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Comorbibities, opportunistic infections, and helminth infections among HIV-positive patients at a small hospital in Delhi, India

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Abstract

Introduction: Immunosuppressed people with HIV/AIDS have increased risk for opportunistic infections (OIs), and poverty can exacerbate this risk. This retrospective cohort study describes the health situation of vulnerable patients receiving care at a small palliative care clinic in Delhi, India, pre-covid-19 pandemic by describing the most frequently occurring OIs, helminth infections, levels of ART adherence, and perceptions of stigma.

Methods: Demographic information, diagnoses, laboratory test results, and outcomes were collected for all 1,101 HIV-positive patients admitted to this clinic over a four-year period. We sampled a small subset of 120 patients for patent helminth infections between July 2016 and June 2018. In September-November 2019, 80 patients in the HBC program were surveyed regarding ART adherence, side effects, and stigma, and an unannounced pill count was conducted for 78 patients participating.

Results: The most frequently diagnosed and treated OIs were tuberculosis and candidiasis. Hemoglobin levels were higher for men than other genders ($F=5.137$; $DF=2$; $p=0.02$). Married individuals had a significantly lower average $CD4^+$ count than single people ($F=8.222$; $DF=2$; $p=0.01$) and widowed people ($p=0.01$). Most patients (59.1%; $n=652$) had $CD4^+$ counts of 350 or less, and women had significantly higher average $CD4^+$ count than men ($F=7.236$; $DF=2$; $p<0.001$). Helminth infections were present among 27 (18%) of the samples and included *Taenia* spp. (37%), *Ascaris lumbricoides* (26%), *Trichuris trichiura* (22%), hookworm (19%), *Strongyloides* spp. (7%), and *Enterobius vermicularis* (4%). Most patients (79%) were not adherent to ART based on pill count, however, 76% of the patients self-reported adherence. Half of the HBC patients surveyed reported stigma, and of those patients, 47% reported that stigma influenced their adherence.

Discussion: Our results are consistent with OIs frequently seen among PLWHA in India; however, our study population demonstrated significant rates of anemia, possibly due to medication adverse effects, anemia of chronic disease, and nutritional iron

deficiency. Knowledge of common helminth infections can inform comprehensive patient health education as helminth infections can exacerbate the effect of OIs and other health effects of HIV and its treatment, especially in situations where ART-associated stigma and side-effects may result in lower adherence than is protective.

Keywords: AIDS, ART adherence, deworming, helminths, HIV, opportunistic infections, palliative care, parasites, PLWHA

Introduction

With a population of 1.1 billion people, and one of the highest reported prevalences of HIV, India accounts for as many as one in eight of the world's HIV infections.[1,2] The National AIDS Control Program (NACP) has taken action resulting in a 37% decline in new infections and 66% reduction in deaths caused by AIDS, but the burden of HIV infections and its effects are not equally distributed.[3] The most vulnerable people in society remain at high risk for new infections and poor outcomes.[1] NACP provides free testing and treatment at Integrated Counselling and Testing Centers (ICTC).[4] However, HIV-associated stigma combined with discrimination related to poverty and LGBTQ+ identity result in disproportionately increased risk to these vulnerable populations.[1,5,6] People living with HIV/AIDS (PLWHA) fear discrimination and rejection by their family and neighbors if their status is discovered, which results in isolation and frequent delays in treatment.[7,8]

Palliative care is a form of comprehensive, supportive, medical care that is focused on the alleviation of symptoms and improvement of quality of life for all people living with chronic diseases. This wholistic support of PLWHA goes beyond the testing and provision of antiretroviral therapies (ART), as patients have a better outcome if they also have access to counseling, nutritional support, financial support, and medical interventions for opportunistic infections common with HIV/AIDS.[7] Medical providers that focus on palliative care, a wholistic approach to healthcare that focuses on maintaining or improving the quality of life for patients with chronic or serious illness (NIH), often provide the supportive interventions that positively impact the physical, mental, and spiritual wellbeing of PLWHA. In these settings, emotional healing and spiritual flourishing can take place, even alongside physical illness.

