2 entries reported a disease-present status of CD4 count < 200 cells/mm³ and < 350 cells/mm³, respectively.

Virologic information

We classified 16 of 51 studies in this category, with five reporting results for multiple diagnostic tests, resulting in a total of 26 entries (Table 4 presents one measure of accuracy and Table 5 presents two measures of accuracy; Fig. 2 (measures of association) all web version only, available at <http://www.who.int/bulletin>). Twenty-one of 26 entries compared HIV RNA quantification and viral

Table 3. Description of included studies for the systematic review of diagnostic tests in HIV management

Variable	Number (%) ^a n = 51
Geographic location	
Africa	38 (75)
Asia	9 (18)
Central America, Mexico, Caribbean	1 (2)
South America	3 (6)
Income level ^b	
Low only	37 (73)
Low-middle only	10 (20)
Middle-high only	3 (6)
Urbanity ^c	
Urban	40 (78)
Rural	1 (2)
Not reported	10 (20)
Treatment ^d	
Antiretroviral therapy	6 (12)
Opportunistic infection prophylaxis	1 (2)
Other	5 (10)
None	3 (6)
Not reported	33 (65)
HIV/tuberculosis co-infection	3 (6)
Types of diagnostic tests evaluated	
Clinical only	0 (0)
Immunologic only	28 (55)
Virologic only	12 (24)
Clinical/immunologic	7 (14)
Clinical/virologic	0 (0)
Immunologic/virologic	2 (4)
Clinical/immunologic/virologic	2 (4)
Measures of test performance	
Sensitivity/specificity	9 (18)
Correlation	28 (55)
Sensitivity/specificity and correlation	14 (28)

^a Percentages may not total 100% due to rounding.

^b Countries were assigned an income-level status (low, low-middle, middle-high, or high) based on gross national income per capita.⁸ One study¹³ was classified as both low and low-middle income.

^c An urban area was defined as a major city and/or the city's outlying areas.

^d Three studies¹⁴⁻¹⁶ had study subjects who were both on and off antiretroviral therapy.

activation markers or reverse transcriptase activity; the remaining five evaluated viral activation markers and clinical staging or immune activation markers (e.g. β -2 microglobulin, CD4 cell count). Fifteen entries evaluated HIV-1 infected study subjects with non-B subtypes, including CRF02_AG and subtypes A, C, D, and G in West Africa; A and D in East Africa; E in Southern Africa; and E in Southeast Asia. None of the studies included HIV-2 infected study subjects. Sensitivity and specificity of diagnostic test performance were reported for only 4 entries,^{19,30} with the remainder reporting correlation coefficients.

Seventeen entries compared commonly used HIV RNA quantification techniques — reverse transcriptase polymerase chain reaction (RT PCR), branched deoxyribose nucleic acid (bDNA) and nucleic acid sequence-based amplification (NASBA). Correlation coefficients for these, comparing both RT PCR and bDNA tests ranged from $r = 0.54$ to $r = 0.90$.^{31,32} Other virologic diagnostic tests examined included viral activation markers (p24 antigen assay) and reverse transcriptase activity. One study reported that concentration of p24 antigen < 1500 fg/ml was 100% sensitive and 91% specific for HIV-1

RNA <400 copies/ml when comparing HIV-1 RNA as measured by RT-PCR and viral activation as measured by heat-denatured p24 antigen assay.³⁰ Four entries evaluated immune and viral activation markers. One study found detectable p24 antigen 72% sensitive for β_2 -microglobulin concentration >5 mg/l as well as 72% sensitive for CD4 count <200 cells/mm³, the same study found detectable p24 antigen 86% sensitive for WHO clinical stage 4.¹⁹ However, the correlation between p24 antigen and CD4 cell count/CDC clinical classification system was low ($r = 0.23$).²⁰

Discussion

Through a systematic review, we identified, selected and critically evaluated 51 studies on clinical, immunologic and virologic strategies for monitoring HIV-infected individuals in developing countries. In the studies we reviewed, over 90% were performed in African and Asian lower income countries and nearly 80% were conducted in urban areas. Monitoring strategies were assessed using a broad range of diagnostic tests, assays or staging systems.

Our review revealed that methods of performance evaluation varied widely across all three types of diagnostic test information categories (clinical, immunologic, virologic). For example, performance measures for “clinical information” were reported primarily as sensitivity and specificity. As expected, most studies reporting performance measures of a patient’s clinical information focused on the relationship between a clinical staging or classification system and lymphocyte subsets (primarily CD4 count <200 cells/mm³). We found that the sensitivity of different clinical staging systems for CD4 cell count varied extensively (Fig. 3, web version only, available from: <http://www.who.int/bulletin>).

In contrast, performance of diagnostic tests using immunologic or virologic status was reported mainly as a correlation coefficient. We found that correlation coefficients ranged from $r^2 = 0.29$ to $r^2 = 0.97$ when comparing different techniques for enumerating CD4 cell count, suggesting relatively robust results among widely differing CD4 count enumeration technologies.^{21,22} However, when assessing the relationship between CD4 and total lymphocyte count, correlation coefficients ranged from $r^2 = 0.05$ to $r^2 = 0.55$, indicating less consistent

findings and greater variation between these two tests.^{26,27} In the few studies reporting the sensitivity of a CD4 cell count enumeration technology, the disease condition primarily was defined as CD4 count <200 cells/mm³. In these studies, sensitivity ranged from 29% to 96%^{17,18} and specificity from 55% to 98%.^{28,33}

The performance of tests used to ascertain virologic status also was generally reported as a correlation coefficient. Correlation coefficients ranged from $r^2 = 0.29$ to $r^2 = 0.81$ when we compared commonly used HIV RNA quantification techniques.^{31,32} Correlations between different HIV RNA quantification techniques for non-B subtypes ranged mainly between $r^2 = 0.49$ and $r^2 = 0.72$.^{34,35} These results suggest robust results among various HIV RNA quantification techniques for HIV-1 B and non-B subtypes. However, due to lack of information on HIV-2-infected subjects, the performance of these tests in such patients is unknown. We identified only one study examining the accuracy of viral activation markers for HIV RNA.³⁰

