Original Article

Drivers of Multi-Drug Resistance to Anti-Tuberculosis Drugs in TB/HIV Co-Infection in Tuberculosis Patients

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Abstract

TB/HIV co-infection is a very heavy burden, and controlling or even eliminating it is a challenge for African countries and their health services. The leading cause of mortality for those with TB/HIV co-infection is still resistance to anti-tuberculosis medications, and the factors leading to it are little known because they are less documented. The main aim of this research was to determine the drivers of multi-drug resistance to anti-tuberculosis drugs in TB/HIV co-infection in tuberculosis patients in a hospital in Kinshasa. A descriptive cross-sectional study analyzed 25 records of patients with TB/HIV co-infection undergoing antiretroviral and anti-tuberculosis treatment at the Saint-Pierre de Kabambarré Hospital in Kinshasa. The mentioned files were analyzed over a period running from October 2023 to January 2024. A descriptive analysis revealed that environmental variables, including alcohol intake, had contributed to 46.6% of patients' development of resistance to anti-tuberculosis medications, loss of sight due to relocation, compared with 40% as a result of economic factors, in particular poverty and geographical inaccessibility. Only 32% of resistance was linked to medical factors: stock-outs of anti-tuberculosis drugs, and 41% of respondents developed resistance as a result of biological factors. On the other hand, only 12% of patients developed resistant relapses due to socio-demographic factors, such as discrimination and the myth surrounding tuberculosis. Poverty combined with the global economic collapse, geographical inaccessibility, stock-outs of anti-tuberculosis drugs and antiretrovirals, increased viral load, discrimination and the myth surrounding tuberculosis are responsible for anti-tuberculosis drug resistance in patients with HIV/TB co-infection.

Keywords: Recurrence, Tuberculosis, HIV, Multidrug resistance, Anti-tuberculosis drugs, Co-infection

Introduction

In nations with inadequate resources, the two most common infectious diseases are tuberculosis (TB) and HIV/AIDS [1]. TB/HIV co-infection affects 14 million individuals globally at the moment, with 70% of those cases occurring in sub-Saharan Africa, which has the largest burden of this co-infection [2, 3]. In 2010, approximately 8.8 million fresh infections of TB were recorded. In 2016, the incidence of TB was estimated at 10.4 million, but only 6.3 million (61%) were screened and put on treatment [4].

Globally, the rate of TB case notification has remained stagnant over a decade. Moreover, 13% of TB patients are co-infected with HIV, and most of these cases originate from Africa [5-8]. With the introduction of preventive measures such as the Calmette-Guérin bile vaccine (more commonly known as BCG), and the discovery of a number of effective antibiotics, the eradication of TB was conceivable by the end of the 20th century [9-11]. All countries are affected, but most cases occur in Africa (30%) and Asia (55%) [12]. Southeast Asia and Africa accounted for nearly two-thirds of all new TB cases (43% and 25%, respectively), with 46% of deaths occurring in Southeast Asia and 39% in Africa in 2020, according to WHO estimates [13]. With 10.6 million new cases, 1.6 million deaths, and 1.7 billion latent infections predicted for 2021, tuberculosis remains a major global health concern [14].

A major cause of death for individuals with HIV is TB [1, 15]. It's true that TB accounts for at least one out of every four fatalities among HIV-positive individuals, and many of

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these deaths take place in nations with low resources [16, 17]. TB associated with HIV infection occupies a very special place in many AIDS-related fields and it is the most frequent opportunistic infection during the course of AIDS worldwide which is one of factors behind the resurgence of tuberculosis [2, 18, 19]. With 69% of all new HIV infections occurring there, sub-Saharan Africa continues to be the area most impacted by the epidemic [1, 20].

TB is a public health problem in the Democratic Republic of the Congo (DRC), which is ranked ninth out of 30 countries with a high TB burden by the WHO. Indeed, the nation reports more than 100,000 susceptible TB cases annually [21, 22]. Unfortunately, HIV and the rise of multi-resistant strains exacerbate the issue [23]. Despite several attempts, the situation in the DRC remains extremely concerning. While there are still many obstacles to overcome, the national AIDS response has achieved strides in a number of areas [24, 25]. In fact, less than 20% of patients have access to antiretroviral medications, services for preventing HIV transmission from mother to child are still only available in a small number of locations, stigmatizing behaviors against individuals living with HIV persist, and 97% of the national response is funded by outside sources [26]. One of the main challenges in identifying and lowering the incidence of TB/HIV co-infection is resistance to anti-tuberculosis medications [27-31].

