REUE | Original Article

Missed opportunities for in-hospital diagnosis of HIV infection in patients with delayed diagnoses from 2015 through 2021

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BACKGROUND AND OBJECTIVE. Unrecognized or late-diagnosed HIV infections create problems for the control of the epidemic and for the health of individuals. This study aimed to identify the rate of missed chances for in-hospital diagnosis of HIV infection in patients finally found to have an advanced stage of infection.

MATERIAL AND METHODS. Retrospective descriptive study including all patients diagnosed with HIV infection between 2015 and 2021 in our catchment area. Late-diagnosed cases were reviewed to determine the reasons the patients sought care in the 3 years prior to diagnosis and evaluating whether visits were missed opportunities for detecting HIV infection.

RESULTS. A total of 358 patients were diagnosed late; 145 (40.5%) of them were diagnosed late in the disease. We identified 139 missed chances to detect HIV infection in 62 (42.8%) of the late-diagnosed patients. Missed chances occurred more than once for 37 (59.7%) of these patients. On average, 15.8 months passed between the first chance of detection and the diagnosis. In 51.8% of the visits before diagnosis, the patient had presented a defining, indicator, or associated condition for HIV infection, and the chance to offer routine testing was missed in 48.2%. The emergency department was the location of the majority of missed chances, with 76 of the lost opportunities (54.7%) in 49 (79%) patients.

CONCLUSIONS. In over 40% of patients diagnosed late, the chance for in-hospital detection of HIV infection in-hospital was missed during the 3 years prior to diagnosis. Good medical practice calls for HIV screening in certain clinical scenarios. Our findings reveal a need to implement new tools for improving the situation identified in this study.

Keywords: Human immunodeficiency virus (HIV). Delayed diagnosis. Undiagnosed infection. Emergency department.

Oportunidades perdidas de diagnóstico de la infección por el VIH en pacientes con diagnóstico tardío en el entorno hospitalario (2015-2021)

OBJETIVO. La infección oculta y el diagnóstico tardío de la infección por VIH constituyen un problema de salud, individual y epidemiológico. El objetivo de este estudio fue conocer las oportunidades perdidas que ocurren en el ámbito hospitalario para el diagnóstico de VIH en los pacientes que debutan con una infección avanzada.

MATERIAL Y MÉTODOS. Estudio descriptivo retrospectivo observacional de pacientes diagnosticados de infección por VIH entre los años 2015 y 2021 en nuestra área de salud. En los pacientes con diagnóstico tardío, se revisaron los episodios de consulta en los servicios hospitalarios en los 3 años previos a la fecha del diagnóstico, para conocer si se produjeron pérdidas de oportunidad de diagnóstico del VIH.

RESULTADOS. De las 358 personas diagnosticadas, 145 (40,5%) presentaron un diagnóstico tardío. En 62 (42,8%) pacientes con diagnóstico tardío se detectaron 139 oportunidades perdidas de diagnóstico del VIH. En 37 (59,7%) pacientes se perdió más de una oportunidad. El tiempo medio entre la primera oportunidad y el diagnóstico fue de 15,8 meses. En el 51,8% de las ocasiones las personas presentaban una enfermedad definitoria, indicadora o asociada al VIH y en el 48,2% se perdió la oportunidad de una oferta rutinaria o dirigida. El servicio en que más pérdidas se produjeron fue el de urgencias hospitalario, con 76 (54,7%) oportunidades en 49 (79%) pacientes.

CONCLUSIONES. En más del 40% de los pacientes con diagnóstico tardío de VIH se perdió la oportunidad de ser diagnosticados en el hospital en los 3 años previos al diagnóstico. La buena praxis médica recomienda cribar el VIH en determinadas situaciones clínicas, por lo que este estudio pone de manifiesto la necesidad de implementar nuevas herramientas que permitan mejorar estos resultados.

Palabras clave: Virus de la inmunodeficiencia humana (VIH). Diagnóstico tardío. Infección oculta. Servicio de urgencias.

