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MAJOR ARTICLE

AIDS-Defining Illnesses at Initial Diagnosis of HIV in a Large Guatemalan Cohort

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Background. Anecdotal evidence suggests that a high proportion of patients diagnosed with HIV in Guatemala present with AIDS. There remain limited data on the epidemiology of AIDS-defining illnesses (ADIs) in Central America.

Methods. We conducted a retrospective cohort study of all patients living with HIV at the largest HIV clinic in Guatemala. Charts were analyzed for clinical and demographic data. Presence of an ADI was assessed by US Centers for Disease Control definitions; patients who presented with an ADI were compared with those without ADI using descriptive statistics.

Results. Of 3686 patients living with HIV, 931 (25.3%) had an ADI at HIV diagnosis, 748 (80.3%) of whom had CD4 counts lower than 200 cells/mm^3. Those with ADIs were more likely to be male (67.5% vs 54.6%; $P < .0001$) and heterosexual (89.4% vs 85.0%; $P = .005$). The most common ADIs were *Mycobacterium tuberculosis* (55.0%), *Pneumocystis jirovecii* pneumonia (13.7%), esophageal candidiasis (13.4%), and histoplasmosis (11.4%). Histoplasmosis and HIV wasting syndrome were both more common among rural patients.

Conclusions. In this large Guatemalan cohort of patients currently living with HIV, a significant portion presented with an ADI. These data inform the most common ADIs diagnosed among survivors, show that histoplasmosis is more commonly diagnosed in rural patients, and suggest that HIV wasting syndrome may reflect missed histoplasmosis diagnoses.

Keywords. AIDS; AIDS-defining illnesses; global health; Guatemala; HIV.

HIV is a significant cause of morbidity and mortality in Guatemala, where the disease prevalence is estimated at 0.5% of the adult population as of 2016 [1]. Patients with late presentation of HIV have higher morbidity and mortality than patients diagnosed with less advanced disease [2]. Although modern antiretroviral therapy (ART) was implemented in Guatemala in the year 2000, deaths due to HIV/AIDS have risen from 13.8 per 100 000 in 1990 to 22.0 per 100 000 in 2012, and the percentage of late presenters and those with AIDS at diagnosis is high [3].

Presence of an AIDS-defining illness (ADI) at HIV diagnosis has been shown to increase health care costs [4]. In the United States and Western Europe, rates of ADIs at diagnosis range from 9.7% to 15.1% [2, 4–11]; the rates of ADIs tend to be higher in developing countries (16.1%–28.9%) [12, 13]. Anecdotally, the experience of HIV providers in Guatemala suggests a high proportion of patients present with an ADI at diagnosis, but this has yet to be the focus of a formal study.

Few studies of the distributions and prevalence of specific ADIs exist in the developing world. A large cohort in French Guiana showed that the most prevalent ADIs in the post-highly active antiretroviral therapy (HAART) era were disseminated histoplasmosis, esophageal candidiasis, cerebral toxoplasmosis, and tuberculosis; this study also noted a decrease of HIV wasting disease and a rise in histoplasmosis when improved histoplasmosis diagnostics were introduced into the country [14]. Our current study sought to identify the proportion of currently living patients presenting with an ADI at the time of HIV diagnosis in a large public hospital in Guatemala City, Guatemala, and to characterize the prevalence of each ADI.

METHODS

We conducted a retrospective cohort study of all patients currently living with HIV at Roosevelt Hospital in Guatemala City, Guatemala. Roosevelt Hospital is a large academic medical center of 900 beds in the capital city; it is publicly funded by the national government, accepts no fees for services performed, and predominantly serves patients with limited economic means. The Roosevelt HIV and Infectious Diseases Clinic is the largest HIV clinic in the country, with a census numbering 4128 active patients and approximately 500 new HIV diagnoses each year. Inclusion criteria were patients age 18 years or older of the Infectious Diseases Clinic at Roosevelt Hospital with a diagnosis of HIV who were still living during the study period and presented for a clinic visit. As all patients have a scheduled

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visit every 3 months, the study period of 4 months was intended to capture the vast majority of the clinic census. There were no exclusion criteria. All patients were naïve to antiretroviral therapy at the time of diagnosis; similarly, no patients were on antifungal therapy at the time of diagnosis. The protocol was approved by the Roosevelt Hospital and Washington University in St Louis institutional review boards with waiver of consent.

