Chronic Cough in Primary Health Care Attendees, Harare, Zimbabwe: Diagnosis and Impact of HIV Infection

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Background. Cough lasting for ⩾3 weeks (i.e., chronic cough) indicates that a patient has suspected tuberculosis (TB). At the primary health care level, the spectrum of disease that causes chronic cough has not been previously investigated in a setting with a high prevalence of human immunodeficiency virus (HIV) infection.

Methods. A total of 544 adults with chronic cough were recruited systematically from 2 primary health care clinics, and they were evaluated using preset first- and second-line investigations and diagnostic case definitions.

Results. The overall prevalence of HIV infection among the study cohort was 83%. TB was the most common diagnosis, with 207 HIV-positive patients (46%) and 27 HIV-negative patients (30%) having confirmed or probable TB. Of these, 145 HIV-positive patients with TB (70%) and 20 HIV-negative patients with TB (74%) had smear-positive cases of TB. Only 17 HIV-positive and 2 HIV-negative patients had smear-negative but culture-positive cases of TB. Lower respiratory tract infections ($n = 178$; HIV prevalence, 79%) and pneumonia ($n = 87$; HIV prevalence, 89%) were the next most common diagnoses. Asthma ($n = 26$; HIV prevalence, 46%), posttuberculous disease and other fibrotic lung disease ($n = 34$; HIV prevalence, 88%), and cardiac disease ($n = 15$; HIV prevalence, 93%) were more common than were *Pneumocystis jiroveci* pneumonia and cryptococcosis ($n = 8$ and $n = 5$, respectively; HIV prevalence, 100%), and we found no cases of nocardiosis or histoplasmosis.

Conclusions. TB was diagnosed for 43% of patients who presented with chronic cough to primary health care clinics in Harare, with 71% having smear-positive disease. The findings of TB culture added relatively little to the findings of fluorescent microscopy of concentrated sputum specimens. The prevalence of HIV infection was high across a range of diagnoses, suggesting that an HIV test should be recommended in the initial investigation of chronic cough.

An integral part of the global tuberculosis (TB)–control strategy promoted by the World Health Organization is that all patients with cough for ⩾3 weeks (i.e., chronic cough) should be considered to have suspected TB and should have sputum microscopy performed for mycobacteria [1]. During the past 2 decades, TB case-notification rates in southern Africa have increased to extremely high levels, mainly because of the HIV epidemic [1, 2]. However, HIV is also likely to have increased the burden of other respiratory opportunistic infections [3–16]. There is also evidence that noninfectious causes of chronic cough, such as asthma and smoking-related lung disease, are increasing in incidence in developing countries [17–19].

The diagnosis of respiratory symptoms in Africa is generally hampered by a lack of available diagnostic facilities, particularly at the level of primary care. Because of this, previous studies of respiratory illnesses in settings with a high prevalence of HIV infection have mostly been based in hospitals [8, 9, 12–16, 20–22] or TB clinics [23–25] or have involved cohorts of patients with known HIV status in research clinics [3–5, 7, 10, 26]. The few studies that have investigated patients in

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the primary health care setting have focused on TB [27, 28] without attempting to identify other common causes of chronic cough.

The aims of the present study were to investigate, at the primary health care level in Zimbabwe, the spectrum of disease that causes cough for ⩾3 weeks and the impact of HIV infection. The proportion of cases of chronic cough that are due to TB has been reported to be very high in studies from urban settings in Kenya [27, 28], Tanzania [22], and Botswana [16]. We were also interested in the burden of smear-negative TB, because the low sensitivity of sputum smears is a prominent feature of HIV-related TB disease in Americans and Europeans [29]. Although routine case-notification data indicate an increasing burden of smear-negative TB disease in African countries with high prevalences of HIV infection [1], a number of research studies have found relatively little impact of HIV infection on the sensitivity of sputum smears among patients with TB in Africa [25, 30–33]. Undiagnosed TB is, however, an extremely common cause of death among HIV-positive Africans [34–37], so case series that are based on registered patients with TB may have underestimated the true burden of smear-negative TB disease.

METHODS

Patients. A prospective cohort of ambulatory patients was recruited from 2 primary health care clinics in Mbare, a high-density suburb of Harare, aiming for a sample size of 550 participants. Inclusion criteria were cough for ⩾3 weeks (regardless of other symptoms) and age ⩾16 years. Potential participants were excluded if they were receiving treatment for TB, had a "danger sign" requiring immediate admission to a hospital (figure 1), were unwilling to undergo confidential HIV testing, or did not usually reside in Mbare. Recruitment was limited to weekdays and to the first 5 patients with chronic cough from each clinic per day.