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Introduction

According to recent estimates, approximately 20,000 people in Spain live with HIV without knowing it[1] — a situation known as undiagnosed infection, which represents a global problem that limits efforts to curb the spread of the epidemic. Undiagnosed individuals are responsible for most new infections,[2] since in Spain, 97.3% of people diagnosed receive antiretroviral treatment, and in more than 90% of these cases, the viral load is undetectable, thus preventing transmission of the virus.[1] Moreover, nearly half of new HIV diagnoses are late,[3] corresponding to advanced infection, defined by fewer than 350 CD4+ T lymphocytes/μL at diagnosis and no evidence of recent infection (i.e., seroconversion within the previous year or acute retroviral syndrome). Late diagnosis (LD) also represents a major individual health problem, as it is associated with a higher incidence of opportunistic diseases and increased mortality.[5] A study conducted in Spain revealed that many patients diagnosed late had previously sought care on multiple occasions at different health care levels, often presenting with clinical or laboratory findings that should have prompted HIV testing.[6] However, the test was not requested, resulting in a missed opportunity for diagnosis.[7]

To identify missed opportunities for diagnosis (MOD) in the Hospital Care Services within our referral area, a retrospective study was conducted reviewing the health records of patients diagnosed with HIV infection between 2015 and 2021 who presented with LD to determine the situations in which these MODs occurred.

Material and methods

We conducted a retrospective, observational, and descriptive study including all patients diagnosed with HIV infection between 2015 and 2021 in a health care area serving 342,000 inhabitants. Cases were obtained from the microbiology laboratory database, excluding individuals not assigned to our health area and those with a prior diagnosis.

From electronic health records, the following variables were collected: sociodemographic data (age, sex, country of origin) and infection-related variables (date of diagnosis, transmission risk factor, and CD4+ T-cell count). Among patients with LD,[4] all hospital visits within the 3 years prior to diagnosis were reviewed, documenting reasons for consultation, services attended, and whether blood tests were performed. Based on this, the presence of a MOD to request an HIV test (serological test for HIV-specific antibodies) was assessed when an indicator disease or HIV-associated condition was present, a defining AIDS condition was diagnosed (Table 1), or when the opportunity was lost to offer the test as routine screening (for individuals aged 20–59 years undergoing blood testing for another reason) or targeted screening (for individuals from high-prevalence countries, Table 2), following the 2014 Ministry of Health Guidelines for HIV Testing in Health care Settings.[6]

For statistical analysis, qualitative variables were expressed as percentages, and quantitative variables as mean ± standard deviation (SD). The chi-square test was used to compare qualitative variables, and the Student's t-test for quantitative ones. A *P*-value < .05 was considered statistically significant.

The study was conducted in full compliance with the ethical standards of the World Health Organization (WHO) (Declaration of Helsinki) for patient data handling, with anonymization procedures ensuring confidentiality. The data were processed in aggregate form, and informed consent was waived. The study was approved by the Hospital Research Ethics Committee (code CEIm: 2023-024-1).

Table 1. Clinical situations[6]

