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## Research Article

# Risk Factors for Mortality in Patients with TB/HIV Co-Infection at the General Provincial Reference Hospital of Kinshasa, Democratic Republic of the Congo

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## Abstract

**Background:** The HIV (human immunodeficiency virus) pandemic has been accompanied by an increase in the incidence of many opportunistic infections like tuberculosis (TB). Despite curative and preventive efforts and free treatment for TB -HIV co-infection, the Democratic Republic of Congo remains the fourth country in Africa where the prevalence of this co-infection remains very high. The aim of this study was to identify the factors that explain mortality in patients with TB/HIV co-infection at the Kinshasa Provincial General Reference Hospital in order to reduce the incidence of complications related to this century's pandemic.

**Methods:** The survey was conducted at the General Provincial Reference Hoisptal of Kinshasa (GPRHK), Kinshasa, DR Congo. This cross-sectional study was conducted between January and November 2018, whereby medical files for patients suffering from TB/HIV co-infection were analyzed. The sample size was determined on the basis of the Fischer formula. Thus, one hundred and forty-four (144) files were selected and consulted. Data were collected based on a pre-established, standardized and anonymous questionnaire. This questionnaire was tested on a sample of 40 files subsequently validated. Descriptive analyses were used to describe the sample profile. The correlational analysis using the Chi-square association test ($X^2$), the confidence interval of the Odds-ratio was performed between different variables. All data were analyzed using SPSS software version 22.0. The p value < 0.05 was considered statistically significant.

**Results:** Multiple regression analysis indicates that the main determinants of mortality in patients with TB/HIV co-infection are as follows: the main predictors of mortality from TB/HIV co-infection were, in order of importance, patients diagnosed with HIV (0.448; p0.05), patients treated with anti-tubercular drugs (0.231; p0.05). The clinical form of tuberculosis ( -0.032; p0.05) and the age of people living with HIV (0.038; p0.05) are not significantly associated with TB-HIV co-infection.

**Conclusion**: The diagnosis of HIV infection in TB patients in the absence of anti-tuberculin prophylaxis, followed by the clinical form of tuberculosis coupled with poor compliance and significant immunosuppression are the major risk factors for mortality.

**Keywords:** TB/HIV co-infection; Risk factors; Kinshasa; Democratic Republic of the Congo

## 1. Introduction

The HIV (human immunodeficiency virus) pandemic has been accompanied by an increase in the incidence of many opportunistic infections like tuberculosis (TB). TB/HIV co-infection remains the leading cause of death among people living with HIV (PLHIV) worldwide. In 2015, the Democratic Republic of the Congo (DRC), which had a TB incidence rate of 254 cases per 100,000 population, was classified as an intermediate country with a burden of TB and HIV/AIDS. In addition, in 2014, 38% of TB patients in the country were infected with HIV and the number of HIV/AIDS-related deaths in the general population is 35,000 cases (13%) worldwide [1].

The rapid spread of the HIV epidemic in many countries has led to an equally dramatic increase in the estimated number of new cases of TB. However, the number of people co-infected with these two diseases continues to increase even in countries with well-organized national tuberculosis control programmes (NTPs) that use the direct observed treatment, short-course (DOTS) approach [2]. South Africa is one of the countries most affected by HIV/AIDS epidemic and it was estimated that in 2013, 74% of the total population was infected, according to Kharsany and Karim [3]. This is associated with the prevalence of tuberculosis bacillus, which is also very high and the highest in the world [4].

Indeed, since HIV/AIDS is the most powerful activator of latent tuberculosis infection to active clinical disease in patients with both diseases, it increases the morbidity and mortality rate of patients. Many studies have shown the importance of TB/HIV co-infection, in 2007 in Southeast Asia, the mortality rate for TB/HIV patients during treatment of this co-infection was particularly high, ranging from 20% to 50% [5]. This rate was reduced to around 30% in Malawi in 2015 [6]. However, among PLHIV, the progression of TB is more serious with a high risk of death due to the interaction between the two diseases. However, the excess mortality among HIV-positive tuberculosis patients is due to: the evolution of the HIV infection itself, drug intolerances or discontinuation [7]. This synergy between the two diseases also has an impact on major societal issues with significant political,

demographic and economic consequences. The WHO [8] points out that nearly 33% or 12 to 15 million of PLHIV are co-infected with TB.

