An Analysis of Three Opportunistic Infections in an Outpatient HIV Clinic in Jamaica

G Barrow[1], TR Clarke[1,2], D Carrington[3], K Harvey[3], EN Barton[1,2]

ABSTRACT

Objectives: *To determine the occurrence of opportunistic infection (OI) in HIV-positive patients and to identify any risk factors which may be associated with such.*

Methods: *A cross-sectional study of all patients attending the HIV out-patient clinic was conducted. Their hospital notes were examined between January 1 and December 31, 2007 inclusive, to identify any occurrence of opportunistic infection. In addition, the patient list was also cross-referenced with all patients hospitalized on the medical wards during the same time period. Clinical and demographic data were collected for all participants. The occurrence of opportunistic infections and the variables of age, gender, CD4 counts and viral loads: (first ever, last in 2007 and at diagnosis of OI [or within six months]), the use of primary and secondary prophylaxis, the discontinuation of prophylactic regimens and the HAART regime at diagnosis of an OI and the diagnostic and treatment protocols of these infections were calculated.*

Results: *Six hundred and three patients participated in the study and 4.7% (n = 28) were found to have experienced at least one opportunistic infection in 2007. Significant associations were found between first and last CD4 cell count, viral load in 2007, year of entry into the clinic and death (*$p < 0.05$*).*

Conclusions: *Opportunistic infections continue to cause significant morbidity and mortality in the HIV-patient population in this study. Earlier entry to treatment facilities and the use of HAART and appropriate prophylaxis can reduce this impact and lead to improved quality of life for HIV-positive individuals.*

Key words: AIDS, HIV, opportunistic infection

Análisis de tres Infecciones Oportunistas en un Paciente Externo de la Clínica de VIH en Jamaica

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RESUMEN

Objetivos: *Determinar la ocurrencia de infecciones oportunistas (IO) en pacientes VIH-positivos e identificar factores de riesgo que puedan estar asociados con ellas.*

Métodos: *Se llevó a cabo un estudio transversal de todos los pacientes que asisten a la clínica externa de VIH. Sus apuntes de hospital fueron examinados entre el 1 de enero y el 31 de diciembre de 2007 inclusive, a fin de identificar cualquier manifestación de infección oportunista. Además, la lista de pacientes fue creada con referencias cruzadas en relación con todos los pacientes hospitalizados en las salas del hospital durante el periodo en cuestión. Se recogieron los datos clínicos y demográficos de todos los participantes. Se realizaron cálculos de la ocurrencia de infecciones oportunistas y las variables de edad, género, conteos de CD4 y las cargas virales: (la primera y la última en 2007 y en el diagnóstico de IO [o dentro de seis meses]), el uso de profilaxis primaria y secundaria, la descontinuación de los regimenes profilácticos y el régimen de TARGA en el diagnóstico de una IO, así como los protocolos de diagnóstico y tratamiento de estas infecciones.*

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Resultados: *Seiscientos tres pacientes participaron en el estudio y se halló que 4.7% (n = 28) habían parecido por lo menos una infección oportunista en 2007. Se hallaron asociaciones significativas entre el primer y el último conteo celular CD4, la carga viral en el 2007, el año de entrada en la clínica y la muerte (*$p < 0.05$*).*

Conclusiones: *Las infecciones oportunistas continúan siendo la causa de morbilidad y mortalidad significativas entre la población de pacientes de VIH de acuerdo a este estudio. El ingreso temprano a los centros de tratamiento y el uso de la terapia de TARGA así como una profilaxis adecuada, puede reducir este impacto y llevar a una mejor calidad de vida de los individuos VIH positivos.*

Palabra clave: SIDA, VIH, infección oportunista

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INTRODUCTION

The primary pathological effect of the HIV virus is the continuous degradation of the human immune system, primarily through a reduction of CD4 positive T-lymphocytes (1). As a consequence, the human body becomes susceptible to pathogens not normally able to cause infection. This transition occurs when the $CD4^+$ cell count is depleted to 200 cells/ml or 14% of total lymphocytes and these pathogens are referred to as opportunistic or AIDS-defining infections. Three opportunistic infections (OIs) which are often associated with AIDS are toxoplasma encephalitis, cryptococcal meningitis and *Pneumocystis jirovecii* pneumonia (PCP). The impact of these infections can be significantly reduced by the use of highly active antiretroviral therapy (HAART) and chemoprophylactic agents (1– 4).

