Opportunistic infections according to the CD4+ T lymphocyte count in patients with HIV at a tertiary care referral center

OSWALDO ENRIQUE AGUILAR-MOLINA, RAÚL ANDRÉS VALLEJO-SERNA, MARIA ANTONIA ESCOBAR-MERA, DANIEL BARONA-ROMY, ESTEFANÍA GARTNER-LÓPEZ, LORENA MATTA-CORTÉS • CALI (COLOMBIA)

DOI: https://doi.org/10.36104/amc.2023.2327

Abstract

Opportunistic infections (OIs) have marked the prognosis in the natural course of patients with human immunodeficiency virus (HIV) infection.

Objective: identifying the most common OIs and determining their relationship with the CD4+ lymphocyte count (CD4+TL) can improve our clinical practice and facilitate early diagnosis, the use of empiric treatments and prompt targeted treatment.

Materials and methods: an observational, retrospective study aimed at describing the characteristics and variations of the OIs diagnosed clinically, using direct or indirect methods, which occur in patients with HIV (related to their CD4+TL count) who are admitted to a tertiary care center in Cali, Colombia. Adult patients hospitalized from January 2018 to January 2019 with a diagnosis of HIV/AIDS and a history or current diagnosis of OI were included. Individuals under the age of 18 and pregnant women were excluded.

Results: a sample of 190 patients with at least one opportunistic infection was obtained, of whom 65.3% were men with a median age of 37 years (29.0-46.0), and the rest were women with a median age of 35.5 years (31.2-43.0). Eighty-three percent had a C3 classification on admission, 86% with a CD4+TL count ≤ 200 cells/mm^3. The most frequent OIs included tuberculosis, with 28.4%, pneumocystosis with 27.9% and toxoplasmosis with 27.4%.

Conclusions: in our population, despite advances in and greater availability of highly-effective antiretroviral therapy, most patients with HIV are hospitalized in advanced stages with opportunistic infections, in some cases with two or more concomitant infections, and with evidence of severe virological and immunological involvement. **(Acta Med Colomb 2022; 48. DOI: https://doi.org/10.36104/amc.2023.2327).**

Key words: *HIV, opportunistic, CD4TL, Colombia*.

Dres. Oswaldo Enrique Aguilar Molina, Raúl Andrés Vallejo-Serna y Daniel Barona-Romy: Especialistas en Medicina Interna y Docentes Universidad del Valle; Dra. María Antonia Escobar-Mera: Residente de Medicina Interna Universidad Libre; Dra. Estefanía Gartner-López: Especialista en Medicina Interna Hospital Universitario del Valle: Dra. Lorena Matta-Cortés: Especialista en Medicina Interna Hospital Universitario del Valle. Vicedecana de Investigación Universidad del Valle. Cali (Colombia).
Correspondencia: Dra. María Antonia Escobar-Mera. Cali (Colombia).
E-Mail: antoniaescobarmera@hotmail.com
Received: 13/IX/2021 Accepted: 22/VII/2022

Introduction

Opportunistic infections (OIs) are an important cause of morbidity and mortality, especially in severely immunocompromised people (1-3). Patients with HIV infection who have a low CD4+ T cell count may develop a variety of OIs with a significant impact on their wellbeing, quality of life, medical care costs and survival (4). In regions like North America, Europe and Australia, *Pneumocystis jirovecii* pneumonia (PJP), Kaposi sarcoma (KS), esophageal candidiasis, cytomegalovirus (CMV), and disseminated *Mycobacterium avium* complex (MAC) infection and related disease were the prevalent OIs prior to the antiretroviral therapy (ART) era (5, 6). In developing regions, the predominant HIV-related OIs prior to the introduction of ART were tuberculosis (TB), candidiasis, infectious diarrhea, bacterial meningitis and recurrent herpes simplex infections (7, 8).

The substantial decrease in OIs with the introduction of ART is evident; however, there are significant differences in the burden of OIs between high-income and limited resource settings. It is important to have information on the reasons for hospital admissions among HIV patients and the type of OIs related to the CD4+ T cell count, in order to improve our clinical practice and favor early diagnosis, the use of empiric therapies and timely targeted therapy, considering that the described epidemiological changes entail different empirical coverage to what is currently used, which can also be influenced by geographic location.

Methodology

This was an observational, descriptive study with retrospective data collection. Adult hospitalized patients with an HIV/AIDS diagnosis and a history of OIs, or at least one OI

at the time of admission, from January 1, 2018, to January 1, 2019, were included. The data were taken from the medical chart database at our institution. Those under the age of 18, pregnant women, those with incomplete medical charts, and cases without a confirmed or presumptive diagnosis of OI were excluded. The sociodemographic conditions, clinical characteristics, reasons for hospitalization, type of OIs and cancers were determined, as well as immunovirological markers (CD4+ T cell count and HIV viral load). The study was approved by the Research and Ethics Committee at Hospital Universitario del Valle (HUV). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2).