PLWHA experiencing poverty are at risk of numerous OI due to viral immune suppression[9,10] and environmental living conditions that facilitate disease transmission.[11,12,13] Soil-transmitted helminths are among the most common infections among people experiencing poverty, with more than one billion people infected,[14] and there is evidence that such infections can impact the outcome of HIV exposures and infections.[15,16] The objective of this study was to characterize the patterns of opportunistic infections (OIs) and parasitic infections among a group of vulnerable patients treated at a small palliative care clinic in Delhi, India prior to the Covid-19 pandemic. We also determined levels of adherence to antiretroviral treatment (ART) for patients in the clinic's home-based care (HBC) program in order to offer suggestions regarding the challenges of working with some of the most vulnerable HIV patients in India.

This clinic works to provide wholistic care to low-income, PLWHA in vulnerable communities, especially those who face multiple layers of stigma and marginalization, such as widows and transgender people living with HIV. This clinic has a medical staff, 10 inpatient beds, a walk-in clinic, and a home-based health care program that focuses on treatment adherence and emotional support. In addition to the medical support, this clinic also provides mental health support and education for family members affected by HIV/AIDS. By understanding patterns of opportunistic infections and parasitic infections among vulnerable populations of low-income

PLWHA, strategies for care in a resource-limited palliative care clinic can be evaluated and focused in order to provide quality care to this patient population.

Materials and Methods

This study was a retrospective cohort analysis of all 1,101 HIV-positive patients who were admitted to a small palliative care clinic in Delhi, India between January 1, 2013 and December 31, 2016. Patients of all ages and demographics were included in the sample who had an HIV-positive status and were admitted within the specified date range. Each patient's physical medical record was used to collect demographic information, all diagnoses, $CD4^+$ counts, and other relevant laboratory data, including hemoglobin (Hgb) level and tuberculosis (TB) sputum acid-fast bacilli (AFB) results. Helminth infections were determined from 120 fecal samples (10g) submitted during outpatient visits or hospitalizations between July 2016 and June 2018. During this time period, the medical staff was interested in learning more about prevalence of parasitic infections among their patients and fecal testing became routine. The on-site lab conducted flotations and direct smears to determine the presence of helminth eggs via microscopy.

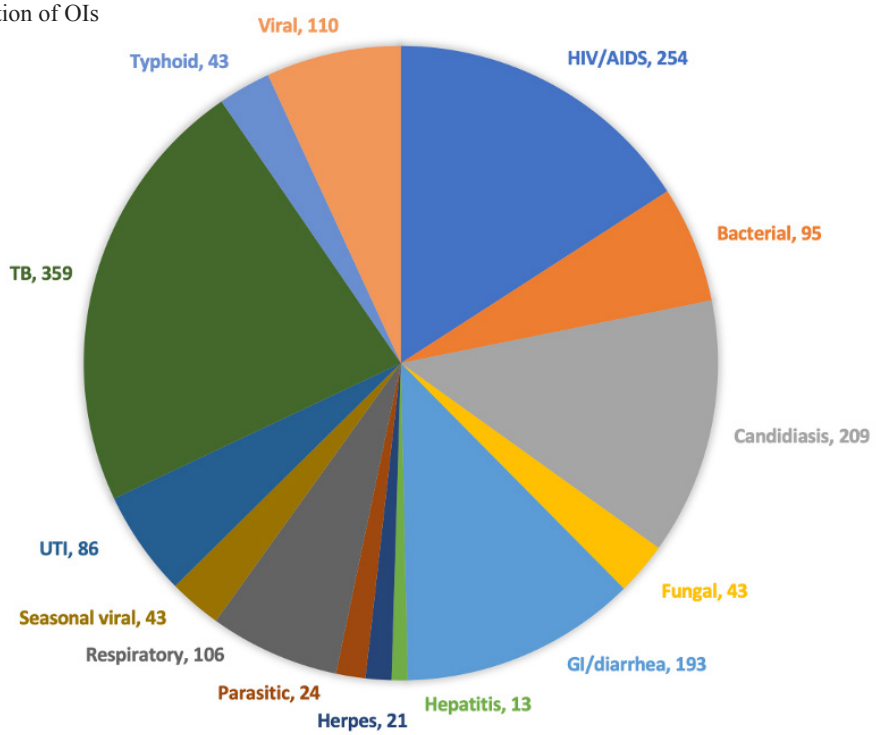
During September to November of 2019, interviews of 80 patients in the HBC program regarding adherence to ART, perceived stigma, and medicine side-effects were conducted. This portion of the study was approved by the Institutional Review Board of Wheaton College, and consent was obtained from all participants. Clinic staff were present during the interviews, and all interviews were conducted in Hindi. In addition to surveys, unannounced pill counts were conducted in 78 patients to determine adherence, defined by the clinic to be the number remaining if the patient was taking medications 100% as prescribed.