Furthermore, DRC is facing a persistent epidemic of HIV infection. Only 27.5% of patients eligible for antiretroviral (ARV) treatment have access to it [32]. In addition, the DRC is also one of the 30 countries most affected by TB, and a growing number of people are dying from TB/HIV co-infection resulting in resistance [33]. The DRC is really still the fourth most prevalent country in Africa, even with free treatment against TB/HIV co-infection and curative and preventative measures [34]. The main aim of this research was to determine the drivers of multi-drug resistance to anti-tuberculosis drugs in TB/HIV co-infection in tuberculosis patients in a hospital in Kinshasa.

Materials and Methods

Study Area

This study was carried out at the Saint-Pierre Hospital in Kabambarré. This health facility is managed by the Bureau Diocesain des Organisations Médicales (BDOM), which is committed to cover medical activities especially the care of HIV patients and it is located in Kinshasa precisely at 116, Kongolo street in Kinshasa municipality.

Study Design and Population

A retrospective cross-sectional investigation was conducted at a hospital with a descriptive design based on hospital files of patients having TB/HIV co-infection. The study was carried out between October 1, 2023 and January 30, 2024. In fact, we retrieved 25 files of patients with TB/HIV co-infection who had relapsed at least once to TB. A questionnaire was used having a multiple-choice questions and the sampling method is accidental non-probability.

Data Collection

Only one category of information was collected: that relating to the recrudescence of multidrug resistance to anti-tuberculosis drugs in TB/HIV co-infection among TB patients treated at the Saint Pièrre de Kabambare hospital in Kinshasa. Environmental, economic, medical, biological and sociodemographic parameters were used as variables in this study. Data were collected from the files of co-infected patients.

Definition of Variables

Independent Variables

Economic Factors

Economic factors are determinants linked to social life and family income that can lead to resistance to anti-tuberculosis drugs due to TB/HIV co-infection. Economic factors were measured using a questionnaire with multiple-choice questions. Each pair of adjectives was presented after the statement: "Have you ever not taken your medication for lack of transport money? The following adjectives were proposed for the measure: Yes or No.

Sociodemographic Factors

Sociodemographic factors are determinants linked to social life and the number of people in the household, which can lead to resistance to anti-tuberculosis drugs through TB/HIV co-infection. Economic factors were measured using a questionnaire with multiple-choice questions. Each pair of adjectives was presented after the statement "How many members does your family consist of?". The following adjectives were proposed for measurement: 2 to 5 respondents and more than 5 respondents.

Medical Factors

The context of access to care is defined by the availability of health services for the management of diarrhea in children. The context of access to care was measured using a questionnaire with open-ended questions. Each pair of adjectives was presented after the following statement: "Do you have access to health care services for children under 5 in case of diarrhea". The following adjectives were proposed to measure intention (yes or no).

Environmental Factors

The immediate environment is the milieu in terms of the place of resistance. The immediate environment was measured using a questionnaire with multiple-choice questions. Each pair of adjectives was presented after the following statement: "The distance separating your household from the health center is more than 5 kilometers". The following adjectives were proposed for measurement: (yes or no).

Biological Factors

Biological factors refer to immune characteristics versus viral load in the occurrence of resistance to anti-tuberculosis drugs. Biological factors were measured using a multiple-choice questionnaire. Each pair of adjectives was presented after the following statement: "Did you relapse from TB during treatment coupled with anti-retrovirals". The following adjectives were proposed for measuring intention: Yes or No.

Dependent Variable

Multi-drug Resistance Tuberculosis in HIV/Tuberculosis Co-Infection

Multi-drug resistance tuberculosis in TB/HIV co-infection is the process by which bacteria are resistant to the first line which is due to the accumulation of acquired resistance to several families of antibiotics, they are only susceptible to a small number of therapeutically useful antibiotics. Multi-tuberculosis drug resistance in TB/HIV co-infection was measured using a questionnaire with multiple-choice questions.

Each pair of adjectives was presented after the following statement: "Have you ever run out of drugs to take in your medical follow-up structure". The following adjectives were proposed for measurement: Yes or No.

Statistical Analysis

The sample profile was described using descriptive statistical methods, including frequency and percentage. Data was analyzed using SPSS version 20 software.

Results and Discussion

Socio-Demographic Parameters

Table 1 presents the sociodemographic attributes of the respondents.

Table 1. Socio-demographic characteristics of respondents

Socio-demographic characteristics	Frequency (n=25)	Percentage (%)
Gender		
Male	12	48
Female	13	52
Education level		
Illiterate	3	12
Primary	7	28
Secondary	5	20
University	10	40
Age (years)		
≤ 42	5	20
≥ 42 ans	20	80
Profession		
Student	3	12
Civil servant	3	12
Private sector	15	60
Others	4	16
Marital status		
Single	13	52
Married	9	36
Divorced	3	12
Widower	0	0

The table shows that the majority of our respondents are female (52%) and only 48% are male. The majority of our respondents have higher education (40%), while only 28% have primary education. On the other hand, 20% of our respondents have secondary education, while only 12% have no secondary education. In addition, the majority of respondents with TB/HIV co-infection were aged 43 or over (80%), while only 20% were aged 42 or under. On the other hand, most of our respondents work in the private sector (60%), while only 12% work in the public sector and are students. However, the majority of our respondents are single (52%) and only 35% are married. A further 12% are divorced, and none are widowed.