Our review had several limitations. We confined our study selection to articles and conferences that were published and/or electronically available, which likely limited incorporation of the most up-to-date data. We also encountered a number of specific challenges in synthesizing this body of information. For example, no universal gold standard has been explicitly defined for monitoring HIV-infected individuals, thereby making identification of the gold standard or reference standard for each study uncertain. The definition of disease and the methods used to assess diagnostic test performance were not consistent across studies. Therefore, we did not evaluate study quality to assess reliability and validity and could not account for bias, reporting error and other methodological limitations of the individual studies.¹¹ While measures of association, such as correlation coefficients, provide researchers with information on the strength of a relationship between two diagnostic tests, they do not provide information that can more easily be translated into clinical decision-making as with measures such as sensitivity and specificity. This is particularly relevant for HIV markers evaluated on a continuous scale, where sensitivity and specificity can be used to identify critical clinical

thresholds when providing antiretroviral therapy or opportunistic infection prophylaxis. Lastly, we did not examine reported assay, instrument and personnel costs or include other biochemical parameters important in the follow-up of HIV-infected individuals receiving treatment,³⁶ as they were beyond the scope of this study.

While HIV care providers in developing countries are working to improve laboratory capacity, key issues, such as where future studies might be conducted (e.g. urban versus rural locales) or the methods used to evaluate diagnostic test performance, have not been addressed.^{37–40} In particular, complete and transparent reporting of participants, test methods, statistical methods, test results and test estimates — as outlined in The Standards for Reporting of Diagnostic Accuracy (STARD) Initiative¹¹ — will play a major role in improving how diagnostic test data are collected and reported. Addressing these issues can provide important information that will assist programme planners and policy-makers in better understanding how diagnostic tests can be used to assess, for example, population-level antiretroviral resistance patterns and HIV RNA distributions. On an individual level, this information can aid in determining not only which diagnostic tests should be used to monitor patients, but also which tests should be employed to initiate HIV management interventions. For example, whether a patient’s clinical information is an appropriate diagnostic tool to initiate opportunistic infection prophylaxis and/or antiretroviral therapy will depend on formal analysis that considers the benefits of treating patients with true positive results as well as the consequences of not treating patients who need treatment (false negatives) and treating patients who do not need treatment (false positives).

Conclusion

We conclude that the broad range of diagnostic tests, the instruments and techniques used to conduct the tests, and the heterogeneity of their reported performance suggest a need for consensus among the research community on how to design studies, and collect and report data in a format that is most useful for decision-makers in developing countries. We recommend the following actions that are critical to successfully scaling up HIV treatment and monitoring efforts

in developing countries: (1) classifying information into clinically relevant categories (clinical, immunologic, or virologic); (2) using a consistent definition of disease across studies; and (3) reporting both measures of association (e.g. correlation coefficients) and measures of accuracy (e.g. sensitivity and specificity). ■

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Résumé

Tests diagnostiques et prise en charge des infections à VIH : revue des méthodes cliniques et analytiques permettant le suivi des personnes contaminées dans les pays en développement

Nous avons réalisé une revue systématique des performances des tests diagnostiques utilisés pour le suivi clinique et biologique des adultes contaminés par le VIH dans les pays en développement. Les résultats de tests diagnostiques recueillis à partir des bases de données informatisées, les données bibliographiques et les informations obtenues sur Internet ont été classés en trois catégories : données cliniques (informations au sujet des malades ne provenant pas des examens en laboratoire), immunologiques (informations fournies par les tests immunologiques en laboratoire) et virologiques (informations fournies par les tests virologiques en laboratoire). Parmi les 51 études sélectionnées pour la revue, 28 évaluaient des tests immunologiques, 12 des tests virologiques et 7 des tests cliniques et immunologiques. L'évaluation des performances méthodologiques se fondait principalement sur la sensibilité et la spécificité pour les données de la catégorie clinique et sur les coefficients de corrélation pour les données appartenant aux catégories immunologique et virologique. Pour la catégorie

clinique, d'après la mesure des performances, la majorité des tests présentaient une sensibilité > 70 % et une spécificité > 65 %. Pour la catégorie immunologique, les coefficients de corrélation allaient de $r = 0,54$ à $r = 0,99$ pour les différentes techniques de numération des CD4, tandis qu'entre la numération des CD4 et celle des lymphocytes totaux, ces coefficients se situaient entre $r = 0,23$ et $r = 0,74$. Pour la catégorie virologique, les coefficients de corrélation entre les différentes techniques de quantification de l'ARN du VIH allaient de $r = 0,54$ à $r = 0,90$. Pour les travaux de recherche à venir, il serait nécessaire de parvenir à un consensus sur les modalités de conception des études et, de collecte et de rapport des données utiles aux décideurs. L'article recommande de classer les informations selon des catégories cliniques pertinentes, en utilisant une définition identique de la maladie dans l'ensemble des études et en fournissant une évaluation de la corrélation et de la précision.

Resumen

Pruebas diagnósticas en el manejo de la infección por VIH: estudio de las estrategias clínicas y de laboratorio empleadas para controlar a las personas infectadas por el VIH en los países en desarrollo

Realizamos una revisión sistemática de la eficacia de las pruebas diagnósticas como medio de seguimiento clínico y de laboratorio de las personas infectadas por el VIH en los países en desarrollo. La información sobre pruebas diagnósticas reunida a partir de bases de datos computarizadas, de las publicaciones y de Internet se clasificó como clínica (información sobre los pacientes distinta de los datos de laboratorio), inmunológica (información sobre pruebas inmunológicas) o virológica (información sobre pruebas virológicas). De los 51 estudios seleccionados para la revisión, 28 evaluaron pruebas inmunológicas, 12 pruebas virológicas, y 7 pruebas clínicas e inmunológicas. Los métodos de evaluación de la eficacia fueron principalmente la sensibilidad y la especificidad en el caso de las pruebas clínicas, y los coeficientes de correlación en el caso de las pruebas inmunológicas y virológicas. Entre las primeras, la mayoría de las medidas de eficacia de las pruebas revelaron

una sensibilidad superior al 70% y una especificidad superior al 65%. En la categoría de pruebas inmunológicas, los coeficientes de correlación oscilaron entre 0,54 y 0,99 para diferentes técnicas de recuento de CD4, mientras que la correlación (r) entre los recuentos de CD4 y de linfocitos totales se situó entre 0,23 y 0,74. En cuanto a las pruebas virológicas, los coeficientes de correlación para diferentes técnicas de cuantificación del ARN del VIH fueron de entre 0,54 y 0,90. A la hora de realizar nuevas investigaciones en el futuro, será necesario consensuar el diseño de los estudios, y reunir y notificar datos de utilidad para las instancias decisorias. Recomendamos clasificar la información en categorías clínicamente pertinentes, utilizar una definición coherente de enfermedad en todos los estudios, y proporcionar medidas tanto de asociación como de exactitud.