The introduction of HAART and prophylaxis of OIs, took place in the early 1990s in the United States of America (5) and most of the developed countries. However, it was not until 2004, through the Global Fund for HIV/AIDS, tuberculosis and malaria, that HAART was available widely in Jamaica (6). Ultimately, the provision of antiretroviral (ARV) medication has lead to significant declines in morbidity and mortality associated with HIV infection (7, 8). However, OIs still exert a significant impact on the lives of HIV-infected persons even though the incidence of non-infectious conditions is increasing (9–11). Pneumocystis pneumonia, in particular, with the highest incidence rates of all OIs in the majority of developed and developing countries, has lead to reductions in quality of life, increased hospitalization and AIDS-associated death in both pre- and post-HAART eras (12–15).

The implementation of prophylaxis for OIs was introduced in the USA in 1995 through guidelines published by the Infectious Disease Society of America (16). These guidelines were adopted by clinicians in the Caribbean but those specific to the region were introduced in 2004 in Jamaica (15). These outlined definitive clinical guidelines for the use of chemotherapeutic agents to reduce the incidence of OIs.

Trimethoprim-sulfamethoxazole (TMP/SMX) has been shown to be an efficient (17) and cost effective (18) prophylactic agent against PCP. It also affords protection against cerebral toxoplasmosis, *S pneumonia*, Salmonella species and Nocardia (19). Chemoprophylaxis against cryptococcal meningitis is more controversial. Fluconazole is one of the mainstays of treatment for cryptococcal meningitis. However, its use as primary prophylaxis, has not been introduced in most developed or developing countries (20).

Access to healthcare and adequate treatment, including prophylaxis are major determinants of the impact of OIs. It is therefore imperative to review the services to HIV-positive patients in order to maximize the quality of care provided. This study looks at the occurrence of three OIs, in a HIV/AIDS population at an outpatient clinic at the University Hospital of the West Indies (UHWI), Jamaica. The diagnostic and treatment modalities used at this facility, including the use and discontinuation of prophylaxis against OIs were also investigated

SUBJECTS AND METHODS

The Centre for HIV/AIDS Research, Education and Services (CHARES) is a HIV specialist clinic at the University Hospital of the West Indies (UHWI), Kingston, Jamaica. The patient population comprises generally people of African descent who are from the lower socio-economic class and have limited education. The study population is generated through referrals from the UHWI, private physicians and referrals from other HIV treatment sites throughout Jamaica. As a result, patients may or may not be ARV naïve when enrolled in the clinic.

The inclusion criteria for this study were:

* Patients enrolled at the clinic (CHARES, UHWI) between January 1, 2007 and December 31, 2007 inclusive.
* Patients admitted to the medical wards at the UHWI and referred to the CHARES team during the defined study period were also included.

A retrospective, cross-sectional study design was instituted. Study participants were identified with use of the medical appointment diary from the clinic as well as a review of all admissions to the medical wards at the UHWI during the study period. Opportunistic Infections (OIs) in hospital admissions were identified using ICD-10 codes. The diagnosis of an OI was usually confirmed with radiological evidence or by direct identification of the causative organism

using staining techniques. However, clinical response to appropriate therapy was also included as a diagnostic modality for PCP. Information on the following variables was collected: patient demographics, CD4 counts and viral loads: (first ever, last in 2007 and at diagnosis of OI [or within six months]), the use of primary and secondary prophylaxis, the discontinuation of prophylactic regimens and the HAART regime at diagnosis of an OI, OI occurrence in 2007 and prior to 2007 and the diagnostic and treatment protocols of these infections.

The occurrence of an OI was the primary outcome of interest. Guidelines used in this project to determine appropriate treatment, including the use of prophylaxis and diagnostic options are taken from the CDC recommendations in 2007 (15, 16).

