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HIV INFECTION AND *MYCOBACTERIUM TUBERCULOSIS* DRUG-RESISTANCE AMONG TUBERCULOSIS PATIENTS IN BURKINA FASO, WEST AFRICA

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RUNNING TITLE: CO-INFECTION WITH HIV AND MDR-TB IN BURKINA FASO

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ABSTRACT

The aim of this study was to compare the drug-resistance patterns of *Mycobacterium tuberculosis* strains among pulmonary tuberculosis patients, according to their HIV serostatus, in Burkina Faso. Tuberculosis (TB) patients were classified in new and previously treated cases by using a structured questionnaire. Susceptibility testing to isoniazid, streptomycin, rifampicin and ethambutol was done by the proportion method. Association between HIV-serostatus and drug-resistant TB was assessed with χ^2 tests, and the statistical significance was set to $P<0.05$. Of 316 (249 new, 67 previously treated) patients included in the study, 68.7% were males and 28.8% were HIV-positive; females (36.4%) were more infected than males (25.3%), ($P=0.04$). The average age of the patients was 37.24±12.76 years [11-75years]. Most of the patients infected with HIV were aged from 15 to 44 years and were females, ($P=0.01$). In the new cases of TB, the difference between HIV-positive and HIV-negative patients was not statistically significant neither for the MDR-TB ($P=0.40$), nor for the resistant-TB to any drug ($P=0.26$). However, the difference was significant for the resistance to isoniazid and streptomycin alone ($P=0.04$). Among the previously treated patients, although there was more MDR-TB and more resistance to any drug in HIV-negative patients than among HIV-positive patients, these differences also were not statistically significant ($P=0.54$ and $P=0.63$, respectively). This study found no significant difference between TB/HIV-negative and TB/HIV-positive patients according to the resistance patterns to anti-TB medications, excepted the resistance to isoniazid in new cases and to isoniazid and streptomycin in all patients took globally. These results encourage the collaboration between the programs against TB and HIV to prevent rapid diffusion of drug-resistant TB and high mortality in patients living with HIV/AIDS as recommended by the World Health Organization.

Keywords: Tuberculosis, HIV, Drug resistance, Burkina Faso

INTRODUCTION

Tuberculosis (TB) is one of the most important opportunistic infections in people living with the human immunodeficiency virus and AIDS (PLHIV/AIDS). The increase of TB cases worldwide was attested by the World Health Organization (1); every second, one new person in the world is infected with *Mycobacterium tuberculosis* and nearly 1% of the world population is newly infected annually. Almost 9 million people develop the disease while 3.4 million die of it. Overall nowadays, one third of the world population is infected and 22 countries account for 80% of cases worldwide. Nearly 2 million annual cases of TB occur in sub-Saharan Africa (1, 2). Since 2009, this region is the most affected by the epidemic of HIV infection in the world. Despite the efforts, the epidemic is stable overall and the number of new infections continues to exceed the number of people put on antiretroviral treatment (3). The epidemic of AIDS contributes to worsen the impact of TB but the extent of the increase varies in different studies (4-6). TB and HIV infection are in fact a complex co-infection; the PLHIV/AIDS are 50 times more likely to develop TB during their lifetime than HIV-negative patients since TB is an early manifestation of infection by HIV (5, 7). TB is the leading cause of death in people infected with HIV. Every 3 minutes, a person with HIV dies of TB worldwide. The negative relationship between TB bacilli resistant to antibiotics and HIV infection has been reported in some parts of the world. Given the poor adherence to TB treatment and the weakness of health systems, the growing epidemic of multidrug-resistant TB (MDR-TB) in HIV-positive patients in the world is a challenge that requires immediate action. PLHIV/AIDS are in fact more likely to be infected by mycobacteria including drug-resistant strains. In addition, HIV infection greatly increases the fatality rate of MDR-TB and ultra drug resistance (XDR) (8, 9). Several countries have reported increasing rates of drug resistance, but in most of low-income countries, the magnitude of the problem remains unknown.