Charts were accessed as patients presented for routine HIV clinic visits, and were examined for clinical and demographic data including sex, age, sexual risk category, date of diagnosis, region of residence in Guatemala, CD4 cell count and viral load at time of diagnosis, presence and type of ADI, and its site at the time of initial presentation. ADI presence was assessed using US Centers for Disease Control and Prevention (CDC) definitions [15]. Specific OIs were diagnosed by a combination of clinical presentation, imaging, and microbiology where available. Cases of histoplasmosis were confirmed by culture. Prior to 2013, cases of tuberculosis and cryptococcal meningitis were confirmed by culture. Starting in 2013, these cases were confirmed using mycobacterial nucleic acid amplification testing (GeneXpert) and cryptococcal antigen assays, respectively. As HIV wasting syndrome is considered a diagnosis of exclusion, those patients who carried a diagnosis of tuberculosis, histoplasmosis, *Pneumocystis jirovecii* pneumonia, *Mycobacterium avium intracellulare*, cryptosporidiosis, or isosporiasis were not considered eligible for a diagnosis of HIV wasting. If patients were charted as having both HIV wasting syndrome and one of the aforementioned, HIV wasting was eliminated as a diagnosis for this analysis. Patients were considered urban dwellers if they resided in the department of Guatemala, which contains Guatemala City and its immediate surroundings; patients from all other departments or from other countries were categorized as rural dwellers. Sexual risk category was defined by the Roosevelt HIV Clinic as either heterosexual, men who have sex with men (MSM), transgender, or sex worker. Data were also collected from patients receiving new HIV diagnoses during the study period.

Data collection and survey implementation occurred during the study period, which ran from June 1, 2015, to September 30, 2015. The on-site data collection was done using a tablet, which allowed staff to upload de-identified clinical data and survey responses directly to REDCap, a secure online application for collecting, storing, and transmitting data from research studies. All transfer of information was performed through the secure platform provided by REDCap, which was maintained by Washington University, and data analysis was performed in the United States.

Data analysis was performed using SPSS (IBM Corp., version 22.0). The chi-square test and the Student *t* test were used for categorical and continuous variables, respectively, to assess associations between clinical and demographic factors and the primary outcome of ADI at HIV diagnosis. The Kruskall-Wallis test was used to assess differences in mean CD4 and mean viral load at diagnosis across the 3 time categories. Statistically significant associations were defined as $P < .05$.

RESULTS

A total of 3686 patients were enrolled during the study period. The patients were 57.9% male with a mean age of 34.4 years, and 931 patients (25.3%) had an ADI at HIV diagnosis (Table 1). Except for one patient diagnosed in 1998, years of HIV diagnosis ranged from 2000 to 2015. Compared with patients without ADI at HIV diagnosis, those with ADIs were more likely to be male (67.5% vs 54.6%; $P < .0001$), more likely to report a heterosexual mode of HIV acquisition (89.4% vs 85.0%; $P = .005$), and were slightly older (mean age, 35.2 years vs 34.1 years; $P = .009$). Mean HIV viral load (VL) at diagnosis was significantly higher in those with ADI (403 100 vs 201 100 copies/mL, $P < .0001$). Of those with ADI, 748 subjects (80.3%) had CD4 counts ≤200

Table 1. Baseline Characteristics of 3686 Patients Living with HIV in Guatemala at Time of Presentation

