Lycke Woittiez

Difficult to treat histoplasmosis (& co-infections with tuberculosis)

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Contents

- Suriname
- HIV, histoplasmosis and TB in Suriname

- Difficult to treat histoplasmosis
- Histoplasmosis and tuberculosis co-infection

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Suriname

- LMIC
- Multi-ethnic population

- Dutch is official language
- Sranan Tongo
- Also: Hindustani, saramaccan, Javanese, Hakka, ….

- Financial crisis

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Healthcare in Suriname

- Primary healthcare
  - RGD
  - Medical Mission
  - Family practitioners

- Hospitals
  - Acacemic Hospital Paramaribo
  - Diakonessenhuis
  - ‘s Lands Hospital
  - St Vincentius Hospital
  - Mungra medical center
  - Marwina hospital

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HIV epidemic in Suriname

- 7200 people living with HIV
- Prevalence in adults 15-49 years: 1.6%

- People living with HIV who know their status: 3600 (51%)
- PLWH who know their status and are on ART: 3100 (86%)
- People with suppressed viral loads: undefined

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HIV epidemic in Suriname

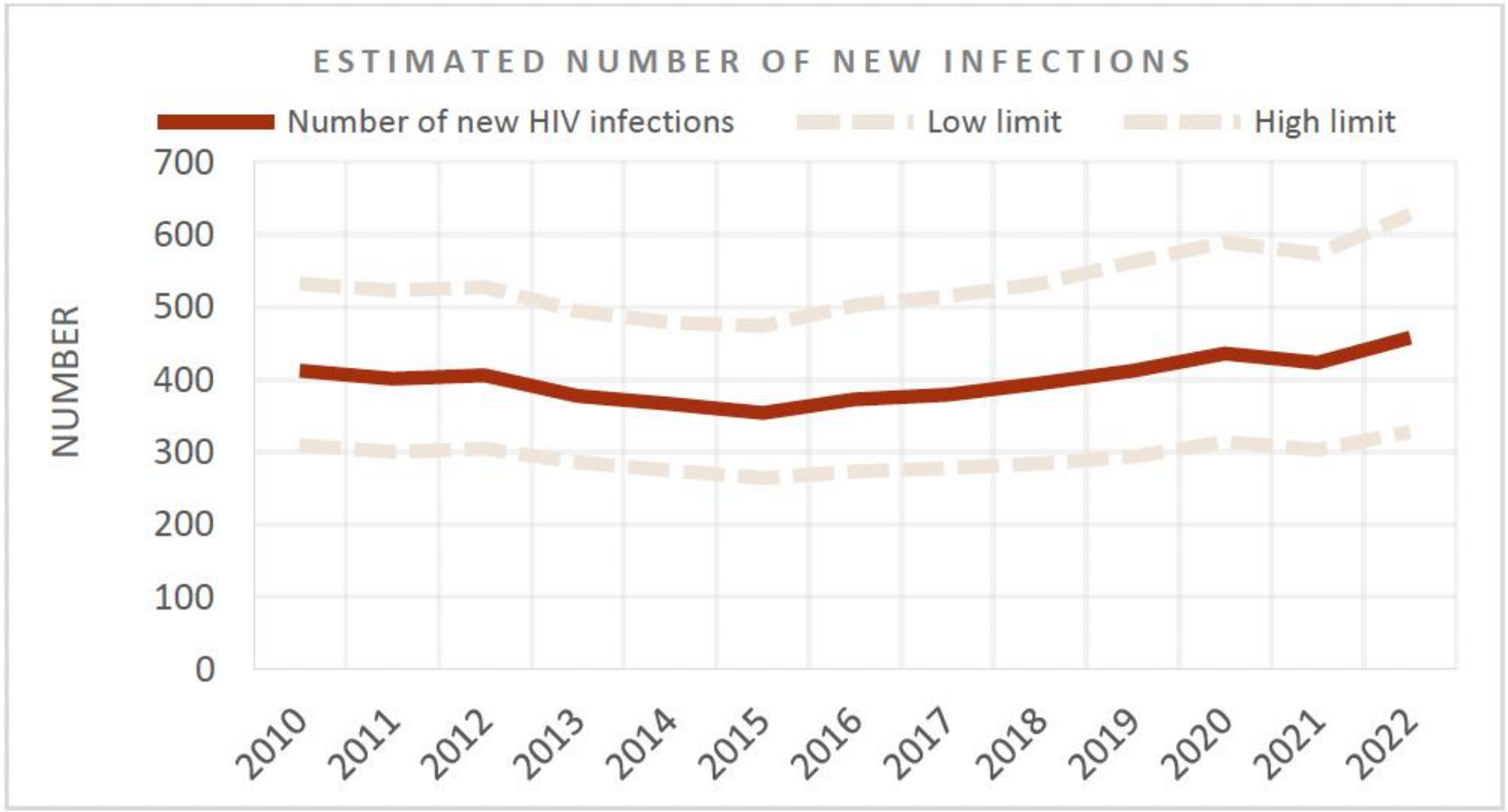

Figure 1:Number of estimated new infection with, 2010-2022

Mid term evaluation Suriname HIV stategic plan

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HIV in Suriname

- Many late presenters
- First presentation often with opportunistic infections
- Diagnosis and treatment hindered by
  - Lack of diagnostic tests for HIV
  - Stock out of CD4 reagens
  - Stock out of ART
  - Limitations in diagnosing opportunistic infections

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Tuberculosis in Suriname

- In 2022 127 new TBC cases
- 73.2% male
- 93.1% drug susceptible TB
- 14.2% HIV positive

Commiesie, 2023

Histoplasmosis in Suriname

- No exact numbers
- Probably most common opportunistic infection

- In 1953: histoplasmin skin test in 43.1% of healthy adults positive
- In 2020: in French Guiana most common opportunistic infection
- Previous investigation in Suriname: in 40% of HIV patients admitted with a CD4 count <100 cells/ul, *H. capsulatum* in bone marrow

Nacher, 2020

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Implementing Histoplasmosis Ag in Suriname

- Culture & PCR: not available
- Histology: challenging
- Buffy coat: sensitivity <30%

- Urine Ag test in studies sensitivity 79-96%, specificity 90-99%

Recent study

- 98 patients included.
- 58 Possible DH, 40 without features of DH
- 20 patients treated for DH

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Implementing Histoplasmosis Ag in Suriname (2)

