ORIGINAL RESEARCH

Clinical characteristics and outcomes in 303 HIV-infected patients with invasive fungal infections: data from the Prospective Antifungal Therapy Alliance registry, a multicenter, observational study

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Abstract: This analysis aimed to characterize the epidemiology, diagnosis, treatment, and outcomes of invasive fungal infections (IFIs) in patients with human immunodeficiency virus (HIV). Data were examined for HIV patients enrolled in the Prospective Antifungal Therapy (PATH) Alliance registry, a multicenter, observational study of patients with IFIs in North America from 2004 to 2008. Patient demographics, clinical characteristics, comorbidities, antifungal therapies, and survival were assessed. In total, 320 fungal isolates were identified from 303 HIV patients with IFIs in the PATH Alliance® registry. These included *Cryptococcus* (50.0%), *Candida* (33.1%), *Histoplasma* (9.1%), and *Aspergillus* (4.4%). *Candida* infection occurred mainly as candidemia (86.0%); *Cryptococcus* as central nervous system infection (76.7%); *Histoplasma* as disseminated infection (74.1%); and *Aspergillus* as pulmonary infection (81.8%). The CD4 cell count was $\leq$200 cells/μL in 91.2% of patients with available data. The majority of patients with *Cryptococcus* (77.9%), *Histoplasma* (100.0%), and *Aspergillus* (71.4%) infections had CD4 cell counts <50 cells/μL compared with 48.9% of patients with *Candida* infections. Patients with candidiasis were more likely to have other conditions requiring medical services compared with patients with other IFIs. Survival probability was lower in patients with *Aspergillus* (0.58) and *Candida* (0.59) infection than in patients with *Histoplasma* (0.84) and *Cryptococcus* (0.81) infection. In the highly active antiretroviral therapy era, traditional opportunistic IFIs such as cryptococcosis and histoplasmosis still mainly occur in HIV patients with CD4 counts <50 cells/μL. Fungal infections remain a clinical challenge in HIV patients with severe immunosuppression. Our data also suggest that HIV patients with CD4 cell counts >200 cells/μL and other underlying conditions may be susceptible to invasive candidiasis.

Keywords: human immunodeficiency virus, invasive fungal infections, Prospective Antifungal Therapy Alliance registry

Introduction

Individuals with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) are at significant risk of invasive fungal infections (IFIs). AIDS-defining fungal infections include pulmonary and esophageal candidiasis, *Pneumocystis jiroveci* pneumonia, disseminated or extrapulmonary coccidioidomycosis, extrapulmonary cryptococcosis, and disseminated or extrapulmonary histoplasmosis.[1] Invasive aspergillosis is relatively rare[2,3] and not considered an AIDS-defining illness.[1]

The advent of highly active antiretroviral therapy (HAART) heralded dramatic improvements in the outcomes for AIDS patients and significant reductions in the incidence of opportunistic infections in North America.[4,5] In a nationwide surveillance project in the US, the incidence of almost all AIDS-defining illnesses decreased significantly between 1992 and 1998.[6,7] By 2007, the average incidence of each AIDS-defining IFI was less than one case per 100 person-years.[8] Despite these advances, opportunistic fungal infections remain common in some patients, such as those with low CD4 cell counts (<250 cells/μL), and those not receiving HAART.[9]

Effective management of IFIs depends on knowledge of current epidemiology, risk factors, rapid diagnostic tests, and optimal treatment regimens. Randomized clinical trials are limited by financial constraints and difficulty in enrolling sufficient numbers of patients with less common IFIs.[10] The development and analysis of large patient databases and registries may overcome these limitations and provide current and relevant clinical information.[11–17]

The Prospective Antifungal Therapy (PATH) Alliance registry is a multicenter, observational registry that collected data on the epidemiologic characteristics, diagnoses, treatment, and outcomes of IFIs in North America.[18] Since its launch in July 2004, data from 6,845 patients have been evaluated, and numerous abstracts, articles, and presentations have been published on the trends and insights gained with regard to these aspects of IFIs in North America.[12,14,18–26] In the present analysis, we explored the clinical characteristics and outcomes of IFIs in the subset of patients with HIV enrolled in the PATH Alliance® registry. Data related to some patients included in this analysis may have been previously reported.[14,19,23,24]

Materials and methods
Data collection
This analysis was based on prospectively collected data from HIV-infected patients with IFIs enrolled from July 1, 2004 to December 31, 2008 in 25 North American centers (23 in the US, two in Canada) participating in the PATH Alliance® registry. This database has been described in detail previously.[21] Briefly, patients with proven or probable IFIs were enrolled and followed prospectively for 12 weeks, or until they died or were lost to follow-up. Inclusion criteria for each specific IFI were adapted from the 2002 guidelines of the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases

Mycoses Study Group.[27] Patient data were accrued using a real-time web-based electronic case report form.