For the initial analysis, BMI was stratified according to the WHO criteria: <17 kg/m^2 (moderate to severe undernutrition), 17 to <18.5 kg/m^2 (mild undernutrition), >18.5-25 kg/m^2 (normal nutrition) and > 25 kg/m^2 (overweight and obesity) (9). The definitions of HIV infection/AIDS, opportunistic infections and HIV/AIDS-related cancers were those established by the United States Centers for Disease Control and Prevention (CDC). *De novo* HIV was defined as those diagnosed for less than three months. The current European definition of late diagnosis (LD) in an individual is a CD4+ T cell count of less than 350 cells/mm^3 and/or an AIDS-defining illness at the time of diagnosis (10, 11). We chose to use WHO's definition of LD: a CD4+ T cell count under 200 cells/mm^3 or a WHO clinical stage 3 or 4 at the time of diagnosis (12).

Imaging (radiology, tomography), microbiological (Gram, India ink, *Cryptococcus* capsular antigen, Ziehl-Neelsen, cultures), serum (VDRL), enzyme (ADA) and histopathological methods allowed the diagnosis of OIs. Studies of lavage and brushing samples were performed in the microbiology laboratory, including Gram, KOH, India ink, Ziehl-Neelsen, aerobic, fungal and mycobacterial cultures, as well as molecular biology for *Mycobacterium tuberculosis* (MTB) and cytomegalovirus. The pathology laboratory processed histopathology and cytology studies using immunohistochemistry, Ziehl-Neelsen, and PAS stains, along with molecular biology studies. For mycobacterial infection diagnoses, direct stains for acid-alcohol fast bacilli were performed, like Ziehl-Neelsen and modified Ziehl-Neelsen, along with *Mycobacterium cultures and* PCR for MTB. Sample seeding for microbiological isolation during the study period was done on solid culture medium (in duplicate for each sample).

To improve sensitivity, molecular identification tests for MTB were run using the Abbott m2000 Real Time MTB® detection test. To determine the disease stage, the most commonly used system is the CDC›s 1993 revision which substitutes the 1986 classification:

- Clinical category A applies to primary infections and asymptomatic patients with or without persistent generalized lymphadenopathy (PGL).
- Category B applies to patients with symptoms of diseases which do not belong to category C, but are related to HIV infection (oral candidiasis; persistent vulvovaginal candidiasis; cervical dysplasia; fever or diarrhea for more than one month; oral hairy leukoplakia; herpes zoster; immune thrombocytopenia; listeriosis; pelvic inflammatory disease; peripheral neuropathy).
- Category C includes patients who have the diseases included in the AIDS-defining illnesses. Patients in categories C1, C2, C3, A3 and B3 are considered to have AIDS (13).

Results

A sample of 444 patients with an HIV diagnosis was obtained during the study period, after applying the exclusion criteria; 190 patients had HIV infection with at least one OI (Figure 1). Of the observed population, 65.3% were men, with a median age of 37 years (29.0-46.0), and 35.5 years (31.2-43.0) for women. Altogether, 81.6% of the patients were from Valle del Cauca Department, and 5.3% were from Cauca Department.

The patients' most common nutritional status was severe undernutrition, with 37.9%; we found an adequate nutritional status in 23.2% of the cases (Table 1). A total of 45.8% of the patients had been diagnosed for less than three months (*de novo*), and 69% of the cases had a late diagnosis (CD4+ T cell count less than 200 cells/mm^3). Of the patients with a prior HIV diagnosis, only 7.76% were found to use OI prophylaxis.

The CD4+ T cell count was less than 200 cells/mm^3 in 86.8% of the cases, with a count lower than 50 cells/mm^3 in 54.7% of the patients, 50-100 cells/mm^3 in 17.4% of the cases, and only 2.1% of the patients having a CD4+ T cell count over 500 cells/mm^3. In 8.4%, the HIV viral load (VL) was undetectable, and in 8.9%, the VL was not reported in the chart (Table 2). Regarding their initial classification, C3 was the most frequent stage, with 87.8% of the cases.