Data were analysed using SPSS version 17.0 for Windows. Medians and inter-quartile ranges were used to describe clinical and demographic data which are not normally distributed and means with 95% confidence intervals for those that were. Categorical variables were compared with OI occurrence using Chi-square tests, all comparisons were 2-tailed and statistical significance was defined as $p < 0.05$. All variables found to be significant in the bivariate analysis were entered into the logistic regression model initially using the block method and a Cox R^2 coefficient calculated.

RESULTS

Describing the Population

A total of 665 patient records were examined, of which 603 (90.7%) met study inclusion criteria. The mean age was 37.7 (36.9 – 37.7) years and there was a slight female predominance amongst the study population, with a male to female ratio of 1:1.2.

A stratification of the first CD4 count ever recorded in these patients revealed that 46.2% (n = 214) had a CD4 count < 200 cells/ml while 84.7% (n = 373) had a CD4 count below 500 cells/ml. Only 16.4% (n = 99) of patients had viral loads done within six months of enrolment to the clinic. However, of those performed, 62.0% (n = 61) had viral load > 10 000 with 27.3% (n = 27) having VL > 100 000 copies, and only 3% (n = 18) were below 50 copies (Tables 1, 2).

By the end of 2007, 76.4% (n = 418) had CD4 counts > 200 cells/ml with 27.6% (n = 151) having CD4 counts > 500 cells/ml. A greater proportion of patients, 64.5% (n = 365) had a VL within six months at the end of 2007. Viral Load (VL) analysis revealed 41.4% (n = 151) < 50 copies, 24.4% (n = 89) were between 10 and 100 thousand copies and 7.4% (n = 27) were > 100 000 copies (Tables 1, 2).

Prior to the rolling out of HAART between 1998 and 2004, 25.7% (n = 155) of patients had already been enrolled in the clinic. Of the 74.3% of patients enrolled in the post-HAART era, 29.4% (n = 177) joined the clinic in 2007.

During the study period, 10 deaths were recorded. Analysis of the association of OI occurrence and death, showed an increased rate, 60% *versus* 40%, of death among those patients without an OI ($p < 0.001$) [Table 4]. However, information on patients lost to follow-up was not available and therefore distinctions between those receiving care at other treatment sites and those who died could not be made. For those patients in whom death was associated with an OI, three patients (75%), had a diagnosis of PCP ($p < 0.001$) [Table 4].

Describing Opportunistic infection Occurrence

In 2007, 4.7% (n = 28) of patients were diagnosed with an opportunistic infection. Of those, 82.2% (n = 23) had PCP, 7.1% (n = 2) had toxoplasma encephalitis, 10.7% (n = 3) had cryptococcal meningitis. At the diagnosis of an OI, CD4 counts < 50 cells/ml occurred in 56% (n = 14) and 80% (n = 20) had CD4 counts < 200 cells/ml (Fig. 2).

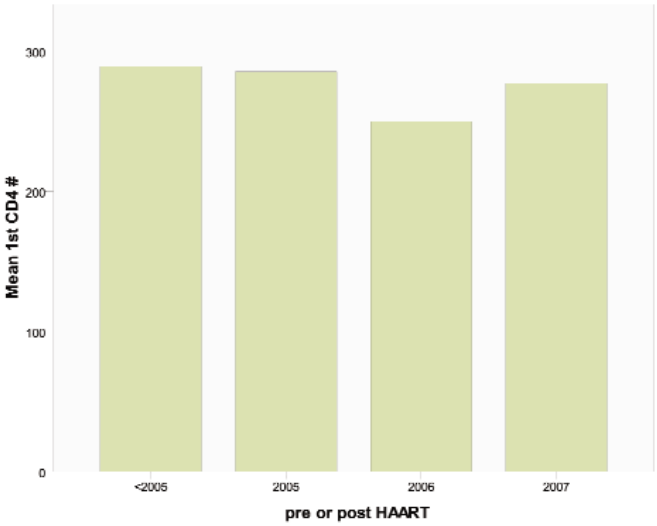

Fig. 1: Comparison of Initial CD4 Count Based on Date of Entry.

