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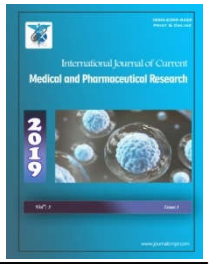

PRIMARY RESISTANCE OF MYCOBACTERIUM TUBERCULOSIS TO ANTI-TUBERCULOSIS DRUGS IN PERSON LIVING WITH HIV (PLHIV) IN KINSHASA/DRC

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ABSTRACT

Background: Up-to-date knowledge of the extent of TB drug resistance in general, and particularly among Person Living with HIV, is important in setting up adequate measures of prevention and control of the disease.
Objective: To determine the frequency and pattern of primary anti-TB drug resistance among HIV-positive individuals in two centers in Kinshasa.
Methods: The sputum of smear-positive tuberculosis patients living with HIV were seeded in Lowenstein Jensen medium and the susceptibility of strains to TB drugs were determined by the proportion technique. The comparison of the data was performed using the Chi-square test or Fisher's exact test as appropriate.
Results: Sixty-eight strains of Mycobacterium tuberculosis, and 2 africanum were isolated from PLHIV. Of these, 38 were resistant to at least one of six anti-tuberculosis drugs tested. Both strains of M.africanum were susceptible to all antituberculosis drugs. Monoresistance was greater for Isoniazid (15.7%) and Streptomycin (10%). On the other hand, that of ethambutol, of loxacin and kanamycin were respectively 1.4%, 4.3% and 2.9%. The frequency of MDR-TB strains was around 4.3% in PLHIV.
Conclusion: The high frequency of primary resistance and the presence of multidrug resistance in PLHIV justify extension of surveillance to the rest of the country in order to define appropriate strategies response.

INTRODUCTION

Resistance to antituberculosis drugs threatens to compromise the effective control of tuberculosis (TB) worldwide, particularly in Africa, where very high levels of resistance is found [1]. The inappropriate use of antituberculous drugs leads to the emergence of multidrug-resistant (MDR-TB) and extensively drug-resistant (XDR-TB) strains of Mycobacterium tuberculosis that may endanger the World Health Organization (WHO) target of eradicate tuberculosis (TB) in the world by 2035 [1-7].Drug-resistant TB is a constant threat, and in 2016 there were 600,000 new cases of resistance to rifampicin (the most effective first-line drug), including 490,000 cases of multidrug-resistant TB [1]. The magnitude of these strains in the population requires early diagnosis to allow rapid implementation of appropriate treatment that improves the patient's prognosis while reducing the risk of transmission of resistant strains that leads to primary resistance defined as a resistance occurring in a patient who has never been treated before or who has been treated for less than 1 month [1-10]. It is therefore a reflection of the importance of the reservoir of resistant strains among the cases already treated and its frequency varies from region to region in the world [1-11].

The Democratic Republic of Congo (DRC), with a population of 79 million, is one of the countries with a high burden of

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drug-resistant tuberculosis and HIV co-infection, known as a multiplier factor as reported in the Global Health Report of WHO on TB 2017. In this report the number of cases of TB is predicted to increase globally by two percent per year [1].

DRC is also among the 30 countries that account for 85% of the global burden of MDR-TB with a 9.7% incidence of rifampicin-resistant tuberculosis (RR-TB) and TB- MR. The same 2017 report estimates that there are 3600 cases of TB-drug-resistant (RR-TB and MDR-TB), including 2.2% for new cases and 17% for retirees [1]. This problem of resistance is a real public health problem in the DRC confirmed by surveys carried out on primary resistance in 2007 and 2009 by Kabedi *et al*. who reported high proportions (43.5% vs. 42.2%) [8-9].

This requires close monitoring to guide decision makers to define standardized chemotherapy protocols [1-6]. It is within this framework that we conducted this study to determine the frequency and the profile of the primary resistance of M. tuberculosis to anti-TB drugs in PLHIV since they constitute a risk group with high frequencies of morbidity and mortality[1-10].

MATERIAL AND METHODS

This prospective study was conducted in two screening and treatment centers (CSDT Saint Alphonse and Mother and Child Center Ngaba) where previous studies of resistance were conducted. The period covered was from January 2014 to July 2015.

