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Late Presentation and Missed Opportunities for HIV Diagnosis in Guatemala

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Abstract
Early HIV diagnosis remains a challenge in many regions with delayed diagnosis resulting in increased morbidity and mortality. We conducted a retrospective cohort study of people living with HIV receiving outpatient care at a large tertiary referral center in Guatemala to describe the proportion of late presenters (LP) and missed opportunities for HIV diagnosis. Of 3686 patients, 2990 (81.1%) were LP who were more likely to be male (60.2% vs. 48.0%, $p < 0.0001$), heterosexual (88.0% vs. 78.0%, $p < 0.0001$) and rural dwellers (43.7% vs. 33.8%. $p < 0.0001$). The proportions of patients who presented late or with AIDS at diagnosis decreased over time. Only 665 patients (18.2%) sought care in the 2 years prior to HIV diagnosis. This study, the first of its kind in Central America to focus on late presenters and missed opportunities for HIV diagnosis, demonstrates extremely high rates of LP in Guatemala. Although in recent years rates of LP have improved somewhat, the need for screening outside of traditional healthcare settings is apparent.

Keywords HIV · Guatemala · Diagnosis · AIDS

Resumen
El diagnóstico precoz del VIH sigue siendo un desafío en muchas regiones, y un diagnóstico tardío está relacionado con aumento de la morbi-mortalidad. Este estudio retrospectivo de una cohorte de personas viviendo con VIH en seguimiento en un centro atención terciaria en ciudad de Guatemala, describe la proporción de presentadores tardíos (PT) y las oportunidades perdidas para diagnosticarlas. De 3686 pacientes analizados, 2990 (81.1%) eran PT, los cuales eran con mayor frecuencia varones (60.2% vs. 48.0%, $p < 0.0001$), heterosexuales (88.0% vs. 78.0%, $p < 0.0001$) y habitantes de un área rural (43.7% vs. 33.8%. $p < 0.0001$). La proporción de PT disminuyó a lo largo del tiempo. Únicamente 665 pacientes (18.2%) buscaron atención médica en los dos años previos al diagnóstico del VIH. Este estudio, el primero en Centro América en enfocarse en presentadores tardios y oportunidades perdidas en el diagnostico del VIH, demuestra una tasa extremadamente alta de PT en Guatemala. A pesar de que en años recientes la tasa de PT ha mejorado, es evidente la necesidad de realizar tamizaje fuera del ambiente sanitario habitual.

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Background

Initiation of potent antiretroviral therapy (ART) has resulted in decreased HIV-associated mortality with life expectancy in people living with HIV (PLWH) approaching that of the general population [1, 2]. However, improvements in morbidity and morbidity in PLWH are dependent on early diagnosis and initiation of ART. Late diagnosis of HIV has been associated with increased healthcare costs arising from higher rates of hospitalization and treatment of opportunistic infections (OIs) added to HIV infection treatment [3]. In addition to poorer patient outcomes, late diagnosis carries significant public health risks resulting from higher rates of transmission [4, 5].

Recent studies in the developed world have identified various risk factors for late presentation, including older age, being a heterosexual man or woman (as compared to men who have sex with men [MSM]) and being born in a country other than the one of current residence [6–8]. The rate of late diagnosis varies considerably between jurisdictions, with rates of 24–39% cited in some developed countries and higher rates seen in developing countries such as Mexico (61%) [3, 6–9]. Studies in developed countries suggest that most patients who present late have been evaluated for symptoms associated with HIV, but the opportunity for diagnosis was lost [10, 11]. In the resource-limited setting, such as Malaysia and Mexico, data suggests missed opportunities occur in up to 50% of patients [12, 13]. At present, no data are available on the rates of late presenters or missed opportunities in Central America.

In 2016, UNAIDS estimated the prevalence of HIV infection in 15–49 year olds in Guatemala at approximately 0.5% [14]. Although the provision of potent ART was implemented in Guatemala in 2000, deaths due to HIV have risen from 13.8 per 100,000 in 1990 to 22.0 per 100,000 in 2012, with a high proportion of newly diagnosed patients presenting with advanced HIV and AIDS [15]. We aimed to describe the proportion of late diagnoses of HIV in Guatemala, and to identify and characterize the missed opportunities for HIV diagnosis, with the goal of improving patient outcomes within the country.