Statistical analyses were conducted using JMP (SAS) Version 14 software. Relevant tests included student's t-tests as well as chi-square tests. Sample sizes were too small to allow for statistical analysis of helminth data, so only summaries and prevalence are reported.

Results

As seen in Figure 1, the most commonly diagnosed and treated OIs were TB (n=359) and candidiasis (n = 209).

Figure 1. Distribution of OIs



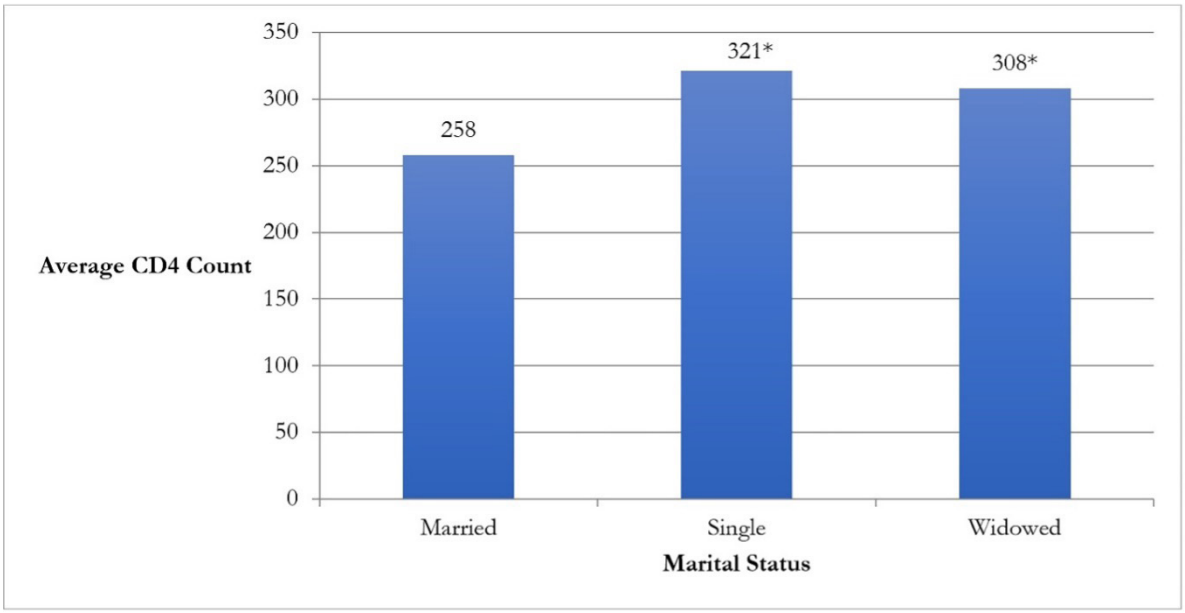
There were 173 new TB diagnoses and 186 admissions for continued treatment of previously diagnosed TB. The most frequently occurring new TB diagnoses were extrapulmonary TB (n=94) followed by pulmonary TB (n=79). In terms of specific TB diagnoses, sputum-positive pulmonary TB (n=37) had the highest number of cases, followed by sputum-negative pulmonary TB (n=31) and disseminated extrapulmonary TB (n=25). Additional frequently occurring OI diagnoses included gastrointestinal infections and diarrhea (n=193), urinary tract infections (n=86), and seasonal viruses including dengue and chikungunya (n=43). Respiratory infections including pneumonias and bronchitis formed another common group of diagnoses (n=106).