Indicator diseases for HIV infection (associated with an undiagnosed HIV prevalence > 0.1%)	Other diseases possibly associated with undiagnosed HIV prevalence > 0.1%
1. Sexually transmitted infection	1. Primary lung cancer
2. Malignant lymphoma	2. Lymphocytic meningitis
3. Anal cancer/dysplasia	3. Oral hairy leukoplakia
4. Cervical dysplasia	4. Severe or atypical psoriasis
5. Herpes zoster	5. Guillain-Barré syndrome
6. Hepatitis B or C (acute or chronic)	6. Mononeuritis
7. Mononucleosis-like syndrome	7. Subcortical dementia
8. > 4-week history of thrombocytopenia or leukocytopenia	8. Multiple sclerosis–type disease multiple
9. Seborrheic dermatitis/exanthema	9. Peripheral neuropathy
10. Invasive pneumococcal disease	10. Unexplained weight loss
11. Fever of unknown origin	11. Idiopathic lymphadenopathy
12. Candidemia	12. Idiopathic oral candidiasis
13. Visceral leishmaniasis	13. Idiopathic chronic diarrhea
	14. Idiopathic chronic renal failure
	15. Hepatitis A
	16. Community-acquired pneumonia
	17. Candidiasis
AIDS-Defining Diseases	
1. Cervical cancer (invasive)	12. >1-month history of isosporiasis (chronic intestinal form)
2. Esophageal candidiasis	13. Progressive multifocal leukoencephalopathy
3. Candidiasis of bronchi, trachea, or lungs	14. Immunoblastic lymphoma
4. Coccidioidomycosis (disseminated or extrapulmonary)	15. Primary cerebral lymphoma
5. Cryptococcosis (extrapulmonary)	16. Burkitt's lymphoma
6. > 1-month history of chronic intestinal cryptosporidiosis	17. Mycobacterium avium complex or Mycobacterium kansasii (disseminated or extrapulmonary)
7. HIV-associated encephalopathy	18. Mycobacterium (other or unidentified species, disseminated or extrapulmonary)
8. Cytomegalovirus disease (excluding liver, spleen, or lymph nodes)	19. Recurrent pneumonia
9. Herpes simplex: chronic ulcers (> 1 month duration) or bronchitis, pneumonitis, or esophagitis	20. Pneumocystis jirovecii pneumonia
10. Recurrent Salmonella septicemia	21. Cytomegalovirus retinitis (with vision loss)
11. Histoplasmosis (disseminated or extrapulmonary)	22. Kaposi's sarcoma
	23. HIV wasting syndrome

Source: Adapted from HIV in Europe, HIDES Group. HIV Indicator Conditions: Guide for Implementing HIV Testing in Adults in Health care Settings. 2013.

Results

During the study period, a total of 358 individuals were diagnosed with HIV infection. The average annual incidence rate was 14.9 cases per 100,000 inhabitants (range, 11.4–17.2). The mean age was 39.2 ± 10.8 years (range, 17–87), and 307 (85.7%) were men. Foreign nationals accounted for 22.1%, and sexual transmission was the main route in 89.9% of cases. At diagnosis, the mean CD4+ T-cell count was 444.2 ± 243.8/μL (range, 1–2046).

Table 2. Countries with HIV prevalence >1% in adults aged 15–49 years according to the UNAIDS Global Report. Data from 2011[6]

Sub-Saharan Africa	Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Chad, Congo, Côte d'Ivoire, Ethiopia, Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Malawi, Mali, Mauritania, Mozambique, Namibia, Nigeria, Central African Republic, United Republic of Tanzania, Rwanda, Sierra Leone, South Africa, South Sudan, Swaziland, Tanzania, Togo, Uganda, Zambia, Zimbabwe
Central and Western Europe	Estonia
South and Southeast Asia	Thailand
Middle East and North Africa	Djibouti
Caribbean	Bahamas, Haiti, Jamaica, Trinidad and Tobago
Latin America	Belize, Guyana

Source: Adapted from UNAIDS. UNAIDS Report on the Global AIDS Epidemic. 2012.

LD occurred in 145 patients (40.5%), of whom 84 (57.9%) had severe immunosuppression (< 200 $CD4^+/\mu L$). The mean age of patients with LD was 44.1 ± 11.6 years (range, 19–87), and 121 (83.4%) were men. Foreigners accounted for 24.1%, and the sexual route was responsible in 87.6%.

The mean age of patients with LD were older than those diagnosed earlier (44.1 ± 11.6 vs 35.7 ± 9.2 years, $P < .05$). LD was observed in 39.4% of men vs 47.1% of women, 44.3% of foreigners vs 39.4% of Spaniards, and 39.4% of sexually transmitted cases vs 50% of other routes, though these differences were not statistically significant ($P > .05$).