Methods

We conducted a retrospective cohort study of all PLWH attending the largest HIV clinic in Guatemala, with a census of 4128 active patients, and approximately 400–600 new HIV diagnoses per year. The clinic is based at a large publicly funded, academic medical center of 900 beds in Guatemala City that predominantly serves patients with limited economic means. The clinic treats patients from all regions of the country. All PLWH 18 years or older who attended the clinic during the study period (including those who were newly diagnosed and attending for the first time) were eligible for enrollment, with no exclusion criteria as long as they could provide verbal consent. The protocol was approved by the institutional review boards of both participating institutions with a waiver of written consent. The study period ran from June 1, 2015 to September 30, 2015.

Subjects were enrolled when they presented for routine HIV clinic visits, and chart review was performed for clinical and demographic data including sex, age, sexual orientation, date of diagnosis, region of residence in Guatemala, CD4 cell count and viral load at time of diagnosis, as well as presence and type of AIDS defining illness (ADI). Presence of ADI was assessed using the CDC definitions [16]. Late presenters were defined as those with CD4 counts less than 350 cells/ml or with an AIDS-defining illness (ADI) at time of HIV diagnosis, according to the European consensus definition [17].

A standardized survey regarding healthcare visits in the 2 years prior to HIV diagnosis was administered by the research assistant to study participants in Spanish; the survey included questions about the presenting symptom, location of care, approximate date of visit, diagnosis received, and if an HIV test was offered, among other questions. The same surveys were administered to those patients who received new HIV diagnoses during the study period.

Continuous and categorical clinical parameters were expressed as mean [standard deviation (SD)] and percentages, respectively. Between group differences were compared using Chi squared test for categorical variables and Student t test for continuous variables; one-way ANOVA was used to compare differences in continuous variables over time. A binary logistic regression model was used to identify significant predictors for late presentation; variables with p value < 0.2 were included in a backward stepwise logistic regression model. In the final models, p values of < 0.05 were considered statistically significant. Data analysis was performed using SPSS (IBM Corp., Version 22.0).

Results

A total of 3686 patients were enrolled, of whom 3628 (98.4%) had available CD4 counts at diagnosis. Of the 58 (1.5%) who did not have a CD4 count available, 9 had ADI's and were included in the late presenter group, the remaining 49 were considered non-late presenter. Overall, 2990 (81.1%) were late presenters, and 2304 (62.5%) had AIDS at diagnosis. With the exception of one patient diagnosed in 1998, all patients enrolled in the study were diagnosed between 2000 and 2015. Baseline characteristics are presented in

Table 1 Baseline characteristics of people living with HIV in Guatemala by disease stage at time of presentation from 2000 to 2015

	Late presenters N = 2990 (%)	Non-late presenters N = 696 (%)	p value	Total cohort N = 3686 (%)
Age at diagnosis, years, mean (SD)	35.2 (10.9)	31.0 (10.3)	< 0.0001	34.4 (10.9)
Sex, male	1799 (60.2)	334 (48.0)	< 0.0001	2133 (57.9)
Sexual risk category				
Heterosexual	2631 (88.0)	543 (78.0)	< 0.0001	3174 (86.1)
MSM	324 (10.8)	140 (20.1)	a	464 (12.6)
Transgender	13 (0.4)	5 (0.7)	a	18 (0.5)
CSW	22 (0.7)	8 (1.1)	a	30 (0.8)
Log(VL at diagnosis), mean (SD)[b]	4.75 (1.08)	3.85 (1.31)	< 0.0001	4.66 (1.10)
CD4 at diagnosis, cells/ml[c]				
< 50	832 (27.9)	0 (0)	< 0.0001	832 (22.9)
50–99	518 (17.4)	0 (0)	a	518 (14.3)
100–199	769 (25.8)	0 (0)	a	769 (21.2)
200–349	800 (26.8)	0 (0)	a	800 (22.1)
350–499	40 (1.3)	351 (54.3)	a	391 (10.8)
500+	22 (0.7)	296 (45.7)	a	318 (8.8)
ADI present at diagnosis	931 (31.1)	0 (0)	N/A	931 (25.3)
Urban dweller	1360 (45.5)	386 (55.5)	< 0.0001	1746 (47.4)
Have sought care in previous 2 years	583 (19.7)	82 (11.8)	< 0.0001	665 (18.2)