There was a seasonal pattern of infections characterized by an increase in vector-borne diseases in the late summer and fall months (X^2 Pearson=228.75; DF=110; likelihood ratio=210.33; p<0.001). Vector-borne diseases peaked in September (n=27) and had increased frequency in August (n=8), October (n=6), and November (n=6). TB was highest in April (n=46) and was elevated in the surrounding months of March (n=36) and May (n=37).

Hemoglobin (Hgb) level (g/dL) was available for 441 patients and of these, 429 (97.27%) reflected anemia with Hgb levels below the normal reference range (male Hgb >13.0 g/dL; female Hgb >12.0 g/dL).[17] Men had a significantly higher average Hgb level (n=241; mean=8.96 g/dL) than women (n=161; mean=8.35 g/dL; F=5.137; DF=2; p=0.017) and transgender people (n=38; mean=8.00; F=5.137; DF=2; p=0.01). There was a significant positive correlation between $CD4^+$ count and Hgb level: as $CD4^+$ count increased, Hgb level also increased (Bivariate linear fit F=28.488; DF=1; p<0.001).

Reliable $CD4^+$ counts were available for 925 patients; CD4+ percentage was not available. 37% of patients had $CD4^+$ counts of 200 or less (n=409), which is an AIDS diagnosis, and 59.1% had $CD4^+$ counts of 350 or less (n=652).

Figure 2. $CD4^+$ count by marital status. Significance is indicated by *.



CD4$^+$ count varied significantly by marital status and married individuals had the lowest average CD4$^+$ count (n=518; mean=258.3) (Figure 2). This is significantly lower than both the average CD4$^+$ counts of single people (n=245; mean=320.7; F=8.222; DF=2; p=0.01) and of widowed people (n=162; mean=307.7; F=8.222; DF=2; p=0.01). Female patients had a significantly higher average CD4$^+$ count (n=321; mean=318.2) than men (n=551; mean=260.4; F=7.236; DF=2; p<0.001).

The helminth infections present among 27 (18%) of the samples included *Taenia* spp. (37%), *Ascaris lumbricoides* (26%), *Trichuris trichiuris* (22%), hookworm (19%), *Strongyloides* spp. (7%), and *Enterobius vermicularis* (4%). One individual (4%) was infected with three different helminths (*Ascaris lumbricoides*, Hookworm, and *Taenia* spp.). Two individuals were infected with two helminths (7%). One had infections with *Taenia* spp. and *Ascaris lumbricoides,* and the other had infections with hookworm and *Strongyloides* spp. More helminth infections were found in samples from men (63%) than women (30%) or transgender people (22%). *Ascaris lumbricoides* infections were more common among samples from men (15%) than women (4%) or transgender people (7%). Hookworm was only found in samples from men (11%) and transgender people (7%). *Trichuris trichiuris* was more common among men (19%) than women (4%) and was not found among transgender people. *Taenia* spp. was more common among women (19%) than men (11%) or transgender people (7%). *Enterobius vermicularis* was only discovered in one sample, and it was from a woman. *Strongyloides* spp. was only found in samples from men.

According to unannounced pill counts, only 17 patients (22%) were adhering to prescribed medication doses, while 61 patients (78%) were not adherent. In contrast, 75% (n=59) reported that they were adherent. The difference in adherence based on pill-count and self-reported adherence is significant (X^2 = 4.99, df=1, p=0.0204). More than half (n=42) of patients reported that they were experiencing physical side effects, and 83% of these patients were not adherent to their ART according to pill count. In addition to physical side effects, half (n=40) of the patients reported experiencing HIV-related stigma, and 47% (n=19) of these patients reported that stigma impacted their adherence to ART.

