



Diagnóstico tardío y mortalidad

El manejo de la enfermedad avanzada en el contexto del continuo de prevención atención del VIH

Dr. Omar Sued

Asesor regional de tratamiento de VIH

Representante de LAC en el cuerpo de gobierno de la IAS

PAHO

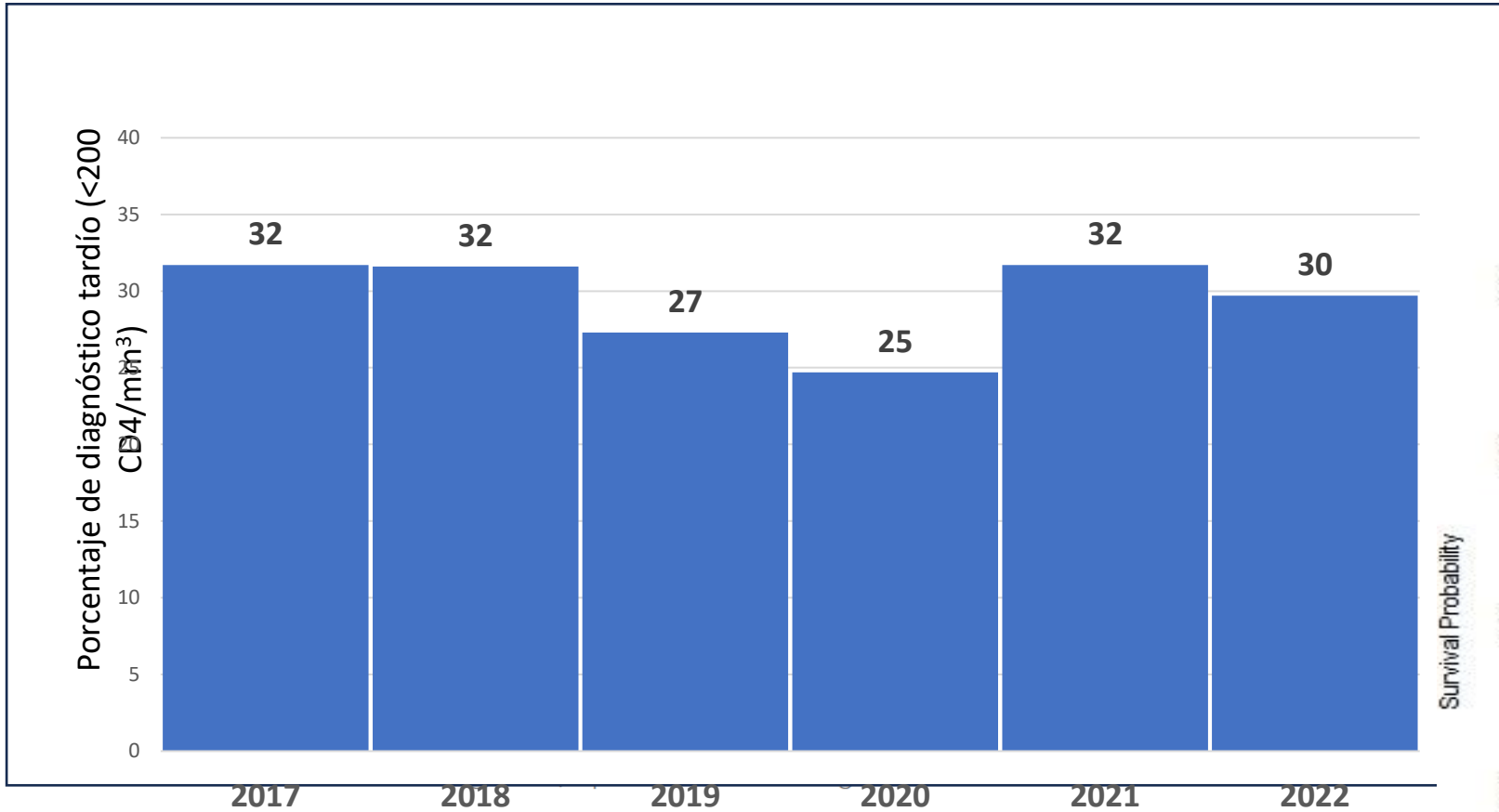


Pan American
Health
Organization



World Health
Organization
REGIONAL OFFICE FOR THE
Americas

Diagnóstico tardío, mortalidad

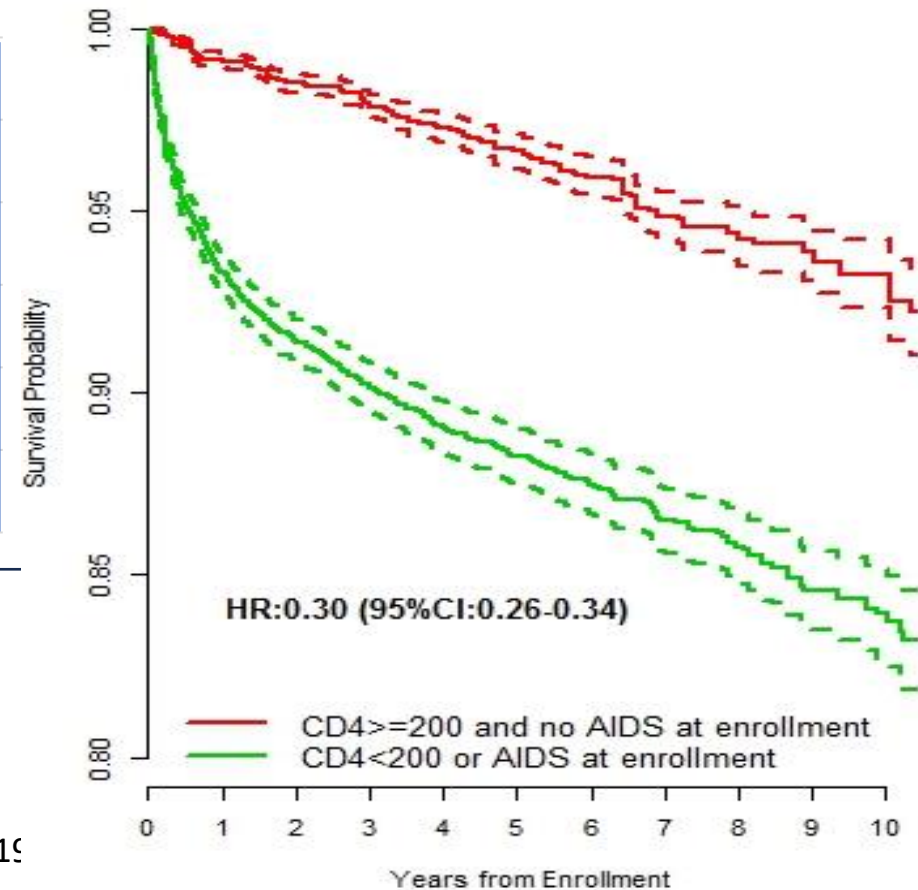


Definición

Al diagnóstico

- < 200 CD4 (hay otras)
- Estadío 3-4 de OMS

A. Late presentation (LP) vs Non-LP



Early mortality in a cohort of people living with HIV in Rio de Janeiro, Brazil, 2004–2015: a persisting problem

Pedro H. A. C. Leite^{1,2*}, Lara E. Coelho², Sandra W. Cardoso², Ronaldo I. Moreira², Valdilea G. Veloso², Beatriz Grinsztejn² and Paula M. Luz^{1,2}

Abstract

Background: Global mortality from AIDS-related diseases has been declining since 2005, resulting primarily from the widespread use and early initiation of combination antiretroviral therapy. Despite the significant improvements, high rates of early mortality, usually defined as that occurring within the 1st year of entry to care, have been observed, especially in resource-limited settings. This analysis draws upon data from an observational cohort of people with HIV (PWH) followed at a reference center for HIV/AIDS care and research in the city of Rio de Janeiro, Brazil, to identify the pattern and factors associated with early mortality.

Methods: The study population includes PWH aged 18 or older followed at the National Institute of Infectious Diseases Evandro Chagas who were enrolled between 2004 and 2015. The primary outcome was early mortality, defined as deaths occurring within 1 year of inclusion in the cohort, considering two follow-up periods: 0 to 90 days (very early mortality) and 91 to 365 days (early mortality). Cox proportional hazards models were used to identify the variables associated with the hazard of very early and early mortality.

Results: Overall, 3879 participants contributed with 3616.4 person-years of follow-up. Of 220 deaths, 132 happened in the first 90 days and 88 between 91 and 365 days. Very early mortality rate ratios (MRR) show no statistically significant temporal differences between the periods 2004–2006 to 2013–2015. In contrast, for early mortality, a statistically significant decreasing trend was observed: mortality rates in the periods 2004–2006 (MR = 5.5; 95% CI 3.9–7.8) and 2007–2009 (MR = 3.9; 95% CI 2.7–5.7) were approximately four and three-fold higher when compared to 2013–2015 (MR = 1.4; 95% CI 0.7–2.7). Low CD4 count and prior AIDS-defining illness were strongly associated with higher hazard ratios of death, especially when considering very early mortality.

Conclusions: The present study shows an excess of mortality in the 1st year of follow-up with no changes in the mortality rates within 90 days among PWH from Rio de Janeiro. We note the significant impact of initiating treatment with immunosuppression, as evidenced by the increased risk of death among those with low CD4 cell count and with AIDS-defining illnesses.