SD standard deviation, *MSM* men who have sex with men, *CSW* commercial sex worker, *VL* viral load, *ADI* AIDS-defining illness

[a]Analyzed with row above

[b]Of 3113 patients with data

[c]Of 3628 patients with data

Table 1. Late presenters were older (average age 35.2 years vs. 31.0 years, p < 0.0001), more likely to be male (60.2% vs. 48.0%, p < 0.0001), and more likely to report a heterosexual mode of HIV acquisition (88.0% vs. 78.0%, p < 0.0001). Of the late presenters, 2928 (97.9%) had CD4 counts of < 350 cells/ml and 931 (31.1%) had an ADI at time of HIV diagnosis. HIV viral load at diagnosis was significantly higher among late presenters (mean 4.75 (standard deviation [SD] 1.08) vs. 3.85 (1.31), p < 0.0001). Urban dwellers were significantly less likely to be late presenters (representing 55.5% of non-late presenters vs. 45.5% of late presenters, p < 0.0001). Of the 665 patients (18.2%) who sought care in the 2 years prior to HIV diagnosis, a higher proportion were late presenters (19.7% vs. 13.1%, p < 0.0001).

Table 2 shows trends in demographics over time in five-year increments between 2000 and 2015. Mean age at diagnosis increased from the time period 2000–2005 compared to the latter periods (33.1 years vs. 35.0 years and 34.5 years, respectively, p < 0.0001), and the proportion of male patients diagnosed increased with each time period (52.7% vs. 54.8% vs. 65.1%, p < 0.0001). There was a large increase in the proportion of MSM patients over the three time periods, with the largest increase in the last 5 years (6.7% vs. 8.4% vs. 21.7%, p < 0.0001). Median CD4 count was identical across the first two time periods and increased in the third period (142 vs. 142 vs. 195, p < 0.0001). The proportion of patients with late presentation, AIDS at diagnosis, or ADI at diagnosis all decreased over time (p < 0.0001), while the proportion who had presented to healthcare in the 2 years prior to diagnosis did not change over time (p = 0.646). The proportion of urban dwellers diagnosed with HIV was significantly higher in the third time period (43.7% vs. 44.7% vs. 53.1%, p < 0.0001).

In univariate analysis, age at diagnosis, male gender, heterosexual risk category, rural dwelling, and having sought care in the 2 years prior to diagnosis were all found to be significantly associated with late presentation, and were included in the multivariate analysis (Table 3). Older age at diagnosis was associated with increased risk of late presentation (aOR 1.41 for each decade increase in age, 95% confidence interval [CI 1.28, 1.54], p < 0.0001), as was male gender (aOR 2.06, 95% CI [1.70, 2.50], p < 0.0001). Compared with heterosexual patients, MSM had a lower risk of late presentation (aOR 0.39, 95% CI [0.30, 0.50], p < 0.0001), as did urban dwellers (aOR 0.71, 95% CI [0.59, 0.84], p < 0.0001). Those who sought care in the 2 years prior to diagnosis had higher risk of late presentation (aOR 1.67, 95% CI [1.29, 2.15], p < 0.0001).

Information on the 665 patients who sought care within the 2 years prior to HIV diagnosis is presented in Table 4.

Table 2 Baseline characteristics of people living with HIV at time of diagnosis categorized by time period in years