In Burkina Faso, 33,437 new cases of TB including all forms, were diagnosed in 2007, with an incidence of 226 cases per 100 000 habitants. This represents 60% of acid fast bacilli (AFB) smear-positive (10). Recent studies have revealed the prevalence of co-infection with *Mycobacterium tuberculosis* and HIV to 31.6% (11). Few studies have been devoted to assessing the resistance of *M. tuberculosis* in TB patients infected with HIV and it is only recently that research on drug-resistant TB began to take a reasonable size.

The aim of this study was to compare the patterns of resistance to anti-TB drugs according to the HIV serostatus of the patients in Burkina Faso, a country where the prevalence of HIV infection is decreasing.

PATIENTS AND METHODS

Patients and study setting

Between April 2005 and September 2006, 316 TB patients who had accepted to be tested for antibodies to HIV, were identified by smears sputa microscopic and cultures. They were included consecutively in two great public centers, "Centre National de Lutte Antituberculeuse" (CNLAT) in Ouagadougou, "Centre Regional de Lutte Antituberculeuse" (CRLAT) in Bobo-Dioulasso, and in two other centers, Dori Hospital Centre and Gorom-Gorom Medical Centre. The careful examination using a structured questionnaire was used to classify the patients into "new" and "previously treated" tuberculosis cases. The study was carried out under anonymous conditions and both Review Board of the University Hospital "CHU Yalgado Ouedraogo" and the National Ethics Committee approvals were obtained.

General laboratory procedures

TB was confirmed by culture; drug susceptibility testing (DST) of *Mycobacterium tuberculosis* complex (MTC) strains as well as HIV-serostatus testing were performed. The non-consenting patients, those with a history of TB treatment has failed to classify them as "never treated" or "already treated", those infected with non-tuberculous mycobacteria (NTM) and patients with bacilli with unknown bacteriological profile were not included in the study.

Bacteriological investigations

Standard procedures were used according to the practice in the country. AFB sputum microscopy, cultures, identification and first-line drugs susceptibility testing (DST) in complex *M. tuberculosis* strains were performed at the CNLAT laboratory. After microscopic analysis, specimens were sent by other Centres to CNLAT laboratory for cultures and DST. They were homogenized and decontaminated using the method of Petroff. The pellet was then inoculated into four media of Lowenstein-Jensen (LJ), including one with 0.4% sodium pyruvate (LJ+Pyruvate) and another one with thiophene-2-carboxylic acid (LJ+TCH). The tubes were incubated and examined after 3 days and then weekly during three months. The isolates were identified by acid-fast stain, growth rate, morphology, resistance to TCH, growth on LJ+Pyruvate and reactions to usual biochemistry tests (niacin, nitrate reductase, catalase activity at 22°C and 70°C). Drug susceptibility testing (DST) was performed by a simplified version of the proportion method described elsewhere (12, 13). The following drugs have been tested: isoniazid (0.2µg/ml), streptomycin (4µg/ml), rifampicin (40µg/ml), ethambutol (2µg/ml). The *M. tuberculosis* H37 ATCC 27294 strain was used for the quality control in DST. Proficiency testing for culture and identification were done in collaboration with the National Reference Center for Mycobacteria in Borstel (Parkallee Borstel, Germany): 10 strains of *M. tuberculosis* Complex strains were used for this control.

HIV testing

A blood sample was collected for HIV testing after counselling and consent had been obtained from the patients. All patients were reassured of the confidentiality of their results. Two rapid tests were performed according to the UNAIDS/WHO recommendations (14): the blood sample was first tested using the Determine™HIV-1/2 (Inverness Medical, Courbevoie Cedex, France). Afterwards, the positive samples were tested with ImmunoComb®II BiSpot HIV-1&2 (PBS Orgenics, Courbevoie Cedex, France) to discriminate among HIV-1, HIV-2, and dual-reactive. Any sample that was nonreactive on the first assay was considered HIV negative.

Statistical analysis

The standard chi-square tests (χ^2) were used to assess statistical relationships between HIV-serostatus and drug-resistant TB by using SPSS 15.0 (SPSS Inc., Paris, France). Linear-by-linear association or likelihood ratio was used to interpret the values. The statistical significance was set at $P<0.05$.