Keywords: HIV, Acquired immunodeficiency syndrome, Survival analysis, Mortality, Risk factors, Cohort studies

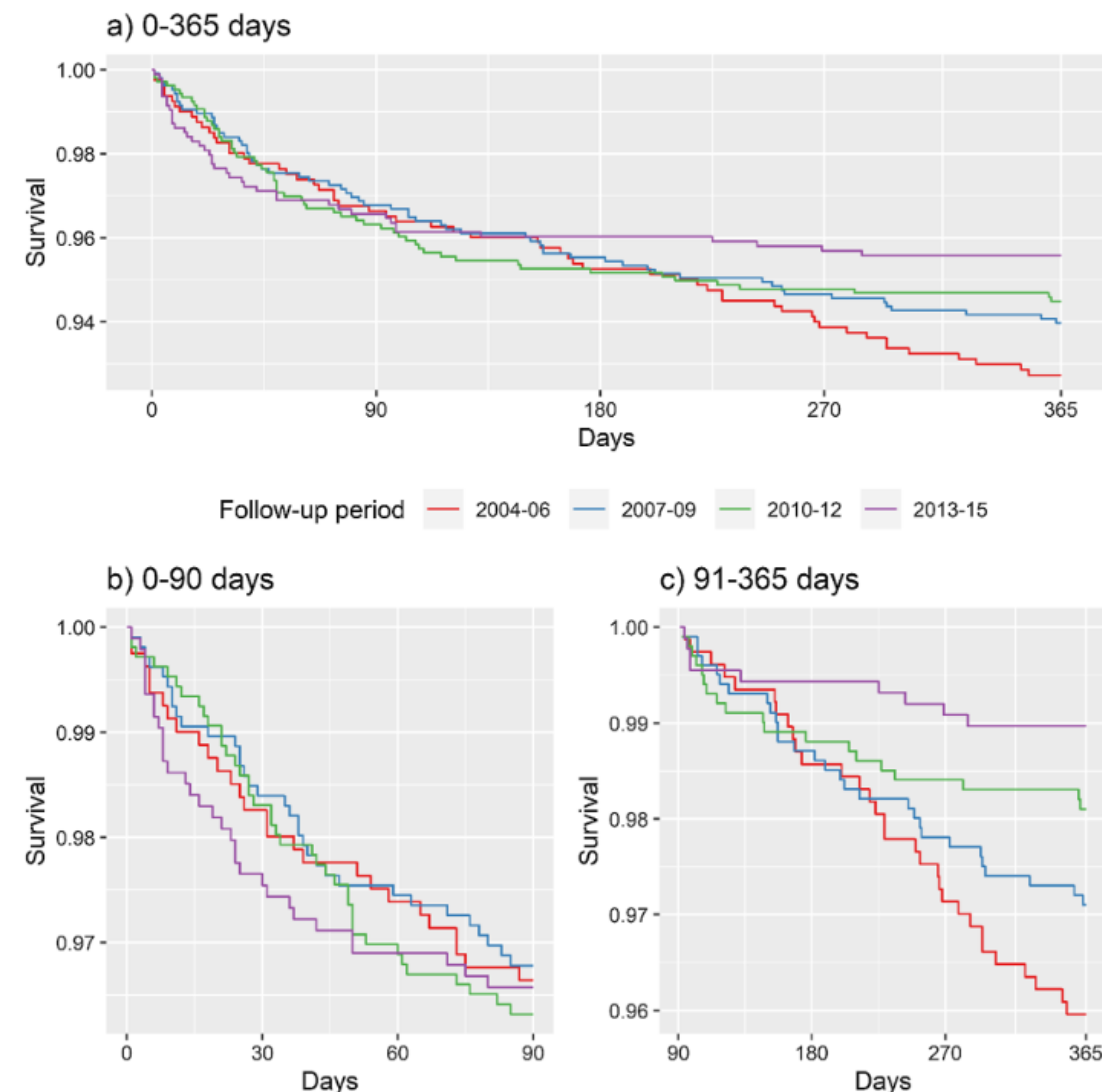


Fig. 1 Kaplan–Meier curves, stratified by year of first visit and follow-up period of cohort participants. INI cohort, 2004–2015 (N = 3879)

●●● Enfermedad avanzada por VIH

Definición

- Personas con <200 CD4
- Menores de 5 años sin TARV
- Estadio 3-4 de OMS

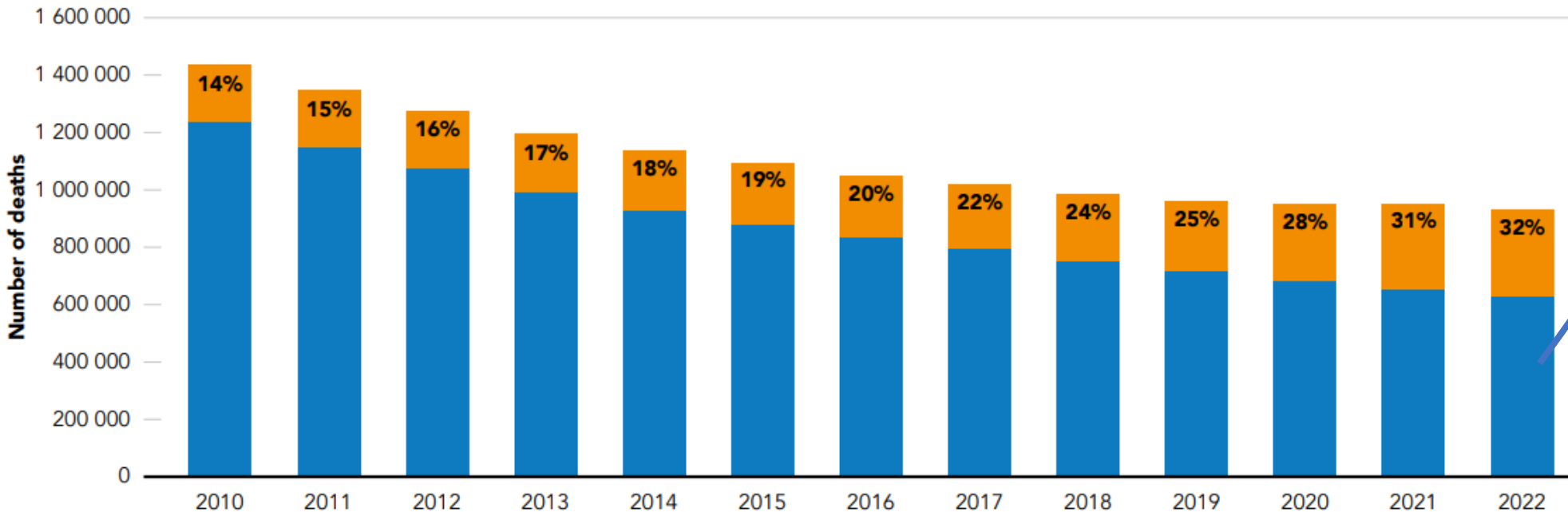
Importancia

- 2/3 de las muertes por VIH todavía se producen por causas prevenibles

Factores asociados

- Edad, sexo
- Pobreza
- Uso de drogas y alcohol
- Poca retención

Figure 2.10 Deaths among people living with HIV, by cause, 2010–2022



Hay muy pocos datos sobre cuáles son las causas de muerte a nivel nacional en personas con VIH de América Latina y El Caribe, pero las infecciones oportunistas siguen teniendo un papel relevante



La mayoría de las personas con enfermedad avanzada ya han sido diagnosticadas pero se perdieron en el seguimiento

Patient characteristics	All patients, n = 551 (100%)	AIDS-defining illness, n = 301 (54.6%)
Age, median (IQR)	37 (30–49)	37 (30–50)
Male	418 (76)	231 (76.7)
Low income	372 (67.5)	225 (74.7)
Lower educational attainment	390 (70.8)	154 (51.1)
New HIV diagnosis	121 (22)	88 (29.2)
ART status		
Receiving ART prior to admission	273 (49.5)	131 (43.5)
Not on ART	278 (50.4)	111 (36.8)
Abandonment of ART	–	59 (19.6)
Adherence to ART ^a	–	83/190 (43.6)
Attending HIV program	–	86 (28.5)
Attending HIV program and receiving ART	–	72(23.9)
CD4 cell count, cells/ μ L Median (IQR)	98 (36.2–98)	59 (24–131)
HIV viral load, copies/mL Median (IQR)	100.278 (1.505–384.250)	179.000 (26.597–622.022)
Anemia ^b	104 (18.9)	76 (25.2)
Past history of TB	88 (20.4)	55 (18.2)

^a Adherence to ART is calculated with patients who had abandoned ART or were rec

^b Anemia was defined using WHO criteria (hemoglobin < 11.0 g/dL for both males and

Table 2 Causes of hospitalization in HIV patients in Medellín, Colombia from August 2014 to July 2015 (N = 551)

Variable	n (%)
AIDS defining illness ^a	301 (54.6)
Tuberculosis	128 (23.3)
Extrapulmonary tuberculosis	84 (15.2)
Pulmonary tuberculosis	44 (8.0)
Esophageal candidiasis	56 (10.1)
Toxoplasma encephalitis	43 (7.8)
Disseminated histoplasmosis	39 (7.1)
CMV infection	36 (6.5)
Extrapulmonary cryptococcosis	32 (5.8)
Pneumonia by <i>P. jiroveci</i>	32 (5.8)
Lymphoma ^b	27 (4.9)
Kaposi's sarcoma	11 (2.0)
Herpes simplex > 1 month	10 (1.8)
Cryptosporidiosis > 1 month	10 (1.8)
HIV Encephalopathy	8 (1.4)
Wasting syndrome	7 (1.3)
MAC	4 (0.7)
Recurrent salmonellosis	2 (0.3)
Adverse drug effect	39 (7.1)
Non-AIDS-defining illness but related to HIV	35 (6.2)
Another cause of hospitalization not related to HIV	176 (31.9)
Bacterial infection	61 (11.0)
Others ^c	115 (20.9)

●●● El impacto del VIH sigue siendo grande en salud

Estudio en 472 personas con VIH admitidas a UCI en 5 hospitales de Medellín 2009-2014.