ملخص

اختبارات تشخيصية في تدبير فيروس العوز المناعي البشري:

مراجعة للاستراتيجيات السريرية (الإكلينيكية) والمختبرية لرصد المصابين بعدوى فيروس العوز المناعي البشري في البلدان النامية

معظم مقاييس أداء الاختبارات تزيد على 70% حساسية وعن 65% نوعية. أما في الفئة المناعية فقد تراوح معامل الترابط بين 0.54 و0.99 بالنسبة لأساليب مختلفة لتعداد الخلايا CD4، فيما تراوح معامل الارتباط بين تعداد الخلايا CD4 وتعداد كامل اللمفاويات يتراوح بين 0.23 و0.74. وفي الفئة الفيروسية، تراوح معامل الارتباط في الأساليب المختلفة لتقدير كمية رنا فيروس العوز المناعي البشري بين 0.54 و0.90. وتمس الحاجة في المستقبل إلى الوصول إلى إجماع حول تصميم الدراسات وجمع المعطيات والإبلاغ عنها مما يفيد أصحاب القرار السياسي. وأوصينا بتصنيف المعلومات إلى فئات مناسبة باستخدام تعاريف متسقة للأمراض في جميع الدراسات وتوفير وسائل للترابط والدقة.

قمنا بمراجعة منهجية لأداء الاختبارات التشخيصية والمختبرية لرصد المصابين بعدوى فيروس العوز المناعي البشري من البالغين في البلدان النامية. جمعنا المعلومات حول الاختبارات التشخيصية من قواعد المعطيات المحوسبة وفهارس المكتبات والإنترنت، وصنفناها إلى اختبارات سريرية (معلومات غير مختبرية حول المرضى)، ومناعية (معلومات من الاختبارات المناعية) وفيروسية (معلومات من المختبرات الفيروسية). ومن بين 51 دراسة اختيرت للمراجعة، كانت 28 دراسة لتقييم الاختبارات المناعية، و12 دراسة لتقييم الاختبارات الفيروسية و7 دراسات لتقييم الاختبارات السريرية والمناعية. أما طرق تقييم الأداء فكانت بشكل رئيسي الحساسية والنوعية للفئة السريرية ومعامل الترابط للفئات الفيروسية والمناعية معاً. وقد كان

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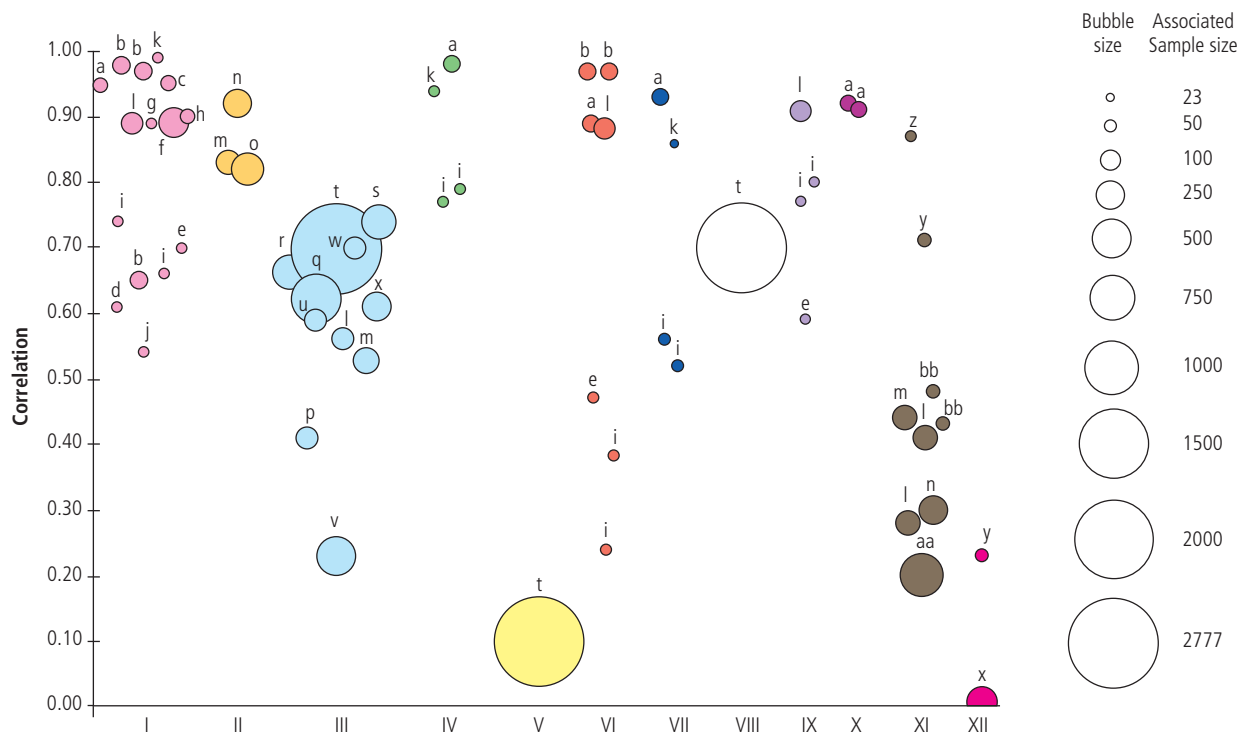
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Call for papers — *Bulletin* theme issue on “health and foreign policy”

The *Bulletin* welcomes submissions on the topic of “health and foreign policy” for a theme issue of the *Bulletin* to be published in March 2007. Public health has become more important to the making and implementing of foreign policy over the past decade. Such explicit links have created both opportunities and challenges for people working in health protection and promotion. We are seeking papers on the historical, theoretical, and practical aspects of pursuing health as a foreign policy objective, and are particularly interested in research or policy and practice papers that provide developing country perspectives on the relationship between health and foreign policy. Papers that use examples or case studies to illustrate how foreign policy actions, instruments, or processes, constitute a determinant of health outcomes are also welcome. Papers submitted will be subject to the *Bulletin's* usual peer review process, and should be written in accordance with the Guidelines for Contributors, available from <http://who.int/bulletin/en>. The deadline for submission is 1 October 2006.