Data for each IFI were collected, including patient demographics and clinical characteristics, comorbidities, existing medications and antifungal therapies, immunologic risk, and concomitant bacterial and viral infections. Patient characteristics included HIV-specific information such as CD4 and CD8 cell counts, and viral load. Detailed information about the IFI was collected and included the specific fungal pathogen and species, infection site, diagnostic tests, antifungal therapy, and outcomes. Incidences of *Pneumocystis* pneumonia were excluded from this analysis since it is not traditionally reported with other IFIs and was therefore likely underreported in the PATH Alliance registry.

Statistical analyses
The day of diagnosis of an IFI was designated as day 1. Descriptive analyses were used for overall patient characteristics and subgroup analyses (eg, pathogen, treatment cohorts). Descriptive survival analyses were used for overall patient survival and subgroup analyses by pathogen. The survival distribution function was estimated using the Kaplan–Meier method.[28] Patients lost to follow-up prior to the week 12 assessment were censored on the day of their last activity documented in the database. Since patient data recorded in the PATH Alliance® registry are not publicly accessible, access to data for statistical analyses was provided to the study investigators by the program sponsor, Astellas Pharma US (Northbrook, IL, USA). Statistical analyses were performed using SAS 9.2/Enterprise Guide version 4.2 (SAS Institute, Inc., Cary, NC, USA).

Results
Overall cohort characteristics
Of the 6,845 patients enrolled in the PATH Alliance® database, 303 (4.4%) were HIV-positive (Table 1). The mean age of the patients was 42.1±0.6 (range 19.0–69.0) years. Most HIV-infected patients in the cohort were adults aged 19–64 years (n=297, 98.0%), male (n=237, 78.2%), and of African-American origin (n=195, 64.4%).

A total of 320 fungal isolates were identified in 303 patients with an HIV infection (Table 2). The most common were *Cryptococcus* (n=160, 50.0% of all infections), *Candida* (n=106, 33.1%), *Histoplasma* (n=29, 9.1%), and *Aspergillus* (n=14, 4.4%). Fifteen patients were documented as having coinfection with two fungal species, ie, *Aspergillus flavus* + *Histoplasma*, *Aspergillus fumigatus* + *Candida glabrata*, *A. fumigatus* + *Histoplasma*, *Candida*

Table 1 Baseline characteristics of 303 patients with human immunodeficiency virus and invasive fungal infections

Characteristic	
Patients, n (%)	303
Age, mean years±SE (range)	42.1±0.6 (19.0–69.0)
Age group, n (%)	
19–64 years	297 (98.0)
≥65 years	6 (2.0)
Male, n (%)	237 (78.2)
Ethnicity, n (%)	
African-American	195 (64.4)
Caucasian	70 (23.1)
Hispanic or Latino	30 (9.9)
Other[a]	8 (2.6)

Note: [a]Includes Alaskan Native, American Indian, Asian, Native Hawaiian, Pacific Islander, other, and unknown.
Abbreviation: SE, standard error.

albicans + C. glabrata (n=3), *C. albicans + Candida krusei*, *C. albicans + Candida tropicalis* (n=2), *C. krusei + C. tropicalis*, *Candida lusitaniae + Candida parapsilosis*, *C. glabrata + C. parapsilosis*, *C. parapsilosis + C. tropicalis*, *C. albicans + Cryptococcus*, and *C. krusei + Mucor*. In addition, one patient had coinfection with *Fusarium + Paecilomyces + Mucor*. The main sites of infection for all fungal pathogens were blood (n=188, 62.0% of patients with positive blood cultures), the central nervous system (n=128, 42.2%), and lung (n=30, 9.9%).