RESULTS

Patient Characteristics

This study did not include patients with negative or uninterpretable cultures, unknown HIV-serostatus in non-tested patients, or infected by nontuberculous mycobacteria. Thus, the population of study comprised 316 patients infected with strains of *M. tuberculosis* complex (MTC) and having DST results. Of the 316 patients examined, 249 were new cases and 67 were previously treated patients. In the latter group of patients, 14 (20.9%) were relapses, 8 (11.9%) returned to treatment after default and 45 (67.2%) were failures. These failures included 31 chronic cases and 14 failures in the 5th and 7/8th months. Among the 316 patients, 217 (68.7%) were male and 99 (31.3%) female. The average age was 37.24±12.76 years [range: 11-75

years]; 25 (14.9) patients were less than 25 years old, 190 (60.1%) were aged from 11 to 44 years and 79 (25%) were more than 44 years old (Table 1).

HIV serostatus of the patients

HIV-serostatus of the patients according to their sex and group age is shown in table 1. Of 316 patients, 91 (28.8%) were HIV-positive, including 78 of the 249 new cases and 13 of the 67 previously treated patients. Globally, female patients (36.4%) were more infected by HIV than male (25.3%), and this difference according to genders was statistically significant (*P=0.04)*. The rate of HIV infection was higher in patients being less than 44 years than in those aged of 45 years old and more.

TABLE 1 HIV SEROSTATUS OF PATIENTS ACCORDING TO THEIR GENDER AND AGE GROUPS

Gende	Age	New cases *(N=249)*			Previously treated *(N=67)*			All patients *(N=316)*		
		HIV+ (%)	Total	*P valu*	HIV+ (%)	Total	*P*	HIV+ (%)	Total	*P*
Male	≤25	4 (16.7)	24		0	6		4 (13.3)	30	
	25-44	31(31)	100	*0.33*	4 (14.8)	27	*0.34*	35 (27.6)	127	*0.223*
	>44	14(28.6)	49		2 (18.2)	11		16 (26.7)	60	
	Total	*49(28.3)*	*173*		*6 (13.6)*	*44*		*55 (25.3)*	*217*	
Female	≤25	3 (21.4)	14		0	3		3 (17.6)	17	
	25-44	24 (47.1)	51	*0.06*	7 (58.3)	12		31 (49.2)		*0.001*
	>44	2 (18.2)	11		0	8		2 (10.5)	19	
	Total	*29 (38.2)*	*76*		*7 (30.4)*	*23*		*36 (36.4)*	*99*	

Drug resistance according to HIV-serostatus

The drug-resistance rate in TB patients according to their HIV-serostatus is shown in Table 2. Seventy-eight (31.3%) patients among the new cases were HIV-positive: among them, 0.8% was MDR versus 2% in TB/VIH-negative *(P=0.40)*. Ten (4%) TB/HIV-positive and 17 (6.8%) TB/HIV-negative were resistant to any drug *(P=0.26)*; 6 (2.4%) TB patients HIV-positive and 4 (1.6%) HIV negative were resistant to isoniazid and streptomycin alone; the rates of resistance to isoniazid was statistically significant *(P=0.046)*.

Thirteen (19.4%) of the 67 patients previously treated were HIV-positive. There was more MDR-TB in HIV-negative patients (n=30; 44.8%) than in HIV-positive patients (n=6; 8.9%), and this difference was not statistically significant (*P=0.54)*. Eight (11.9%) TB/HIV-negative were resistant to all or any drug versus 37 (55.2%) in HIV-negative patients *(P=0.63)*.

According to genders, 4.6% of male and 8.1% of female, all HIV-positive, were resistant to any drug *(P=0.27* and *P=0.85*, respectively).

DISCUSSION

According to the UNAIDS' report on the global HIV/AIDS epidemic in 2007, women were more infected than men: 61% of adults living with HIV in sub-Saharan Africa were women, while this rate was 58% in 2004 and 37% in 2001(15). In this study realized in Burkina Faso, females TB patients also were more infected than males, particularly those aged from 15 to 44 years old.