A total of 139 MODs were identified in the hospital setting, involving 62 patients (42.8%) with LD in the three years prior to diagnosis, averaging 2.2 ± 1.5 MODs per person (range, 1–7). In 37 patients (59.7%), there was > 1 MOD. The average time between the MOD and HIV diagnosis was 15.8 months (range, 3 days to 3 years).

Table 3 details the clinical entities associated with missed opportunities. In 72 instances (51.8%), these occurred in patients with AIDS-defining, indicator, or HIV-associated diseases, while in 67 cases (48.2%), the opportunity was missed to offer routine or targeted testing. One patient presented with cytomegalovirus colitis (an AIDS-defining illness) that had initially been diagnosed as probable Crohn's disease. Another patient from Ghana was not offered HIV testing on 3 separate occasions—in Gastroenterology, Otolaryngology, and Emergency Services.

The emergency department (ED) accounted for the largest number of MODs, with 76 (54.7%) MODs in 49 patients (79%). Table 4 lists the chief complaints leading to these missed testing opportunities in the ED. Among other hospital departments, the Gastroenterology Service recorded 15 MODs (10.8%) (8 routine, 6 indicator/associated/defining, and 1 targeted) in 10 patients (16.1%), and the Dermatology Service recorded 13 MODs (9.3%) (8 indicator/associated and 5 routine) in 8 patients (12.9%).

Table 3. Reason for consultation in the 139 occasions when there was a missed opportunity for diagnosis in the hospital setting

Reason	139 Missed Opportunities n (%)
Defining diseases	**1 (0.7)**
Cytomegalovirus colitis	1 (0.7)
Indicator diseases	**29 (20.9)**
Fever of unknown origin	6 (4.3)
Sexually transmitted infection	6 (4.3)
Herpes zoster	6 (4.3)
Rash	5 (3.6)
Idiopathic pancytopenia	4 (2.9)
Mononucleosis-like syndrome	2 (1.4)
Possibly associated diseases	**42 (30.2)**
Unexplained weight loss	10 (7.2)
Community-acquired pneumonia	10 (7.2)
Chronic diarrhea	9 (6.5)
Idiopathic lymphadenopathy	7 (5.0)
Peripheral neuropathy	3 (2.1)
Lymphocytic meningitis	1 (0.7)
Oral candidiasis	1 (0.7)
Atypical psoriasis	1 (0.7)
Routine offer	64 (46.0)
Targeted offer	3 (2.2)

Discussion

Although the incidence rate of HIV infection has shown a declining trend in recent years, both in Spain and in neighboring countries, the proportion of patients diagnosed with advanced or late-stage infection remains high.[3] LD poses a significant problem not only for individual health but also for public health, as well as for the health care system, given the increased costs associated with opportunistic diseases that characterize advanced HIV infection.[8] There are guidelines recommending HIV testing in clinical situations where HIV infection is more prevalent. However, as demon-

Table 4. Reason for consultation in the 76 occasions when there was a missed opportunity for diagnosis in the hospital emergency department

Reason	76 Missed Opportunities n (%)
Reason	**17 (22.4)**
Indicator diseases	6 (7.9)
Fever of unknown origin	2 (2.6)
Sexually transmitted infection	4 (5.3)
Herpes zoster	3 (3.9)
Rash	1 (1.3)
Idiopathic pancytopenia	1 (1.3)
Mononucleosis-like syndrome	**28 (36.8)**
Possibly associated diseases	8 (10.5)
Unexplained weight loss	8 (10.5)
Community-acquired pneumonia	5 (6.6)
Chronic diarrhea	3 (3.9)
Idiopathic lymphadenopathy	2 (2.6)
Peripheral neuropathy	1 (1.3)
Lymphocytic meningitis	1 (1.3)
Oral candidiasis	**30 (39.5)**
Routine offer	1 (1.3)
Targeted offer	