Investigations. All participants completed a questionnaire and provided a specimen for confidential HIV testing, with written, informed consent. Diagnostic evaluation followed a preset algorithm of first- and second-line management (figure 1). Physical examination for all patients included inspection of the skin and palate for Kaposi sarcoma, palpation for enlarged lymph nodes (biopsies of which were performed if the nodes were hard or unilateral), and full respiratory and cardiac examination.

Case definitions. Definitions are summarized in Appendix.

Radiology. Radiographs were obtained on day 1 and again on day 7 if the findings were abnormal or if clinical deterioration had occurred, and they were obtained again after 1 month for patients with TB and patients with persisting symptoms who still had not received a diagnosis. Radiographs were graded independently by 2 readers [38] without reference to the working diagnosis and with initial discrepancies resolved by consensus.

Laboratory methods. Confidential HIV testing was performed using Determine tests (Abbott), with all positive results and 1 in 10 negative results confirmed with Unigold (Trinity Biotech).

For TB microscopy, concentrated sputum smears were stained with auramine and were examined under fluorescent light independently by 2 microscopists. Slides were not reported to have positive results unless the results were confirmed with Ziehl-Neelsen stain. Mycobacterial culture was performed with Lowenstein-Jensen slopes and Kirchner's media, after decontamination with 4% sodium hydroxide. The identification of isolates was based on colonial morphology and band hybridization with IS*6110* probes following DNA extraction.

Bacterial pathogens were identified by use of Gram staining and subculture after inoculation onto blood, chocolate, and MacConkey agars. *Streptococcus pneumoniae* was identified using colonial morphology, α haemolysis on blood agar, appearance of the Gram stain, and susceptibility to optochin. *Haemophilus* species were identified on the basis of the appearance of the Gram stain, satellitism, and requirement for factors V and X for growth.

Blood and chocolate agar plates were kept for 14 days in CO_2 at 37°C for *Nocardia.* Yeasts, isolated on Sabouraud's agar, were investigated for germ tube formation, urease production, morphology on yeast extract agar, and biochemical profile if they were urease positive (bioMérieux API 20C). Potentially pathogenic, filamentous fungi growing from the inoculation point were identified by morphology and potassium hydroxide staining.

Pneumocystis jiroveci was identified from sputum specimens induced with 5% sodium chloride, using Grocott's stain and direct immunofluorescence (Merifluor Pneumocystis; Meridian). Latex agglutination (Murex; Remel) was used to detect cryptococcal antigens in diluted serum from all patients undergoing second-line investigations (figure 1).

Ethics considerations. The study was approved by the ethics committees of the London School of Hygiene and Tropical Medicine (London, United Kingdom), Biomedical Research and Training Institute (Harare, Zimbabwe), City Health Department (Harare, Zimbabwe), and Medical Research Council of Zimbabwe (Harare, Zimbabwe). Written, informed consent was obtained from all patients. Voluntary counseling and testing was made available separately and was recommended to all participants, who were then referred for follow-up care if they were found to be HIV positive.

Data analysis. Data were analyzed with STATA software, version 7.0 (STATA Corporation). Fisher's exact test was used