CD4 cell counts were available for 146 patients (48.2%; Table 3). The majority of these patients (n=101, 69.2%) had an absolute CD4 count <50 cells/μL. Very few patients

Table 2 Fungal pathogens and species

Pathogen	Number of isolates[a]
Overall, n	320
Cryptococcus, n (%)	160 (50.0)
Candida spp., n (%)	106 (33.1)
C. albicans	48 (15.0)
C. glabrata	25 (7.8)
C. parapsilosis	11 (3.4)
C. tropicalis	10 (3.1)
C. dubliniensis	5 (1.6)
C. krusei	5 (1.6)
C. lusitaniae	1 (0.3)
Unknown *Candida* spp.	1 (0.3)
Histoplasma, n (%)	29 (9.1)
Aspergillus spp., n (%)	14 (4.4)
A. fumigatus	11 (3.4)
A. flavus	2 (0.6)
Other *Aspergillus* spp.	1 (0.3)
Other yeasts and molds,[b] n (%)	11 (3.4)

Notes: [a]From 303 patients with microbiology records; [b]includes *Mucor* (n=2), *Rhizomucor* (n=1), an unknown *Zygomycetes* spp. (n=1), *Coccidioides* (n=1), *Fusarium* (n=2), *Paecilomyces* (n=1), one other mold (n=1), an unknown endemic fungus (n=1), and one other yeast (n=1).

(n=13, 8.9%) had an absolute CD4 count >200 cells/μL. The median CD4 cell count was 24 cells/μL (range 0–1,468). The median CD4:CD8 ratio was 0.1 (0.0–1.9). Median CD4 cell counts and CD4:CD8 ratios were highest in patients with *Candida* infections (Table 3).

HIV viral load counts were available for 116 patients (38.3%; Table 3). Most of these patients (n=114, 98.2%) had HIV viral loads of ≥50 copies/mL. Median HIV viral load was 92,100 copies/mL (range 0–4,306,000). Median viral loads were highest in patients with *Cryptococcus* and *Histoplasma* infections (Table 3).

Some patients presented with other underlying conditions in addition to HIV as summarized in Table 4. Overall, 30 patients underwent nontransplant surgery, 18 presented with a hematologic malignancy, 15 presented with a solid tumor, four required a solid organ transplant, and one received hematologic stem cell therapy. Of the remaining patients, 167 had conditions classified under general medicine services, and predisposing or comorbid conditions were not reported in 112 patients.

Of all patients with HIV, those with candidiasis presented with the highest incidence of other conditions (Table 4). Sixteen patients with this IFI required surgery, 12 presented with a hematologic malignancy, 11 presented with a solid tumor, and five required either solid organ (n=4) or hematologic stem cell (n=1) transplantation. Only 15 patients with candidiasis presented with no underlying condition other than HIV.

Specific pathogens
Cryptococcosis
Cryptococcosis was the most frequently reported IFI (n=159, 52.5% of all patients). Median CD4 cell count and HIV viral load in patients with *Cryptococcus* infection were 17 cells/μL (range 0–391) and 117,000 copies/mL (0–4,306,000), respectively (Table 3). The CD4 count was <50 cells/μL in 77.9%, and ≤200 cells/μL in 97.4% of the patients with cryptococcosis. The main sites of infection were not mutually exclusive and included central nervous system (n=122), blood (n=83), and lung (n=11). *Cryptococcus* infection was diagnosed in the majority of patients by culture (n=119), antigen test (n=108), and/or histopathologic examination (n=9). On day 3, 69 patients (43.4%) with cryptococcosis had received monotherapy with either lipid-based amphotericin B (n=37), fluconazole (n=18), amphotericin B deoxycholate (n=12), or 5-fluorocytosine (n=3). An additional 67 patients (42.1%) received combination therapy with lipid-based amphotericin B and 5-fluorocytosine (n=31), amphotericin B deoxycholate and 5-fluorocytosine (n=24), or other combinations (n=12).