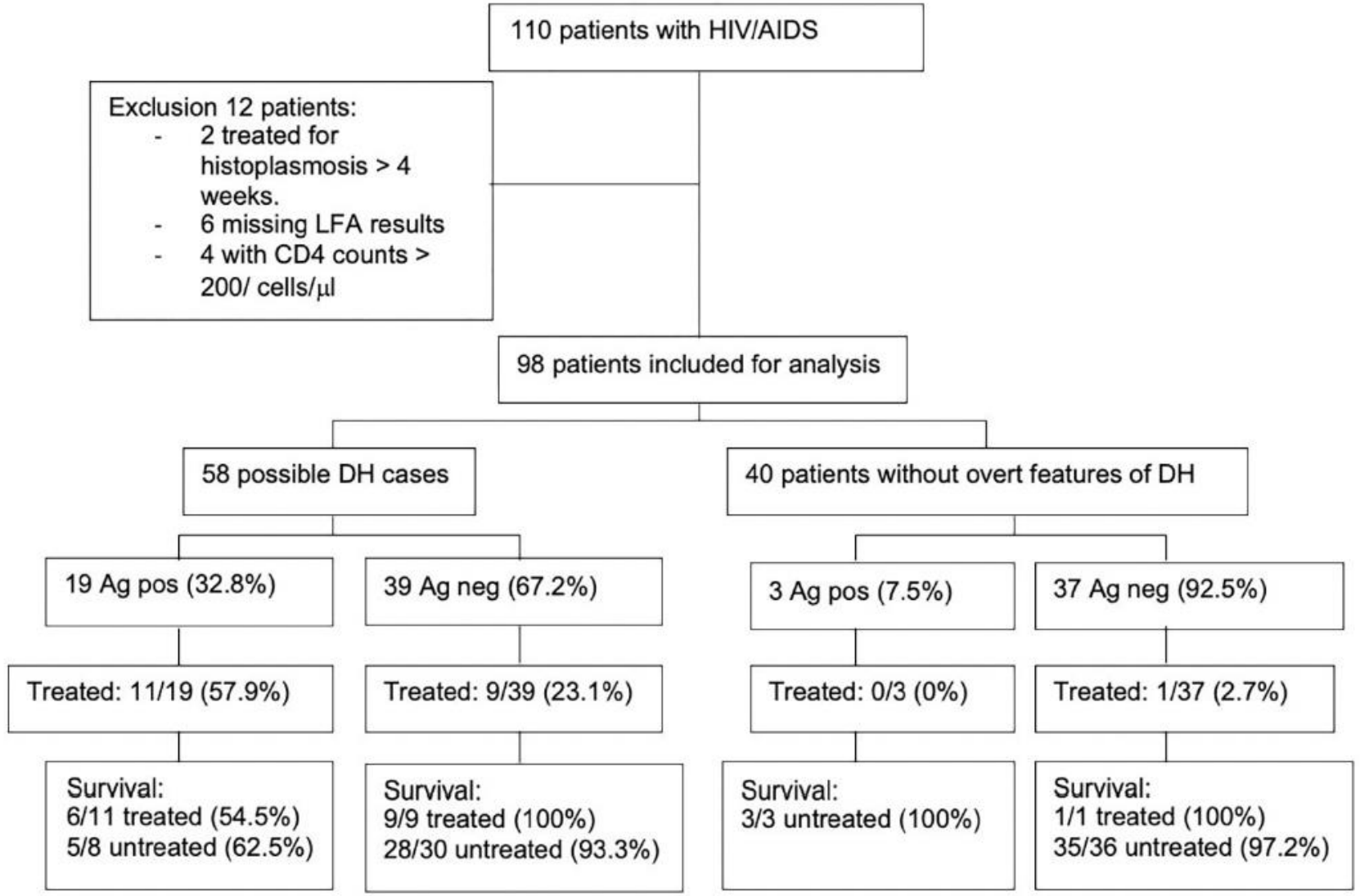

Fig 1. Flowchart of patient population. DH: disseminated histoplasmosis.

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Implementing Histoplasmosis Ag in Suriname (2)

22 patients with positive LFA

19 possible DH cases
- 11 treated
- 8 patients untreated
  - Symptoms attributed to other illness
  - Treated with fluconazole or only ART

3 patients without features of DH had positive LFA
- None of them treated
- All of them remained free of symptoms

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Implementing Histoplasmosis Ag in Suriname (3)

Conclusion

- LFA good addition to diagnostic options in Suriname
- Currently over- and underdiagnosis of DH
- Combining clinical signs with LFA results enhances diagnostic accuracy
- Implementing LFA is cost-effective

Woittiez, 2024

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Difficult to treat histoplasmosis

- No definition available
- Unclear how prevalent it is

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Usual treatment regimen histoplasmosis

Disseminated histoplasmosis

Induction therapy
- liposomal amphotericin B 3 mg/kg for 2 weeks

Or, in resource constrained settings
- Deoxycholate amphotericin B 0.7 – 1 mg/kg for 2 weeks

Followed by itraconazole 200mg 2 times daily

Duration: minimum 12 months

Perez, 2021

Prognosis disseminated histoplasmosis

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- High mortality (30.2%)
- Due to first episode or relapse
- Relapse often due to drug nonadherence (itraconazole or ART)

Damasceno, 2014

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Complications / disadvantages of usual treatment regimen histoplasmosis

- Erratic absorption
- Dose-limiting toxicity
- Drug-drug interactions
- Poor long term tolerability

- New treatment options?
  - Other presentation

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Histoplasmosis and tbc co-infections

- Very similar clinical characteristics
- Rare occurrence (?)
- Prevalence very location dependend

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Histoplasmosis and tbc co-infections - review

J Fungi (Basel). 2019 Aug 9;5(3):73. doi: 10.3390/jof5030073

Histoplasmosis and Tuberculosis Co-Occurrence in People with Advanced HIV

Diego H Caceres [1,2,*,†], Audrey Valdes [3,*,†]

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PMCID: PMC6787747 PMID: 31404979