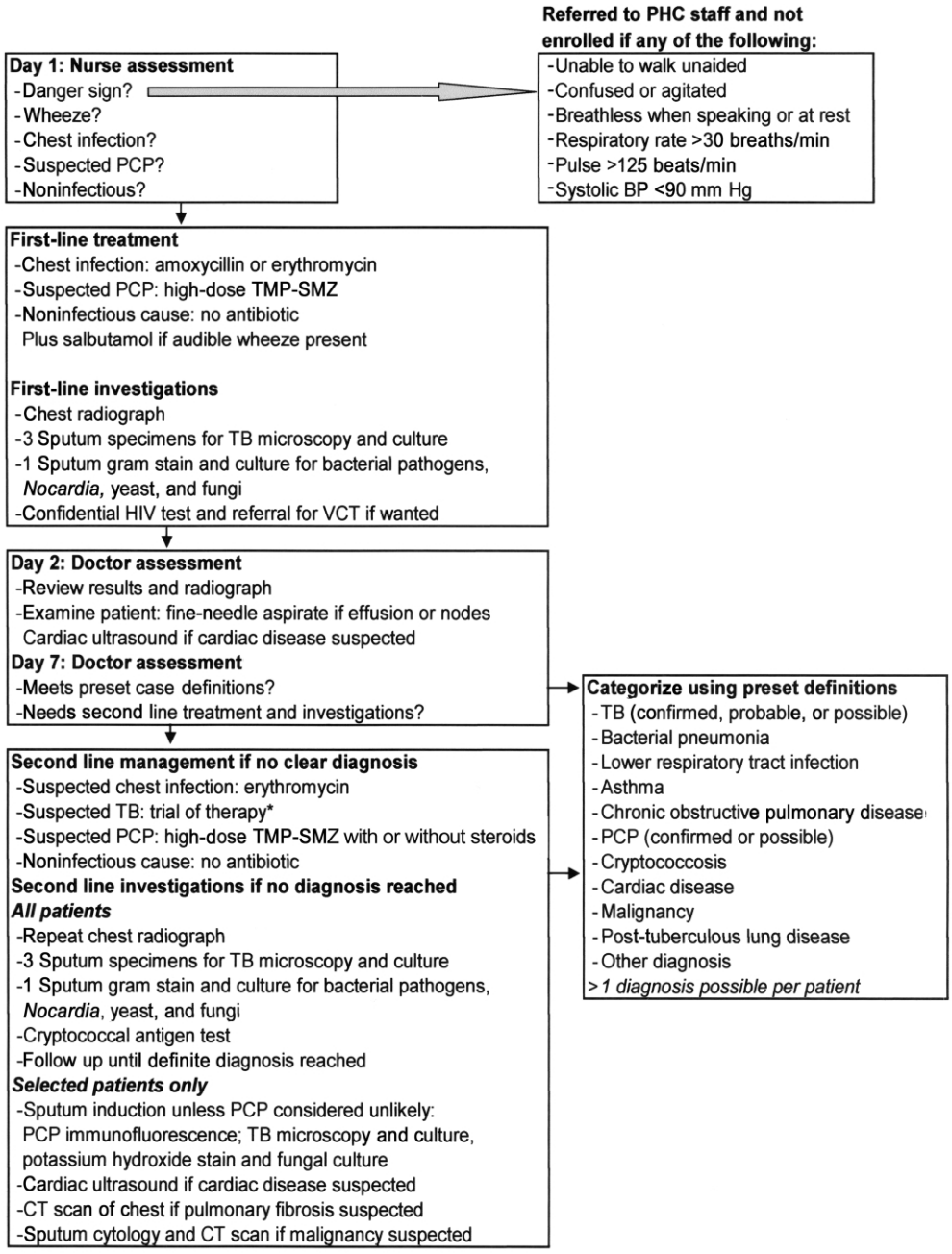

Figure 1. Summary of first-line and second-line investigations and management. TMP-SMZ, trimethoprim-sulfamethoxazole. *In accordance with National TB Programme guidelines, trials of TB treatment were with isoniazid, pyrazinamide, and ethambutol for 1 month, after which rifampicin was added to the regimens of patients who had a clinical or radiological response.

to investigate the significance of between-group differences in categorical variables. Tests for trend were calculated for variables with >2 categories by use of likelihood ratio tests. κ Tests were used to compare results of smear microscopy with results of culture.

RESULTS

Of the 550 participants recruited, there were incomplete data for 6 patients (3 were lost to follow-up after day 1, and 3 had undetermined HIV status). Baseline characteristics of the other 544 patients are shown by HIV status in table 1. The prevalence of HIV infection was 83%. The median age in both HIV status groups was 33 years. There was no significant difference by HIV status in sex, duration of cough, antibiotic treatment in the previous 3 weeks, smoking status, indoor smoke exposure, or reported household contact with a patient with TB. A total of 35% of HIV-positive participants and 34% of HIV-negative participants had received antibiotics in the previous 3 weeks,

Table 1. Baseline characteristics of participants in a study of African patients with suspected tuberculosis (TB).