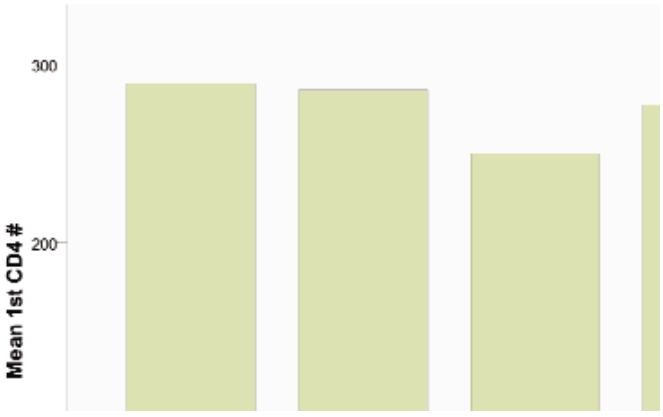

Fig. 2: Comparison of CD4 count at the Diagnosis of an Opportunistic Infection.

Previous opportunistic infections occurred in 12.1% (n = 73) of patients. The majority were diagnosed with PCP, 83.5% (n = 61) and 8.2% (n = 6) were diagnosed with toxoplasma encephalitis and cryptococcal meningitis.

The diagnosis of PCP was made in 91.3% (n = 21) of cases based on clinical suspicion and X-ray findings alone while the remaining 8.7% (n = 2) utilized silver staining of sputum. All of the cases of toxoplasma encephalitis were diagnosed with contrast computed tomography of the brain which revealed multiple ring enhancing lesions and *Cryptococcus neoformans* was identified with CSF examination using India Ink stain.

Patients in whom an OI occurred, 35.7% (n = 10) were not on any HAART, 50% (n = 14) were on a NNRTI-based regime and 14.3% (n = 4) were on a PI-based regime.

Prophylaxis

During the study period, primary prophylaxis was offered to 39.9% (n = 241) of all patients and 11.6% (n = 70) received secondary prophylaxis. Trimethoprim-sulfamethoxazole was the most popular agent accounting for 97.5% (n = 235) and 91.4% (n = 64) of all primary and secondary prophylaxis respectively. Patients who were sensitive to TMX/SMX were usually offered dapsone as an alternative, in 2.5% and 5.7% of patients receiving primary and secondary prophylaxis respectively. Fluconazole, only accounted for 2.9% (n = 2) of all secondary prophylaxis being offered (Table 3).

Using the aforementioned guidelines, the appropriate use of these agents was assessed and it was found that only 2.0% (n = 12) were not receiving appropriate primary prophylaxis while 1.0% (n = 6) were not receiving appropriate secondary prophylaxis. There were 38.9% (n = 121) of patients who were receiving either primary or secondary prophylaxis in 2007 who had their prophylaxis discontinued. However, in 13.8% (n = 43) of cases, this discontinuation was inappropriate. An additional point of note, was that 50% (n = 11) of patients who developed either PCP or toxoplasma infection in 2007, were being prescribed TMX/SMX. However, compliance with medication regimes was not assessed. By the end of 2007, 57.7% (n = 348) of all patients were being offered some form of prophylaxis.

First and last CD4 cell count, last viral load, year of entry into the clinic and death were all found to be significant on bivariate analysis. The multivariate logistic regression analysis included all significant variables identified on bivariate analysis. The total number of cases entered in this model was 270 (44.7%). Only CD4 count at the end of 2007, remained a significant variable ($p = 0.015$) in a model which explained 4.2% of the variation in OI occurrence. To increase the number of cases entered in the model, VL assessments were removed. The number of cases entered in the model increased to 423 (70.1%), however, the R^2 coefficient increased to only 0.079. This coefficient was not affected by the method of entry of the variables into the model.