	ADI at Diagnosis (n = 931), No. (%)	No ADI at Diagnosis (n = 2755), No. (%)	*P* Value	Total Cohort (n = 3686), No. (%)
Mean age (±SD), y	35.2 (10.3)	34.1 (11.1)	.01	34.4 (10.9)
Male sex	628 (67.5)	1505 (54.6)	<.0001	2133 (57.9)
Sexual risk category			.005	
Heterosexual	832 (89.4)	2342 (85.0)		3174 (86.1)
MSM	87 (9.3)	377 (13.7)		464 (12.6)
Transgender	3 (0.3)	15 (0.5)		18 (0.5)
Sex worker	9 (1.0)	21 (0.8)		30 (0.8)
Mean VL at diagnosis (±SD), 1000 copies/mL	403.1 (920.0)	201.1 (517.5)	<.0001	253.0 (651.7)
CD4 count at diagnosis[a]			<.0001	
0–50	400 (43.4)	446 (16.5)		846 (23.3)
51–100	181 (19.6)	338 (12.5)		519 (14.2)
101–200	167 (18.1)	596 (22.0)		763 (21.0)
201–350	112 (12.1)	687 (25.4)		799 (22.0)
>350	62 (6.7)	639 (23.6)		701 (19.3)

Abbreviations: ADI, AIDS-defining illness; MSM, men who have sex with men; VL, viral load.

[a]Of the 3628 patients (922 with ADI at diagnosis, 2706 with no ADI at diagnosis) with available CD4 count at diagnosis.

cells/mm^3, while the remaining 183 (19.7%) had CD4 counts >200 cells/mm^3.

The frequencies of individual ADIs are included in Table 2. The most common ADIs were *Mycobacterium tuberculosis* (55.0% of those with ADI at diagnosis, 13.9% of the entire HIV cohort), *Pneumocystis jirovecii* pneumonia (13.7%, 3.5%), esophageal candidiasis (13.4%, 3.4%), disseminated histoplasmosis (11.4%, 2.9%), toxoplasmosis (10.8%, 2.7%), extrapulmonary cryptococcosis (8.7%, 2.2%), and HIV wasting syndrome (7.8%, 2.0%). Less common ADIs included HSV (7.5%, 1.9%) and CMV retinitis (2.8%, 0.7%).

The proportion of patients presenting with an ADI at time of HIV diagnosis was similar in urban and rural populations (P = .382) (Table 2). However, there were differences in prevalence of specific ADIs. Tuberculosis was the most common ADI in both populations; however, there was a significantly higher rate of central nervous system toxoplasmosis among the urban patients (14.0% vs 9.2%; P = .018). Rural patients had higher rates of histoplasmosis (13.3% vs 7.8%; P = .013) and HIV wasting syndrome (9.2% vs 5.3%; P = .037).

Trends in the most common ADIs over time are displayed in Table 3. Patients were grouped by year of diagnosis (1998–2005, 2006–2010, and 2011–2015). Overall incidence of any ADI at diagnosis among survivors decreased with time (P < .001). Mean CD4 count at diagnosis significantly increased with time (P < .001); mean viral load at diagnosis also increased with time (P < .001), but only with a magnitude of 0.1 log. There were also significant increases over time in incidence of tuberculosis (P = .001), histoplasmosis

Table 2. Frequency of AIDS-Defining Illnesses Among HIV Cohort in Guatemala

AIDS-Defining Illness	Rural Patients (n = 610), No. (%)	Urban Patients (n = 321), No. (%)	*P* Value	Patients With ADIs (n = 931), No. (%)	Percentage of Entire HIV Cohort (n = 3686)
Any	610 (100)	321 (100)	.378	931 (100)	25.2
Mycobacterium tuberculosis	339 (55.6)	173 (53.9)	.662	512 (55.0)	13.9
Pneumocystis jirovecii pneumonia	85 (13.9)	43 (13.4)	.835	128 (13.7)	3.5
Esophageal candidiasis	90 (14.8)	35 (10.9)	.068	125 (13.4)	3.4
Histoplasmosis	81 (13.3)	25 (7.8)	.013	106 (11.4)	2.9
Toxoplasmosis	56 (9.2)	45 (14.0)	.018	101 (10.8)	2.7
Cryptococcosis	53 (8.7)	28 (8.7)	.974	81 (8.7)	2.2
HIV wasting syndrome	56 (9.2)	17 (5.3)	.037	73 (7.8)	2.0
HSV	39 (6.4)	31 (9.7)	.07	70 (75)	1.9
CMV retinitis	17 (2.8)	9 (2.8)	.982	26 (2.8)	0.7
Recurrent bacterial infections	17 (2.8)	5 (1.6)	.243	22 (2.4)	0.6
Cryptosporidiosis	16 (2.6)	6 (1.9)	.476	22 (2.4)	0.6
Primary CNS lymphoma	7 (1.1)	0 (0)	.103	7 (0.8)	0.2
Other ADI[a]	25 (4.1)	18 (5.6)	N/A	43 (4.6)	1.2