Characteristic	HIV-positive participants (n = 454)	HIV-negative participants (n = 90)	P
Male sex	214 (47)	48 (53)	.3
Age, years			<.001
16–24	44 (10)	18 (20)	
25–34	225 (50)	31 (34)	
35–44	117 (26)	14 (16)	
45–54	47 (10)	9 (10)	
⩾55	20 (4)	18 (20)	
Duration of cough, weeks			.83
3–4	100 (22)	23 (26)	
4–7	121 (27)	22 (24)	
8–12	62 (14)	10 (11)	
⩾13	171 (38)	35 (39)	
Incomplete follow-up			.3
Died during diagnostic evaluation	7 (2)	0 (0)	
Lost to follow-up	5 (1)	0 (0)	
Previous TB treatment	92 (20)	5 (6)	<.001
Smoker			.79
Current	34 (7)	8 (9)	
Former	77 (17)	13 (14)	
Never smoked	343 (76)	69 (77)	
Median pack-year history if ever smoked	3	2.8	.35
Household contact of TB patient (ever)	314 (69)	62 (69)	1
Asthma ever diagnosed	7 (2)	0 (0)	.24
Received antibiotics during previous 3 weeks	160 (35)	31 (34)	1
Abnormal findings of chest radiography[a]	319 (70)	45 (50)	<.001
Symptoms and signs			
Purulent sputum	144 (32)	25 (28)	.53
Hemoptysis	90 (20)	16 (18)	.77
Felt feverish	426 (94)	73 (81)	<.001
Night sweats	415 (91)	75 (83)	.032
Loss of weight	431 (95)	75 (83)	<.001
Pyrexial[b]	345 (76)	55 (61)	.006
Respiratory rate >20 breaths/min at rest	126 (28)	13 (15)	.008

NOTE. Data are no. (%) of patients, unless otherwise indicated.

[a] Radiographs were lost before formal reading for 5 HIV-positive participants and 1 HIV-negative participant.

[b] Temperature, >37.5°C.

with the most common drugs being low-dose trimethoprim-sulfamethoxazole (121 patients), doxycycline (35 patients), and amoxicillin (31 patients). A personal history of previous TB treatment was significantly more common among HIV-positive participants (20%) than among HIV-negative participants (5%) (P < .001). Previously diagnosed asthma was rare (2% of HIV-positive participants and no HIV-negative participants). Fever, hemoptysis, weight loss, and night sweats were reported by the majority of patients, but each symptom was significantly more common among HIV-positive participants. A total of 76% of HIV-positive participants and 61% of HIV-negative participants were febrile (P = .006), and a respiratory rate of ⩾20 breaths/min was documented for 28% of HIV-positive participants and 15% of HIV-negative participants (P = .008).

The final diagnoses are summarized in table 2. HIV prevalence by diagnosis is shown in table 3. TB and bacterial chest infections were the predominant causes of chronic cough in the present study. TB was significantly more common among HIV-positive participants than among HIV-negative participants (P = .007), whereas lower respiratory tract infections

Table 2. Diagnoses according to HIV status.

Diagnosis, class or pathogen	No. (%) of participants		
	HIV-positive (n = 454)	HIV-negative (n = 90)	P
Tuberculosis	**207 (46)**	**27 (30)**	**.007**
Smear positive[a]	145 (70)[a]	20 (74)[a]	
Culture positive, smear negative	17 (8)	2 (7)	
Smear and culture negative	45 (22)	5 (19)	
Bacterial pneumonia	**77 (17)**	**10 (11)**	**.21**
Streptococcus pneumoniae	9 (12)	1 (10)	
Gram-negative bacilli	12 (16)	0 (0)	
Staphlococcus aureus	11 (14)	1 (10)	
Haemophilus species	7 (9)	0 (0)	
Branhamella catarrhalis	14 (18)	2 (20)	
Cryptococcus species	2 (26)	0 (0)	
No potential pathogen isolated	33 (43)	6 (60)	
LRTI	**140 (31)**	**38 (42)**	**.049**
Streptococcus pneumoniae	19 (14)	1 (5)	
Gram negative-bacilli	18 (13)	4 (18)	
Staphlococcus aureus	23 (16)	8 (21)	
Haemophilus species	6 (4)	2 (5)	
Branhamella catarrhalis	34 (24)	12 (32)	
Cryptococcus species	0 (0)	1 (0)	
No potential pathogen isolated	65 (46)	16 (42)	
Fibrotic lung disease	**30 (6.6)**	**4 (4)**	**.63**
Posttuberculous disease	28 (6.2)	2 (2)	
Idiopathic diffuse fibrosis	2 (0.4)	2 (2)	
Asthma	**12 (2.6)**	**14 (16)**	**<.001**
PCP	**8 (1.8)**	**0 (0)**	
Cryptococcosis	**5 (1.1)**	**0 (0)**	**.32**
Heart failure	**14 (3)**	**1 (1)**	**.3**
Cancer	**3 (0.4)**	**2 (2)**	**.13**
Pulmonary KS	0 (0)	0 (0)	
Cutaneous KS	3 (0.7)	0 (0)	
Primary bronchus	0 (0)	1 (1)	
Metastatic breast	0 (0)	1 (1)	
Other[b]	**7 (1.5)**	**2 (2)**	**.67**
Uncertain	**9 (2)**	**1 (1)**	**1**
>1 diagnosis made[c]	**57 (13)**	**9 (10)**	**.6**