Altogether, 42.1% (80) of the patients were on ART, but only 31% of these adhered to the instated treatment; among the patients who had ART ordered, the two most frequently used schemes were a combination of a non-nucleoside reverse transcriptase inhibitor (NNRTI) and two nucleoside reverse transcriptase inhibitors (NRTIs), and a combination of two NRTIs with a potentiated protease inhibitor. One hundred

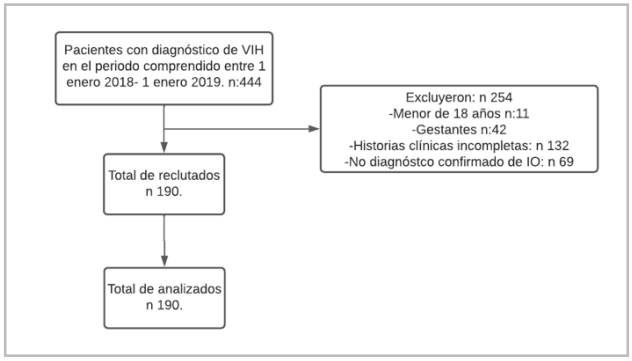

Figure 1. *Patient sample.*

Table 1. *General characteristics of the population.*

Variables	Female	Male	General
Sex	66 (34.7)	124 (65.3)	190
Age	35.5 (31.2 - 43.0)	37.0 (29.0 - 46.0)	37.0 (30.0 - 44.8)
Place of origin			
Valle	57 (86.4)	98 (79.0)	155 (81.6)
Cauca	2 (3.0)	8 (6.5)	10 (5.3)
Nariño	2 (3.0)	4 (3.2)	6 (3.2)
Other	5 (7.6)	14 (11.3)	19 (10.0)
Time since diagnosis			
Novo	26 (39.4)	61 (49.2)	87 (45.8)
Less than one year	9 (13.6)	18 (14.5)	27 (14.2)
1 - 5 years	11 (16.7)	17 (13.7)	28 (14.7)
5 - 10 years	10 (15.2)	14 (11.3)	24 (12.6)
More than 10 years	10 (15.2)	13 (10.5)	23 (12.1)
Vertical	0	1 (0.8)	1 (0.5)
Nutritional status			
Adequate	20 (30.3)	24 (19.4)	44 (23.2)
Mild undernutrition	0	1 (0.8)	1 (0.5)
Severe undernutrition	17 (25.8)	55 (44.4)	72 (37.9)
No data	29 (43.9)	44 (35.5)	73 (38.4)

Table 2. *Virological and immunological status.*

Variables	Female	Male	General (%)
Stage on admission			
C1	2 (3.0)	2 (1.6)	4 (2.1)
C2	13 (19.7)	8 (6.5)	21 (11.1)
C3	51(77.2)	114 (91)	165 (86.8)
Viral load (Copies/mL)			
50 - 10,000	6 (9.1)	18 (14.5)	24 (12.6)
10,000- 100,000	14 (21.2)	37 (29.8)	51 (26.8)
100,000 - 500,000	17 (25.8)	29 (23.4)	46 (24.2)
More than 500,000	15 (22.7)	21 (16.9)	36 (18.9)
Undetectable	8 (12.1)	8 (6.5)	16 (8.4)
No data	6 (9.1)	11 (8.9)	17 (8.9)
Count (CD4 cells/mm^3)			
Less than 50	31 (47.0)	73 (58.9)	104 (54.7)
50 - 100	9 (13.6)	24 (19.4)	33 (17.4)
100 - 200	11 (16.7)	17 (13.7)	28 (14.7)
200 - 500	13 (19.7)	8 (6.5)	21 (11.1)
More than 500	2 (3.0)	2 (1.6)	4 (2.1)

sixty-five patients (86.8%) had had an OI on their last recorded hospitalization.

The most common OIs in the whole group were tuberculosis with 28.4%, pneumocystosis with 27.9%, and toxoplasmosis with 27.4%; oral candidiasis, histoplasmosis and crypotcoccosis were reported in 4.2%, 11.1%, and 11.6%, respectively. The least common OIs were CMV with 3.7% and MAC with 0.5% of the cases (Table 3). Altogether, 223