- 28% diagnóstico VIH en la internación
- 83% <200 CD4
- 80% Infecciones oportunistas
- 55% recibió TARV alguna vez

Impacto

- 21 días media de ingreso
- 49% mortalidad

Histoplasmosis y criptococosis fueron más frecuentes entre los que no sobrevivieron (16% vs. 20% y 13% vs. 23%, respectivamente).

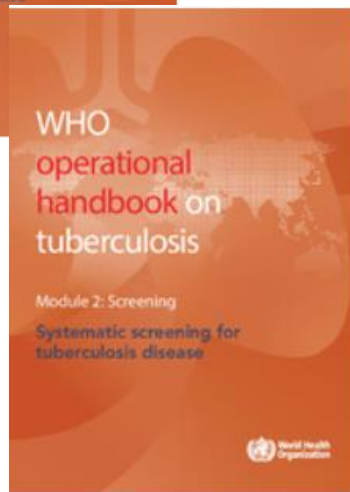
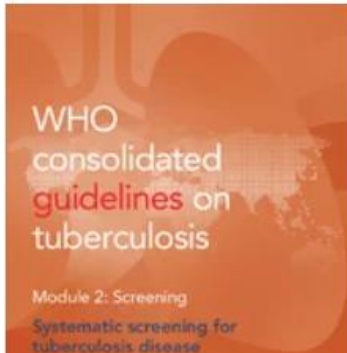
Causes for ICU admission	Total (n = 472) n (%)
Admission due to*:	
Respiratory failure	268 (57)
Sepsis and septic shock	139 (30)
CNS compromise	129 (27)
Post-operative care	35 (7)
Hypovolemic shock	27 (6)
Metabolic disorder	23 (5)
Cardiovascular	9 (1.9)
GI hemorrhage	7 (1.5)
Trauma	6 (1.3)
ICU admission for OI**:	
Pulmonary TB	144/376 (38.3)
<i>P. jirovecii</i>	134/376 (35.6)
Extrapulmonary TB	85/376 (22.6)
Toxoplasmosis	71/376 (18.9)
Candidiasis	69/376 (18.4)
Histoplasmosis	69/376 (18.4)
Cryptococcosis	68/376 (18)
CMV infection	67/376 (17.8)
Kaposi sarcoma	8/376 (2.1)
HSV	8/376 (2.1)
Salmonellosis	7/376 (1.9)
Cryptosporidiosis	5/376 (1.3)
MAC infection	4/376 (1.1)
More than one OI	252/376 (67)
ICU admission for non-opportunistic infection	
	42 (9)
Non-infectious ICU admission***	
	54 (11)



Tuberculosis

Recomendaciones para el tamizaje

Las personas con VIH deben tamizarse sistemáticamente para la enfermedad tuberculosa activa en cada visita a la clínica (*Recomendación fuerte, muy baja calidad de evidencia*)



- **Prueba de los cuatro síntomas de la OMS:** Tos, fiebre, sudores nocturnos y pérdida de peso (Recomendación firme) Para niños: Tos actual, fiebre, escaso aumento de peso o contacto cercano con un paciente con TB (Recomendación firme)
- **Proteína C reactiva** utilizando un punto de corte de $>5\text{mg/L}$ (Recomendación condicional)
- **Radiografía de tórax digital** (Recomendación condicional) con detección asistida por ordenador (Recomendación condicional)
- **Pruebas moleculares rápidas** para el cribado de la tuberculosis (Recomendación condicional)
- **LAM en orina** en personas con VIH internados o <200 CD4





Effect on mortality of point-of-care, urine-based lipoarabinomannan testing to guide tuberculosis treatment initiation in HIV-positive hospital inpatients: a pragmatic, parallel-group, multicountry, open-label, randomised controlled trial

Jonny G Peter*, Lynn S Zijenah*, Duncan Chanda*, Petra Clowes*, Maia Lesosky, Phindile Gina, Nirja Mehta, Greg Calligaro, Carl J Lombard, Gerard Kadzirange, Tsitsi Bandason, Abidan Chansa, Namakando Liusha, Chacha Mangu, Bariki Mtafya, Henry Msila, Andrea Rachow, Michael Hoelscher, Peter Mwaba, Grant Theron, Keertan Dheda

Una intervención de 15 minutos reduce la mortalidad en pacientes internados con VIH

Lancet 2016; 387: 1187-97

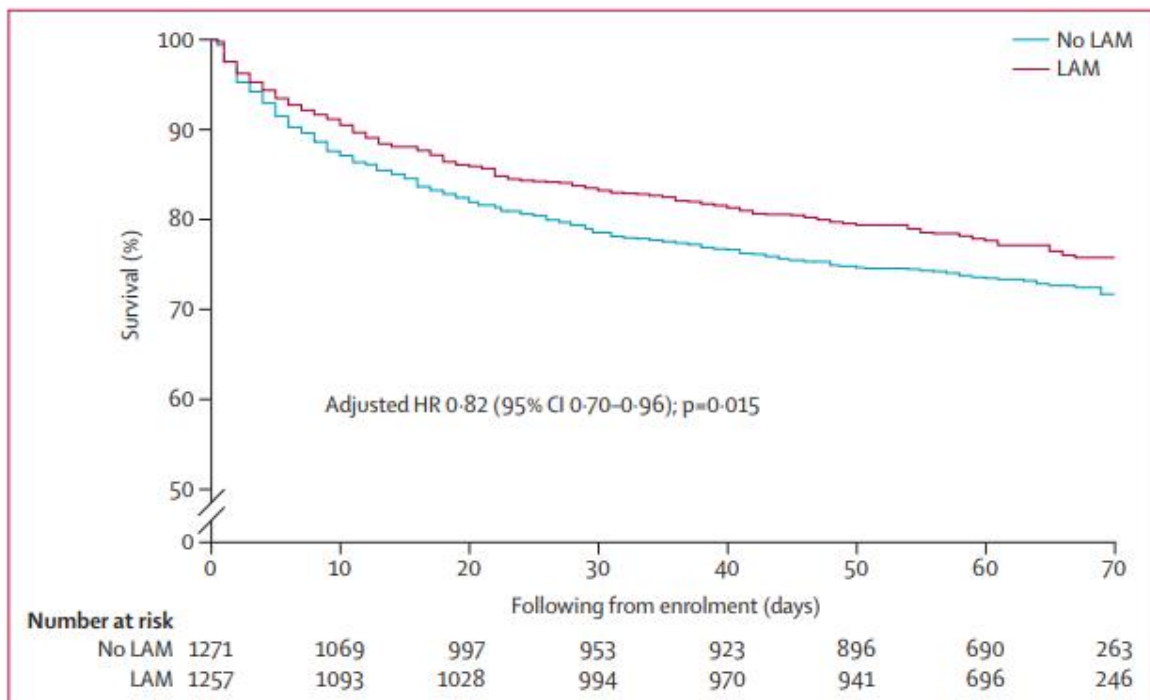
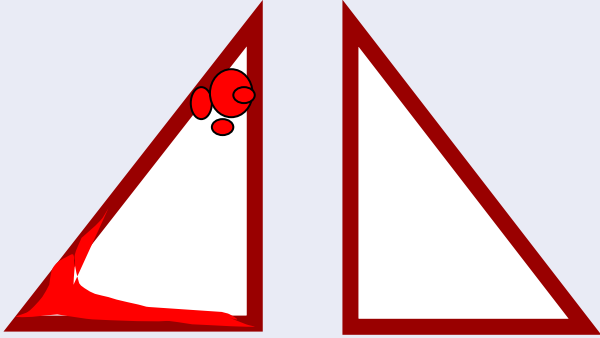
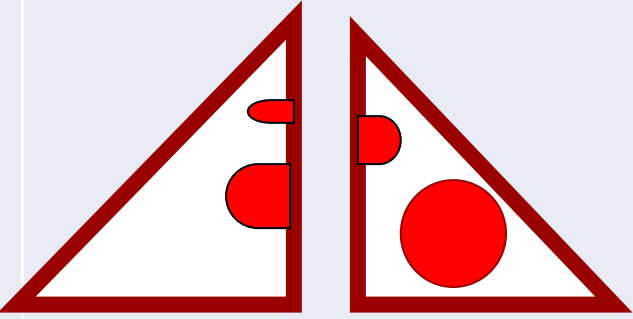
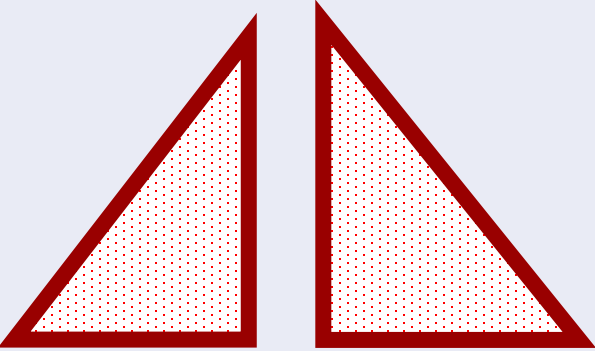


Figure 2: Time to 8-week all-cause mortality

HR=hazard ratio. LAM=lipoarabinomannan. Data are overall HRs and p values for study groups adjusted for country.