NOTE. Data in boldface type indicate the numbers and percentages of patients with the specified diagnosis. KS, Kaposi sarcoma; LRTI, lower respiratory tract infection; PCP, *Pneumocystis* pneumonia.

[a] At least 1 positive result of smear confirmed by Ziehl-Neelson staining.

[b] For HIV-positive patients: severe anemia in 1 patient, pulmonary embolus in 1 patient, aspiration following cerebrovascular accident in 1 patient, and anxiety after household contact with tuberculosis (TB) in 4 patients. For HIV-negative patients: anxiety after household contact with TB in 1 patient.

[c] Multiple diagnoses were as follows. Among HIV-positive patients, TB and LRTI in 22 patients, TB and bacterial pneumonia in 3 patients, TB and asthma in 1 patient, TB and Kaposi sarcoma in 2 patients, TB and posttuberculous lung disease in 1 patient, bacterial pneumonia and asthma in 1 patient, bacterial pneumonia and posttuberculous lung disease in 9 patients, LRTI and asthma in 2 patients, LRTI and Kaposi sarcoma in 1 patient, LRTI and heart failure in 1 patient, LRTI and posttuberculous lung disease in 12 patients, LRTI and PCP in 1 patient, and LRTI and pulmonary embolus in 1 patient. Among HIV-negative patients, TB and carcinoma of bronchus in 1 patient, TB and LRTI in 3 patients, asthma and LRTI in 1 patient, bacterial pneumonia and posttuberculous lung disease in 1 patient, LRTI and posttuberculous lung disease in 1 patient, and LRTI and pulmonary fibrosis in 2 patients.

Table 3. Prevalence of HIV infection, by diagnostic category.

Diagnosis	HIV prevalence, %
Tuberculosis	88
Bacterial pneumonia	89
LRTI	79
Fibrotic lung disease	88
Asthma	46
PCP	100
Cryptococcosis	100
Heart failure	93
Cancer	60
Overall	83

NOTE. LRTI, lower respiratory tract infection; PCP, *Pneumocystis* pneumonia.

(LRTIs) ($P = .049$) and asthma ($P < .001$) were more common among HIV-negative participants. More than 1 diagnosis was given to 57 HIV-positive participants (13%) and 9 HIV-negative participants (10%).

TB was the most common diagnosis, with 207 HIV-positive participants (46%) and 27 HIV-negative participants (30%) having cases that met case definitions for confirmed or probable TB disease. Of these, 145 HIV-positive participants (70%) and 20 HIV-negative participants (74%) had ⩾1 positive result(s) of smears, and an additional 17 HIV-positive participants with TB (8%) and 2 HIV-negative participants with TB (7%) had negative results of smears but positive results of cultures (table 2). Numbers of positive results of smears versus numbers of positive results of cultures for patients with TB are shown in table 4.

Abnormal findings of radiological examinations were present for all but 5 (1 HIV-negative participants and 4 HIV-positive participants; 10%) of the 50 participants with smear- and culture-negative TB. The findings of radiological examinations were highly suggestive of TB in 38 participants (76%), with the most notable abnormality being pleural effusion in 23 participants, cavitation in 2 participants, pericardial effusion in 1 participants, miliary shadowing in 1 participant, and intrathoracic adenopathy in 11 participants. An additional 5 participants, all of whom had negative results of cryptococcal antigen tests, did not respond to empirical TB treatment and were categorized as having an uncertain diagnosis.