	2000–2005 N = 776	2006–2010 N = 1654	2011–2015 N = 1256	p value	Total cohort N = 3686 (%)
Age at diagnosis, years, mean (SD)	33.05 (10.15)	35.01 (10.82)	34.39 (11.31)	< 0.0001	34.4 (10.88)
Sex, male	409 (52.7)	906 (54.8)	818 (65.1)	< 0.0001	2133 (57.9)
Sexual risk category					
Heterosexual	719 (92.7)	1489 (90.0)	966 (76.9)	< 0.0001	3174 (86.1)
MSM	52 (6.7)	139 (8.4)	273 (21.7)	[a]	464 (12.6)
Transgender	3 (0.4)	10 (0.6)	5 (0.4)	[a]	18 (0.5)
CSW	2 (0.3)	16 (1.0)	12 (1.0)	[a]	30 (0.8)
Log(VL at diagnosis), mean (SD)[b]	4.82 (1.00)	4.82 (1.20)	4.58 (1.19)	< 0.0001	4.66 (1.10)
CD4 at diagnosis, cells/ml, median (IQR)[c]	142 (56, 281)	142 (49, 272)	195 (71, 362)	< 0.0001	
0–49	177 (23.2)	415 (25.1)	240 (19.8)	< 0.0001	832 (22.9)
50–99	127 (16.6)	250 (15.1)	141 (11.6)	[a]	518 (14.3)
100–199	166 (21.8)	370 (22.4)	233 (19.2)	[a]	769 (21.2)
200–349	167 (21.9)	360 (21.8)	273 (22.5)	[a]	800 (22.1)
350–499	66 (8.7)	155 (9.4)	170 (14.0)	[a]	391 (10.8)
500+	60 (7.9)	104 (6.3)	154 (12.7)	[a]	318 (8.8)
Urban dweller	339 (43.7)	740 (44.7)	667 (53.1)	< 0.0001	1746 (47.4)
Late presentation (CD4 < 350 or ADI at diagnosis)[c]	663 (85.4)	1419 (85.8)	908 (72.3)	< 0.0001	2990 (81.1)
AIDS at diagnosis (CD4 < 200 or ADI present)[c]	538 (69.3)	1105 (66.8)	661 (52.6)	< 0.0001	2304 (62.5)
ADI present at diagnosis	257 (33.1)	425 (25.7)	249 (19.8)	< 0.0001	931 (25.3)
Have sought care in previous 2 years[d]	146 (19.0)	288 (17.4)	231 (18.4)	0.65	665 (18.2)

SD standard deviation, *MSM* men who have sex with men, *CSW* commercial sex worker, *VL* viral load, *IQR* interquartile range, *ADI* AIDS-defining illness, *AIDS* acquired immunodeficiency syndrome

[a] Analyzed with row above

[b] Of 3113 patients with data

[c] Of 3628 patients with data

[d] Of 3654 patients with data

Table 3 Multivariate logistic regression of factors associated with late presentation on univariate analysis

Variable	OR (95% CI)	aOR (95% CI)	p value
Age at diagnosis (by decade)	1.51 (1.38, 1.65)	1.41 (1.28, 1.54)	< 0.0001
Gender, male	1.64 (1.39, 1.93)	2.06 (1.70, 2.50)	< 0.0001
Sexual risk category			
Heterosexual	Reference	Reference	N/A
MSM	0.49 (0.38, 0.59)	0.39 (0.30, 0.50)	< 0.0001
Transgender	0.54 (0.19, 1.51)	0.48 (0.17, 1.37)	0.17
CSW	0.57 (0.25, 1.28)	0.60 (0.26, 1.38)	0.23
Urban	0.66 (0.56, 0.78)	0.71 (0.59, 0.84)	< 0.0001
Sought care in previous 2 years[a]	1.82 (1.42, 2.34)	1.66 (1.29, 2.15)	< 0.0001

OR odds ratio, *CI* confidence interval, *aOR* adjusted odds ratio, *MSM* men who have sex with men, *CSW* commercial sex workers

[a] Among 665 patients who presented to healthcare

Of those that sought care, 55.6% presented only one time, while the remaining 44.4% presented two or more times. Late presenters were more likely to present to healthcare multiple times (p = 0.019).