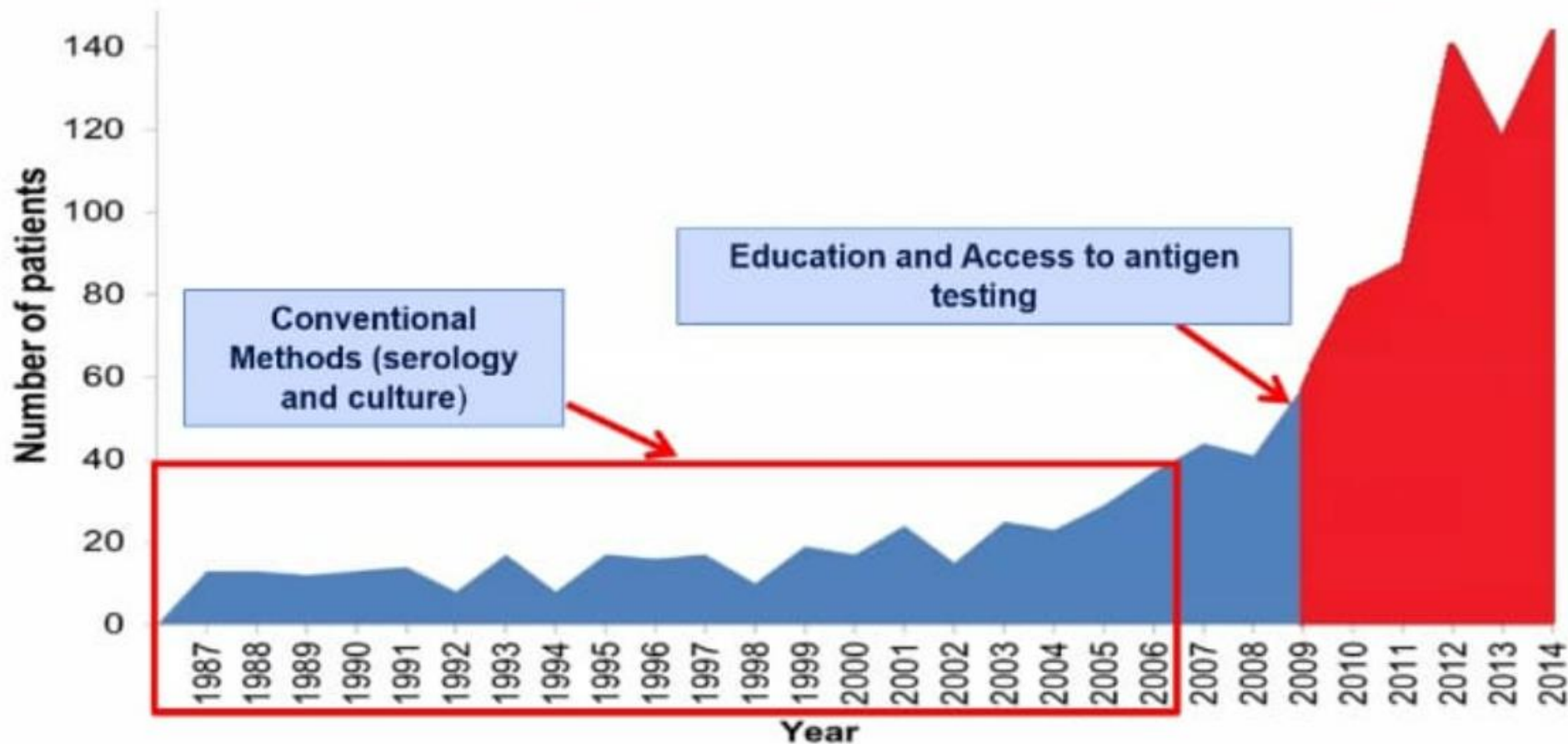
● ● ● Valor adicional de combinar Xpert y LAM-TB

Cd4 >500	CD4 500-200	CD4 <200
Asymptomatic Cough	Fever, lymph node	Fever, lymph node, weight loss, night sweats
		
Pulmonar	Pulmonar atypical	Extrapulmonary
Xpert POSITIVO	Xpert POSITIVO o NEGATIVO	Xpert NEGATIVO
LAM NEGATIVO	LAM POSITIVO o NEGATIVO	LAM POSITIVO

La combinación tiene >90% de sensibilidad
Aumento 36% en la capacidad de detectar la enfermedad

Histoplasmosis

El que busca encuentra: historia del diagnóstico en Colombia



Caceres et al. Am J Trop Med Hyg. 2015 Sep;93(3):662-7.

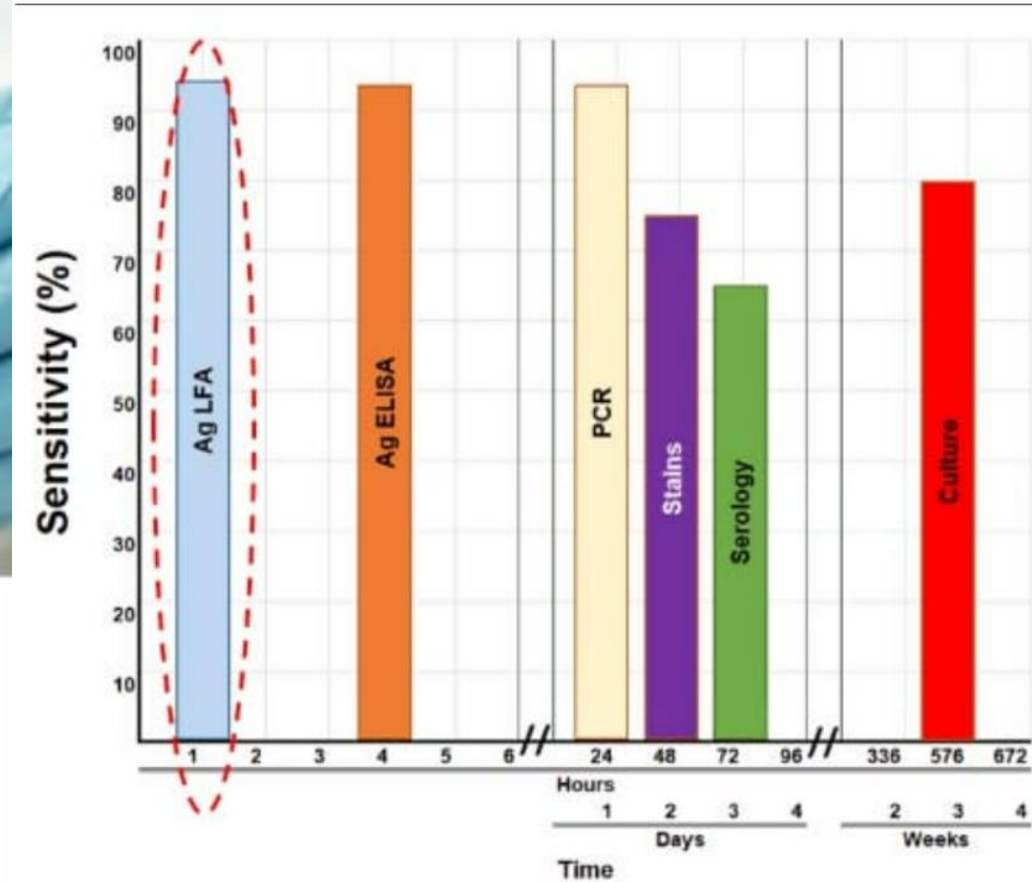
●●● Antígeno en orina para Histoplasmosis



Sensitivity	Specificity
98%	97%

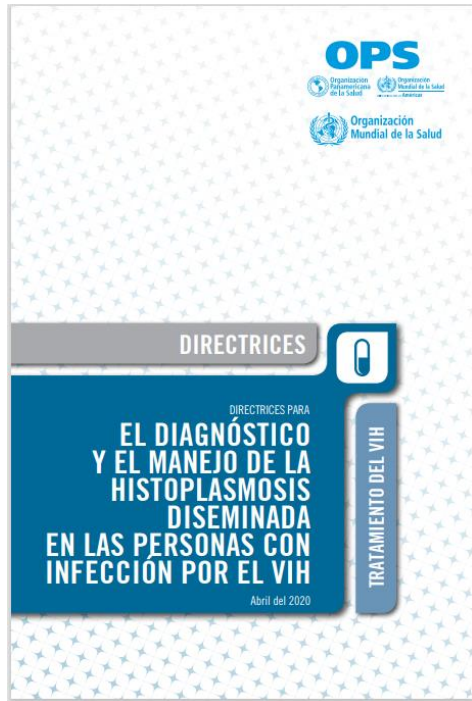


Sensibilidad y especificidad mayor al 90%



Cáceres DH et al. J Clin Microbiol. 2018

● ● ● Resumen de la guía de histoplasmosis de la OPS/OMS



1. Diagnóstico de la histoplasmosis diseminada en las personas con infección por el VIH: En las personas con infección por el VIH, la histoplasmosis diseminada debería diagnosticarse mediante la detección de antígenos circulantes de *Histoplasma* (*recomendación condicional; evidencia con un grado de certeza bajo*).