Fig. 1. Performance of immunologic diagnostic tests for monitoring HIV-infected individuals: measures of association



Correlation coefficients (on the y-axis) range from 0 to 1, with performance measures grouped by type of diagnostic tests compared. Twelve groups were defined and represented as I–XII on the x-axis, as follows: (I) CD4 cell count versus CD4 cell count; (II) CD4 cell count versus CD4%; (III) CD4 cell count versus total lymphocyte count (TLC); (IV) CD4% versus CD4%; (V) CD4% versus TLC; (VI) CD8 cell count versus CD8 cell count; (VII) CD8% versus CD8%; (VIII) CD8% versus TLC; (IX) CD4/CD8 versus CD4/CD8; (X) CD3 cell count (CD3%) versus CD3 cell count (CD3%); (XI) CD4 cell count versus clinical and/or other immunologic information; and (XII) immunologic and/or clinical information versus virologic information. Groups I–X reflect measures of association between different sources of immunologic information only. Group XI reflects measures of association between immunologic and/or clinical information and/or clinical information and/or immunologic information. Group XII reflects measures of association between immunologic and/or clinical information and virologic information. The area of each bubble is proportional to the sample size of the study from which a correlation was abstracted. The letter(s) above each marker denote the associated reference of the point estimate.

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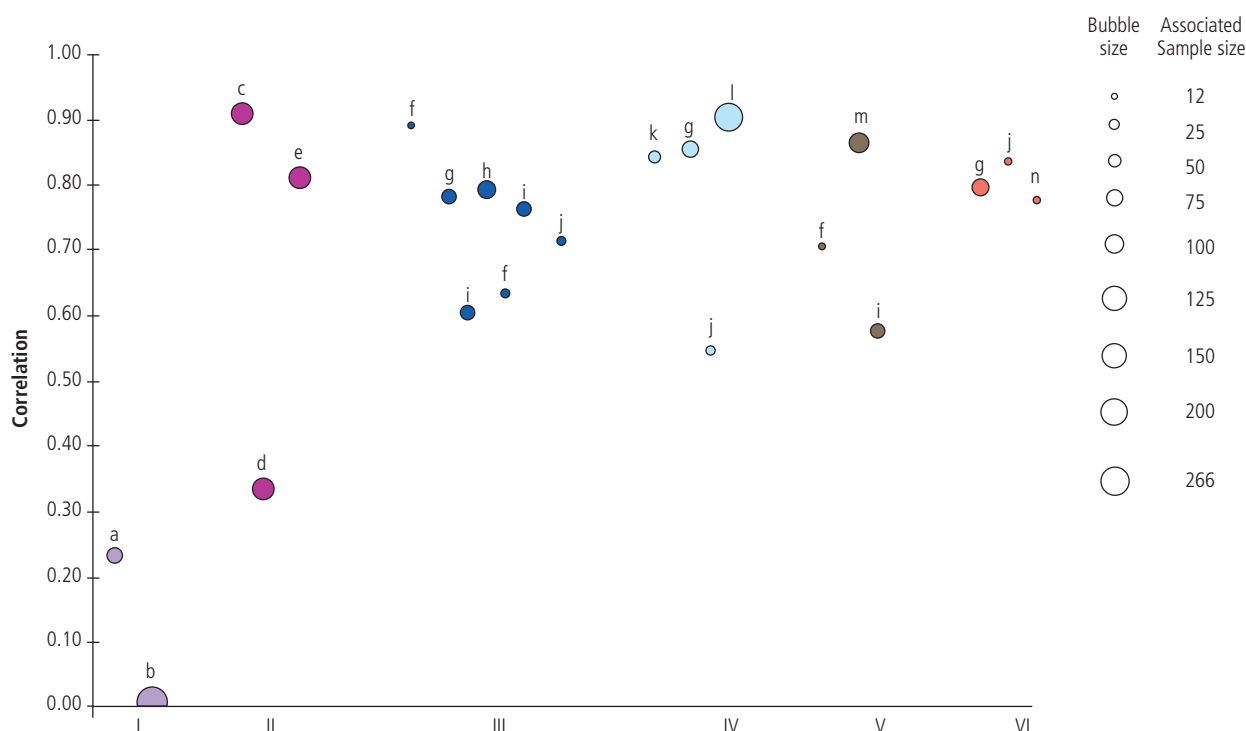
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Fig. 2. Performance of virologic diagnostic tests for monitoring HIV-infected individuals: measures of association



Correlation coefficients (on the y-axis) range from 0 to 1, with performance measures grouped by type of diagnostic tests compared. Six groups were defined and represented as I–VI on the x-axis, as follows: (I) Virologic information compared to clinical and/or immunologic information, (II) HIV RNA and p24 antigen, (III) HIV-1 RNA (RT-PCR) versus HIV-1 RNA (NASBA), (IV) HIV-1 RNA (RT-PCR) versus HIV-1 RNA (bDNA), (V) HIV-1 RNA (RT-PCR) versus HIV-1 RNA (RT-PCR or RT enzyme activity), and (VI) HIV-1 RNA (NASBA) versus HIV-1 RNA (bDNA). Group I reflects measures of association between virologic information and clinical and/or immunologic information. Groups II–VI reflect measures of association between different sources of virologic information only. The area of each bubble is proportional to the sample size of the study from which a correlation was abstracted. The letter above each marker denotes the associated reference of the point estimate.