In some parts of sub-Saharan Africa, up to 70% of TB patients also have HIV. It is estimated that up to 33% of AIDS-related deaths worldwide are directly attributable to TB, while in sub-Saharan Africa this proportion rises to 50%. According to the Congolese Ministry of Health [9], the Democratic Republic of Congo (DRC) with a high tuberculosis burden with a prevalence ranging from 392 cases per 100,000 inhabitants. In addition, in 2008, 30% of patients were diagnosed with TB and received an external redox partner 2,6 dicholoroindophenol (DCIP). Of those patients, 63% were tested for HIV+. The National Programme to Combat HIV/AIDS illustrates that, of all the opportunistic infections encountered in health facilities in the city of Kinshasa in 2010, tuberculosis accounted for 39.75% of cases leading to TB/HIV co-infection. Indeed, dermatoses and enteritis represent 17.85% and 16.86% of cases respectively. While toxoplasmosis represents only about 1% of cases. The aim of this study was to identify the factors that explain mortality in patients with TB/HIV co-infection at the General Provincial Reference Hospital of Kinshasa (GPRHK) in order to reduce the incidence of complications related to this century's pandemic.

## 2. Materials and methods

### 2.1. Study area

This study was carried out at the GPRHK located in Kinshasa, DRC. This health facility offers curative and preventive care against TB/HIV co-infection.

### 2.2. Population of study and criteria

We included all records of HIV patients co-infected with TB who had benefited with or without anti-tuberculosis treatment associated with antiretroviral drugs and followed up in the care units of the internal medicine department. Indeed, the follow-up time for each patient was 8 months from the diagnosis and initiation of treatment with anti-tuberculosis drugs, regardless of the treatment regimen administered.

### 2.3. Study design and sample size

This is a cross sectional and correlational study having a retrospective insight. This allowed to use the records of patients hospitalized in 2018 in this hospital setting. It concerned patients suffering from TB-HIV co-infection whose microscopic and radiological results were positive. The sample size was determined on the basis of the Fischer formula according to Ancell [10]. Thus, 144 files were selected and the literature review was used with a questionnaire designed based on the files.

### 2.4. Data collection

Data were collected based on a pre-established, standardized and anonymous questionnaire. This questionnaire was tested on a sample of 40 files subsequently validated. These files were obtained from the archives of various care units likely to receive patients co-infected with TB/HIV and from the consultation registers of the internal medicine department of this hospital. At GPRHK, most diagnoses of extra-pulmonary tuberculosis are based on clinical evaluation (due to limited access to specific diagnostic tools) and in comparison to the favourable response to empirical anti-tuberculosis treatment. Mixed patients are those who had lung diseases associated with any form of pulmonary tuberculosis.

Several variables were searched namely: TB/HIV co-infection (dependent variable), socio-demographic data (gender, age and education level), clinical data (positive microscopy pulmonary TB (PMPTB), negative microscopy pulmonary TB (NMPTB), extra-pulmonary TB, Mixed TB, new reprocessing cases, sputum examination, CSF examination) and therapeutic data (management protocols for these patients, cotrimoxazole prophylactic (CPT), level of treatment compliance, treatment initiation times). In addition, psychosocial workers (PSAs) in two ways conducted the assessment of therapeutic compliance found in the files. It involved both TB and HIV treatments: i) either patients had missed more than one dose of medication in the last 7 days before the meeting with PSA; or patients had missed one week or more of their treatment in the month before the start of the meeting or since the initiation of therapy according to Blanc et al. [11]. Unfortunately, either by the ratio between the number of prescriptions dispensed and the theoretical number of prescriptions expected (corresponding to the number of months of treatment follow-up), the patient was declared non-compliant when the said ratio was less than 0.95 according to Essomba et al. [12].