2. Esquemas de tratamiento antimicótico de inducción y mantenimiento para la histoplasmosis diseminada en las personas con infección por el VIH

3. Momento oportuno para iniciar el tratamiento antirretroviral: el tratamiento antirretroviral debe iniciarse cuanto antes en las personas con histoplasmosis diseminada si no presentan afectación del sistema nervioso central presunta o confirmada (*recomendación condicional; evidencia con un grado de certeza muy bajo*).

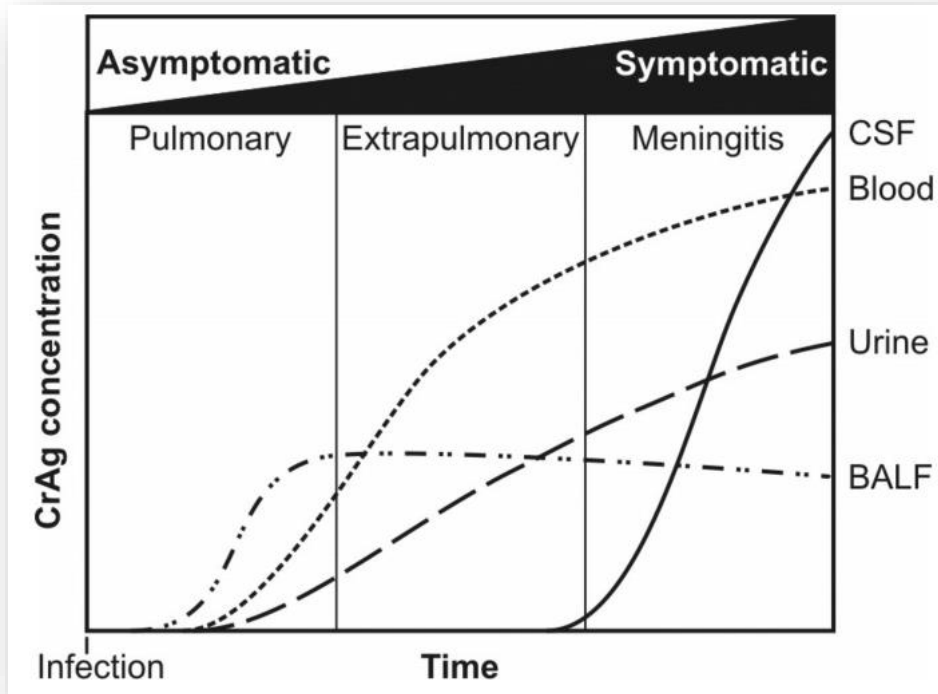
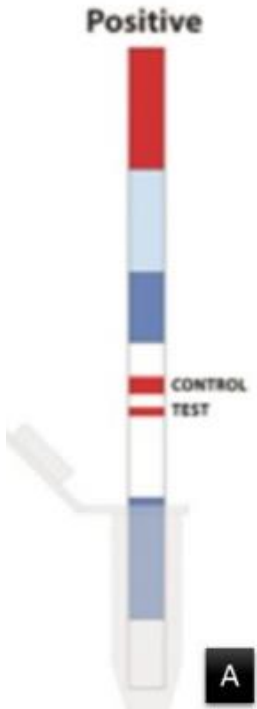
4. Tratamiento de la tuberculosis en las personas coinfectadas por la tuberculosis, el VIH y la histoplasmosis: las personas con coinfección por el VIH, la tuberculosis y la histoplasmosis deben recibir tratamiento contra la tuberculosis en conformidad con las directrices de tratamiento de la OMS (*recomendación condicional; evidencia con un grado de certeza muy bajo*).



Criptococosis

Posibilidad de detectarla temprano con Ag

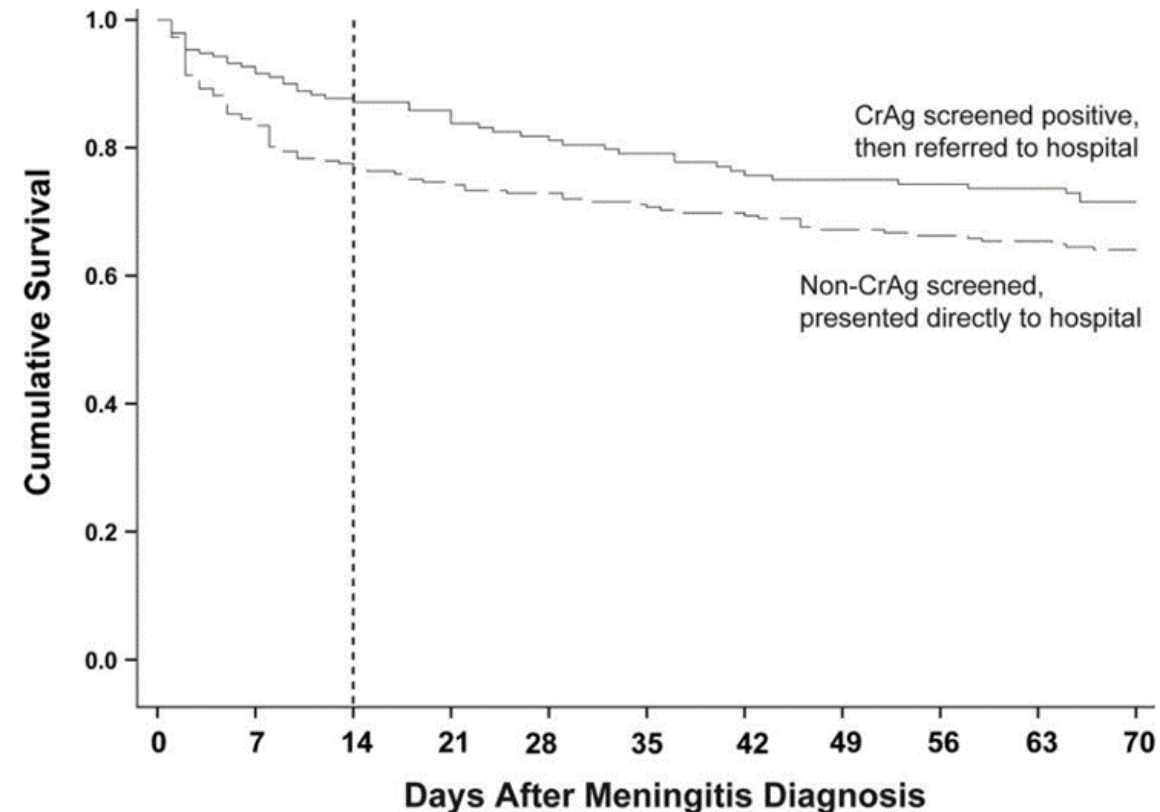
- Primera causa de meningitis en jóvenes en áreas de alta prevalencia de VIH
- Responsable de 2.400 muertes en LAC/año
- 100% de fatalidad sin tratamiento, 30% con tratamiento



Pais	Prevalencia	Autor
Paraguay	10%	G. Aguilar y cols
Guatemala	4.8%	N. Medina y cols
Argentina	8.1%	C. Frola y cols
Brazil	12%	Ferreira y cols
Brazil	3%	Vidal y cols

Outpatient Cryptococcal Antigen Screening Is Associated With Favorable Baseline Characteristics and Improved Survival in Persons With Cryptococcal Meningitis in Uganda

Anna E. Levin,¹ Ananta S. Bangdiwala,² Elizabeth Nalintya,³ Enock Kagimu,³ John Kasibante,³ Morris K. Rutakingirwa,³ Edward Mpoza,³ Samuel Jjunju,⁴ Edwin Nuwagira,⁴ Rose Naluyima,³ Paul Kirumira,³ Cody Hou,^{1,6} Kenneth Ssebambulidde,³ Abdu K. Musubire,³ Darlisha A. Williams,¹ Mahsa Abassi,^{1,6} Conrad Muzoora,⁴ Katherine H. Hullsiek,² Radha Rajasingham,^{1,6} David B. Meya,^{1,3,5,a} David R. Boulware,^{1,a} and Caleb P. Skipper^{1,3,a,6}



Se puede reducir la mortalidad con tamizaje sistemático en personas con menos de 200 CD4

La mortalidad por subgrupos a los 14 días fue:

12%
tamizados con CrAg y positivos

21%
sin tamizar para CrAg y que se presenta-ron con meningitis

($p = 0,005$).