In the group overall, the most common symptoms were weight loss (73.8%), fever/chills (63.8%), diarrhea (57.1%), vomiting (30.5%), and loss of appetite (18.9%). Late presenters were more likely to present with weight loss (73.3% vs. 63.4%, p = 0.022), diarrhea (59.0%

Table 4 Presenting symptoms and diagnoses given to HIV patients who sought care in Guatemala in the 2 years prior to HIV diagnosis

	Late presenters N = 583 (%)	Non-late presenters N = 82 (%)	p value	Total cohort seeking care N = 665 (%)
Number of times care sought				
1	316 (54.2)	54 (65.9)	0.02	370 (55.6)
2–4	197 (33.8)	23 (28.0)	a	220 (33.1)
5+	70 (12.0)	5 (6.1)	a	75 (11.3)
Symptom				
Constitutional				
Weight loss	439 (73.3)	52 (63.4)	0.02	491 (73.8)
Fever/chills	371 (63.6)	59 (72.0)	0.14	424 (63.8)
Loss of appetite	119 (20.4)	7 (8.5)	0.01	126 (18.9)
Night sweats	28 (4.8)	4 (4.9)	1	32 (4.8)
Gastrointestinal				
Diarrhea	344 (59.0)	36 (43.9)	0.01	380 (57.1)
Vomiting	184 (31.6)	19 (23.2)	0.12	203 (30.5)
Nausea	59 (10.1)	9 (11.0)	0.81	68 (10.2)
Abdominal pain	21 (3.6)	3 (3.7)	1	24 (3.6)
Pulmonary				
Cough	64 (11.0)	3 (3.7)	0.040	67 (10.1)
Shortness of breath	9 (1.4)	1 (1.2)	1	9 (1.4)
Neurological				
Headache	94 (16.1)	17 (20.7)	0.30	111 (16.7)
Confusion	11 (1.9)	1 (1.2)	1	12 (1.8)
Vision problems	9 (1.5)	0 (0)	0.61	9 (1.4)
Seizure	9 (1.5)	0 (0)	0.61	9 (1.4)
Other				
Rash	55 (9.4)	10 (12.2)	0.43	65 (9.8)
Dysuria	10 (1.7)	1 (1.2)	1	11 (1.7)
Lymphadenopathy	5 (0.9)	3 (3.7)	0.06	8 (1.2)
Diagnosis given				
Gastrointestinal				
Intestinal parasites	79 (13.6)	4 (4.9)	0.03	83 (12.4)
Stomach virus	55 (9.4)	8 (9.8)	0.93	63 (9.5)
Gastritis	6 (1.0)	1 (1.2)	0.68	7 (1.1)
H. pylori	5 (0.8)	0 (0)	1.00	5 (0.8)
Irritable bowel syndrome	3 (0.5)	0 (0)	1.00	3 (0.5)
"Empacho"	3 (0.5)	0 (0)	1.00	3 (0.5)
Peptic ulcer	2 (0.3)	0 (0)	1.00	2 (0.3)
Pulmonary/respiratory				
Common cold	49 (8.4)	10 (12.2)	0.30	59 (8.9)
Pneumonia	12 (2.1)	0 (0)	0.38	12 (1.8)
Tonsillitis/amygdalitis	4 (0.7)	3 (3.7)	0.04	7 (1.1)
Sinusitis	2 (0.3)	0 (0)	1.00	2 (0.3)
Infectious				
Dengue fever	9 (1.5)	5 (6.1)	0.02	14 (2.1)
Typhoid fever	3 (0.5)	0 (0)	1.00	3 (0.5)
Malaria	2 (0.3)	0 (0)	1.00	2 (0.3)
UTI	3 (0.5)	0 (0)	1.00	3 (0.5)
Mucocutaneous				
Herpes zoster	4 (0.7)	0 (0)	1.00	4 (0.6)
Oral herpes	3 (0.5)	0 (0)	1.00	3 (0.5)

Table 4 (continued)

	Late presenters N = 583 (%)	Non-late presenters N = 82 (%)	p value	Total cohort seeking care N = 665 (%)
Genital herpes	2 (0.3)	0 (0)	1.00	2 (0.3)
Oral thrush	2 (0.3)	0 (0)	1.00	2 (0.3)
Other				
Allergic reaction	4 (0.7)	1 (1.2)	0.48	5 (0.8)
Anemia	2 (0.3)	0 (0)	1.00	2 (0.3)
Other diagnoses[b]	12 (2.1)	5 (6.1)	0.03	17 (2.6)

Patients could present with multiple symptoms at a given visit, and also could have multiple visits

HIV human immunodeficiency virus, *Empacho* local term roughly translating to indigestion, *UTI* urinary tract infection