DISCUSSION

The majority of patients in this study presented to the HIV treatment site at very advanced stages of HIV disease, with 46.1% of patients presenting with AIDS. The average CD4 cell counts at presentation to the clinic appear to be remaining fairly constant, despite the date of entry to the clinic. Studies from both developed and developing countries have also shown similar statistics. For example, in Barbados between 2004 and 2006, Kumar *et al* were able to show that 48% of all admissions were in patients with CD4 < 200 cells/ml and that 40% of these cases had their initial diagnosis of HIV made on admission to hospital (21). Other studies (22) have shown stability in statistics including a retrospective study conducted in Italy by Manfredi *et al* highlighting no difference in the spectrum of OIs or in the level of underlying immunodeficiency at presentation between pre- and post-HAART eras (23). Other studies have presented conflicting findings. One such study from the MAC cohort revealed an 81% reduction in the diagnosis of an OI as the presenting AIDS event and a 77% reduction for secondary infections with an OI, between the pre-and post-HAART eras (4). Unfortunately, differences in the type of OIs included in these studies preclude their direct comparison. As previously discussed, increases in CD4 counts above 200 cells/ml can lead to improvements in the prognosis of HIV disease. However, the Euro SIDA study group were able to show that even after immune reconstitution, CD4 cell count nadir is still associated with significant increases in the risk for disease progression and OI development (24).

Among the study population, there was a very small percentage, 16.4% (n = 99) of VL assessments ordered at the time of enrolment to the clinic. This is in keeping with the national guidelines where VL assessments are not generally performed prior to the commencement of HAART. However, the results do mimic the CD4 findings, with presentation at advanced HIV disease, with 61.6% of patients having VL > 10 000 copies and 27.3% having VL > 100 000 copies. In a randomized study, ACTG 772, looked at the predictive value of VL assessment for the development of an OI and found that there was a RR of 2.2 for every 1 log increase in baseline VL and a RR of 15 for a 1 log increase in VL at anytime for the development of an OI (25).

By the end of 2007, the profile of the population had changed with increases in CD4 counts and decreases in VL (Table 1, 2). These findings highlight the impact of HAART on immune restoration and the invaluable contribution of specialized clinics in the care of HIV patients.

The positive benefits of prophylaxis cannot be understated. The use of cotrimoxazole especially, has been associated with prolonged life, decreases in morbidity and cost, as well as delays in HIV disease progression (2). Conversely, a lack of appropriate prophylactic regimens contributes to the development of OIs even after patients have accessed care (26). It is noteworthy that the overwhelming

majority of patients in this study, between 98–99%, were receiving appropriate primary or secondary prophylaxis respectively. The use of cotrimoxazole prophylaxis has also been associated with improved outcomes even in patients whose CD4 counts were greater than 200 cells/ml and for diseases other than PCP or toxoplasma. Several studies out of Africa have shown additional benefits from the use of TMP/SMX prophylaxis in HIV-infected persons co-infected with TB, malaria and diarrhoeal disease (27). Prophylaxis against cryptococcal meningitis still remains outside of many national guidelines especially in resource-poor settings. A Cochrane review showed efficacy of fluconazole in preventing cryptococcal infection but no overall reduction in mortality. It went on to highlight that even with the paucity of published research on the matter, areas with low disease prevalence are less likely to show cost-effectiveness (20).

The clinical manifestations of OIs in the HIV-positive population can vary widely. Therefore, definitive laboratory confirmation of diagnoses in a timely manner is very advantageous to the clinician. In this study setting, the diagnostic options for PCP are limited and mostly rely on the managing physician's clinical acumen in making the diagnosis. The introduction of tests with high sensitivities, for example immune-fluorescent assays which can indentify both cysts and trophozoite forms of *Pneumocystis jirovecii* can greatly assist the physician in making accurate diagnoses (28).