Table 3 Immunologic and viral load status in different fungal infections

Parameter	Overall	*Cryptococcus*	*Candida* spp.	*Histoplasma*	*Aspergillus* spp.
CD4 cell count, n	146	77	47	9	7
<50 cells/μL	101 (69.2)	60 (77.9)	23 (48.9)	9 (100.0)	5 (71.4)
50–100 cells/μL	16 (11.0)	8 (10.4)	7 (14.9)		
101–200 cells/μL	16 (11.0)	7 (9.1)	7 (14.9)		1 (14.3)
201–350 cells/μL	4 (2.7)	1 (1.3)	2 (4.3)		1 (14.3)
>350 cells/μL	9 (6.1)	1 (1.3)	8 (17.0)		
Mean cells/μL±SD	82±186	41±63	170±298	14±14	64±93
Median cells/μL (range)	24 (0–1,468)	17 (0–391)	50 (0–1,468)	13 (1–38)	32 (3–254)
CD4:CD8 ratio, n	92	48	34	2	3
Mean±SD	0.30±0.40	0.16±0.33	0.38±0.45	0.05±0.05	0.25±0.32
Median (range)	0.08 (0.00–1.86)	0.05 (0.00–1.7)	0.21 (0.00–1.86)	0.05 (0.01–0.08)	0.08 (0.04–0.62)
HIV viral load, n	116	56	35	15	4
<50 copies/mL, n (%)	2 (1.4)	1 (1.8)			1 (25.0)
≥50 copies/mL, n (%)	114 (98.2)	55 (98.2)	35 (100.0)	15 (100.0)	3 (75.0)
Mean copies/mL±SD	243,416±521,206	340,921±701,986	130,885±240,011	239,547±248,836	25,485±41,191
Median copies/mL (range)	92,100 (0–4,306,000)	117,000 (0–4,306,000)	16,600 (50–750,000)	110,000 (1,580–750,000)	7,720 (0–86,500)

Abbreviations: HIV, human immunodeficiency virus; SD, standard deviation.

By day 3, three patients had died, and treatment records were incomplete for the remaining 19 patients due to missing data and loss to follow-up.

Candidiasis

Candidiasis was the second most frequently reported IFI (n=93, 30.7% of all patients). The most common *Candida* species was *C. albicans*, which accounted for 45.3% of all *Candida* species. Median CD4 cell count and median viral load in these patients were 50 cells/μL (0–1,468) and 16,600 copies/mL (50–750,000), respectively. The CD4 count was <50 cells/μL in 48.9% and ≤200 cells/μL in 78.7% of the patients with candidiasis. The majority of cases presented as candidemia (n=80, 86.0%). Other infection sites were not mutually exclusive and included skin (n=4), abdomen (n=3), and lung (n=2). *Candida* infection was diagnosed by culture or tissue biopsy in all patients. On day 3, monotherapy with echinocandins (n=28) or fluconazole (n=22) were commonly

used for the treatment of candidemia, but amphotericin B (lipid-based; n=5) and combination therapy (n=5) were rarely used. By day 3, nine patients had died, and treatment records were incomplete for the remaining 24 patients due to missing data and loss to follow-up.

Histoplasmosis

Histoplasmosis was the third most frequently reported IFI (n=27, 8.9% of all patients). Median CD4 cell count and median viral load in these patients were 13 cells/μL (1–38) and 110,000 copies/mL (1,580–750,000), respectively. The CD4 count was <50 cells/μL in all patients with histoplasmosis. The sites of infection were not mutually exclusive and included blood (n=20), lung (n=4), abdomen (n=3), central nervous system (n=2), and skin (n=1). The majority of cases of infection with *Histoplasma* were diagnosed through culture (n=24). The other three infections were diagnosed by antigen test (n=1), histopathologic examination (n=1), or both (n=1).

Table 4 Other underlying conditions

Condition[a]	Overall	*Cryptococcus*	*Candida* spp.	*Histoplasma*	*Aspergillus* spp.
Overall, n	303	159	93	27	11
Hematologic malignancy, n (%)	18 (5.9)	2 (1.3)	12 (12.9)	0 (0.0)	2 (18.2)
Hematopoietic stem cell transplant, n (%)	1 (0.3)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)
Surgical (nontransplant), n (%)	30 (9.9)	8 (5.0)	16 (17.2)	3 (11.1)	0 (0.0)
Solid organ transplant, n (%)	4 (1.3)	0 (0.0)	4 (4.3)	0 (0.0)	0 (0.0)
Solid tumor, n (%)	15 (5.0)	3 (1.9)	11 (11.8)	0 (0.0)	0 (0.0)
General medicine, n (%)	167 (55.1)	73 (45.9)	62 (66.7)	17 (63.0)	5 (45.5)
None of the above (HIV only), n (%)	112 (37.0)	82 (51.6)	15 (16.1)	8 (29.6)	5 (45.5)

Note: [a]Categories are not mutually exclusive.
Abbreviation: HIV, human immunodeficiency virus.