[a]Analyzed with row above

[b]Other diagnoses include one case each of: acute otitis, bronchitis, flu, food poisoning, gangrene, HIV, papillomatosis, prostatitis, rheumatoid arthritis, hemorrhoids, low platelets, lymphoma, no diagnosis, prenatal visit, rubeola, uterine myoma, viral infection

vs. 43.9%, p = 0.01), loss of appetite (20.4% vs. 8.5%, p = 0.01), and cough (11.0% vs. 3.7%, p = 0.039). No symptoms were more common among non-late presenters. The most common diagnoses given were intestinal parasites (12.4%), stomach virus (9.5%), common cold (8.9%), Dengue fever (2.1%), and pneumonia (1.8%).

Locations where patients sought care prior to HIV diagnosis are shown in Supplementary Table SI, and no type of facility appeared to be associated with significantly higher rates of missed opportunities. Overall, an HIV test was offered at only 4.4% of visits, with no individual location type offering one at more than 15% of visits (data not shown). The most common was private clinics (70.2% for late presenters vs. 64.6% for non-late presenters, p = 0.17), followed by puestos de salud (or publicly funded local health outposts; 13.6% for late presenters vs. 14.6% for early presenters, p = 0.73), and public emergency rooms (10.7% for both groups, p = 1.00). Only social security clinics showed a significant difference (p = 0.036) between the two groups, but the number of patients [11] was small at this location.

Locations of residence of patients at the time of HIV diagnosis can be found in Supplementary Table S2. Guatemala was by far the most represented department with 1746 patients (47.4% of the cohort), and Escuintla was the second most common department with 541 patients (14.7%).

Discussion

Here we present one of the largest cohorts of PLWH in Central America to date and the largest to examine late presentation and missed opportunities for diagnosis. A high proportion (81.1%) of patients present late, with CD4 count < 350 cells/ml or with an ADI at the time of HIV diagnosis; to our knowledge, this is the highest rate of late presenters reported internationally to date. In keeping with our findings, data published from the MANGUA cohort in Guatemala indicated that almost three quarters of patients had signs of advanced HIV infection at study enrollment [18]. In our study, 62.5% had AIDS at diagnosis. These results closely mirror those from a similar study in Mexico, where 61% presented with AIDS [9], but are much higher than rates in developed countries, where the rates range between 23 and 47% [19–24].

The most compelling aspect of our data is the fact that a low percentage of patients with HIV presented for care in the 2 years prior to diagnosis, regardless of early or late presentation. This stands in stark contrast to many studies in the developed world, where a large majority (62–99%) of patients have seen a provider within the 1–3 years prior to their HIV diagnosis [10, 21–24]. Studies from the United States have shown 60–72% of patients had missed opportunities for HIV diagnosis [10, 20]. In a recent Israeli study, the authors felt that 100% of patients presenting late with HIV disease had a missed opportunity [19]. Another Chinese study concluded that 99% of their HIV cohort had a missed opportunity for HIV diagnosis, though time to diagnosis from prior healthcare visit to the diagnostic visit has gone down over time [25].

Male sex was associated with late presentation and has previously been described as risk factor in developed counties [26]. Interestingly, over time, the rates of males being diagnosed with HIV has increased. We hypothesize that the difference in gender risk over time may be attributable to higher rates of diagnosis of female in the earlier time periods due to the introduction of routine prenatal HIV screening of women, though a recent study in Mexico, where prenatal screening is mandated, showed that 61% of women diagnosed late with HIV reported never receiving an HIV test while pregnant [13]. A Guatemalan study looking at

women receiving pre-natal HIV screening showed decreasing rates of HIV diagnosis over time, but also a decrease in median CD4 count over time, suggesting that perhaps pre-natal screening did not necessarily translate to earlier HIV diagnoses [27].

Similarly, MSM and younger patients were also found to have lower rates of late presentation. This trend has been shown in studies from developed countries [19, 20, 26], and may indicate that these groups are more likely to receive screening due to the perception that they are a higher risk population. The sizable increase in the proportion of MSM over time in our cohort raises some concerns as it is unclear if this indicates an epidemic in this risk group or simply represents improvements in accurate reporting of HIV risk, with further work required to clarify this.