Las pruebas son costo-efectivas

TB-LAM

Cost/DALY averted 4.6 euros

Criptococo

Cost/DALY averted USD 21
Costo por vida salvada USD 662

Histoplasmosis

Costo/año/vida con Amph-D USD 26
Costo/año/vida con Amph-L USD 607

RESEARCH ARTICLE

Cost-effectiveness of diagnostic algorithms including lateral-flow urine lipoarabinomannan for HIV-positive patients with symptoms of tuberculosis

Nadia Yakhelele^{1,2*}, Martine Audibert², Gabriella Ferazzo^{3†}, Joseph Sitenei^{4,5†}, Steve Wanjala^{6†}, Francis Varaine^{3†}, Maryline Bonnet^{1,6†}, Helena Huerga^{1,6†}

1 Epicentre, Paris, France, **2** Université Clermont Auvergne, CNRS, CERDI, Clermont-Ferrand, France, **3** Médecins Sans Frontières, Paris, France, **4** Division of National Strategic Health Programs, Ministry of Health, Nairobi, Kenya, **5** Médecins Sans Frontières, Nairobi, Kenya, **6** IRD UMI 233 TransVIHMI—UM-INSEERM U1175, Montpellier, France

* These authors contributed equally to this work.
† These authors also contributed equally to this work.
* nadiayakhelele@hotmail.com



OPEN ACCESS

Citation: Yakhelele N, Audibert M, Ferazzo G, Sitenei J, Wanjala S, Varaine F, et al. (2020) Cost-effectiveness of diagnostic algorithms including lateral-flow urine lipoarabinomannan for HIV-positive patients with symptoms of tuberculosis. PLOS ONE 15(1): e0227138. <https://doi.org/10.1371/journal.pone.0227138>

Editor: Frederick Quinn, The University of Georgia, UNITED STATES

Received: July 22, 2019

Accepted: December 12, 2019

Published: January 30, 2020

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: <https://doi.org/10.1371/journal.pone.0227138>

Copyright: © 2020 Yakhelele et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All relevant data are within the manuscript and its Supporting Information files.

Abstract

Background

Tuberculosis (TB) is the leading cause of death among HIV-positive patients. We assessed the cost-effectiveness of including lateral-flow urine lipoarabinomannan (LF-LAM) in TB diagnostic algorithms for severely ill or immunosuppressed HIV-positive patients with symptoms of TB in Kenya.

Methods

From a decision-analysis tree, ten diagnostic algorithms were elaborated and compared. All algorithms included clinical exam. The costs of each algorithm were calculated using a 'micro-costing' method. The efficacy was estimated through a prospective study that included severely ill or immunosuppressed (CD4<200cells/μL) HIV-positive adults with symptoms of TB. The cost-effectiveness analysis was performed using the disability-adjusted life year (DALY) averted as effectiveness outcome. A 4% discount rate was applied.

Results

The algorithm that added LF-LAM alone to the clinical exam lead to the least average cost per TB case detected (€47) and was the most cost-effective with a cost/DALY averted of €4.6. The algorithms including LF-LAM, microscopy and X-ray, and LF-LAM and Xpert in sputum, detected a high number of TB cases with a cost/DALY averted of €6.1 for each of them. In the comparisons of the algorithms two by two, using LF-LAM instead of microscopy (clinic&LAM vs clinicµscopy) and using LF-LAM along with GeneXpert in sputum instead of GeneXpert in urine along with GeneXpert in sputum, (clinic&LAM&Xpert_sputum

RESEARCH ARTICLE

Evaluation of a national cryptococcal antigen screening program for HIV-infected patients in Uganda: A cost-effectiveness modeling analysis

Radha Rajasingham^{1*}, David B. Meya², Gregory S. Greene³, Alexander Jordan⁴, Mina Nakawuka⁵, Tom M. Chiller⁶, David R. Boulware⁷, Bruce A. Larson⁸

1 Division of Infectious Diseases & International Medicine, University of Minnesota, Minnesota, United States of America, **2** Infectious Diseases Institute, Makerere University, Kampala, Uganda, **3** Mycotic Diseases Branch, Centers for Disease Control, Atlanta, Georgia, United States of America, **4** AIDS Control Program, Ministry of Health, Kampala, Uganda, **5** Department of Global Health, Boston University School of Public Health, Boston, Massachusetts, United States of America

* radha@umn.edu



OPEN ACCESS

Citation: Rajasingham R, Meya DB, Greene GS, Jordan A, Nakawuka M, Chiller TM, et al. (2019) Evaluation of a national cryptococcal antigen screening program for HIV-infected patients in Uganda: A cost-effectiveness modeling analysis. PLOS ONE 14(1): e0210105. <https://doi.org/10.1371/journal.pone.0210105>

Editor: Eileen Stillwagon, Gettysburg College, UNITED STATES

Received: November 27, 2018

Accepted: December 16, 2018

Published: January 10, 2019

Copyright: This is an open access article, free of all copyright, and may be freely reproduced, distributed, transmitted, modified, built upon, or otherwise used by anyone for any lawful purpose. The work is made available under the [Creative Commons CC0 public domain dedication](https://creativecommons.org/licenses/by/4.0/).

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: RR is supported by the National Institute of Allergy and Infectious Diseases (K23AI138851). RR is supported by the CDC foundation. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the funding agencies. The source of this information is the Global Cryptococcal

Abstract

Background

Cryptococcal meningitis accounts for 15% of AIDS-related mortality. Cryptococcal antigen (CrAg) is detected in blood weeks before onset of meningitis, and CrAg positivity is an independent predictor of meningitis and death. CrAg screening for patients with advanced HIV and preemptive treatment is recommended by the World Health Organization, though implementation remains limited. Our objective was to evaluate costs and mortality reduction (lives saved) from a national CrAg screening program across Uganda.

Methods

We created a decision analytic model to evaluate CrAg screening. CrAg screening was considered for those with a CD4<100 cells/μL per national and international guidelines, and in the context of a national HIV test-and-treat program where CD4 testing was not available. Costs (2016 USD) were estimated for screening, preemptive therapy, hospitalization, and maintenance therapy. Parameter assumptions were based on large prospective CrAg screening studies in Uganda, and clinical trials from sub Saharan Africa. CrAg positive (CrAg+) persons could be: (a) asymptomatic and thus eligible for preemptive treatment with fluconazole; or (b) symptomatic with meningitis with hospitalization.

Results

In the base case model for 1 million persons with a CD4 test annually, 128,000 with a CD4<100 cells/μL were screened, and 8,233 were asymptomatic CrAg+ and received preemptive therapy. Compared to no screening and treatment, CrAg screening and treatment in the base case cost \$3,356,724 compared to doing nothing, and saved 7,320 lives, for a cost of \$459 per life saved, with the \$3.3 million in cost savings derived from fewer patients

RESEARCH ARTICLE

Cost-effectiveness evaluation of routine histoplasmosis screening among people living with advanced HIV disease in Latin America and the Caribbean

Radha Rajasingham¹, Narda Medina², Gabriel T. Mousquer³, Diego H. Caceres^{4,5}, Alexander Jordan⁶, Mathieu Nacher⁷, Diego R. Falci^{8,9}, Ayanna Sebro¹⁰, Alessandro C. Pasqualotto^{11,12}, Omar Sued¹³, Tom Chiller⁹, Freddy Perez^{9,11,13*}

1 Division of Infectious Diseases & International Medicine, Department of Medicine, University of Minnesota, Minneapolis, Minnesota, United States of America, **2** ASRT, Inc., Mycotic Diseases Branch, Division of Foodborne, Waterborne, and Environmental Diseases (DFWED), Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America, **3** Graduate Program in Biosciences, Federal University of Health Sciences of Porto Alegre (FUCSPA), Porto Alegre, Brazil, **4** Center of Expertise in Mycology Radboudumc/CWZ, Nijmegen, The Netherlands, **5** Studies in Translational Microbiology and Emerging Diseases (MICROES) Research Group, School of Medicine and Health Sciences, Universidad del Rosario, Bogotá, Colombia, **6** Mycotic Diseases Branch—Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America, **7** Center for Clinical Investigation Antilles-Guyane, Inserm 1424, Cayenne Hospital, Cayenne, French Guiana, France, **8** Infectious Diseases Unit, Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil, **9** School of Medicine, Pontifical Catholic University of Rio Grande do Sul, Porto Alegre, Brazil, **10** National AIDS Coordinating Committee Secretariat, Port of Spain, Trinidad & Tobago, **11** Federal University of Health Sciences of Porto Alegre, Porto Alegre, Brazil, **12** Communicable Diseases Laboratory, Santa Casa de Misericórdia de Porto Alegre, Porto Alegre, Brazil, **13** Communicable Diseases Prevention, Control, and Elimination Department, Pan American Health Organization, District of Columbia, United States of America

* perezf@paho.org



OPEN ACCESS

Citation: Rajasingham R, Medina N, Mousquer GT, Caceres DH, Jordan A, Nacher M, et al. (2020) Cost-effectiveness evaluation of routine histoplasmosis screening among people living with advanced HIV disease in Latin America and the Caribbean. PLOS Glob Public Health 3(8): e0001861. <https://doi.org/10.1371/journal.pgph.0001861>

Editor: Stefan Kohler, Heidelberg University, GERMANY

Received: January 30, 2023

Accepted: July 3, 2023

Published: August 15, 2023

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: <https://doi.org/10.1371/journal.pgph.0001861>

Copyright: This is an open access article, free of all copyright, and may be freely reproduced, distributed, transmitted, modified, built upon, or otherwise used by anyone for any lawful purpose. The work is made available under the [Creative Commons CC0 public domain dedication](https://creativecommons.org/licenses/by/4.0/).

Data Availability Statement: Data is available within the manuscript.