There were 0 cases of Burkitt's lymphoma, immunoblastic lymphoma, or lymphoid interstitial pneumonia.

Abbreviations: CMV, cytomegalovirus; CNS, central nervous system; HIV, human immunodeficiency virus; HSV, herpes simplex virus.

[a]Other ADI includes invasive cervical cancer, recurrent pneumonia, *Mycobacterium avium intracellulare*, disseminated nontuberculous mycobacterium, Kaposi sarcoma, HIV encephalopathy, isosporiasis, CMV disease, recurrent Salmonella septicemia, disseminated coccidioidomycosis, progressive multifocal leukoencephalopathy, and pulmonary candidiasis.

Table 3. Trends of CD4 Count, Viral Load, and Most Common AIDS-Defining Illnesses Over Time

	Patients With ADIs From 1998–2005 (n = 776), No. (%)	Patients With ADIs From 2006–2010 (n = 1654), No. (%)	Patients With ADIs From 2011–2015 (n = 1256), No. (%)	*P* Value
Mean CD4 count at diagnosis[a] (±SD)	199 (192)	188 (179)	253 (239)	<.001
Mean viral load at diagnosis[b] (±SD), 1000 copies/mL	217.9 (299.0)	225.0 (536.2)	309.4 (885.4)	<.001
ADI at HIV diagnosis	257 (33.1)	425 (25.7)	249 (19.8)	<.001
Mycobacterium tuberculosis	116 (45.1)	251 (59.0)	145 (58.2)	.001
Pneumocystis jirovecii pneumonia	36 (14.0)	53 (12.5)	39 (15.7)	.504
Esophageal candidiasis	45 (17.5)	49 (11.5)	31 (12.4)	.074
Histoplasmosis	17 (6.6)	50 (11.8)	39 (15.7)	.006
Toxoplasmosis	31 (12.1)	36 (8.5)	34 (13.7)	.086
Cryptococcosis	32 (12.4)	24 (5.6)	25 (10.0)	.006
HIV wasting syndrome	19 (7.4)	43 (10.1)	11 (4.4)	.028
HSV	37 (14.4)	30 (7.1)	3 (1.2)	<.001
CMV retinitis	8 (3.1)	12 (2.8)	6 (2.4)	.89

Abbreviations: ADI, AIDS-defining illness; CMV, cytomegalovirus; HIV, human immunodeficiency virus; HSV, herpes simplex virus.

[a]Of the 3628 patients with available CD4 count at diagnosis.

[b]Of the 3113 patients with available viral load at diagnosis.

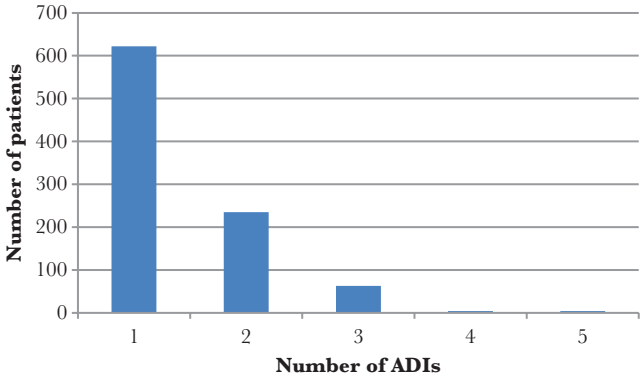

Figure 1. Distribution of number of ADIs diagnosed in individual patients. This figure shows the frequency of the number of ADIs among patients diagnosed with at least 1 ADI at the time of HIV diagnosis (total = 931). Abbreviation: ADI, AIDS-defining illness.