The most common antifungal therapy used for histoplasmosis on day 3 was monotherapy with either lipid-based amphotericin B (n=12) or an azole (itraconazole, fluconazole, or voriconazole; n=6). Combination therapy was not used to treat *Histoplasma* infection. By day 3, two patients had died, and records were incomplete for the remaining seven patients due to missing data and loss to follow-up.

Invasive aspergillosis

Invasive aspergillosis was reported in 14 patients (4.6%), three of whom also had infections with fungal pathogens other than *Aspergillus* spp. Of the *Aspergillus* spp., the most common were *A. fumigatus* (78.6%) and *A. flavus* (18.2%). In the 11 patients with *Aspergillus* spp. infections only, median CD4 cell count and median viral load were 32 cells/μL (3–254) and 7,720 copies/mL (0–86,500), respectively. The CD4 count was <50 cells/μL in 71.4% and ≤200 cells/μL in 85.7% of these patients. The most common site of infection was the lung (n=9). Other sites of infection were not mutually exclusive and included central nervous system (n=2) and single cases from skin, sinus, and eye. Of the 14 *Aspergillus* infections, eight were proven and six were probable, and were confirmed by culture (n=11), histopathologic or cytopathologic examination (n=7), computed tomography scan (n=7), magnetic resonance imaging (n=3), and/or galactomannan antigen (n=2). On day 3, treatment records indicated that two patients received monotherapy with either lipid-based amphotericin B or voriconazole; three patients received combination therapy with voriconazole and echinocandins; or voriconazole and amphotericin B; or with amphotericin B and echinocandins. By day 3, one patient had died, and records were incomplete for the remaining five patients due to missing data and loss to follow-up.

Survival

The Kaplan–Meier plots in Figure 1 show overall survival, as well as survival for each fungal pathogen. Overall, the 30-day and 90-day survival probabilities for all patients were 0.80 and 0.72, respectively. The survival probabilities in patients with *Aspergillus* (0.70 at day 30 and 0.58 at day 90) and *Candida* (0.67 at day 30 and 0.59 at day 90) infections were lower than those observed with *Histoplasma* (0.84 at day 30 and 0.84 at day 90) and *Cryptococcus* (0.89 at day 30 and 0.81 at day 90) infections.