Bacterial pneumonia was diagnosed in 77 (17%) of the HIV-positive participants and 10 (11%) of the HIV-negative participants, and LRTIs that responded to treatment with antibiotics were diagnosed in 140 (31%) of the HIV-positive participants and 38 (42%) of the HIV-negative participants. The results of sputum cultures are shown in table 2. However, only a minority of potential pathogens isolated from sputum samples had Gram stain results that supported their clinical significance. Supportive microscopy was most often associated with pneumococcal infection, with 60% of patients with LRTIs and 40% of patients with pneumonia from whom *S. pneumoniae* was isolated having a predominance of gram-positive diplococci in the sputum sample. Evidence of significance from microscopy was much lower for gram-negative isolates (from 17% of patients with pneumonia and 9% of patients with LRTIs), *Staphylococcus aureus* (0% of patients with pneumonia and 10% of patients with LRTIs) and *Branhamella catarrhalis* (6% of patients with pneumonia and 11% of patients with LRTIs). For *Haemophilus* isolates, 71% of patients with pneumonia and 12.5% of patients with LRTIs had gram-negative coccobacilli confirmed by microscopy.

Cryptococci were isolated from the initial sputum specimens of 3 patients (2 HIV-positive patients and 1 HIV-negative patient) who recovered with the use of antibiotics alone and who were cryptococcal antigen negative and did not have any subsequent cryptococcal isolates. These patients were classified as having a bacterial disease etiology (2 patients had pneumonia, and 1 had a LRTI), with the cryptococcal isolate being of unproven significance.

Only 5 patients (1% of HIV-positive patients) had cases that met the criteria for confirmed cryptococcal disease. The diagnosis was based on cryptococcal isolates from culture in 4 patients (1 who had growth from sputum and CSF samples, 2 who had growth from CSF samples only, and 1 who had growth from lymph node aspirate only) and on the positive results of cryptococcal antigen tests and response to treatment in 1 patient. One patient had a positive result of a cryptococcal antigen test and positive results of TB smears and cultures and was classified as having TB only, although treatment with fluconazole was started for cryptococcal meningitis within 6 months.

Empirical treatment for *Pneumocystis* pneumonia (PCP) as both first-line and second-line therapy was initiated if there was a strong clinical suspicion of PCP (see Appendix). Although 13 (2.9%) of the HIV-positive patients and no HIV-negative patients were treated for PCP, only 1 case was confirmed microscopically, and, on review, only 7 of the other cases met case definitions for possible PCP.

Table 4. Smear and culture results for all patients with tuberculosis.

No. of positive results of smears	No. of positive results of cultures			
	0	1	2	⩾3
0	51	5	12	2
1	2	20	6	5
2	2	0	21	13
⩾3	0	1	1	93

NOTE. $\kappa = 0.7$; $P < .001$. Results are shown per patient, not per specimen. Up to 13 specimens were obtained from each patient.

No isolates of *Nocardia* were grown. Filamentous fungi grew at the inoculation point in 8 (9%) of the HIV-negative patients and 11 (2%) of the HIV-positive patients ($P = .007$) but were not thought to be pathogenic in any case. This includes 1 patient with a single colony of *Histoplasma* species, with no subsequent isolates on repeated cultures or cultures of induced sputum specimens.

The remaining diagnoses were those of noninfectious conditions, of which posttuberculous lung disease affected 28 (6%) of the HIV-positive patients and 2 (2%) of the HIV-negative patients. In most cases, the patients presented with an acute exacerbation. There were also 4 patients (2 HIV-positive patients and 2 HIV-negative patients) with diffuse pulmonary fibrosis of uncertain etiology. No patient received a diagnosis of chronic obstructive pulmonary disease, but a diagnosis of asthma was given for 12 (3%) of the HIV-positive patients and 14 (16%) of the HIV-negative patients. Cardiac disease was diagnosed for 14 (3%) of the HIV-positive patients and 1 (1%) of the HIV-negative patients. Cardiac ultrasonography showed cardiomyopathy in 14 patients and mitral valve stenosis in 1 patient. Other, less common conditions were cutaneous Kaposi sarcoma with no pulmonary involvement (in 2 patients), other malignancies (in 2 patients), severe microcytic anemia (in 1 patient), pulmonary embolus (in 1 patient), aspiration post–cerebrovascular accident (in 1 patient), and probable psychogenic cough following household exposure to TB (6 patients).