Discussion

The patterns we observed regarding opportunistic infections were similar to what would be expected in an urban poor setting in India.[9,17,18,20] TB and candidiasis were the most frequently diagnosed and treated OIs, which is consistent with the most common OIs diagnosed among other Indian HIV patients.[9,18] Seasonal patterns of diagnoses were found that support the conclusion that vector-borne diseases follow monsoon seasonal patterns.[19,20,21] The higher average CD4$^+$ count of female patients is also consistent with findings among other HIV patients in India[18,22]; however, significantly lower CD4$^+$ counts for married people has not been reported in the literature. Patients at this clinic report feeling stigmatized and isolated by their diagnosis,[8] and this could result in delayed or inconsistent treatment, and a lack of adherence to ART.[22,23] HIV patients generally must have a > 95% adherence rate to maintain a satisfactory quality of life,[23,24] but only 22% of the home-based care patients at this clinic adhere to the prescribed protocols. When asked if stigma impacted their adherence, 47% of the patients reporting stigma stated it did impact their adherence to ART.

While patterns of OIs were not surprising, the levels of anemia (97%) were very high, and this has serious implications for the patients at this clinic. Anemia is a prevalent HIV comorbidity worldwide,[25] and is strongly linked to both HIV and TB.[26] Low hemoglobin is predictive for TB infections and morbidity from HIV-related TB.[26] The etiology of the extremely high rates of anemia in this population is multifactorial, with likely contributing factors of: anemia of chronic disease (ACD) related to HIV itself,[27] adverse effects of early generation ART such as AZT (particularly zidovudine), and antituberculosis therapy, as well as iron deficiency related to nutritional deficiencies.[28]

In fact, further evidence that first line ART could be contributing to the anemia of the patients in our study is that in a small study of this same patient population, it was found that patients taking first line ART were more likely to have chronic musculoskeletal pain, which is an indicator of anemia.[29] Understanding the levels of anemia as related to CD4 and opportunistic infections is important evidence that patients in our study may need to be transitioned to alternative HIV therapies. In fact, in the Gatenah et al. study,[28] patients experiencing anemia related to AZT were transitioned to alternate HIV therapy, and the result was a lower burden of adverse effects. The problem of anemia as it relates to opportunisitic infections like TB and ACD, unfortunately, is common among early-generation ART,[28] which are the HIV treatments readily available to patients in this study population. Patients with chronic infections and prolonged inflammation, such as HIV, are frequently affected by ACD, an inflammatory process in which hepcidin (the enzyme that regulates iron homeostasis) limits absorption of iron in the duodenum.[26] This form of anemia has been shown to be related to bacterial loads and the dissemination of TB among HIV/AIDS patients.[26] This specific form of anemia is best treated by managing the underlying cause of inflammation and treating the chronic disease itself.[27] This is reflected in our finding that there is a positive correlation between improving $CD4^+$ count and increased Hgb.

Other factors that may contribute to anemia in this population may be bone marrow suppression in the setting of acute opportunistic infections, blood loss anemia related to cancer and normal menstruation, and nutritional deficiencies due to a lack of iron-rich foods that cannot be accessed due to financial constraints in this resource-limited setting. While IV iron infusions are effective in treating iron-deficiency anemia, they can be cost-limiting. Oral iron supplementation is a more affordable alternative and is necessary to offer patients with iron-deficiency, along with treating the underlying cause of their anemia.[30]

Patients at this clinic, also, are impacted by infections with soil-transmitted helminths, which can exacerbate anemia and impact the immune system by switching the predominant immune response from the T-helper 1 (Th1)-type to the Th2-type.[16] As a result, the ability of the immune system to respond adequately to HIV is reduced, and progression of the infection could accelerate as indicated by decreasing $CD4^+$ counts.[16,31] Helminths are known to activate the Th2 cytokine profile and increase IgE levels.[31] For people living with HIV, this is important because elevated IgE levels are related to the onset of opportunistic infections.[32] The helminth-induced imbalance of Th1/Th2 profiles combined with elevated IgE levels could facilitate HIV transmission due to elevated plasma HIV.[33,34] The most common parasites seen among patients in our study were *Ascaris lumbricoides, Trichuris trichiura,* and hookworm which are also the most common helminth infections described among PLWHA. However, in our study, the prevalence of each of these infections, *A. lumbricoides* (26%), *T. trichiura* (22%), and hookworm (19%), were much higher than the 5-8% prevalence reported in a meta-analysis of global studies.[35] Each of these species have a fecal-oral transmission and are common in locations with poor sanitation. Thus, this finding is not surprising among the patients in our study who live without access to sufficient sanitation.