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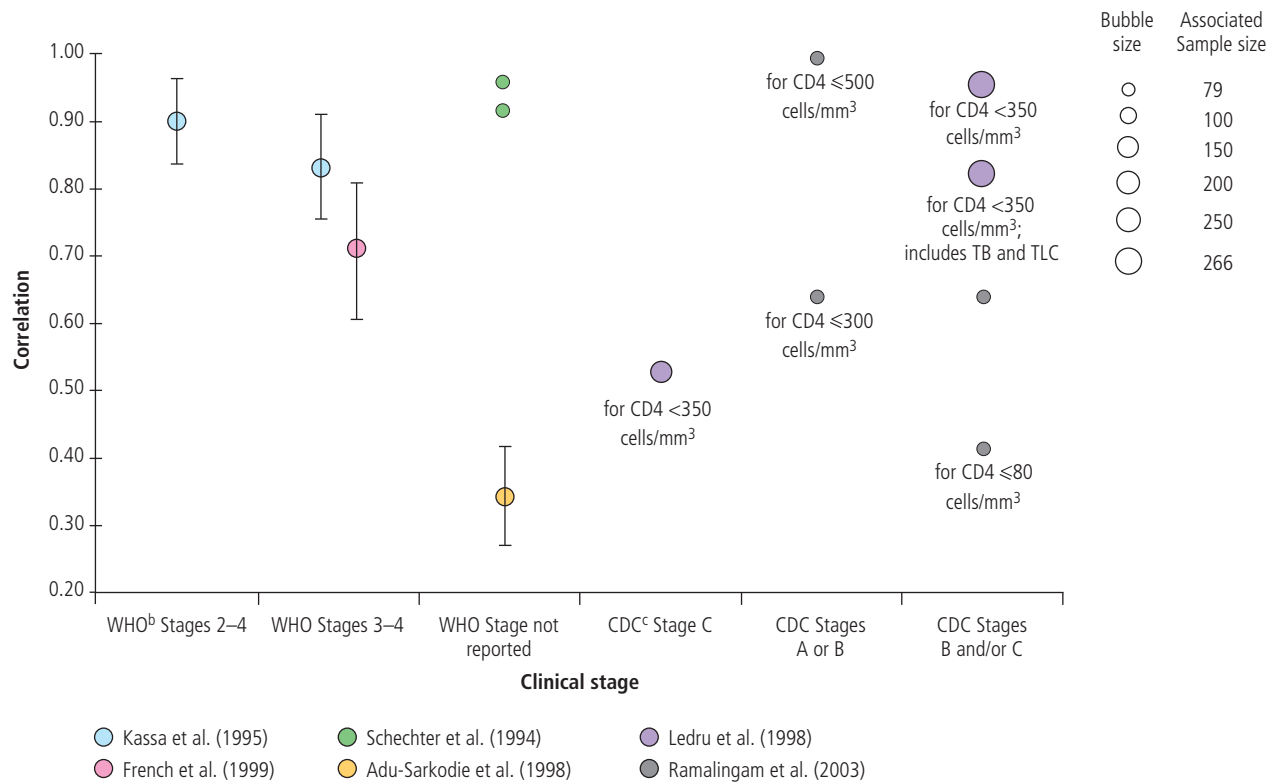
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Fig. 3. Sensitivity of different clinical staging systems for CD4 cell count^a



^a All values are compared to CD4 (cluster differentiation 4) count <200 cells/mm³ unless otherwise specified. The size of each marker is proportional to the sample size of the study.

^b WHO = World Health Organization.

^c CDC = Centers for Disease Control and Prevention.

Kassa et al. (1995) = Kassa E, Rinke de Wit TF, Hailu E, Girma M, Messele T, Mariam HG, et al. Evaluation of the World Health Organization staging system for HIV infection and disease in Ethiopia: association between clinical stages and laboratory markers. *AIDS* 1999;13:381-9.

French et al. (1999) = French N, Mujugira A, Nakiyingi J, Mulder D, Janoff EN, Gilks CF. Immunologic and clinical stages in HIV-1-infected Ugandan adults are comparable and provide no evidence of rapid progression but poor survival with advanced disease. *J Acquir Immune Defic Syndr* 1999;22:509-16.

Schechter et al. (1994) = Schechter M, Zajdenverg R, Machado LL, Pinto ME, Lima LA, Perez MA. Predicting CD4 counts in HIV-infected Brazilian individuals: a model based on the World Health Organization staging system. *J Acquir Immune Defic Syndr* 1994;7:163-8.

Adu-Sarkodie et al. (1998) = Adu-Sarkodie Y, Sangaré A, d'Almeida OA, Kanmogne GD. Distribution of CD4+ T-lymphocytes levels in patients with clinical symptoms of AIDS in three West African countries. *J Clin Virol* 1998;11:173-81.

Ledru et al. (1998) = Ledru E, Diabougua S, Meda N, Sanou PT, Dahourou H, Ledru S, et al. A proposal for basic management of HIV disease in West Africa: use of clinical staging and haemogram data. *Int J STD AIDS* 1998;9:463-70.

Ramalingam et al. (2001) = Ramalingam S, Kannangai R, Zachariah A, Mathai D, Abraham C. CD4 counts of normal and HIV-infected south Indian adults: do we need a new staging system? *Natl Med J India* 2001;14:335-9.

Table 4. Performance of clinical diagnostic tests for monitoring HIV-infected individuals: measures of accuracy

Author (year of publication)	Diagnostic tests			Test characteristics				
	Reference standard	Index	Value	Sensitivity [P(T+ D+)] ^a		Specificity [P(T- D-)] ^b		
				Positive test	Disease	Value	Negative test	No disease
Clinical information versus virologic information								
Hofer et al. (1994) ^c	WHO ^d staging system	p24 ^e antigen	86%	p24 positive (detectable)	WHO stage 4	–	p24 negative	WHO stages 1–3
Clinical information versus immunologic information								
Adu-Sarkodie et al. (1998) ^f	WHO staging system, Bangui definition	CD4 ^g	34%	<200 cells/mm ³	WHO Bangui definition of AIDS ^h	–	≥200 cells/mm ³	WHO Bangui definition of non-AIDS
French et al. (1999) ⁱ	CD4	WHO staging system	71%	WHO stage ≥3	<200 cells/mm ³	68%	WHO stage <3	>200 cells/mm ³
Kassa et al. (1999) ^j	CD4	WHO staging system	83%	WHO stage ≥3	<200 cells/mm ³	71%	WHO stage ≤2	>200 cells/mm ³
Ramalingam et al. (2001) ^l	CD4	CDC ^k classification system	64%	CDC classification groups B or C	≤200 cells/mm ³	55%	CDC classification group A	>200 cells/mm ³
Ghate et al. (2000) ^m	CD4	Oral candidiasis	29%	Oral candidiasis	≤200 cells/mm ³	96%	No oral candidiasis	>200 cells/mm ³
Ramalingam et al. (2001) ^l	CD4%	CDC classification system	73%	CDC classification groups A or B	≤14%	65%	CDC classification group C	>14%
Ramalingam et al. (2001) ^l	TLC ⁿ	WHO staging system	46%	Not reported	1000–2000 cells/mm ³	65%	Not reported	<1000 or >2000 cells/mm ³
Clinical and immunologic information versus immunologic information								
Schechter et al. (1994) ^o	CD4	WHO staging system, TLC, WBC ^p	96%	Not reported, <1000 cells/mm ³ , <40%	≤200 cells/mm ³	83%	Not reported, >1000 cells/mm ³ , >40%	>200 cells/mm ³
Ledru et al. (1998) ^q	CD4	CDC classification system, pulmonary tuberculosis, TLC	82%	CDC classification ≥B OR BAAR ^r positive sputum; ≤2500 cells/mm ³	<350 cells/mm ³	70%	CDC classification <B OR BAAR negative sputum; >2500 cells/mm ³	>350 cells/mm ³
Sehgal et al. (2002) ^s	CD4, CDC classification system	TNF-α ^t receptor	95%	>550 pg/ml	≤200 cells/mm ³ , CDC group 3	–	<550 pg/ml	>200 cells/mm ³ , CDC groups 1 & 2