DISCUSSION

The present study shows a high burden of TB, cases of which were mostly smear-positive, in patients presenting to primary health care clinics in urban Harare, and an even higher burden of underlying HIV infection. TB was diagnosed for 43% of participants, and the prevalence of HIV infection was 83% overall and 88% among patients with TB. A high burden of TB in patients with chronic cough has been reported from other urban sites in this region [16, 22, 28]. Pneumonia and LRTIs, presumed to be bacterial, were also common and were strongly associated with HIV infection. TB was often complicated by bacterial superinfection, with partial response to broad-spectrum antibiotics reported by 10% of patients with TB—a potential diagnostic pitfall that has been described elsewhere [39]. Nonbacterial, HIV-related opportunistic infections that are difficult to diagnose and treat were reassuringly uncommon. The results of the present study support other findings that PCP and cryptococcosis are the most frequent opportunistic infections after TB and bacterial infections in southern Africa [8, 14, 16]. Even including treated patients whose cases did not meet case definitions, the combined prevalence of PCP and cryptococcosis was only 3%, and we found no patients with pulmonary Kaposi sarcoma, nocardiosis, or histoplasmosis. The presence of PCP in a small minority of patients with chronic cough is compatible with reports from elsewhere in the region [16, 24, 40], although the prevalence was lower than the equivalent figures from hospital-based series of inpatients with smear-negative respiratory disease [14, 21, 41].

Overall, TB was diagnosed for 43% of all participants, with 32% of all HIV-positive participants and 22% of all HIV-negative participants having smear-positive TB. HIV infection had little effect on smear status, with 70% of HIV-positive patients with TB and 74% of HIV-negative patients with TB being smear positive. TB culture results added relatively little to the results of microscopy: only 3.7% of HIV-positive participants and 2.2% of HIV-negative participants received a diagnosis of smear-negative but culture-positive TB disease. This outcome is likely to reflect the sensitivity of the microscopy techniques used (i.e., concentrated smears examined under fluorescent microscopy by 2 readers) and the protocol encouraging frequent collection of sputum specimens until TB disease was confirmed or excluded. Similar findings of a high prevalence of smear-positive disease in both HIV-positive patients with TB and HIV-negative patients with TB and a low added yield from culture have been made by other research groups who used highly sensitive microscopy in Africa [27, 30, 42, 43].

Limited access to TB culture is often perceived as being a major obstacle to diagnosis of TB in resource-poor settings. TB culture, however, is technically demanding, and the management of results is also logistically demanding because of the high potential for delayed and false-positive results. The findings from the present study would be more supportive of a move toward improving the sensitivity of smears, with radiology, and not culture, as the second-line investigation. Radiological abnormalities were present for 68% of participants overall and for 91% of patients with TB. For smear-negative patients with TB, radiological abnormalities were present for 87% and were strongly suggestive of TB for 76%, whereas results of cultures were positive for only 28%. Operational research to identify the most cost-effective approach to TB diagnosis is needed, particularly in countries like Zimbabwe that have a high prevalence of HIV infection but low rates of primary drug-resistance in patients with TB [44].

Patients with smear-negative TB outnumbered patients with nonbacterial opportunistic infections by >5-fold, but special consideration of PCP and cryptococcosis is still needed. Cryptococcosis is becoming more relevant with the increasing access to fluconazole in Africa. PCP is a relatively uncommon opportunistic infection among African adults [45], but the infection responds well to a low-cost and ubiquitous antibiotics if treatment is started early; symptoms progress rapidly and case-fatality rates increase considerably when the diagnosis is delayed. There is considerable overlap in the clinical and radiological features of TB and PCP [46], and liberal use of

empirical PCP treatment has become standard practice in Zimbabwe, even when HIV status is unknown, because of the grave consequences of delayed diagnosis. Our diagnostic algorithm allowed for treatment for PCP among patients not known to be HIV negative who had a combination of predetermined symptoms and signs, including fever and exertional dyspnea [46]. Treatment was given to a small minority of patients, most of whom responded well to therapy. PCP was only confirmed in 1 patient, but we used microscopy of induced sputum samples and not bronchoscopy, and so were anticipating a low diagnostic sensitivity [47]. Current guidelines for investigation of chronic cough do not include clinical criteria for the trial use of PCP treatment during the diagnostic evaluation [48]. The consistent identification of PCP in a minority of African patients with suspected TB and consistent identification of exertional dyspnea as a distinguishing feature between TB and PCP suggest that this would be a valuable addition that would rationalize an already common practice and may improve patient outcomes [16, 21, 24, 40, 41, 46].