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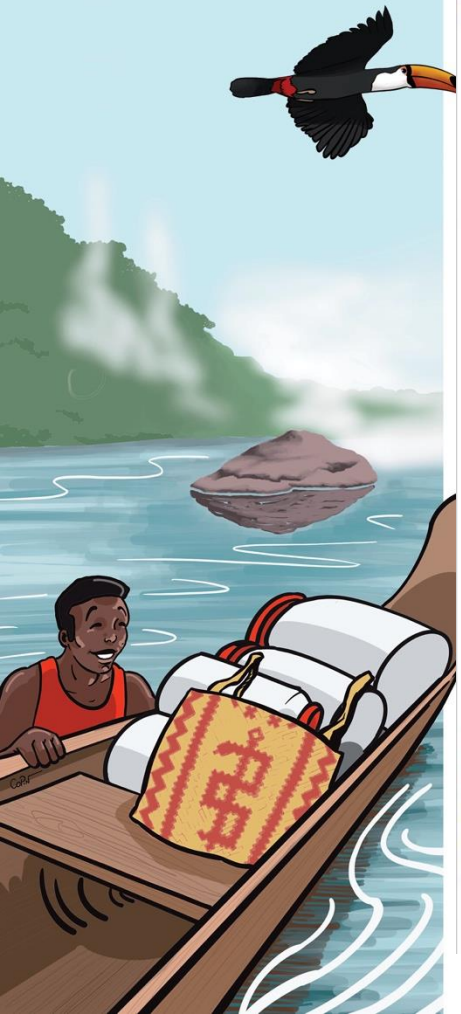
Histoplasmosis and tbc co-infections - review



Reference	Study period	Country	% (# TB and # histoplasmosis)	Comments
López AG, et al [17]	2009–2014	Argentina	9% (16/171)	Histoplasmosis patients median CD4 T cell: 29 cells/mm^3
Boigues B, et al [18]	2011–2016	Brazil	26% (6/23)	Histoplasmosis patients median CD4 T cell: 19 cells/mm^3
Falci DR, et al [19]	2016–2018	Brazil	15% (19/123)	Multicenter study, 11 Brazilian cities.CD4 T cell: 39 cells/mm^3
Caceres DH, et al [20]	2008–2011	Colombia	35% (16/45)	Histoplasmosis patients median CD4 T cell: 30 cells/mm^3
Velásquez G, et al [25]	1998–2004	Colombia	16% (7/44)	Histoplasmosis patients median CD4 T cell: 30 cells/mm^3
Huber FN, et al [21]	1982–2007	French Guiana	8% (16/200)	Histoplasmosis patients median CD4 T cell: 63 cells/mm^3
Samayoa B, et al [22]	2005–2009	Guatemala	26% (26/101)	Histoplasmosis patients median CD4 T cell: 25 cells/mm^3
Caceres DH, et al [26]	2017	Panama	38% (18/48)	Diagnosed by *Histoplasma* antigen and lateral flow lipoarabinomannan assays
Pérez G, et al [23]	1996–2014	Peru	11% (3/23)	Histoplasmosis patients median CD4 T cell: 30 cells/mm^3
Mata SC, et al [24]	2000–2005	Venezuela	2% (1/53)	Histoplasmosis/TB co-occurrence including non-HIV patients was 5%

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Histoplasmosis and tbc co-infections - review

Patients with co-infections

1. Highly immunosuppressed (median CD4: 30 cells/mm3)
2. Treatment failures frequently reported

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Histoplasmosis and tbc co-infections - symptoms

- Fever most common (75%)
- Lymph node involvement (50%)
- Gastrointestinal / abdominal pain (50%)
- Respiratory symptoms (50%)

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Histoplasmosis and tbc co-infections - diagnosis

- Differentiation based on clinical signs / symptoms: difficult
- Studies from French Guiana and Colombia: more GI tract involvement in DH, more pulmonary involvement in TBC

- However: not possible to differentiate based on clinical signs

- TBC PCR
- Histoplasmosis LFA?

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Treatment

- Interaction between itraconazole and tuberculosis treatment
- Rifampicin and rifabutin can decrease itraconazole levels
- Itraconazole may increase rifabutin levels

- Possible fluoroquinolone as alternative?