($P = .006$), decreases in HIV wasting syndrome ($P = .028$) and herpes simplex virus ($P < .001$), and a change over time in cryptococcosis ($P = .006$) that was not consistently in one direction.

Data examining co-infection rates are displayed in Figure 1. Of the 931 patients who were diagnosed with an ADI, 622 (66.8%) were diagnosed with a single ADI, 235 (25.2%) were diagnosed with 2 ADIs, 63 (6.8%) were diagnosed with 3 ADIs, 4 (0.4%) were diagnosed with 4 ADIs, and 4 (0.4%) were diagnosed with 5 ADIs.

DISCUSSION

In this large cohort of living HIV patients in Guatemala, a significant proportion (25.2%) presented with an ADI at the time of HIV diagnosis. The percentage of patients presenting with an ADI decreased over time, a trend that was also associated with an increase in mean CD4 at diagnosis over time. This suggests that some progress has been made in diagnosing HIV earlier among our population. While viral load at diagnosis also increased over time and reached statistical significance, this increase was approximately 0.1 log, and therefore is of questionable clinical significance. *M. tuberculosis* was present in more than half of survivors with ADI at diagnosis, which was much higher than expected. Of note, many of the most common ADIs in our cohort of survivors, including tuberculosis and histoplasmosis, showed a significant increase over time. We hypothesize that this is due to a combination of improved diagnostics (as mycobacterial GeneXpert was implemented in 2013) and survival bias (as patients with these ADIs were perhaps less likely to survive to the study period, and ART was more readily available in Guatemala in the later time periods). We are unaware of any prior studies reporting the prevalence of ADIs among survivors with HIV in Central America.

In a study of ADI distribution in French Guiana, the authors had high suspicion that in the pre-HAART era many patients diagnosed with HIV wasting syndrome in fact had disseminated histoplasmosis that was undiagnosed. In the HAART era, which also corresponded with access to histoplasma antigen diagnostics in French Guiana, the incidence of disseminated histoplasmosis increased while the incidence of all other ADIs decreased [14]. It is possible, therefore, that a proportion of our cohort with HIV wasting syndrome also represented undiagnosed disseminated histoplasmosis. The fact that both histoplasmosis and HIV wasting syndrome were significantly higher in the rural portion of our cohort supports this hypothesis. Improvements in histoplasmosis diagnostics, including the enzyme-linked immunosorbent assay developed by the CDC [16], as well as an anticipated lateral flow assay in the near future, may prove that histoplasmosis is a more common ADI than previously appreciated in Central America. Improved diagnostics are available at another HIV clinic in Guatemala City, but have not been successfully implemented at Roosevelt Hospital to date [17].

The strengths of our study include the large cohort size and the fact that it was performed in an area without previous data on ADIs at the time of HIV diagnosis. Limitations include the largely retrospective nature of the study (only a small percentage were new HIV diagnoses during the study period) and the fact that it is from a single center, so the conclusions may not be generalizable to the population of Guatemala as a whole. Another limitation is that data were only gathered from patients who were living during the study period and are still receiving care. This precludes any conclusions about the true prevalence of ADIs among HIV patients at diagnosis.

In conclusion, our study documents the significant burden of ADIs at the time of HIV diagnosis among survivors in a large Guatemalan cohort and identifies the most common ADIs diagnosed in this group. We show significant differences between rural and urban populations in terms of ADIs diagnosed and propose that histoplasmosis may play a larger role than currently estimated based on limited diagnostic capability.

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Ethical approval. This study protocol was approved by the Roosevelt Hospital and Washington University in St Louis institutional review boards with waivers of consent.

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Conflicts of interest. Dr. Powderly reports grants and personal fees from Merck, as well as personal fees from Gilead, outside the submitted

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