There are still aspects of treatment of OIs which need further clarification. The cessation of OI prophylaxis in patients who have shown good immune reconstitution is one area which has been receiving some attention. Several studies have been conducted involving the investigation of various OIs and the safety of cessation of prophylaxis (29–34) and guidelines have adopted these theories (16). The findings of this study indicate that these guidelines are generally also being followed at this site. The 43 cases of inappropriate discontinuation however, remain of some concern and highlight an area with room for improvement. This is not a situation unique to this site (35). Several reasons have been identified for inappropriate prophylaxis use, implicating mainly the failure to restart prophylaxis after discontinuation following immune restoration (35). The timing of HAART in patients presenting with an OI has also been a topical issue. Reports on the recent ACTG A5164 study have provided valuable insights into commencement of HAART regimes in the face of an OI (36). They were able to prove significant reductions in clinical progression and death among patients who commenced HAART within 14 days of presenting with an OI *versus* those who deferred therapy. In addition, the SAPiT (37) study was also able to prove that earlier initiation of therapy in the setting of TB co-infection lead to improved outcomes in these patients. These studies provide valuable insights into answering this important clinical issue. However, in the ACTG A5164 study, the majority of participants enrolled were diagnosed with PCP. These patients were perhaps more likely to be on steroid therapy which may impact the development of IRIS (38). Therefore, further investigation focussing on individual OIs is still needed.

The population examined in this study was limited to only those managed by the CHARES team. The patients who were admitted to the UHWI but not referred to CHARES were not included. Additionally, patients who demised before a referral could be made, generally within the first 24–48 hours post-admission, as well as those admitted to services other than to the Medical wards, were also not included. Patient selection is most likely the reason for the modest OI rate of 4.6% described in this study. The tracking of patients in this setting also provides a significant challenge but an important one to overcome for both management purposes and research. The lack of this information provides major impediments to the ability to design cohort studies with robust statistical techniques. The introduction of integrated web-based information technology systems in order to capture patient movements between clinics, loss to follow-up and death can provide this valuable information.

CONCLUSIONS

Late presentation for HIV care remains a significant barrier to improved outcomes among this HIV population and earlier diagnosis of HIV is needed to reduce the incidence of OIs. Prompt enrolment to treatment sites is needed to allow the assessment of CD4 counts and other baseline investigations and hasten the commencement of appropriate antiretroviral therapy. Timely recommended prophylaxis, both primary and secondary, can decrease the incidence of OIs and will subsequently lead to declines in HIV-related morbidity and mortality.

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APPENDICES

Table 1: Demographics based on OI occurrence

	OI Present	OI Absent	Total Population
Age	34.1 (31.6 – 36.6)	37.9 (37.1 – 38.7)	37.7 (36.9 – 37.7)
Gender M/F	39.3/60.7	46.5/53.5	46.1/53.9
CD4: – Initial	104.5 (35.3 – 186.0)	280.3(70.75 – 403.0)	233.0 (69.0 – 389.0)
– End of 2007	154.0 (35.3 – 186.0)	357.5 (235.7 – 527.5)	348.0 (217.7 – 518.0)
– At OI Diagnosis	92.0 (44.8 – 139.2)		

Table 2: Variations in viral load counts during the course of HIV disease

Percentages (%)	Percentage of Total Population	< 50	50–10 000	10 000 –100 000	> 100 000
Viral load:- Initial	16.4	18.2	20.2	34.3	27.3
– End of 2007	60.5	41.4	24.1	24.4	10.1
– At OI Diagnosis	14.3	50.0	0.0	25.0	25.0

Table 3: The use of chemoprophylaxis in the total population

	Primary Prophlaxis (%)	Secondary Prophylaxis %	Total (%)
Bactrim	41.0	10.7	51.7
Dapsone	1.0	0.7	1.7
Fluconazole	N/A	0.3	0.3

Table 4: Significant associations with opportunistic infection occurrence

VARIABLE	Percentage (%)	*p* value
First CD4 count:		0.013
– < 50	34.8	
– 50 – 200	43.5	
– 200-500	21.7	
– > 500	0.0	
Last CD4 count in 2007:		< 0.001
– < 50	25.0	
– 50 – 200	50.0	
– 200 – 500	20.8	
– > 500	4.2	
Last Viral Load in 2007:		0.036
< 10 000	35.7	
> 10 000	64.3	
Diagnosis of HIV in Pre-HAART versus Post-HAART era:		0.043
– 1998 – 2004	32.1	
– 2005	21.4	
– 2006	3.6	
– 2007	42.9	
Deceased:		< 0.001
– OI present	40.0	
– OI absent	60.0	
Deceased:		< 0.001
– PCP	75.0	
– Toxoplasma	0.0	
– Cryptococcus	25.0	