Concerning the DST results in Table 1, the most notable results and most disturbing are the high resistance to any anti-TB and multidrug resistance (MDR) observed in previously treated cases, although the resistance rates were not significantly different in both groups of HIV-positive and HIV-negative. The resistance in HIV-positive new cases is lower than in HIV-negative patients. The high rates of resistance to INH and streptomycin STM are frequent within the strains of MTC. These strains were subjected for a long time to the pressure of antibiotics, what resulted in a more important resistance to INH and STM (16). In Burkina Faso, the combinations of anti-TB drugs include these antibiotics; the health workers have to remind themselves that 10% of the TB patients are spontaneously resistant to INH. As it is retained in standard treatments, patients and health workers must take greater control of all treatments started to avoid the maximum loss of generators and irregular treatment resistance. Resistance to streptomycin was also high but this drug is replaced in the second phase by ethambutol. In this study, the resistance rate to anti-TB drugs in HIV-negative and HIV-positive patients was not statistically different according to genders and age ranges, suggesting that the epidemiology of resistance at the phenotypic level in West Africa is similar. With or without HIV, the treatment success of patients with MDR tuberculosis is lower than that of drug-susceptible cases, but nevertheless it reached 70% (17).

Although the rates of TB/HIV co-infection and resistance strains to anti-TB were high in our patients (28.8%), MDR-TB was not significantly associated with HIV infection; this corroborates the

results of other African studies (18-20). It is possible that many cases are not detected in patients with HIV because all AFB-positive identified patients were not included in the study; more particularly those who had refused HIV serological testing, which is always done in patients who accept it after their counselling. The TB patients included in the study were not under antiretroviral treatment when they had been diagnosed as HIV-positive. Contrary to our results, those obtained in industrialized countries had found a significant association between HIV infection and MDR-TB (21-24). The association between HIV infection and drug-resistant tuberculosis is complex and multifaceted (25, 26). HIV co-infection in TB patients is not believed to increase the rate at which spontaneous resistance-conferring mutations occur. However, it might increase the number of mutants that arise overall by enlarging the pool of individuals with active tuberculosis disease (27).

TABLE 2: COMPARISON OF TB PATIENTS ACCORDING TO HIV SEROSTATUS AND THE RESISTANCE TO FIRST-LINE ANTI-TB THERAPY

Resistance	Resistance in New cases			Resistance in Previously treated cases			Resistance in All patients		
	HIV+ (n=78)	All cases (N=249)	*P value*	HIV+ (n=13)	All cases (N=67)	*P value*	HIV+ (n=91)	All cases (N=316)	*P value*
To all drugs	10 (4)	29 (11.6)	-	8 (11.9)	45(67)	-	18 (5.7)	74 (23.4)	-
To each drug									
H	8 (3.2)	20 (8)	*0.39*	8 (11.9)	37(55.2)	*0.63*	16 (5.1)	65 (20.6)	*0.39*
R	1 (0.4)	7 (2.8)	*0.29*	6 (8.9)	30(44.8)	*0.54*	7 (2.2)	43 (13.6)	*0.04*
E	1 (0.4)	7 (2.8)	*0.29*	6 (8.9)	30(44.8)	*0.54*	7 (2.2)	43 (13.6)	*0.04*
S	4 (1.6)	13 (5.2)	*0.98*	7 (10.4)	24(35.8)	*0.54*	11 (3.5)	44 (14)	*0.56*
Monoresistance									
H only	6 (2.4)	12 (4.8)	*0.09*	0	2(2.9)	-	6 (1.9)	12 (3.8)	*0.99*
R only	0	0	-	0	0	-	0	0	-
E only	0	1 (0.4)	-	0	0	-	0	1 (0.3)	-
S only	2 (0.8)	6 (2.4)	*0.90*	0	0	-	2 (0.6)	6 (1.9)	*0.797*
Total	8 (3.2)	19 (7.6)	*0.14*	0	2(2.9)	-	8 (2.5)	19 (6)	*0.18*
MDR									
RH	0	2 (0.8)	-	0	5 (7.5)		0	7 (2.2)	-
RHE	0	0	-	1 (1.5)	4 (5.9)	*0.53*	1 (0.3)	4 (1.3)	*0.80*
RHS	0	0	-	0	0	-	0	0	-
RHES	1 (0.4)	4 (1.6)	*0.94*	5 (7.5)	27(40.3)	*0.50*	6 (1.6)	31 (9.8)	*0.13*
Total	1 (0.4)	6 (2.4)	*0.4*	6 (8.9)	36(53.7)	*0.54*	7 (2.2)	42 (13.3)	*0.05*
Other patterns									
HE	0	2 (0.8)	-	0	3 (4.5)	-	0	5 (1.6)	-
HS	1 (0.4)	2 (0.8)	*0.58*	2 (2.9)	2 (2.9)	-	3 (0.9)	4 (1.3)	*0.040*
HSE	0	0	-	0	2 (2.9)	-	0	2 (0.6)	-
RE	0	0	-	0	0	-	0	0	-
RS	0		-	0	0	-	0		-
RES	0	0	-	0	0	-	0	0	-
ES	0	0	-	0	0	-	0	0	-
Total	1 (0.4)	4 (1.6)		2 (2.9)	7 (10.4)		3 (0.9)	11(3.9)	
Resistance to									
1 drug	8 (3.2)	19 (7.6)		0	2 (2.9)		8 (2.5)	21 (6.6)	
2 drugs	1 (0.4)	6 (2.4)		2 (2.9)	10(14.9)		3 (0.9)	16 (5.1)	
3 drugs	0	0		1 (1.5)	6 (8.9)		1 (0.3)	6 (1.9)	
4 drugs	1 (0.4)	4 (1.6)		5 (7.5)	27(40.3)		6 (1.6)	31 (9.8)	
Total	10 (4)	29 (11.6)	*0.26*	8 (11.9)	45(67)	*0.63*	18 (5.7)	74 (23.4)	*0.60*