Description of Study Variables

Factors in Multidrug Resistance to Anti-Tuberculosis Drugs in TB/HIV Co-Infection

Different factors leading to the multidrug resistance is presented in the **Table 2** below.

Table 2. Factors in multi-drug resistance to anti-tuberculosis drugs in TB/HIV co-infection

Factors in multi-drug resistance to anti-tuberculosis drugs in HIV/TBC co-infection	Frequency (n=25)	Percentage (%)
Have you forgotten to take your medicine because it is out of stock?	6	24
Have you not been vaccinated against tuberculosis since you were a child?	2	8
During your course of anti-tuberculosis treatment, have you had any relapses?	13	52
Have you suffered from opportunistic infections several times since your diagnosis of HIV or tuberculosis?	12	48
Do you live far from health facilities that treat patients with HIV or tuberculosis?	14	56
Have you ever forgotten to take your medication?	22	88
Sometimes you are not seen by the medical team	0	0

It was found that 88% of our respondents had forgotten their TB/HIV co-infection medication, while 56% had failed to take their anti-tuberculosis medication because of the distance between their home and the place of care. In addition, 52% have relapsed from their co-infection and 48% have developed an opportunistic infection during treatment.

Only 24% had forgotten to take their medication due to stock-outs, compared with 8% who had not been vaccinated against tuberculosis during childhood. On average, 39.4% of those surveyed knew what causes multi-drug resistance to anti-tuberculosis medications in cases of TB/HIV co-infection.

Biological, Medical and Sociodemographic Factors

Table 3 presents biological, medical and sociodemographic factors.

Table 3. Biological, medical and sociodemographic factors

Different factors	Frequency (n=25)	Percentage (%)
Biological factors		
Relapse and emergence of multi-resistant bacilli	13	52
Individual's innate immune defences reduced due to lack of antibodies	2	8
Treatment failure with anti-tuberculosis drugs	13	52
Dissemination of germs	13	52
Medical Factors		
Stock shortages	15	60
Lack of qualified healthcare staff	11	44
Absence of internist antibiogram tests	5	20
Socio-demographic factors		
Illiteracy	3	12
Discrimination and myths	5	20

In fact, 52% of our respondents had complications resulting from relapse and emergence of multidrug-resistant bacilli, therapeutic failure with anti-tuberculosis drugs and dissemination of germs, compared with only 8% who had missed the innate immune defenses of the individual reduced for lack. On average, 41% of those surveyed had biological characteristics that contribute to TB/HIV co-infected individuals' multidrug resistance to anti-tuberculosis medications.

However, with regard to medical factors, 60% of our respondents are victims of stock shortages, while 40% experience the absence of qualified health personnel. In summary, 32% of our respondents are resistant to anti-tuberculin drugs in TB/HIV co-infection, due to medical factors. In addition, 12% of our respondents suffer from illiteracy as a sociodemographic factor.

Economic, Environmental and Behavioral Factors

Table 4 presents economic, environmental and behavioral factors.

Table 4. Economic, Environmental and behavioral factors

Different factors	Frequency (n=25)	Percentage (%)
Economic factors		
Economic inaccessibility	15	60
Health insurance	5	20
Environmental and behavioural factors		
Geographical inaccessibility	20	80
Loss of sight due to relocation	12	48
Alcohol consumption	14	56
Trips	10	40
Negligence	14	56
Forget	20	80

Unfortunately, 60% of our respondents have resistance complications due to economic inaccessibility, compared with only 20% who have missed out on health insurance. Regarding multi-drug resistance to anti-tuberculosis medications in TB/HIV co-infected individuals, an average of 40% of our respondents cited economic considerations. However, in relation to environmental and behavioral factors, 80% of our respondents are victims of geographical inaccessibility, while 40% do not respect travel-related care. In other words, the majority of our respondents experienced resistance as a result of forgetfulness (80%), compared with 56% who had it as a result of neglect. In summary, on average 42% of our respondents are resistant to anti-tuberculin drugs in TB/HIV co-infection, due to environmental and behavioral factors.

The primary substantial risk factor for having an MDR-TB infection is co-infection with HIV. The most deadly syndemic illness in human history is thought to be the co-infection of TB and HIV, which work together to increase the disease's burden [35, 36].