Limitations of the present study are that bronchoscopy was not available (although sputum induction was), that we excluded patients who required immediate hospitalization, and that we did not enroll participants outside of normal working hours or during weekends. The results of the present study cannot, therefore, be generalized to patients with chronic cough who are acutely ill or are in a critical condition at the time of presentation. There is also potential for recruitment bias to have occurred, because enrollment was restricted to 5 patients per day per clinic. However, one clinic rarely had as many as 5 patients presenting with chronic cough on any one day, and the other rarely had <10 patients. The results from the present study may not be applicable to rural areas, where TB may be a much less prominent pathogen [7].

With these limitations in mind, the present study and several other studies have found TB to be the single most common cause of chronic cough in urban settings with a high prevalence of HIV infection [16, 22, 28]. Our data support the continued use of diagnostic algorithms based on the results of smear cultures, radiology, and the response to antibiotics in resource-poor settings with a high prevalence of HIV infection, but the data highlight the need to add a trial of PCP treatment for patients with smear-negative TB who report experiencing dyspnea. Also apparent is the urgent need to increase capacity for HIV testing at the primary health care level and to move toward HIV testing before rather than after the final diagnosis is made, because the impact of HIV was apparent across a wide range of diagnoses [49].

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APPENDIX

CASE DEFINITIONS USED DURING THE PRESENT STUDY

Confirmed TB: Two or more positive results of sputum smears or cultures, plus compatible illness.

Probable TB: One positive result of sputum smear and/or positive result of culture with compatible clinical or radiological illness, failure to respond to broad-spectrum antibiotics, and response to TB treatment by 1 month.

Probable smear- and culture-negative TB: Either (1) suggestive radiological disease (such as pleural effusion), failure to respond to broad-spectrum antibiotics, and radiological response to TB treatment by 1 month, or (2) clinical features suggestive of TB (e.g., drenching night sweats and progressive weight loss) with nonspecific or no radiological changes; no other cause found during first-line and second-line investigation; no response to first-line and second-line treatment with broad-spectrum antibiotics; clinical response to TB treatment by 1 month.

Bacterial pneumonia: Presenting symptoms that included ⩾2 of the following: fever, purulent sputum, pleuritic chest pain, leucocytosis plus airspace consolidation observed on radiographs of the chest performed at presentation, in addition to symptoms and radiological changes resolving with broad-spectrum antibiotics. Patients with cases meeting these definitions were followed-up after 8 weeks and were discharged if their symptoms had resolved and the results of TB cultures were negative.

LRTI: Same as definition of bacterial pneumonia, but with no radiological changes.

Definite PCP: *Pneumocystis* organisms detected in induced sputum specimens.

Possible PCP: HIV infection, exertional dyspnea, elevated respiratory rate at rest or minimal exertion, bilateral midzone ground-glass or interstitial shadowing, radiological and clinical response to high-dose trimethoprom-sulfamethoxazole.

Definite pulmonary cryptococcosis: Compatible radiological changes plus *Cryptococcus neoformans* isolated from sputum or CSF samples, in addition to radiological response to fluconazole.

Possible pulmonary cryptococcosis: Compatible radiological changes with positive results of a serum cryptococcal antigen test at 1:8 dilution or higher or *Cryptococcus* species grown

from CSF samples, in addition to radiological response to fluconazole by 1 month with no other cause of symptoms found.

Bacterial empyema: Pleural effusion with evidence of pyogenic infection on microscopy or culture.

Bronchial asthma: With or without acute respiratory tract infection: a history of recurrent wheeze or chest tightness on waking, sleeping, or during exercise; audible wheeze at examination; and symptomatic relief achieved through the use of oral salbutamol.

Chronic obstructive pulmonary disease: With or without accompanying respiratory tract infection: a history of cigarette smoking and at least 2 indications of chronic respiratory illness (i.e., recurrent wheeze, chest tightness, or breathlessness limiting ability to exercise during the previous 12 months; cough productive of sputum of at least 3 months' duration during the past 2 or more years; and radiological evidence of hyperinflation).

Pulmonary Kaposi sarcoma: Biopsy-confirmed palatal or cutaneous Kaposi sarcoma and suggestive radiographic abnormalities that failed to resolve with treatment with broad-spectrum antibiotics and for which no other cause was found.

Posttuberculous lung disease: History of previous TB treatment with static radiological changes of focal scarring or bronchial wall thickening and >2 previous chest infections requiring antibiotics since the time that TB treatment was completed, in addition to production of purulent sputum during infections.

Cardiac cause: Clinical findings of cardiac failure and evidence of cardiomyopathy or valve lesions found on cardiac ultrasound examination.

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