After oral consent, all patients never treated for tuberculosis, and who had at least two Ziehl-positive bacilloscopies during the study period, were included. HIV status should be known after two rapid tests (To Determine and Unigold) [10]. Each subject answered standardized questionnaire to determine any previous exposure to anti-TB drugs.

Sputum specimens were inoculated on Lowenstein-Jensens medium after 4% sodium hydroxide treatment [12]. Cultures were monitored for 48-72 hours for signs of contamination [12]. The antibiogram was performed using the proportion technique and the direct method [12]. The following antituberculous drugs were used at the following critical concentrations: Isoniazid (INH): 0.2 µg / ml; Rifampicin (RMP): 40 µg / ml; Streptomycin (SM): 4 µg / ml; Ethambutol (EMB): 2 µg / ml; Kanamycin (KM): 30 µg / ml and Ofloxacin (OFX): 4 µg / ml (12). The antibiogram reading was performed on days 28 and 42, respectively, after incubation [12]. Strain identification was based on classical cultural and biochemical criteria [12].

Ethical consideration

The study received the approval of the Ethics Committee of the School of Public Health of the University of Kinshasa (N ° ESP / CE / 081/2010).

Data analysis

The data was recorded in the laboratory register and then transferred to the Excel software. They were analyzed using the Epi info version 5 software. Ficher's exact test and Pearson's chi-square were used as needed. The significance level was set at 5% and the confidence interval (CI) at 95%.

RESULTS

Seventy Ziehl positive sputum from 70 PLHIV patients were recorded between January 2014 and July 2015 in selected CDST. These samples were from Category I (NC) patients. Thirty-two samples (45.7%) came from CDST St Alphonse and 54.3% from the Ngaba Mother and Children Center (38). The average age of patients was 35.91 with extremes ranging from 8 to 74 years.

Table 1 Distribution of tuberculosis patients by age group and sex

Age Group Sex	Men		Women		Total	
	n	%	n	%	n	%
8-18	5	11.9	2	7.1	7	10
19-29	13	30,9	7	25	20	28.6
30-40	13	30,9	10	35.7	23	32.9
41-51	4	9.5	4	14.3	8	11.4
52-62	5	11.9	3	10.7	8	11.4
63-73	1	2.4	2	7.1	3	4.3
≥74	1	2.4	0	0	1	1.4
Total	42	60	28	40	70	100

There were more men than women (60% vs. 40%, p = 0.12) with a sex ratio of 1.5. Sixty-eight strains of Mycobacterium tuberculosis and two africanum were isolated on LJ. 54.3% were resistant to at least one anti-TB drug (38) and of these resistant strains, 4.3% (n = 3) were both resistant to rifampicin and Isoniazid (MDR-TB). The age group of 19 to 62 years was the most affected by primary resistance; the MDR-TB strains were prevalent in the 19-40 age group. The monoresistance profile is shown in Figure 1.

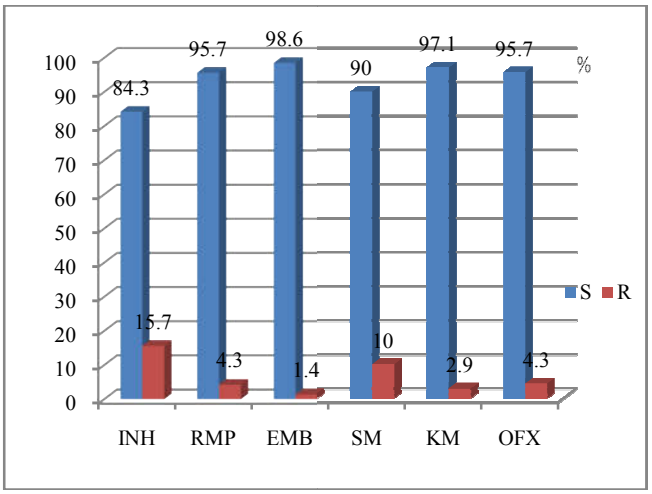

Figure 1 Monoresistance profile of strains isolated in PLHIV

INH: Isoniazid; RMP: Rifampicin; EMB: Ethambutol; MS: Streptomycin; KM: Kanamycin; OFX: Ofloxacin; S: Sensible; R: Resistant.