Discussion

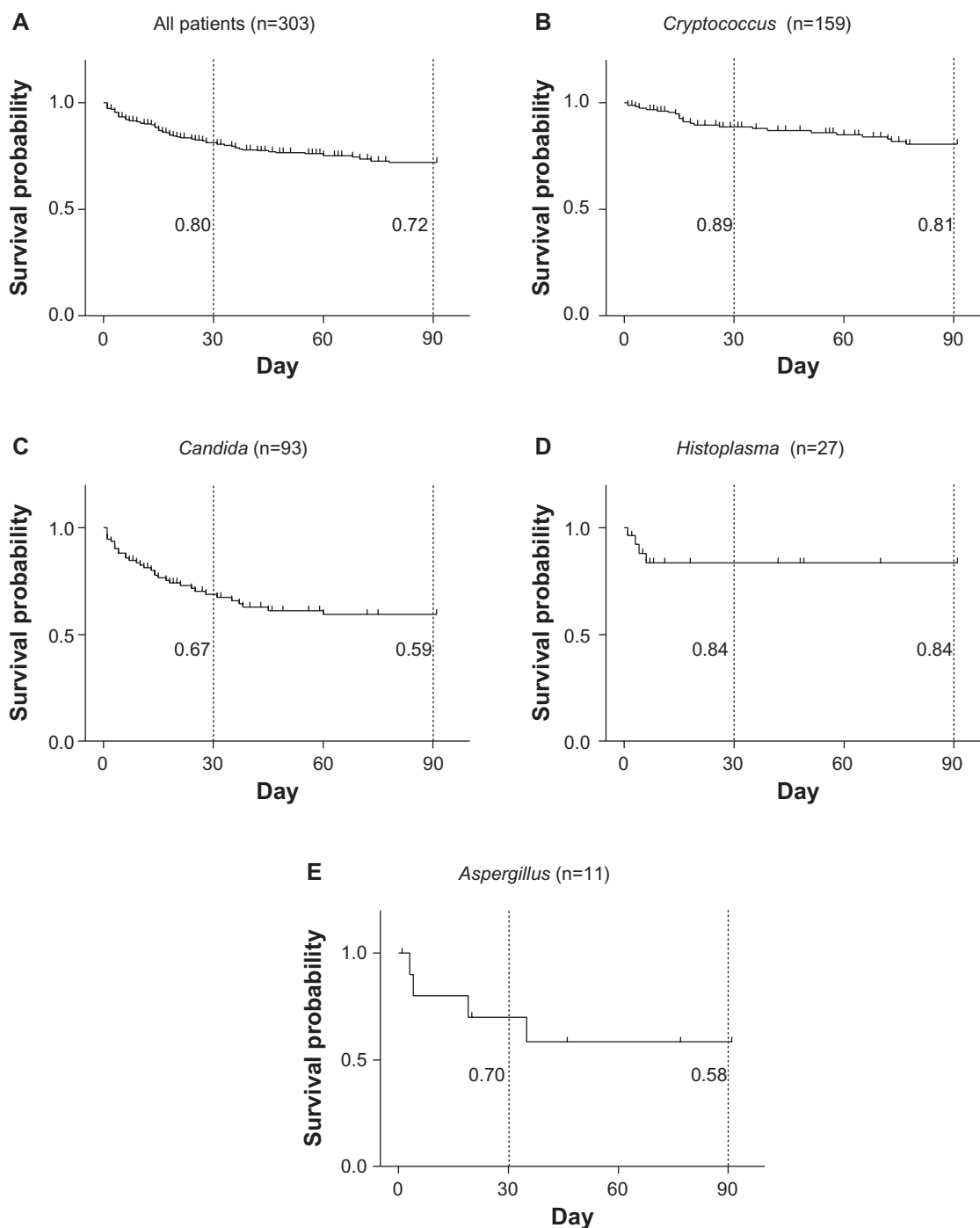This is the first analysis of the PATH Alliance® registry emphasizing the epidemiology and outcomes of IFIs in HIV-infected patients. Our findings highlight the occurrence of IFIs in a subset of patients with low CD4 cell counts and high viral loads despite the availability of HAART.

Most patients in the cohort were adults aged 19–64 years, male, and of African-American origin, which is consistent with the epidemiology of patients with HIV in the US.[29] HIV was not well controlled in this cohort, as evidenced by the high proportions of patients with low CD4 cell counts (≤200 cells/μL) and detectable HIV viral load (≥50 copies/mL). At least 91% of patients in this cohort had AIDS by virtue of a CD4 count ≤200 cells/μL. Almost 70% had CD4 counts <50 cells/μL and were at significant risk of developing an opportunistic IFI.[1,7,30] In the present analysis, the majority of patients with *Cryptococcus*, *Histoplasma*, and *Aspergillus* infections had extremely low CD4 counts, which is consistent with earlier reports.[30–33] Cryptococcosis most often occurs with CD4 counts <50 cells/μL;[30] disseminated histoplasmosis usually occurs in patients with CD4 counts <150 cells/μL;[31,34] and HIV-associated aspergillosis typically occurs with CD4 counts <100 cells/μL.[35] Although candidemia has also been reported in patients with HIV and very low CD4 cell counts (ranging from ~10 cells/μL[36] to 125 cells/μL[37]), over 20% of the patients in this cohort with candidiasis had CD4 counts >200 cells/μL.

HAART has emerged as the standard of care among patients with CD4 cell counts <500 cells/μL and is associated with marked reductions in the incidence of IFIs in patients with HIV.[7] Results from this query of the PATH Alliance registry suggest that the majority of HIV patients with an IFI were either not receiving or were nonadherent to HAART. However, information on antiretroviral therapy was not collected to confirm this hypothesis.