Table 3. *Opportunistic infections.*

Variables	Female	Male	Total
Type of presentation			
History of OI	11 (16.7)	14 (11.3)	25 (13.2)
Prior OI on admission	55 (83.3)	110 (88.7)	165 (86.8)
Toxoplasmosis			
Not present	46 (69.7)	92 (74.2)	138 (72.6)
Present	20 (30.3)	32 (25.8)	52 (27.4)
Pneumocystosis			
Not present	49 (74.2)	88 (71.0)	137 (72.1)
Present	17 (25.8)	36 (29.0)	53 (27.9)
Cryptococcosis			
Not present	59 (89.4)	109 (87.9)	168 (88.4)
Present	7 (10.6)	15 (12.1)	22 (11.6)
Histoplasmosis			
Not present	57 (86.4)	112 (90.3)	169 (88.9)
Present	9 (13.6)	12 (9.7)	21 (11.1)
Candidiasis			
Not present	63 (95.5)	119 (96.0)	179 (94.2)
Present	3 (4.5)	5(6.2)	8 (4.2)
Tuberculosis			
Not present	48 (72.7)	88 (71.0)	136 (71.6)
Present	18 (27.3)	36 (29.0)	54 (28.4)
CMV infection			
Not present	64 (97.0)	119 (96.0)	183 (96.3)
Present	2 (3.0)	5 (4.0)	7 (3.7)
MAC infection			
Not present	66 (100)	123 (99.2)	189 (99.5)
Present	0	1 (0.8)	1 (0.5)
Coccidia infections			
Not present	64 (97.0)	121 (97.6)	185 (97.4)
Present	2 (3.0)	3 (2.4)	5 (2.6)
Defining neoplasm			
Not present	59 (89.4)	106 (85.5)	165 (86.8)
Present	7 (10.6)	18 (14.5)	25 (13.2)
Non-defining neoplasm			
Not presente	65 (98.5)	122 (98.4)	187 (98.4)
Present	1 (1.5)	2 (1.6)	3 (1.6)

OIs were recorded, with 48 patients having more than one OI; in this group, the most frequent associations were histoplasmosis associated with pneumocystosis, tuberculosis associated with pneumocystosis, and tuberculosis associated with toxoplasmosis.

Regarding the association of OIs in relation to the CD4+ T cell count, 91% of the OIs occurred in patients with fewer than 200 cells/mm^3 and only 1.8% of the OIs in those with lymphocyte counts greater than 500 cells/mm^3.

Sixty-three percent of the cerebral toxoplasmosis cases were found in patients with CD4+ T cell counts less than 100 cells/mm^3 and 62% of the pneumocystosis cases were found in patients with CD4+ T cell counts less than 50 cells/mm^3, as were 100% of the *Histoplasma* infections (21). Tuberculosis was found in all ranges, with more patients in the CD4+ T cell range of less than 50 cells/mm^3 (52%) (Table 4, Figure 2).

Discussion

Human immunodeficiency virus infection is a public health problem due to its high economic impact (14). In the described population, OIs were more frequent in men (65.3 vs. 34.7%) and at a general age ranging from 33 to 44 years, similar to populations described in other cities in our country and other countries in Latin America and Europe (4-16). The overall prevalence of undernutrition was high (37.9%), comparable to the undernutrition rate of patients hospitalized with AIDS in similar groups (18, 19), probably due to most of the admitted patients being severely immunocompromised, with a CD4+ T cell count <200 cells/mm^3, which is known to be related to undernutrition (20).

Most AIDS diagnoses and deaths are preventable, and one of the main predictors of HIV morbidity and mortality is late diagnosis of HIV infection. Altogether, 69.6% met the definition of LD, much higher than the 53% recorded in the European population, but similar to some African registers (10, 21). A total of 86.8% of the patients with OIs had a CD4+ T cell count ≤200 cells/mm^3; counts under 50 cells/mm^3 were found in 54.7% of the patients, and only 42.1% were on an ART scheme at the beginning of the study, very far from the 90-90-90 WHO 2020 objective and from the 81% reported in some cohorts in industrialized countries (22). For ART to be effective (reach undetectable plasma VLs), at least 95% of the daily doses must be taken; in our study, treatment adherence was measured with a patient survey which indicated that only 31% of the patients had adequate adherence, which could explain the very low percentage of undetectable VLs (8%).

Our study shows that the most common OIs were tuberculosis with 28.4%, followed by pneumocystosis with 27.9% and toxoplasmosis with 27.4%; oral candidiasis, histoplasmosis and cryptococcosis were reported in 4.2, 11.1 and 11.6%, respectively. This spectrum has varied widely from population to population and depends on some factors like access to ART or adequate affiliation to a social security system. Tuberculosis has already been described as the main OI in other data published in our country (23). Human immunodeficiency virus infection is known to have fostered a dramatic increase in the incidence of TB in many areas of the world, in some of which it is 10 times greater in people infected with HIV than in the general population (24).