^a P(T+|D+): P(positive test|disease condition present), or the probability that the specified value or condition as measured by the index test reflected the value or condition as measured by the index test.

^b P(T-|D-): P(negative test|disease condition absent), or the probability that the absence of the value or condition as measured by the index test reflected the absence of the value or condition as measured by the reference standard.

^c Hofer CB, Pinto ME, Zajdenverg R, Schechter M. p24 antigenaemia in HIV-1 infected Brazilians correlates with other markers of disease progression. *J Infect* 1994;29:129-31.

^d WHO = World Health Organization.

^e p24 = protein 24.

^f Adu-Sarkodie Y, Sangaré A, d'Almeida OA, Kanmogne GD. Distribution of CD4+ T-lymphocytes levels in patients with clinical symptoms of AIDS in three West African countries. *J Clin Virol* 1998;11:173-81.

^g CD4 = cluster differentiation 4.

^h AIDS = acquired immunodeficiency syndrome.

ⁱ French N, Mujugira A, Nakiyingi J, Mulder D, Janoff EN, Gilks CF. Immunologic and clinical stages in HIV-1-infected Ugandan adults are comparable and provide no evidence of rapid progression but poor survival with advanced disease. *J Acquir Immune Defic Syndr* 1999;22:509-16.

^j Kassa E, Rinke de Wit TF, Hailu E, Girma M, Messele T, Mariam HG, et al. Evaluation of the World Health Organization staging system for HIV infection and disease in Ethiopia: association between clinical stages and laboratory markers. *AIDS* 1999;13:381-9.

^k CDC = Centers for Disease Control and Prevention.

^l Ramalingam S, Kannangai R, Zachariah A, Mathai D, Abraham C. CD4 counts of normal and HIV-infected south Indian adults: do we need a new staging system? *Natl Med J India* 2001;14:335-9.

^m Ghate MV, Mehendale SM, Mahajan BA, Yadav R, Brahme RG, Divekar AD, et al. Relationship between clinical conditions and CD4 counts in HIV-infected persons in Pune, Maharashtra, India. *Natl Med J India* 2000;13:183-7.

ⁿ TLC = total lymphocyte count.

^o Schechter M, Zajdenverg R, Machado LL, Pinto ME, Lima LA, Perez MA. Predicting CD4 counts in HIV-infected Brazilian individuals: a model based on the World Health Organization staging system. *J Acquire Immune Defic Syndr* 1994;7:163-8.

^p WBC = white blood cells.

^q Ledru E, Diabougba S, Meda N, Sanou PT, Dahourou H, Ledru S, et al. A proposal for basic management of HIV disease in West Africa: use of clinical staging and haemogram data. *Int J STD AIDS* 1998;9:463-70.

^r BAAR = acid-alcohol resistant bacillus.

^s Sehgal S, Datta U, Mujtaba S, Sood A, Vinayak VK. Cellular and serological markers of disease activity in Indian patients with HIV/AIDS. *Methods Cell Sci* 2002;24:107-14.

^t TNF-α = tumour necrosis factor-alpha.

Table 5. Performance of immunologic diagnostic tests for monitoring HIV-infected individuals: measures of accuracy