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Histoplasmosis and tbc co-infections

Open Access | Article

A Rapid Screening Program for Histoplasmosis, Tuberculosis, and Cryptococcosis Reduces Mortality in HIV Patients from Guatemala

by Narda Medina [1,2,†], Ana Alastruey-Izquierdo [1,†], Oscar Bonilla [3,†], Osmar Gamboa [2,†], Danicela Mercado [3,†], Juan C. Pérez [3,†], Luis Roberto Salazar [2,†], Eduardo Arathoon [2,3,†], David W. Denning [4,5,6,†] and Juan Luis Rodriguez-Tudela [6,*,†]

J. Fungi, 2021

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Histoplasmosis and tbc co-infections

- 2017 – 2018
- All newly diagnosed HIV patients

- Smear microscopy
- Sputum culture
- Blood culture
- In house PCR for *M. tuberculosis* and *H. capsulatum*
- LFA for *H. capsulatum*
- Cryptococcal Ag LFA

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Histoplasmosis and tbc co-infections

- 2127 newly diagnosed HIV patients, 1821 full screening
- Median age 31 years
- Median CD4 187

- 385 patients with opportunistic infections
- 36.4% histoplasmosis
- 31.4% tuberculosis
- 20.3% Cryptococcal disease
- 8.1% multiple OIs

- Of these with multipole OIs
  - Histoplasmosis / cryptococcosis 35.5%
  - Histoplasmosis / tuberculosis 32.3%
  - Cryptococcosis / tuberculosis 12.9%

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Histoplasmosis and tbc co-infections

- After 180 days: 213 (10%) died
- 18.3% due to histoplasmosis
- 12.7% due to tuberculosis
- 7.0% to multiple OIs

- Significant higher mortality in those with OIs (29.7 % vs 5.9%)

- 7% reduction in OI mortality in 2018 compared to 2017, with simultaneous increase in OI treatment
- Attributable to earlier diagnosis?

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Histoplasmosis and TB co-infection

Trans R Soc Trop Med Hyg 2024; **118**: 391–398
https://doi.org/10.1093/trstmh/trad104 Advance Access publication 27 January 2024

Clinical characteristics, diagnosis, treatment and outcomes of patients living with HIV and co-infected with tuberculosis and histoplasmosis: a 5-y retrospective case series

María Eugenia Castellanos Reynosa [a,*,†], Maria Eugenia Caal [b,†], Danicela Mercado [c], Narda Medina [b], Juan Carlos Pérez [b], Theophilus I. Emeto [a], and Eduardo Arathoon [b,c]

[a]Public Health and Tropical Medicine, College of Public Health, Medical and Veterinary Sciences, James Cook University, Townsville, Queensland, Australia; [b]Asociación de Salud Integral, Guatemala City, Guatemala; [c]Clínica Familiar Luis Ángel García, Hospital General San Juan de Dios, Guatemala City, Guatemala

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Retrospective study

- Guatemala city
- Retrospective study, 2017 – 2021
- ≥ 18 years
- Laboratory confirmed histoplasmosis and TB within a 4-month interval

- Primary outcome: mortality at 6 months
- 26 patients identified
- 21 met inclusion criteria

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Retrospective study

- 86% male
- 81% heterosexual
- Median age 37 years
- 62% newly diagnosed
- 7 patients (33%) had discontinued ART for at least 90 days

- 11 patients extrapulmonary TB and disseminated histo
- 8 pulmonary tb and disseminated histo
- 2 pulmonary co-infections