In other countries, for example the United States, Djawe et al. describe pneumocystosis and Kaposi sarcoma as the most frequently reported OIs of all times (prior to and after the beginning of effective ART) (25). Among the systemic mycoses, cryptococcosis is most often found in patients with AIDS, especially in the form of meningoencephalitis. One of the most significant risk factors for opportunistic mycotic infections in patients with HIV infection is a CD4+ T cell

Table 4. *Opportunistic infections according to CD4 T cell count.*

Opportunistic infections	CD4 T lymphocyte count				
	Less than 50	50 - 100	100 - 200	200 - 500	More than 500
Toxoplasmosis	24 (17.9)	9 (22.5)	15 (51.7)	3 (18.7)	1 (25)
Pneumocystosis	33 (24.6)	12 (30)	5 (17.2)	2 (12.5)	1 (25)
Cryptococcus	15 (11.1)	5 (12.5)	0	1 (6.25)	1 (25)
Histoplasma	21 (15.7)	0	0	0	0
Candida	6 (4.5)	0	0	2 (12.5)	0
Tuberculosis	28 (20.9)	11 (27.5)	6 (20.7)	8 (50)	1 (25)
CMV	3 (2.2)	3 (7.5)	1 (3.4)	0	0
MAC	0	0	1 (3.4)	0	0
Coccidia	4 (2.9)	0	1 (3.4)	0	0
Total	**134**	**40**	**29**	**16**	**4**

A total of 223 OIs were recorded; 48 patients had more than one OI and the three most common associations were histoplasmosis associated with pneumocystosis, tuberculosis associated with pneumocystosis and tuberculosis associated with toxoplasmosis.

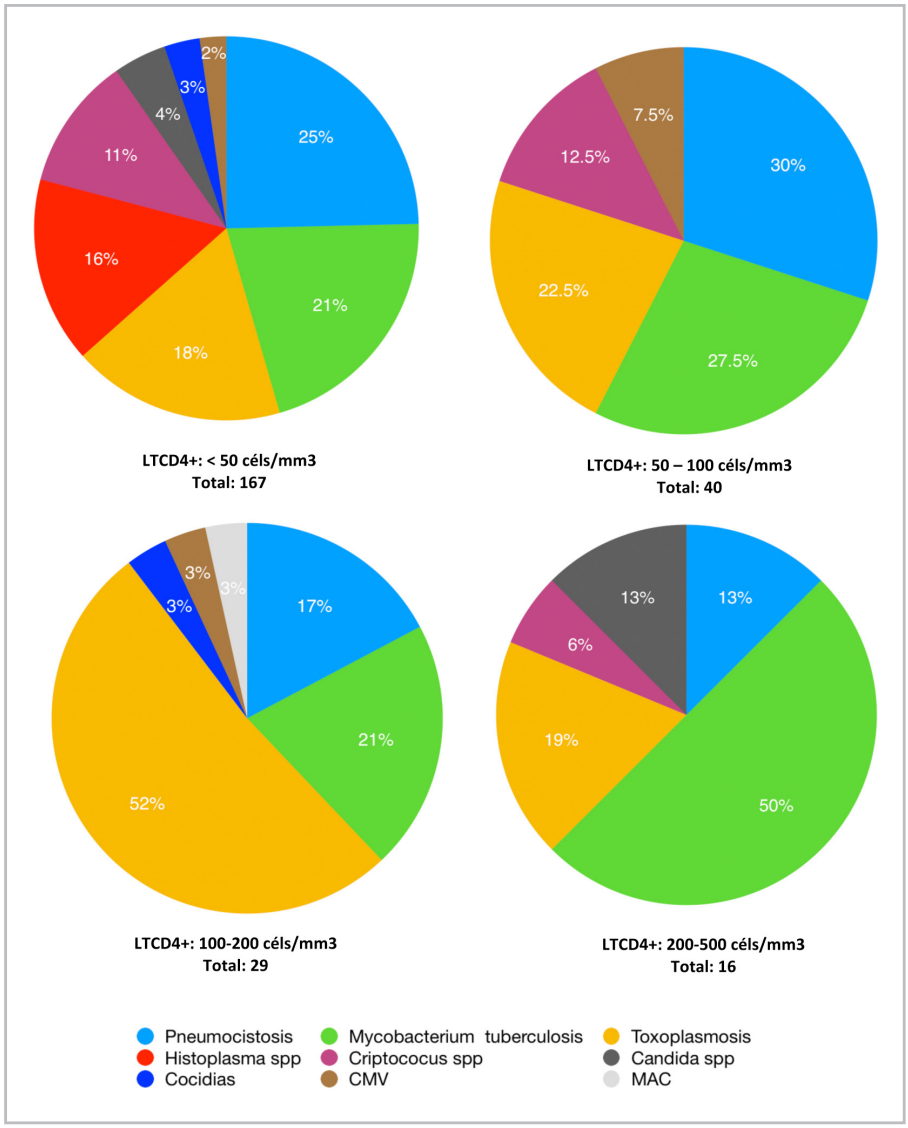

Figure 2. *Opportunistic infections according to CD4 T cell count.*

count less than or equal to 200 cells/mm^3 (26), which was corroborated in our study.