Abstract

Histoplasma antigen can be detected in people with advanced HIV disease (AHD), allowing for early and accurate diagnosis of histoplasmosis. The aim of this analysis was to assess the cost-effectiveness of routine histoplasmosis screening using antigen detection, among people with AHD. We developed a decision analytic model to evaluate *Histoplasma* antigen screening among people with AHD. The model estimated the costs, effectiveness, and cost-effectiveness of routine screening for *Histoplasma* antigen compared to the current practice of no routine *Histoplasma* antigen screening. The model includes stratification by symptoms of histoplasmosis, severity of presentation, and estimates of 30-day mortality. Data sources were taken from the Pan American Health Organization (PAHO) Strategic Fund databases on public purchases of medicines, and published literature on treatment outcomes. Outcome measures are life years saved (LYS), costs (US dollars), and incremental cost-effectiveness ratios (ICERs). Routine *Histoplasma* antigen screening averts an estimated 17% of deaths in persons with advanced HIV disease, and is cost-effective compared to no histoplasmosis screening, with an ICER of \$26/LYS. In sensitivity analysis assuming treatment for histoplasmosis with liposomal amphotericin, *Histoplasma* antigen screening remains cost-effective with an ICER of \$607/LYS. *Histoplasma* antigen screening among people

¿Qué hacer?

Enf. Avanzada recién diagnosticada
Diagnóstico tardío

Enf. Avanzada por progresión post-abandono de TARV

Expandir testeo

Detectar EAH

Detectar y prevenir IO

Inicio TARV

Revincular perdidos

Utilizar las diferentes modalidades disponibles

Pruebas de CD4 en el punto de atención



Implementar el paquete expandido de enfermedad avanzada

Apoyo especial para pacientes inestables

Inicio rápido
Uso de dolutegravir en adultos y niños

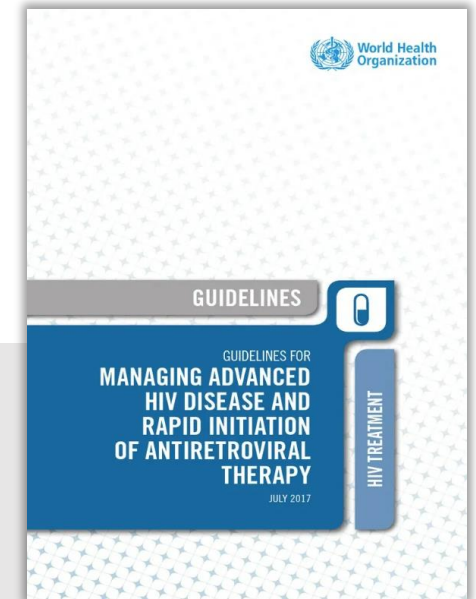
- Servicios diferenciados
- Estrategias de adherencia
- Apoyo social
- Incentivos
- Búsqueda comunitaria
- Frascos multimeses (6 meses)

Recomendación de OMS (2021)

Los programas de VIH deben implementar intervenciones para buscar las personas que se han desconectado de la Atención y proporcionarle apoyo para su re-vinculación.

Paquete de enfermedad avanzada

- Buscar síntomas de posibles enfermedades oportunistas
- En asintomáticos, **tratamiento preventivo para TB**
- Si hay síntomas de tuberculosis:
 - Xpert en esputo y otras muestras si se sospecha TB extrapulmonar
 - Rx, Rx digital o Proteína C.Reactiva si está disponible
- **Tamizaje sistemático de antígenos para TB, Criptococosis e Histoplasmosis**
- Profilaxis con TMS
- Inicio rápido del TARV
- Monitoreo del síndrome de respuesta inflamatoria sistémica
- **Tratamiento de Infecciones oportunistas**



Más vale prevenir que curar

- 6 a 9 meses de INH diaria
- 4 meses de rifampicina
- 1 mes de rifapentina-INH
- **12 tomas (una por semana) de rifapentina-INH**

 = Vitamin B6  = INH/RPT

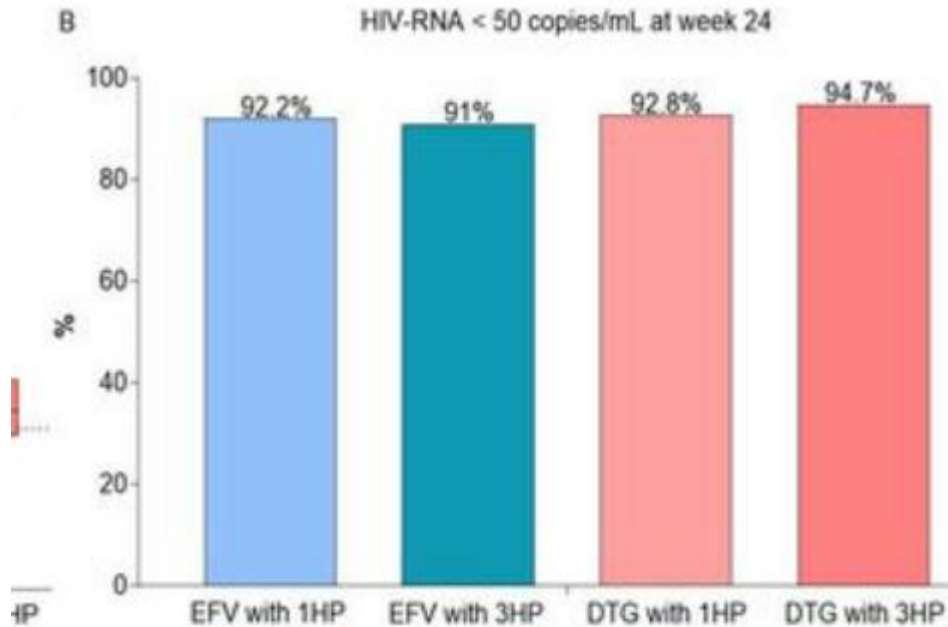
*Pill count with the Macleods product:
INH/RPT fixed-dose combination
(INH 300 mg, RPT 300 mg)*

3HP



●●● Segura y efectiva en pacientes con Dolutegravir

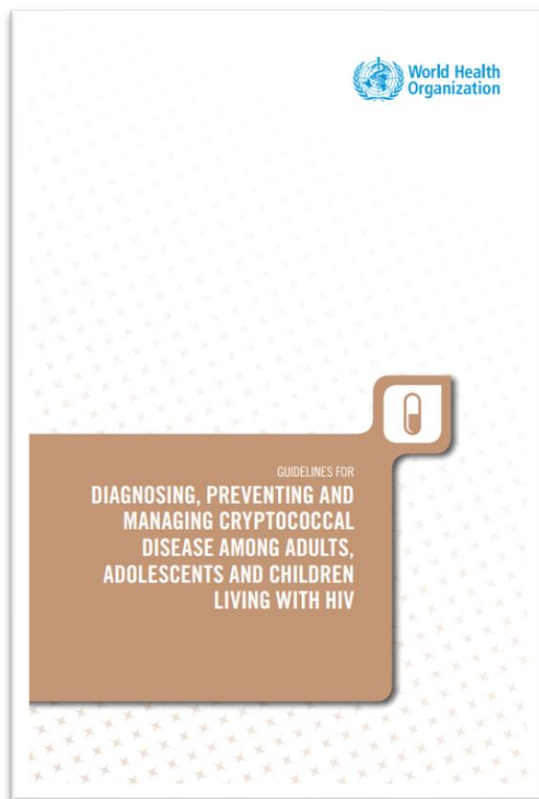
Supresión virológica durante el TARV en personas utilizando rifapentina y dolutegravir



¿Porque no se comienza la profilaxis apenas se confirma la infección y se descarta la infección?

- En personas con <200 CD4 hay una alta tasa de anergia cutanea
- En personas con >200 CD4 hacer PPD si esta disponible
- Si no esta disponible ofrecer TPT

Hubo cambios en la recomendaciones de tratamiento de Criptococosis, OMS 2022



Dosis única de anfotericina liposomal

+

5-fluocitosina

+

Fluconazol

Menor toxicidad

Similar eficacia

Induction therapy (2022 recommendations)

A single high dose (10 mg/kg) of liposomal amphotericin B with 14 days of flucytosine (100 mg/kg per day divided into four doses per day) and fluconazole (1200 mg/daily for adults; 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily) should be used as the preferred induction regimen for treating people with cryptococcal meningitis.

Strong recommendation; moderate-certainty evidence for adults and low-certainty evidence for children

Alternative induction regimens

If liposomal amphotericin B is not available:

A seven-day course of amphotericin B deoxycholate (1 mg/kg per day) and flucytosine (100 mg/kg per day, divided into four doses per day) followed by seven days of fluconazole (1200 mg daily for adults and 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily).

Strong recommendation; moderate-certainty evidence for adults and low-certainty evidence for children and adolescents

If no amphotericin B formulations are available:

14 days of fluconazole (1200 mg daily, 12 mg/kg per day for children and adolescents) + flucytosine (100 mg/kg per day, divided into four doses per day).

Strong recommendation; moderate-certainty evidence

Note: fluconazole + flucytosine is the only recommended oral combination regimen and has been associated with lower mortality compared with amphotericin B deoxycholate + fluconazole (3).

If flucytosine is not available:

14 days of liposomal amphotericin (3–4 mg/kg per day) + fluconazole (1200 mg daily, 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily).

Strong recommendation; moderate-certainty evidence for adults

If liposomal amphotericin B and flucytosine are not available:

14 days of amphotericin B deoxycholate (1 mg/kg per day) + fluconazole (1200 mg daily, 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily).

Strong recommendation; moderate-certainty evidence

Note: flucytosine-containing regimens are superior, and steps should be taken to ensure access to this drug.