Our cohort also showed differences in geographic risk for late presentation, with a lower proportion of late presentations amongst urban dwellers compared to those living in rural settings. Rural dwellers are likely at higher risk of late presentation due to reduced access to care, with potential contributions of education level and socioeconomic status that were not measured in our dataset.

When the data are examined over time, they show that the proportion of late presenters has decreased and median CD4 count at diagnosis has increased. HIV viral load also decreased over time, although the clinical relevance of the magnitude of the reduction is unclear. These trends provide some evidence that efforts to diagnose patients earlier are having some effect, although the proportion of late presenters was 72% in the most recent time frame; this proportion remains high and indicates further work is required to achieve earlier HIV diagnoses.

Among patients presenting for care, the most common symptoms were weight loss, fever, and diarrhea. Weight loss and diarrhea were both more common among late presenters, and could represent "triggers" for healthcare providers in Guatemala to consider HIV testing. While the majority of patients sought care only one time, 44% sought care multiple times, suggesting that improved screening at healthcare visits could, in fact, result in earlier HIV diagnoses for a small subset of the population.

The diagnoses given to patients were various, with intestinal parasites and stomach virus being the most common. The only diagnosis that was more common in late presenters was intestinal parasites, consistent with the increased rates of diarrhea seen in this group. As above, this suggests that in patients presenting with chronic diarrhea, making providers aware that HIV should be considered as an alternative to intestinal parasites may help with earlier diagnoses in some patients. Data from this cohort also showed high prevalence of tuberculosis, *Pneumocystis jirovecii* pneumonia, esophageal candidiasis, and histoplasmosis at HIV

diagnosis, suggesting these diagnoses should also prompt HIV testing [28].

While data on missed opportunities in the developing world are lacking, a recent study from Uganda showed that only 21% of all patients diagnosed with HIV, and 28% of late presenters, had received care in a medical clinic at any time prior to diagnosis [29]. Our data are more in line with a single center study in Spain, where only 14% of late presenters had a missed diagnostic opportunity, though a much higher percentage (46%) had presented for care in the year prior to HIV diagnosis [26]. This represents a pressing public health issue for Guatemala, which saw 3700 new HIV infections in 2015, more than three times the number of any other Central American country that year [30].

The strengths of our study include the large cohort size and the fact that it was performed in an area without previous data on missed opportunities for HIV diagnosis. The are several limitations, including that it was largely retrospective (only a small percentage, 5.4%, were new HIV diagnoses during the study period, the remainder were established clinic patients) and therefore is subject to the inherent biases associated with this study design. Secondly, it is a single center study, so the conclusions may not be generalizable to the population of Guatemala as a whole. However, it should be noted that Roosevelt Hospital draws patients from every part of the country, and that every district was represented in our sample. Third, data were only gathered from patients who were living during the study period and are still receiving care. This creates a bias against patients who were more severely ill at time of diagnosis and did not live until the study period. We expect this resulted in the proportion of late presenters, as well as the proportion of patients with ADI at diagnosis, being underestimations of the true rates in the population. Fourth, the data on healthcare presentations prior to HIV diagnosis are gathered from retrospective surveys, and patients' memories of such encounters may not be entirely accurate. Fifth, we do not have data on socioeconomic status or education level of the study participants, which may have provided more information about risk, especially between rural and urban dwellers. Sixth, we do not have data on prior antenatal screening for HIV among female patients in our cohort to verify our suspicion that this accounts for the gender difference in our study.

Our data indicate that, although a significant portion of PLWH are diagnosed late in disease, relying on patients to present to healthcare settings will not allow for sufficient screening of the population. Models developed for screening in other healthcare jurisdictions may have limited impact based on the data reported herein that lower rates of patients are seeking care in the years prior to diagnosis compared to other countries. Alternative approaches to screening outside of standard healthcare associated models

may need to be implemented in order to diagnose patients earlier. Expanded screening will likely be necessary for Guatemala to see significant decreases in late HIV presentation through earlier diagnosis.

Compliance with Ethical Standards

Conflict of interest WP has received research grants through his institution from Merck & Co. and has served on advisory board for Merck & Co. and Gilead Sciences. JM, SR, JOH, AS and AAC declare that they have no relevant conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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