Sociodemographic Characteristics

As for the sociodemographic factors, the majority of respondents are female (52%) and 48% are male, 40% have a higher education and 12% are illiterate, while the majority of respondents was old i.e. more than 42 years old (80%), 60% work at the private sector and last 52% were divorced. Palambwa *et al*. [37] reported that 53.5% were female, 50.7% had a secondary education, the range age was 16-66 years old, 60% worked in the private sector, 52% were single. It should be noted that the difference may reside in the sample size.

Drivers in Multi-Drug Resistance to Anti-Tuberculosis Drugs in TB/HIV Co-Infection

Treatment of multidrug-resistant tuberculosis (MDR TB) is especially difficult in people with HIV. Drug-resistant

tuberculosis (DR-TB) occurs when microorganisms that cause TB are resistant to one or more anti-TB drugs. Polydrug-resistant TB (poly-DR-TB), rifampicin-resistant TB (RR-TB), multidrug-resistant TB (MDR-TB), extensively drug-resistant TB (XDR-TB), and mono-drug-resistant TB (mono-DR-TB) are the several types of DR-TB. In order to effectively control MDR TB in people with HIV, ART is essential [30, 38]. In light of the growing body of recent research supporting a positive relationship between HIV and MDR-TB, a revised assessment of the extent of the link is required [38, 39].

In fact, 88% of respondents forget to take their TB/HIV co-infection medication, while 56% fail to take their anti-tuberculosis drugs because of the distance between their home and the healthcare facility. International immigration is one of the main causes of the rise in TB cases in affluent nations with low incidence rates [39, 40]. Another a fact is that maybe those patients are afraid of side effects (adverse effects) due to the combination of both therapies (ARVs/TB treatment) considering the drug-drug interactions and this may lead to this forgetfulness. Anticipate and aggressively manage adverse medication responses since they may contribute to the worse TB treatment results seen in HIV patients. These reactions can be caused by overlapping toxicities and drug-drug interactions [41]. This situation may worsen the condition of the patient and weakens his immune system and may be exposed to other opportunistic diseases precisely nosocomial infections occurring in the healthcare facility.

Moreover, 52% of respondents relapsed following co-infection, and 48% developed an opportunistic infection during treatment. Only 24% forgot to take their medication due to stock-outs, compared with 8% who did not receive TB vaccination during childhood. Besides these classic factors, other factors have recently been incriminated like smoking and forgetting to take medication, by inducing bronchial inflammation and altering alveolar macrophages, appear to be responsible for a higher chance of contracting TB and developing the illness [42, 43].

Biological, Medical and Socio-Demographic Factors

In fact, 52% of respondents had complications resulting from relapse and emergence of multi-resistant bacilli, therapeutic failure with anti-tuberculosis drugs and dissemination of germs, while 8% who had missed the innate immune defenses of the individual reduced for lack. Moreover, the association between poverty and TB is well established [44, 45]. The rate of increase of this chronic infection, due to Koch's bacillus and most often found in the lungs, is estimated at nearly 12% compared to what was known during the 1980s [46, 47]. The wide inter-individual variability observed in clinical practice is linked to genetic variability in the control of defense against TB/HIV co-infection [48, 49].

On the other hand, in relation to medical factors, 60% of respondents were victims of stock shortages, while 40% of respondents experienced the absence of qualified health personnel. In short, 32% of respondents are resistant to anti-tuberculosis drugs in TB/HIV co-infection, due to medical factors. The vast majority of people suffering from TB have the poorest medical services. This results in poor treatment adherence by patients, thus risks of relapse and emergence of resistant bacilli [50].

Economic, Environmental and Behavioral Factors

In fact, 60% of respondents' present complications of resistance to co-infection due to economic inaccessibility, compared with only 20% who missed out on health insurance. poverty and destitution are the main causes of TB/HIV co-infection due to the poor medical services [2, 18]. On the other hand, in relation to environmental and behavioral factors, 80% of respondents are victims of geographical inaccessibility, compared with 40% who do not respect travel-related care. In other words, the majority of respondents experienced resistance as a result of forgetfulness (80%), compared with 56% who had it as a result of neglect.

Conclusion

The descriptive analysis carried out to identify the key factors in the multi-resistance of people living with TB/HIV coinfection to anti-tuberculosis drugs were: poverty added to the collapse of the global economic fabric, the consumption of alcohol and drugs thus delaying anti-tuberculosis actions on the other hand, geographical inaccessibility, stock-outs of anti-TB drugs and antiretrovirals.

In addition, the increase in viral load resulting from refusal to take anti-tuberculosis drugs, discrimination and the myth surrounding TB are responsible for resistance to anti-tuberculosis drugs in patients suffering from TB/HIV co-infection. This leads to an upsurge in relapses and, by the same token, resistance to anti-tuberculosis drugs, quadrupling the probability of death for people living with HIV/AIDS and pulmonary TB.

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