In our study, 22 cases of *Cryptococcus* infection were documented, 20 of which were in patients with CD4+ T cell counts under 200 cells/mm^3, which corresponds to 12.1% of all patients in this CD4+ T cell range; only two cases were documented in patients with CD4+ T cell counts greater than 200 cells/mm^3. We underscore a low percentage of OIs due to *Candida*, which suggests a low rate of diagnosis at our center. These data are similar to local studies in which a prevalence of *Candida* infection of up to 5.5% has been estimated in patients with HIV (27).

We highlight the fact that patients with CD4 counts <50 cells/mm^3 were more prone to having more than one OI (often three), compared with all the patients studied, which concurs with other reviews (28-29).

Conclusions

Despite the availability of highly-effective ART, OIs continue to cause considerable morbidity and mortality in patients infected with HIV. Accessibility to ART should be improved, delayed diagnosis reduced, and above all, lack of adherence to treatment should be impacted (the latter derived from psychosocial and economic factors, including low educational level, poverty and unemployment) (30). Instating certain measures like regular medical visits, evaluating barriers prior to beginning ART, using ART with a high genetic resistance barrier, simplified dosing schemes (including the single-pill regimen), and multidisciplinary approaches including social work, are important strategies which need to be disseminated more (31, 32).

In our population, most patients are hospitalized in advanced stages with OIs and with evidence of severe viral

and immunological compromise. Our study contributes valid information regarding the main OIs affecting this population, which should therefore be thoroughly checked for, along with cancers, when evaluating patients with HIV infection.