- Mean BMI at baseline 19.4 kg/m2

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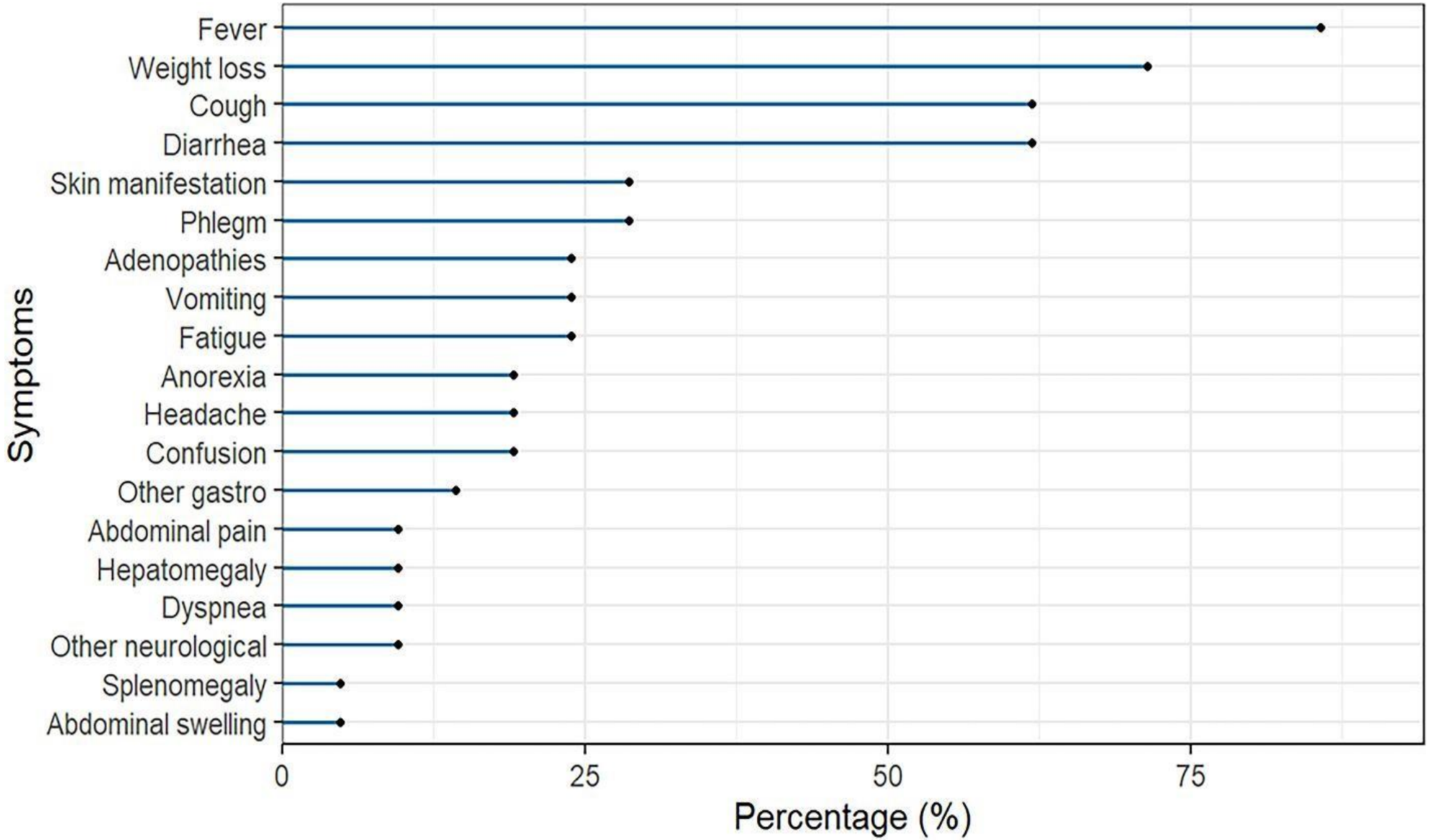
Retrospective study



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Retrospective study - lab

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Lab:

- Median CD4 20
- Median HIV load 438.560

• Anemia	95%
• High LDH	80%
• High gGT	75%

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Retrospective study - outcomes

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- 6 month mortality rate 57.1%
- 23.8% died within 30 days

Characteristics	Total (N=21)	Dead (n=12)	Survivors (n=9)	p-Value[a]
Received ART	16/21(76)	7/12 (58)	9/9 (100)	0.045
Received antifungal therapy	18/21(86)	9/12 (75)	9/9 (100)	0.2
Received amphotericin B as induction therapy	16/21 (76)	8/12 (67)	8/9 (89)	0.3
Received TB treatment	19/21 (90)	10/12 (83)	9/9 (100)	0.5
Initiation phase was completed	13/21 (62)	4/12 (33)	9/9 (100)	0.005
Continuation phase was completed	9/21 (43)	0/12 (0)	9/9 (100)	<0.001

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Conclusion / take home message

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- Histoplasmosis common opportunistic infection
- Signs and symptoms can be aspecific
- Treatment can be difficult

- Co-infections with histoplasmosis and tuberculosis are relatively uncommon
- However – high lever of suspicion needed

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Questions?