As shown figure 1, the highest resistance was observed with INH (15.7%), followed by Streptomycin (10%). The frequency of resistance to rifampicin and ofloxacin was the same (4.3%) that of kanamycin was 2.9% and 1.4% for Ethambutol. The exhaustive profile of the 38 resistant strains identified is reproduced in Table 2

Table 2 Resistance profile among the 38 strains identified in PLHIV

Antituberculosis drug	Number of strains (%)
Monoresistance type	
SM	**7 (10)**
INH	**11 (15.7)**
RMP	**3(4.3)**
EMB	**1(1.4)**
KM	**2(2.9)**
OFX	**3(4.3)**
Total	**27(38.6)**
Type of resistance association:	
INH+RMP	**3(4.3)**
INH+RMP+EMB	**1(1.4)**
INH+RMP+SM	**4(5.7)**
Total	**8 (11.4)**
Resistance association INH and others	
INH+SM	**4(5.7)**
INH+EMB	**1(1.4)**
INH+EMB+SM	**3(4.3)**
INH + OFX	**3 (4.3)**
Total	**11(15.7)**
Other type of association	
RMP+EMB	**1(1.4)**
Total	**1(1.4)**

Legend:SM=Streptomycin;INH=Isoniazid ; RMP=Rifampicin ;EMB = Ethambutol; KM = Kanamycin; OFX: Ofloxacin

Table 2 illustrates that monoresistance was observed for 27 strains (38.6%) and multidrug resistance (MDR-TB) concerned 3 strains (4.3%) while other forms of resistance associating Isoniazid with other molecules than Rifampicin revealed a frequency of less than 15.7%.

DISCUSSION

In many countries of the world, resistance of *Mycobacterium tuberculosis* to anti tuberculosis drugs is a major challenge for the prevention and control of tuberculosis [1]. However, the growing concern around the world about TB drug resistance and the emergence of extensively drug-resistant TB strains underscores the vital role of resistance surveillance. In a given population, the more patients with acquired resistance, the higher the primary resistance rate [4-14].

The greater the secondary resistance for a large number of antibiotics, the higher the primary resistance because of the difficulty of treatment, especially with HIV-infected patients [7-9,11-14]. Thus, the frequency and severity of primary resistance are indicators of the quality of management of TB patients in a country [4-9,11-14].

Thus, the survey was initiated to determine the frequency and pattern of primary resistance in TB-MR patients who constitute a high-risk group. The survey reports primary resistance of 54.3% and MDR-TB around 4.3%. The highest resistance was observed for Isoniazid (15.7%) followed by Streptomycin (10%), that of rifampicin and ofloxacin was the same (4.3%) and kanamycin 2.9%. The lowest resistance was 1.4% for Ethambutol.

The low preponderance of the male sex (60%) in this survey, although not statistically significant (p = 0.12), corroborates findings of some authors who think that the difference is due to insufficient reporting women cases in developing countries [15-16]. They also showed that men would be easier to screen than women because of certain socio-cultural barriers [15-16]. On the other hand, other authors think that men are the most exposed as a result of their daily activities [17-18].

The high incidence of HIV co-infected patients (72.9%) in the 19 to 51 age group is in line with many WHO reports which show that tuberculosis mainly affects the social strata of the population. more mobile and more economically active [1-7]. This shows that the risk of co-infection increases with age [13-14].

However, the impact of HIV / AIDS on the radiological, immunological and clinical picture of pulmonary tuberculosis is a known problem [7-9,13-14]. Several studies have shown that HIV is an important factor in the emergence of tuberculosis, and that HIV-related immunodeficiency is associated with the transition from latent TB to active TB [1-14]. Therefore, late detection of co-infection would be the leading cause of death for co-infected patients.

The work of Nicolas Veziris *et al*. have shown that HIV-infected patients have a higher risk of resistance to anti-TB drugs (13,19). This is consistent with our findings in this survey which show a high frequency of primary resistance (54.3%) among PLHIV. This frequency is greater than 43.5% and 42.2% reported by Kabedi *et al*. in previous surveys of the entire surveyed population irrespective of their HIV status [8-9].

However, this proportion is lower than that observed in other African countries [17-18]. The difference could be explained by different years of study, sample size (300, 161 and 70) and may be overestimated resistance cases of category I inherent in our definition of new cases as our survey did not use appropriate molecular tool to properly justify the cases and relied on patient anamnestic data.