References

1. **Holmes, C. B.; Losina, E.; Walensky, R. P.; Yazdanpanah, Y.; Freedberg, K. A.** Review of Human Immunodeficiency Virus Type 1–Related Opportunistic Infections in Sub-Saharan Africa. *Clin. Infect. Dis.* **2003**, *36* (5), 652–662. https://doi.org/10.1086/367655.
2. **Kouanfack, O. S. D.; Kouanfack, C.; Billong, S. C.; Cumber, S. N.; Nkfusai, C. N.; Bede, F.; Wepngong, E.; Hubert, C.; Nguefack-Tsague, G.; Singwe, M. N.** Epidemiology of Opportunistic Infections in HIV Infected Patients on Treatment in Accredited HIV Treatment Centers in Cameroon. *Int. J. Matern. Child Health AIDS* **2019**, *8* (2), 163–172. https://doi.org/10.21106/ijma.302.
3. **Dereje, N.; Moges, K.; Nigatu, Y.; Holland, R.** Prevalence And Predictors Of Opportunistic Infections Among HIV Positive Adults On Antiretroviral Therapy (On-ART) Versus Pre-ART In Addis Ababa, Ethiopia: A Comparative Cross-Sectional Study. *HIVAIDS Auckl. NZ* **2019**, *11*, 229–237. https://doi.org/10.2147/HIV.S218213.
4. **O Iroezindu, M.** Prevalence and Risk Factors for Opportunistic Infections in HIV Patients Receiving Antiretroviral Therapy in a Resource-Limited Setting in Nigeria. *J. AIDS Clin. Res.* **2013**, *01* (S3). https://doi.org/10.4172/2155-6113.S3-002.
5. **Iroezindu, M.** Disparities in the Magnitude of Human Immunodeficiency Virus-Related Opportunistic Infections between High and Low/Middle-Income Countries: Is Highly Active Antiretroviral Therapy Changing the Trend? *Ann. Med. Health Sci. Res.* **2016**, *6* (1), 4. https://doi.org/10.4103/2141-9248.180234.
6. **Rosenblum, L.; Buehler, J. W.; Morgan, M. W.; Costa, S.; Hidalgo, J.; Holmes, R.; Lieb, L.; Shields, A.; Whyte, B. M.** The Completeness of AIDS Case Reporting, 1988: A Multisite Collaborative Surveillance Project. *Am. J. Public Health* **1992**, *82* (11), 1495–1499. https://doi.org/10.2105/AJPH.82.11.1495.
7. **Rubaihayo, J.; Tumwesigye, N. M.; Konde-Lule, J.** Trends in Prevalence of Selected Opportunistic Infections Associated with HIV/AIDS in Uganda. *BMC Infect. Dis.* **2015**, *15* (1), 187. https://doi.org/10.1186/s12879-015-0927-7.
8. **Rubaihayo, J.; Tumwesigye, N. M.; Konde-Lule, J.; Wamani, H.; Nakku-Joloba, E.; Makumbi, F.** Frequency and Distribution Patterns of Opportunistic Infections Associated with HIV/AIDS in Uganda. *BMC Res. Notes* **2016**, *9* (1), 501. https://doi.org/10.1186/s13104-016-2317-7.
9. **World Health Organization.** Nutrition Requirements for People Living with HIV/AIDS: Report of a Technical Consultation. Geneva: WHO; 2003.
10. **European Centre for Disease Prevention and Control/WHO Regional Office for Europe**. (2019). HIV/AIDS Surveillance in Europe 2019–2018 Data.
11. Late presenters working group in COHERE in EuroCoord; Mocroft, A.; Lundgren, J.; Antinori, A.; Monforte, A. d'Arminio; Brännström, J.; Bonnet, F.; Brockmeyer, N.; Casabona, J.; Castagna, A.; Costagliola, D.; De Wit, S.; Fätkenheuer, G.; Furrer, H.; Jadand, C.; Johnson, A.; Lazanas, M.; Leport, C.; Moreno, S.; Mussini, C.; Obel, N.; Post, F.; Reiss, P.; Sabin, C.; Skaletz-Rorowski, A.; Suarez-Loano, I.; Torti, C.; Warszawski, J.; Wittkop, L.; Zangerle, R.; Chene, G.; Raben, D.; Kirk, O. Late Presentation for HIV Care across Europe: Update from the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) Study, 2010 to 2013. *Euro Surveill. Bull. Eur. Sur Mal. Transm. Eur. Commun. Dis. Bull.* **2015**, *20* (47). https://doi.org/10.2807/1560-7917.ES.2015.20.47.30070.
12. **Ngongo, N. M.; Nani-Tuma, H. S.; Mambimbi, M. M.; Mashi, M. L.; Izizag, B. B.; Ndolumingu, F. K.; Maes, N.; Moutschen, M.; Darcis, G**. Decrease in Late Presentation for HIV Care in Kinshasa, DRC, 2006–2020. *AIDS Res. Ther.* **2021**, *18*, 41. https://doi.org/10.1186/s12981-021-00366-8.
13. **Ward, M., Buehler, M. J. W., Jaffe, M. H. W., & Berkelman, R. L.** (1993). 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS among Adolescents and Adults.
14. Fondo Colombiano de Enfermedades de Alto Costo, Cuenta de Alto Costo (CAC). Situación del VIH en Colombia 2019; Bogotá D.C. 2020.
15. **Agudelo-Gonzalez, S.; Murcia-Sanchez, F.; Salinas, D.; Osorio, J**. Infecciones Oportunistas En Pacientes Con VIH En El Hospital Universitario de Neiva, Colombia. 2007-2012. *Infectio* **2015**, *19* (2), 52–59. https://doi.org/10.1016/j.infect.2014.11.008.
16. **Montalvo, R. H.; Mejía, J. R.; Ramírez, P.; Rojas, E.; Serpa, H.; Tiza, V.** Infecciones Oportunistas Post Inicio de Tratamiento Antirretroviral En Pacientes Con VIH/SIDA En Un Hospital Público de Perú. *Rev. Fac. Cienc. Salud UDES* **2018**, *5* (1), 19. https://doi.org/10.20320/rfcsudes.v5i1.103.