Author (year of publication)	Diagnostic tests		Test characteristics					
	Reference standard	Index	Value	Sensitivity [P(T+ D+)] ^a		Specificity [P(T- D-)] ^b		
				Positive test	Disease	Value	Negative test	No disease
Immunologic information versus clinical information								
Ghate et al. (2000) ^c	CD4 ^d	Oral candidiasis	29%	Oral candidiasis	≤200 cells/mm ³	96%	No oral candidiasis	>200 cells/mm ³
Adu-Sarkodie et al. (1998) ^e	WHO ^f staging system, Bangui definition	CD4	34%	≤200 cells/mm ³	WHO Bangui definition of AIDS ^g	–	>200 cells/mm ³	WHO Bangui definition of non-AIDS
Kassa et al. (1999) ^h	CD4	WHO staging system	83%	WHO stage ≥3	<200 cells/mm ³	71%	WHO stage ≤2	>200 cells/mm ³
French et al. (1999) ⁱ	CD4	WHO staging system	71%	WHO stage ≥3	<200 cells/mm ³	68%	WHO stage <3	>200 cells/mm ³
Ramalingam et al. (2001) ^j	CD4	CDC ^k classification system	64%	CDC classification groups B or C	≤200 cells/mm ³	55%	CDC classification group A	>200 cells/mm ³
Ramalingam et al. (2001) ^j	CD4%	CDC classification system	73%	CDC classification groups A or B	≤14%	65%	CDC classification group C	>14%
Ramalingam et al. (2001) ^j	TLC ^l	WHO staging system	46%	Not reported	1000–2000 cells/mm ³	65%	Not reported	<1000 or >2000 cells/mm ³
Immunologic information versus immunologic information^m								
Ledru et al. (1998) ⁿ	CD4	Eosinophil	35%	0 cells/mm ³	<350 cells/mm ³	87%	>0 cells/mm ³	≥350 cells/mm ³
Gernow et al. (1995) ^o	CD4 (FC _D) ^p	CD4 (bead) ^q	100%	≤200 cells/mm ³	≤200 cells/mm ³	70%	>200 cells/mm ³	>200 cells/mm ³
Lisse et al. (1997) ^r	CD4 (FC _D)	CD4 (IA) ^s	81%	<300 cells/mm ³	<200 cells/mm ³	96%	≥300 cells/mm ³	≥200 cells/mm ³
Hosp et al. (2000) ^t	CD4 (FC) ^u	CD4 (IA)	83%	<350 cells/mm ³	<200 cells/mm ³	87%	≥350 cells/mm ³	≥200 cells/mm ³
Lisse et al. (1997) ^r	CD4	CD4%	91%	<20%	<300 cells/mm ³	73%	≥20%	≥300 cells/mm ³
Kumarasamy et al. (2004) ^v	CD4	TLC	72%	TLC increase	CD4 increase	75%	TLC decrease	CD4 decrease
Mbanya et al. (2002) ^w	CD4	TLC	76%	<2000 cells/mm ³	<200 cells/mm ³	47%	≥2000 cells/mm ³	≥200 cells/mm ³
Mane et al. (2003) ^x	CD4	TLC	43%	<1200 cells/mm ³	<200 cells/mm ³	98%	≥1200 cells/mm ³	≥200 cells/mm ³
Kimani et al. (2003) ^y	CD4	TLC	56%	<1500 cells/mm ³	<200 cells/mm ³	83%	>1500 cells/mm ³	>200 cells/mm ³
Kumarasamy et al. (2002) ^z	CD4	TLC	73%	<1400 cells/mm ³	<200 cells/mm ³	88%	≥1400 cells/mm ³	≥200 cells/mm ³
Kassa et al. (1999) ^h	CD4	TLC	52%	<1000 cells/mm ³	<200 cells/mm ³	97%	≥1000 cells/mm ³	≥200 cells/mm ³
van der Ryst et al. (1998) ^{aa}	CD4	TLC	78%	<1500 cells/mm ³	<200 cells/mm ³	80%	≥1500 cells/mm ³	≥200 cells/mm ³
Guarner et al. (1996) ^{bb}	CD4	TLC	62%	<1500 cells/mm ³	<200 cells/mm ³	76%	≥1500 cells/mm ³	≥200 cells/mm ³
Post et al. (1996) ^{cc}	CD4	TLC	68%	<1250 cells/mm ³	<200 cells/mm ³	89%	>1250 cells/mm ³	≥200 cells/mm ³
Hosp et al. (2000) ^t	CD4	TLC	69%	<2000 cells/mm ³	<200 cells/mm ³	60%	>2000 cells/mm ³	≥200 cells/mm ³
Badri & Wood (2003) ^{dd}	ΔCD4 ^{ee}	ΔTLC ^{ff}	83%	TLC increase or decrease	Similar CD4 count trend	87%	TLC increase or decrease	Similar CD4 count trend
Lisse et al. (1997) ^r	CD4% (FC _D)	CD4% (IA)	89%	<20%	<14%	95%	≥20%	≥14%
van der Ryst et al. (1998) ^{aa}	CD4%	TLC	59%	<2000 cells/mm ³	<20%	44%	≥2000 cells/mm ³	≥20%

(Table 5, cont.)

Author (year of publication)	Diagnostic tests			Test characteristics				
	Reference standard	Index	Value	Sensitivity [P(T+ D+)] ^a		Specificity [P(T- D-)] ^b		
				Positive test	Disease	Value	Negative test	No disease
Immunologic information versus clinical and immunologic information								
Sehgal et al. (2002) ^{9g}	CD4, CDC classification system	TNF- α ^{hh} receptor	95%	>550 pg/mL	\leq 200 cells/mm ³ , CDC group C	–	<550 pg/mL	>200 cells/mm ³ , CDC groups 1 & 2
Ledru et al. (1998) ⁿ	CD4	CDC classification system, pulmonary tuberculosis, TLC	82%	CDC classification \geq B OR BAAR ⁱⁱ positive sputum; \leq 2500 cells/mm ³	<350 cells/mm ³	70%	CDC classification <B OR BAAR negative sputum; >2500 cells/mm ³	>350 cells/mm ³
Schechter et al. (1994) ^{jj}	CD4	WHO staging system, TLC, WBC ^{kk}	96%	Not reported, <1000 cells/mm ³ , <40%	\leq 200 cells/mm ³	83%	Not reported, >1000 cells/mm ³ , >40%	>200 cells/mm ³
Immunologic information and/or clinical information versus virologic information^m								
Hofer et al. (1994) ^{ll}	β - ₂ microglobulin	p24 antigen ^{mmm}	72%	p24 positive (detectable)	>5 mg/l	–	p24 negative	<5 mg/l
Hofer et al. (1994) ^{ll}	CD4	p24 antigen	72%	p24 positive (detectable)	\leq 200 cells/mm ³	–	p24 negative	>200 cells/mm ³

^a P(T+|D+) = P(positive test|disease condition present), or the probability that the specified value or condition as measured by the index test reflected the value or condition as measured by the index test.

^b P(T-|D-) = P(negative test|disease condition absent), or the probability that the absence of the value or condition as measured by the index test reflected the absence of the value or condition as measured by the reference standard.

^c Ghate MV, Mehendale SM, Mahajan BA, Yadav R, Brahme RG, Divekar AD, et al. Relationship between clinical conditions and CD4 counts in HIV-infected persons in Pune, Maharashtra, India. *Natl Med J India* 2000;13:183-7.

^d CD4 = cluster differentiation 4.

^e Adu-Sarkodie Y, Sangaré A, d'Almeida OA, Kanmogne GD. Distribution of CD4+ T-lymphocytes levels in patients with clinical symptoms of AIDS in three West African countries. *J Clin Virol* 1998;11:173-181.

^f WHO = World Health Organization.

^g AIDS = acquired immune deficiency syndrome.

^h Kassa E, Rinke de Wit TF, Hailu E, Girma M, Messele T, Mariam HG, et al. Evaluation of the World Health Organization staging system for HIV infection and disease in Ethiopia: association between clinical stages and laboratory markers. *AIDS* 1999;13:381-9.