Propuesta de implementación

Pacientes con un nuevo diagnóstico de VIH

Pacientes que abandonaron el TARV y vuelven a la consulta

Síntomas

ó

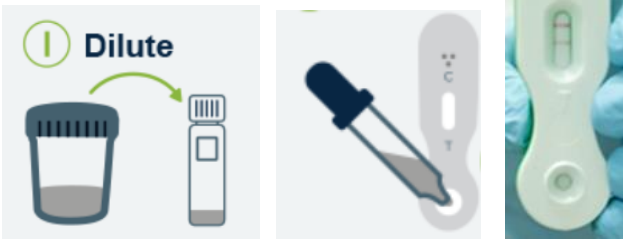
CD4 <200

Tira de CD4 rápido



Sensibilidad 92.6%
Especificidad 89.8%

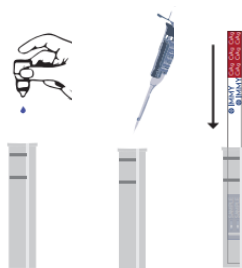
Miravista LFA Histo
Urine, 40'



Histoplasmosis

Sensibilidad 96%
Especificidad 96%

IMMY LFA Crypto

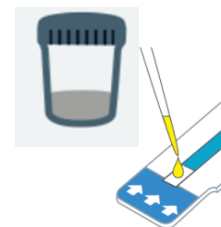


Blood Serum
10'

Criptococosis

Sensibilidad 99%
Especificidad 100%

TB-Alere
Urine, 25'



Tuberculosis (LAM + Xpert)

Sensibilidad combinada 90%
Especificidad 86%

Xpert
Sputum,
CSF, biopsy,
90'



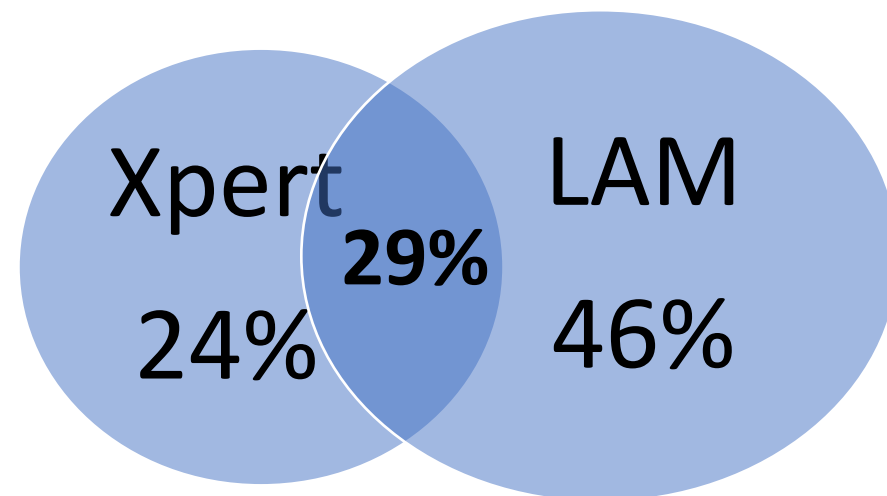
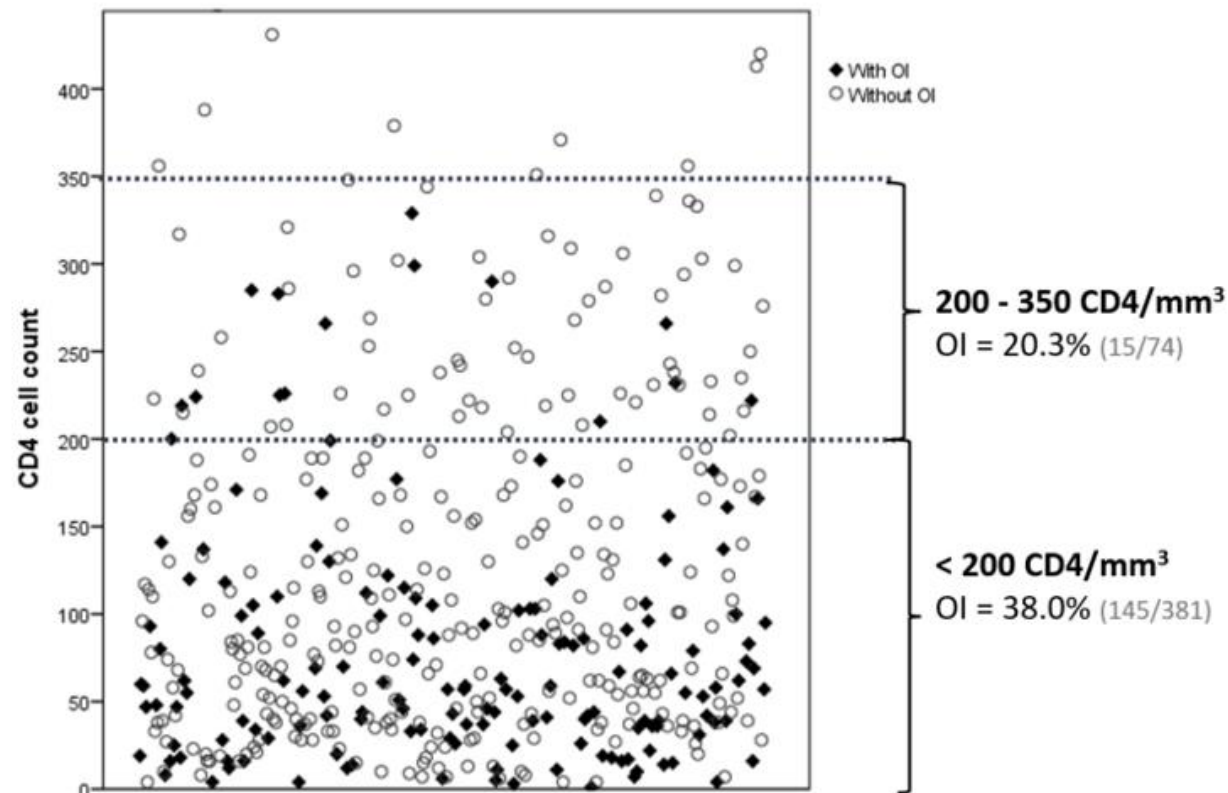
Paraguay

Frecuencia de infecciones oportunistas en personas con enfermedad avanzada (síntomas o <200 CD4)

Opportunistic infection ¹		CD4 cell count					
		Overall	< 50	50–99	100–199	200–350	>350
Histoplasmosis	+	43	20	13	4	5	0
	Screened	464	144	116	103	68	25
	%	9.2%	13.9%	11.2%	3.9%	7.4%	0.0%
Cryptococcosis	+	52	23	16	11	2	0
	Screened	485	148	117	110	74	27
	%	10.7%	15.5%	13.7%	10.0%	2.7%	0.0%
Tuberculosis	+	92	41	21	20	9	0
	Screened	474	145	117	108	71	26
	%	19.4%	28.3%	17.9%	18.5%	12.7%	0.0%

Pruebas positivas

Diagnostic assay	Histoplasmosis (n=43)		
	Tested	+	%
Urine Ag	464	43	9.3%
	Cryptococcosis (n=52)		
Serum LFA-CrAg	484	51*	10.5%
CSF LFA-CrAg	34	21	61.8%
CSF culture	22	11	50.0%
CSF India ink	23	4	17.4%
	Tuberculosis (n=92)		
TB-LAM	467	72	15.4%
TB GeneXpert	204	35	17.1%
TB Culture	102	22	21.6%
TB-LAM + GeneXpert	197	62	31.4%



Brasil (n=410) Diagnóstico

Método	Histoplasmose			Criptococose			Tuberculose		
	n	+	%	n	+	%	n	+	%
Ag Urina	406	41	10,1						
Histopatologia	27	1	3,7						
Ag Soro				407	47	11,5			
Ag LCR				48	8	16,6			
Cultura				117	30	25,6			
TB Lam							401	106	26,4
GeneXpert							395	68	17,2
Baciloscopia							240	21	8,75
TB Lam + GeneXpert							247	19	7,7



● ● ● En conclusión

- Las infecciones oportunistas y las muertes prevenibles son una falla en nuestros sistemas de salud
- El diagnóstico tardío es un reflejo de nuestras políticas de testeo y la enfermedad avanzada por faltas en las estrategias de retención
- Los enfoques integrados permiten el diagnóstico rápido de las infecciones oportunistas más frecuentes
- Estos cambios, junto con el inicio rápido del tratamiento antirretroviral con nuevos esquemas y la mejora de la Atención hospitalaria de las infecciones oportunistas puede ayudar a reducir las muertes prevenibles.

● ● ● Pero....

Frente a las enfermedades que genera la miseria, frente a la tristeza, la angustia y el infortunio social de los pueblos, los microbios, como causas de enfermedad, son unas pobres causas.

Ramon Carillo

- Ninguna prueba diagnóstica en el punto de atención va a reducir la mortalidad si no se acompaña de:
 - Acceso a tratamientos de enfermedades oportunistas
 - Rápido inicio del tratamiento antirretroviral
 - Apoyo y acompañamiento para asegurar la adherencia



Muchas gracias por su atención

suedoma@paho.org

Agradecimientos al equipo de la Unidad de VIH, TB , HV e ITS OPS WDC

Equipos de investigación en implementación de Paraguay, Brasil y Trinidad y Tobago
Ecuador, Guyana y República Dominicana



<https://www.campusvirtualsp.org/en/course/tbhiv-coinfection>

<https://www.campusvirtualsp.org/es/curso/coinfeccion-tbvih>