17. **Gueler, A.; Moser, A.; Calmy, A.; Günthard, H. F.; Bernasconi, E.; Furrer, H.; Fux, C. A.; Battegay, M.; Cavassini, M.; Vernazza, P.; Zwahlen, M.; Egger, M**. Life Expectancy in HIV-Positive Persons in Switzerland: Matched Comparison with General Population. *Aids* **2017**, *31* (3), 427–436. https://doi.org/10.1097/QAD.0000000000001335.
18. **Hailemariam, S.; Bune, G. T.; Ayele, H. T.** Malnutrition: Prevalence and Its Associated Factors in People Living with HIV/AIDS, in Dilla University Referral Hospital. *Arch. Public Health* **2013**, *71* (1), 13. https://doi.org/10.1186/0778-7367-71-13.
19. **Alebel, A.; Demant, D.; Petrucka, P.; Sibbritt, D.** Effects of Undernutrition on Mortality and Morbidity among Adults Living with HIV in Sub-Saharan Africa: A Systematic Review and Meta-Analysis. *BMC Infect. Dis.* **2021**, *21*, 1. https://doi.org/10.1186/s12879-020-05706-z.
20. **Mulu, H.; Hamza, L.; Alemseged, F.** Prevalence of Malnutrition and Associated Factors among Hospitalized Patients with Acquired Immunodeficiency Syndrome in Jimma University Specialized Hospital, Ethiopia. *Ethiop. J. Health Sci.* **2016**, *26* (3), 217. https://doi.org/10.4314/ejhs.v26i3.4.
21. **Assen, A.; Molla, F.; Wondimu, A.; Abrha, S.; Melkam, W.; Tadesse, E.; Yilma, Z.; Eticha, T.; Abrha, H.; Workneh, B. D.** Late Presentation for Diagnosis of HIV Infection among HIV Positive Patients in South Tigray Zone, Ethiopia. *BMC Public Health* **2016**, *16* (1), 558. https://doi.org/10.1186/s12889-016-3263-y.
22. **Sezgin, E.; Van Natta, M.; Thorne, J.; Puhan, M.; Jabs, D.** Secular Trends in Opportunistic Infections, Cancers and Mortality in Patients with AIDS during the Era of Modern Combination Antiretroviral Therapy. *HIV Med.* **2018**, *19* (6), 411–419. https://doi.org/10.1111/hiv.12609.
23. **Montúfar Andrade, F.; Quiroga, A.; Builes, C.; Saldarriaga, C.; Aguilar, C.; Mesa, M.; Zuleta Tobón, J.** Epidemiología de La Infección Por El Virus de Inmunodeficiencia Humana En Pacientes Hospitalizados En Una Institución de Alta Complejidad y Enseñanza Universitaria En Medellín, Colombia. *Infectio* **2016**, *20* (1), 9–16. https://doi.org/10.1016/j.infect.2015.05.004.
24. **Corbett, E. L.; Watt, C. J.; Walker, N.; Maher, D.; Williams, B. G.; Raviglione, M. C.; Dye, C.** The Growing Burden of Tuberculosis. *Arch. Intern. Med.* **2003**, *163* (9), 1009. https://doi.org/10.1001/archinte.163.9.1009.
25. **Djawe, K.; Buchacz, K.; Hsu, L.; Chen, M. J.; Selik, R. M.; Rose, C.; Williams, T.; Brooks, J. T.; Schwarcz, S.** Mortality Risk after AIDS-Defining Opportunistic Illness among HIV-Infected Persons-San Francisco, 1981-2012. *J. Infect. Dis.* **2015**, *212* (9), 1366–1375. https://doi.org/10.1093/infdis/jiv235.
26. **González Ángel, Tobón Ángela María.** Infecciones micóticas oportunistas en pacientes con VIH/SIDA. *Infect.* [Internet]. 2006 Dec [cited 2022 Mar 08] ; **10(4):**279-287.
27. **Martinez LL, Cardona-Arias JA.** Infecciones fúngicas en un hospital público de referencia para la atención de personas con VIH/SIDA, Medellín 2013-2017. MÉD.UIS. 2020;**33(2):**17-24. doi: 10.18273/revmed.v33n2-2020002
28. **Tilak, A.; Shenoy, S.; Varma, M.; Kamath, A.; Tripathy, A.; Sori, R.; Saravu, K.** Opportunistic Infection at the Start of Antiretroviral Therapy and Baseline CD4+ Count Less than 50 Cells/Mm3 Are Associated with Poor Immunological Recovery. *J. Basic Clin. Physiol. Pharmacol.* **2019**, 30 (2), 163–171. https://doi.org/10.1515/jbcpp-2018-0105.
29. **Gautam, H.; Bhalla, P.; Saini, S.; Uppal, B.; Kaur, R.; Baveja, C. P.; Dewan, R**. Epidemiology of Opportunistic Infections and Its Correlation with CD4 T-Lymphocyte Counts and Plasma Viral Load among HIV-Positive Patients at a Tertiary Care Hospital in India. *J. Int. Assoc. Physicians AIDS Care Chic. Ill 2002* **2009**, 8 (6), 333–337. https://doi.org/10.1177/1545109709346881.
30. **Benson, C.; Wang, X.; Dunn, K. J.; Li, N.; Mesana, L.; Lai, J.; Wong, E. Y.; Chow, W.; Hardy, H.; Song, J.; Brown, K**. Antiretroviral Adherence, Drug Resistance, and the Impact of Social Determinants of Health in HIV-1 Patients in the US. *AIDS Behav.* **2020**, 24 (12), 3562–3573. https://doi.org/10.1007/s10461-020-02937-8.
31. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents | AIDS Education and Training Centers National Coordinating Resource Center (AETC NCRC) https://aidsetc.org/resource/guidelines-use-antiretroviral-agents-hiv-1-infected-adults-and-adolescents (accessed 2021 -08 -22).
32. **Holmes, C. B.; Losina, E.; Walensky, R. P.; Yazdanpanah, Y.; Freedberg, K. A.** Review of Human Immunodeficiency Virus Type 1–Related Opportunistic Infections in Sub-Saharan Africa. *Clin. Infect. Dis.* **2003**, *36* (5), 652–662. https://doi.org/10.1086/367655.