Patients with invasive candidiasis were more likely to have another condition requiring clinical services such as malignancy, nontransplant surgery, hematologic stem cell therapy, or solid organ transplantation. The presence of central venous catheters is a significant independent risk factor for candidemia in patients with HIV[36–38] and it is possible that these patients were more likely to have central venous catheters due to the additional condition. However, information on the use of central venous catheter was not collected.

Culture and antigen tests were the most frequently used diagnostic tests for IFIs in this patient group. All cases of candidemia were diagnosed with traditional culture methods,[39] similar to previous reports of candidemia in patients with HIV.[36,37] However, cases of *Candida* infection in the lung or skin reported here may not be classified as IFIs as per revised 2008 guidelines.[40] Diagnosis of cryptococcosis is most often

A All patients (n=303)

B *Cryptococcus* (n=159)

C *Candida* (n=93)

D *Histoplasma* (n=27)

E *Aspergillus* (n=11)

Figure 1 Ninety-day post-diagnosis survival.

made by latex agglutination test for capsular polysaccharide, and/or by blood or cerebrospinal fluid culture.[41] The majority of *Cryptococcus* infections in this study were detected by one or both of these methods.

In general, treatment strategies adhered to current guideline recommendations. Lipid-based amphotericin B is the recommended first-line treatment for disseminated histoplasmosis[30] and was administered most frequently in this cohort. Based on the results of a number of randomized clinical trials,[42–45] echinocandins or fluconazole are the preferred treatments for invasive candidiasis[46] and were administered most frequently in this cohort. Voriconazole is recommended for invasive aspergillosis,[47] and was received by most treated patients in this cohort. Notably, voriconazole was also prescribed in combination with either amphotericin B or echinocandins in some patients. By contrast,

induction therapy with amphotericin B and 5-fluorocytosine is recommended for *Cryptococcus* infection, but was used in fewer than half of patients with cryptococcosis.

Survival in this cohort was highest in patients with cryptococcosis and histoplasmosis. Survival in patients with HIV and cryptococcosis generally ranges from 75% to 90%,[48,49] which is similar to survival reported in the present analysis. Although survival in patients with disseminated histoplasmosis is typically poor (50%–65% for *Histoplasma* infection),[50,51] survival rates in the PATH Alliance® registry were higher. Survival in patients with invasive aspergillosis was lower compared with patients with cryptococcosis and histoplasmosis, but was better than existing data that report long-term survival rates <30%.[2,3] In contrast, survival in patients with invasive candidiasis was poor and similar to previous reports of 40%–60% survival in patients with HIV.[36,37]

We acknowledge that our analysis has significant limitations. Although the database was designed to capture CD4 cell count and HIV viral load data, these parameters were available for <50% of patients. Furthermore, the database did not capture HIV therapy, so we were unable to analyze the presence or absence of antiretroviral therapy. However, we believe that most patients in this cohort were not adherent to antiretroviral therapy. Although the initial sample size was reasonable, analysis regarding treatment and outcomes was limited by incomplete treatment information and loss of follow-up in a significant number of patients. In addition, the 2002 guidelines of the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group were used for this analysis, but when the guidelines were revised in 2008, the new guidelines could not be adopted in totality. All skin and lung *Candida* infections in the PATH Alliance® registry are listed in this manuscript as IFIs; however, not all cases may have histologic evidence of invasive disease, and this is also a limitation. Finally, since this was a database of patients with IFIs and not a database of HIV patients, we were unable to determine incidence and prevalence rates.

Conclusion

In the HAART era, traditional opportunistic IFIs such as cryptococcosis and histoplasmosis still occur in HIV patients with CD4 cell counts <50 cells/µL. Fungal infections remain a clinical challenge in HIV patients with severe immunosuppression. Our data also suggest that HIV patients with CD4 cell counts >200 cells/µL and other conditions may be at an increased risk for invasive candidiasis. Survival rates for HIV patients with cryptococcosis and histoplasmosis have improved compared with survival rates for invasive candidiasis and aspergillosis, which remain poor. Clinicians should remain vigilant for IFIs in HIV patients with low CD4 cell counts, even in the HAART era.

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