strated in our study—where MODs for HIV diagnosis were observed in 42.8% of patients with LD (with 79% occurring in the ED)—these recommendations are not always followed, due to logistical issues, oversight, or lack of awareness. Two previous Spanish studies have reported similar findings.[7,9] In a study conducted in Aragón (2011–2015) analyzing MODs within the 3 years prior to HIV diagnosis—in primary care, emergency departments, and inpatient settings—86.2% of patients diagnosed with HIV had at least 1 MOD. Among them, 77.8% of patients with LD had visited an ED at least once, and 21.2% had been hospitalized. In a multicenter study conducted in Spanish EDs in 2019, among 159 patients who had attended the ED within 5 years prior to diagnosis with a condition associated with HIV infection, 74.2% had not been tested.

In 2020, the Spanish Society of Emergency Medicine (SEMES) launched a program to promote routine HIV testing in non-urgent settings within EDs, targeting 6 specific clinical conditions associated with higher HIV prevalence[10]. This initiative has been highly successful, achieving a cultural shift among emergency physicians and encouraging their engagement in this issue. However, the program remains insufficient—first, because there are other clinical conditions linked to HIV prevalence > 0.1% in which testing should also be offered; and second, because some patients present with other pathologies in which routine testing could lead to diagnosis. In our study, HIV testing would have been ordered in only 15 of the 76 MODs in the ED based on this recommendation—meaning that > 80% of potential diagnoses would have been missed. Therefore, we believe it would be advisable to broaden the range, of clinical situations for which HIV testing is recommended, including routine offers of testing.

The publication of HIV testing recommendations for health care settings has not been sufficient to reduce rates of LD. To meet the WHO's goal of ending the AIDS epidemic by 2030, new improvement strategies are needed. The high number of missed opportunities in hospital settings—and likely in primary care as well—indicates substantial room for improvement.

Since our study did not include primary care visits, the actual number of missed opportunities is likely even higher. In hospital settings, potential barriers to test ordering may include insufficient training and up-to-date knowledge among health care professionals, particularly in services where patients often present with conditions associated with HIV; overcrowding in emergency departments, where such cases may go unnoticed; and the requirement for specific informed consent, which could act as an additional obstacle. Therefore, establishing programs that enhance staff training and automate the HIV test request process in conditions for which testing is recommended could be a valuable strategy to reduce late diagnoses and benefit the health care system, since screening for HIV in conditions where prevalence exceeds 0.1% has been proven cost-effective.

Furthermore, 2 meta-analyses have demonstrated that not only opportunistic screening but also universal HIV screening in emergency departments is cost-effective.[12,13] Additionally, although cost-effectiveness studies are typically based on prevalence, in high-income countries, growing evidence shows that population-based screening can yield significant cost-effectiveness benefits, even when prevalence is low.[14] We believe that HIV testing in health care settings should not be treated differently from other diagnostic tests. Chadwick *et al*.[15] argue that the exceptionalism surrounding HIV testing and consent procedures is no longer justified, given the high rates of undiagnosed infection and LD, as well as advances in treatment. Despite the limitations of our study—given its retrospective design and the exclusion of primary care data—we identified several areas for improvement. We consider that there are ethical arguments supporting the normalization of HIV testing, treating it similarly to other chronic, manageable infections, and ensuring that testing is offered even when it might otherwise be omitted due to oversight or lack of awareness. Conducting HIV tests in the clinical scenarios outlined in the Ministry of Health's recommendations[6] should be regarded as part of good medical practice.

Conclusions

In conclusion, many opportunities to diagnose HIV infection are missed in hospital settings, even in situations where testing is recommended, which contributes to the persistently high rate of late diagnoses. As the Emergency Department is where most missed opportunities occur, it represents a key setting for implementing screening strategies. Implementing evidence-based strategies to improve testing practices is essential for reducing LD, improving individual health outcomes, lowering health care costs, and achieving control of the AIDS epidemic, which remains a public health challenge.

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