ⁱ French N, Mujugira A, Nakiyingi J, Mulder D, Janoff EN, Gilks CF. Immunologic and clinical stages in HIV-1-infected Ugandan adults are comparable and provide no evidence of rapid progression but poor survival with advanced disease. *J Acquir Immune Defic Syndr* 1999;22:509-16.

^j Ramalingam S, Kannangai R, Zachariah A, Mathai D, Abraham C. CD4 counts of normal and HIV-infected south Indian adults: do we need a new staging system? *Natl Med J India* 2001;14:335-9.

^k CDC = Centers for Disease Control and Prevention.

^l TLC = total lymphocyte count.

^m For those entries comparing the same diagnostic test (e.g., CD4 cell count as both the reference and index tests), the assay used is listed in parentheses.

ⁿ Ledru E, Diagbouga S, Meda N, Sanou PT, Dahourou H, Ledru S, et al. A proposal for basic management of HIV disease in West Africa: use of clinical staging and haemogram data. *Int J STD AIDS* 1998;9:463-70.

^o Gernow A, Lisse IM, Böttiger B, Christensen L, Brattegaard K. Determination of CD4+ and CD8+ lymphocytes with the cytosphere assay: a comparative study with flow cytometry and the immunoalkaline phosphatase method. *Clin Immunol Immunopathol* 1995;76:135-41.

^p FC_D = dual-platform flow cytometry.

^q bead = bead-based manual counting.

^r Lisse IM, Böttiger B, Christensen LB, Knudsen K, Aaby P, Gottschau A, et al. Evaluation of T cell subsets by an immunocytochemical method compared to flow cytometry in four countries. *Scand J Immunol* 1997;45:637-44.

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(Table 5 references, cont.)

- ^s IA = immunoalkaline phosphatase method.
- ^t Hosp M, Lisse IM, Quigley M, Mwinga AM, Godfrey-Faussett P, Porter JDH, et al. An evaluation of low-cost progression markers in HIV-1 seropositive Zambians. *HIV Med* 2000;1:125-7.
- ^u FC = flow cytometry (whether single- or dual-platform not specified).
- ^v Kumarasamy N, Chaguturu SK, Balakrishnan P, Mayer KH, Solomon S, Flanigan TP. Low-cost strategies to monitor highly active antiretroviral therapy in resource-limited settings [Abstract 589]. 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, CA, 8–11 February 2004. Available from: <http://www.retroconference.org/2004/cd/Abstract/589.htm>. Accessed on 8 May 2006.
- ^w Mbanya DN, Assah FK, Kaptue LN. Correlation between total lymphocyte counts and CD4 counts in HIV-1 positive adults in Yaounde [Abstract MoPeB3099]. XIV International AIDS Conference, Barcelona, Spain, 7–12 July 2002. Available from: http://www.iasociety.org/abstract/show.asp?abstract_id=1991. Accessed 9 May 2006.
- ^x Mane A, Patel A, Pujari S, Gupte N, Patel J, Patel K, et al. Total lymphocyte counts (TLC) is a poor surrogate for CD4 counts amongst asymptomatic HIV infected patients in resource limited settings [Abstract 481]. The 2nd IAS Conference on HIV Pathogenesis and Treatment, Paris, France, 13–16 July 2003. Available from: http://www.iasociety.org/abstract/show.asp?abstract_id=10643. Accessed on 9 May 2006.
- ^y Kimani J, Irungu E, Thottingal P, Njeri J, Kariri A, Wachihi C, et al. Is a total lymphocyte count a surrogate marker for absolute CD4+ cells count among HIV-1 infected patients in Nairobi, Kenya [Abstract 139]. The 2nd IAS Conference on HIV Pathogenesis and Treatment, Paris, France, 13–16 July 2003. Available from: http://www.iasociety.org/abstract/show.asp?abstract_id=10190. Accessed on 9 May 2006.
- ^z Kumarasamy N, Mahajan AP, Flanigan TP, Hemalatha R, Mayer KH, Carpenter CC, et al. Total lymphocyte count (TLC) is a useful tool for the timing of opportunistic infection prophylaxis in India and other resource-constrained countries. *J Acquir Immune Defic Syndr* 2002;31:378-3.
- ^{aa} van der Ryst E, Kotze M, Joubert G, Steyn M, Pieters H, van der Westhuizen M, et al. Correlation among total lymphocyte count, absolute CD4+ count, and CD4+ percentage in a group of HIV-1-infected South African patients. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998;19:238-44.
- ^{bb} Guarner J, Sanchez-Mejorada-Fernandez G, del Rio-Chiriboga C, Mohar A. [Simplified CD4+ T-lymphocyte count in patients with HIV/AIDS in Mexico]. *Salud Publica Mex* 1996;38:207-11.
- ^{cc} Post FA, Wood R, Maartens G. CD4 and total lymphocyte counts as predictors of HIV disease progression. *QJM* 1996;89:505-08.
- ^{dd} Badri M, Wood R. Usefulness of total lymphocyte count in monitoring highly active antiretroviral therapy in resource-limited settings. *AIDS* 2003;17:541-5.
- ^{ee} Δ CD4 = change (increase or decrease) in CD4 cell count.
- ^{ff} Δ TLC = change (increase or decrease) in TLC.
- ^{gg} Sehgal S, Datta U, Mujtaba S, Sood A, Vinayak VK. Cellular and serological markers of disease activity in Indian patients with HIV/AIDS. *Methods Cell Sci* 2002;24:107-14.
- ^{hh} TNF- α = tumour necrosis factor-alpha.
- ⁱⁱ BAAR = acid-alcohol resistant bacillus.
- ^{jj} Schechter M, Zajdenverg R, Machado LL, Pinto ME, Lima LA, Perez MA. Predicting CD4 counts in HIV-infected Brazilian individuals: a model based on the World Health Organization staging system. *J Acquir Immune Defic Syndr* 1994;7:163-8.
- ^{kk} WBC = white blood cell count.
- ^{ll} Hofer CB, Pinto ME, Zajdenverg R, Schechter M. p24 antigenaemia in HIV-1 infected Brazilians correlates with other markers of disease progression. *J Infect* 1994;29:129-31.
- ^{mmm} p24 = protein 24.

Note: Because the references for the table are numerous, they have been numbered separately from the text.