On the other hand, other studies carried out in the world as well as the World Report on the Surveillance of the Resistance (WHO and Union) did not find the relation of cause and effect between HIV and resistance. However, it is clear that resistance has an impact on the management of cases, especially those co-infected with HIV, with a risk of therapeutic failure for the patient and transmission of resistant bacilli to subjects living with them [20-21].

Thus, it is important to prevent the spread of antibiotic-resistant strains of M. tuberculosis, which is based on the fastest adequate treatment after early detection of resistance.

Another explanation supported by some authors is that resistance is more marked in HIV-coinfected patients who constitute a vulnerable layer [13-14,17-18]. This high frequency shows a significant threat that could reverse current efforts in the fight against tuberculosis.

Therefore, WHO recommends maximizing detection and early treatment of cases, strengthening TB infection control activities, and properly implementing the DOTS strategy to reduce the burden of MDR-TB. [2-6,20]. Primary resistance varies from country to country as a result of poor treatment practices and implementation of inappropriate control programs in the past [1-7,11,13-14,17-1-19, 21]. However, when WHO recommendations are met, the proportion of primary resistance is less than 10% [11].

As we can see in the surveys carried out in the following countries: Fatemeh *et al* (Iran 2016); Sangaré *et al* (Burkina Faso 2010); Nicolas Vezins *et al* (France 2012); Millet *et al* (West Indies-Guyanne 2014); Hamusse *et al* (Ethiopia 2016) and Umubyeyi and others (Rwanda 2007) reported 11.1%,

12.4%, 9.9%, 11.8%, 15.3% and 3.5% respectively [22,17,19,23-24,18].

With regard to MDR-TB, which is a reflection of the mismanagement of tuberculosis, the control of its emergence is a health reality in the world and a challenge for tuberculosis control activities, especially in developing countries where the problem of early diagnosis to ensure adequate case management arises [1-11, 13-14, 17-21].

The 4.3% incidence of MDR-TB observed among PLHIV in this survey provides sufficient evidence that the threat exists with a risk of mortgaging the expected benefit. Several studies reported cases of MDR-TB, RR-TB and XDR-TB in PLHIV [7-9,13-14,20-28]. Suchindran *et al*. could not demonstrate an overall association between MDR-TB (including its acquired form) and HIV, but their findings suggested that HIV infection was associated with primary MDR-TB [25]. This can be explained by the complexity of case management in PLHIV [25-28].

The survey shows that the resistance concerned more the age group of 19-62 years including men and women and it is this same segment of population where 4.3% of MDR-TB is found. These results are in line with surveys conducted by WHO and some authors who show that this age group is the most affected by the disease and 80% of deaths are also found in this age group [1.8- 9,17-18,23-24].

The study of the resistance profiles of tubercle bacilli shows that resistance involving at least Isoniazid and Streptomycin are the most frequently found (15.7% and 10%). The predominance of resistance to these two antituberculosis drugs is an observation reported in many countries and there are wide disparities in the world reflecting an heterogeneous management of patients. [13.17-28].

The frequencies of resistance to rifampicin and ofloxacin were reported in 4.3% of strains for each and that of kanamycin was 2.9%. This can be explained by frequent use of these drugs in the past, especially Streptomycin, which has been used to treat other infectious diseases.

It is also likely that these high proportions are the result of infection of patients with a strain of *M. tuberculosis* from a patient who developed resistance during inappropriate treatment. In contrast, the survey reports a low proportion of resistance to ethambutol (1.4%). This frequency is greater than 1% observed by Umumbyi *et al*. (Rwanda 2007) and is above 5.19% reported by Adane *et al* (Ethiopia 2015) [18,29].

Regarding 2.8% of M. africanum strains reported in this survey, we believe that these people were infected by patients who developed M.africanum tuberculosis found in West Africa.

It is important to take into account certain limitations in the interpretation of our results. First only two TB screening centers were involved therefore the findings cannot reflect the reality at the community level. The second limitation concerns the small size of the sample.

However, the survey is strengthened by its prospective nature and the protocol presented could be used as a basis for further analysis on a larger sample of PLHIV for better interpretation.

CONCLUSION

Proportion of drug-resistant strains of *M. tuberculosis* observed in PLHIV must be monitored continuously, given the vulnerability of this group which require early diagnosis and appropriate treatment to improve patient's prognosis while reducing the risks of transmission of the resistant strains which lead to primary resistance.

Conflicts of interest: None

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