Quality of life could be improved by incorporating deworming protocols into healthcare strategies for HIV/AIDS patients.[36] Despite being recommended for children, systematic deworming of adult HIV patients is not common globally even though some studies demonstrate deworming can result in marked increases in $CD4^+$ or influence the outcome of TB infections.[15,37] The cost of deworming patients is relatively low,[38] and the authors have heard from patients that the opportunity to receive treatment for worm infections gives them dignity and hope that their situation could improve. Any improvement in the status of OIs that could increase energy also results in the ability to retain jobs and contribute to the

greater community.[35] The kinds of results that decrease stigma and alienation might even be the most important result of any HIV intervention. The possibility for the improvement in health status through deworming is a very low-cost addition to any health intervention and should be considered.[39]

The high frequency of both TB and anemia found in this study points to the very common situation of vulnerable populations of PLWHA. While ART is freely available in India, many people living with HIV face significant stigma and, at times, rejection in healthcare settings, which can lead to poorer health outcomes and can delay diagnosis or implementation of ART.[2] The practitioners at the clinic described in this study provide not only vital medical resources to low-income PLWHA, but they also offer dignifying, person-centered care to those who have faced rejection in familial and healthcare settings due to their HIV status, poverty, or their LGBTQ identity. Perhaps most importantly, this clinic provides hope and healing to a population in need and builds community and vital social connection through support groups and mental wellness initiatives. Those in the most vulnerable situations include women affected by HIV and cancer, who often are not able to pursue day labor given progressive illness. This organization's economic empowerment program and emergency food distribution system work to meet the needs of the most vulnerable and to mitigate the risk of further progression of disease related to hunger. While the need to provide quality medical care to people living with HIV in India remains great, funding for this work has decreased in recent years. In order to continue this organization's vital work, the staff seeks international, grant funding and crowd-source support from local church communities. The impact of this clinic's work is evidenced by the stories of patients who attribute their survival and healing to the care that these practitioners provide and the hope that has been infused into their lives. The palliative care approach taken by this clinic improves the quality of life for patients with chronic or serious illness, but more importantly results in patients who trust their caregivers. Because this clinic invests in the lives of their patients beyond the treatment of disease, they may be able to work against stigma and begin to address the problems of low adherence to ART which could improve the outcome of OIs and anemia. Patients who trust their medical providers may be more willing to maintain their treatment. The care that is provided to the patients at this clinic in Delhi, India provides a model for the ways that palliative care promotes emotional healing and spiritual flourishing and, ultimately, can improve physical health.

Conclusions

Patterns of opportunistic and helminth infections among patients cared for at this small clinic in Delhi, India are characteristic of those reported among PLWHA in India.[9,18] Additionally, patterns of CD4+ counts were consistent with findings among other patients in India.[18, 22] However, the levels of anemia (97%) were very high, and the implications for care are significant especially because the most common helminth infections found were those that exacerbate anemia. Finally, patients at this clinic report stigma associated with their diagnosis, and there is evidence that side effects and stigma contribute to a decreased adherence to ART. The work of this clinic among the significantly impoverished patients in Delhi improves the quality of life of these patients as well as empowering them to work against stigma. Palliative care provides patients with supportive medical care that is focused on alleviating symptoms and improving the quality of life going beyond testing and provision of ART. Patient outcomes at this clinic are improved because of the provisison of counseling, nutritional, and financial support. Most importantly, emotional healing and spiritual flourishing can take place, even alongside physical illness.

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