H: isoniazid; R: rifampicin; E: ethambutol; S: streptomycin; MDR: multidrug-resistance;

If immunosuppression is not very advanced, then the response to anti-TB treatment is usually similar in HIV-negative and HIV-positive patients, whereas HIV-positive patients have greater risk of suffering from drug toxicity and to die during the treatment (20, 28). This is well illustrated by the study conducted in KwaZulu-Natal in South Africa (29). The possible association between HIV and drug-resistant MTC strains can be mainly explained by the fact that antiretroviral treatment could interfere with anti-TB drugs and make them less effective, or lead to resistance to these drugs (30). Patients with HIV-associated TB could have diminished adherence to treatment due to increased pill burden, overlapping toxic effects (31, 32). There is also the problem of malabsorption; therefore, they are prone to having subtherapeutic concentrations of anti-TB drugs (33).

Often there is a dilemma when the treatment of TB/HIV-positive cases was not well codified: treat TB first or treat TB and HIV together, knowing that some antiretroviral drugs interfere with TB drugs (34). The protease inhibitors and non-nucleoside reverse transcriptase inhibitors are known to interact with rifampicin, a drug included in many major associations for the treatment of TB.

In this work in Burkina Faso, the HIV testing was done during the study without knowledge on the patients' serostutus before. Moreover, it was possible that HIV-positive patients and those having drug-resistant TB shared similar risk factors, such as the environmental conditions. Indeed, many outbreaks of drug-resistant TB were triggered in areas where relatively large numbers of HIV infected people were in close contact with each other, such as hospitals or prisons. However, information regarding the transmission of tuberculosis in these settings can be used to predict the spread of drug resistant tuberculosis in the general population. HIV infection and TB form a lethal combination when the degree of immunosuppression is advanced (5, 35). Studies of outbreaks in the early 1990s could show that patients with the acquired immunodeficiency syndrome (AIDS) and multidrug-resistant tuberculosis had a median survival of 4 to 16 weeks (36, 37).

This study had not found a significant difference between TB/HIV-negative and TB/HIV-positive patients according to the resistance patterns to anti-TB medications, excepted the resistance to INH in new cases and to INH and STM in all patients took globally. Indeed HIV infection increases TB epidemiology, but it cannot be responsible for the MDR-TB resurgence. Other serious factors may be implicated.

To reduce the number of people with this dual infection, it is important to diagnosis contagious pulmonary TB patients early and to prevent transmission in the places where infected people are in close contact with each other, such as hospitals and prisons. Collaboration between the better and stronger programs against TB and HIV is needed to prevent rapid transmission of drug-resistant tuberculosis and high mortality in communities heavily affected by HIV. To this end, the WHO has recommended expanding the scope of collaborative TB/HIV (10).

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