### 2.5. Data analysis

Descriptive analyses (frequency, mean, standard deviation and percentage) were used to describe the sample profile. The correlational analysis using the Chi-square association test ($X^2$), the confidence interval of the Odds-ratio was performed between different variables. All data were analyzed using SPSS software version 22.0. The p value $< 0.05$ was considered statistically significant.

### 2.6. Ethical considerations

Ethical permission for this study was obtained from the Research and Ethics committee of the University of Kinshasa (Faculty of Medicine, Public Health School) along with the informed consent and confidentiality was the golden rule. This research study was conducted in strict compliance according to the protocol approval of the ethical review committee.

## 3. Results

3.1 Sociodemographic and clinical parameters

Table 1 presents the sociodemographic and clinical parameters of the respondents.

**Table 1: Sociodemographic and clinical parameters of respondents**

| **Sociodemographic Parameters** | **(n=144) /n (%)** |
|---|---|
| **Sex** | |
| Female | 77 (53.5) |
| Male | 67 (46.5) |
| Age (years): 18 à 66 | |
| 18-45 | 70 (48.6) |
| 46-66 | 74 (51.4) |
| Mean ± DS | 39.6 ± 13.4 |
| **Level of education** | |
| Primary | 59 (41.0) |
| Secondary | 73 (50.7) |
| University | 12 (8.3) |
| **Clinical forms of TB** | |
| Positive Pulmonary | 85 (59.0) |
| **Negative** Pulmonary | 45 (31.3) |
| Extrapulmonary | 14 (9.7) |
| **Bacillary microscopic diagnostic examination** | |
| Positive | 70 (48.6) |
| Négative | 67 (46.5) |
| Positive after a week of specific exam | 7 (4.9) |
| **Radiological diagnostic examination performed** | |
| Positive Congestion | 69 (47.9) |
| Normal | 75 (52.1) |

Table 1 shows that the participants in this study were aged between 18 and 66 years with an average age of 39.6 ±13.4 years. More than two thirds of them were female (53.5%). The majority had only secondary education (50.7%), but it should be noted that 41.0% had at the primary level.

The majority of respondents developed in clinical pulmonary form of tuberculosis (active disease), 59.0% compared to 31.3% which did not develop the disease. More than half, 48.6%, had positive bacillary microscopic diagnostic tests and only 46.5% of these participants were tested negative. Last, 47.9% of the participants in the radiological diagnostic examination performed showed positive congestion and 52.1% were negative.

### 3.2 Therapeutic profiles, risk factors and mortality

The therapeutic profile of respondents is presented in table 2.

**Table 2:** Therapeutic description of anti-tuberculosis drugs and the patient's fate

| **Parameters** | (n=144)/n (%) |
|---|---|
| **TB treatment received** | |
| RHZ | 68 (47.2) |
| SHM | 76 (52.8) |
| **Diagnosed HIV** | |
| Positive | 69 (47.9) |
| Negative | 75 (52.1) |
| **Final fate of HIV patients** | |
| Deceased | 67 (46.5) |
| Healed | 77 (53.5) |

**Legend:** RHZ: Rifampicin, Isoniazid and Pyrazinamide, SHM: Streptomycin, Isoniazid and Ethambutol

As observed, the table above shows that the majority of participants (47.2%) were treated with RHZ (combination of three drugs) for tuberculosis compared to only 52.8% who were placed on SHM. In addition, 47.9% of respondents tested positive for HIV. Unfortunately, 46.5% of our participants died of TB-HIV co-infection compared to only 53.5% who recovered. The bivariate analysis between the diagnosed HIV and the final fate of the PLHIV showed a perfect statistically significant relationship: p= 0.000. Thus, rather than HIV diagnosis, the sooner antiretroviral therapy is started to reduce the viral load.

The bivariate analysis on the relationship established between the diagnosed TB/HIV co-infection and the gender of TB patients is presented in the table below.

**Table 3:** Bivariate analysis of TB/HIV and gender of TB patients

| **Parameters** | **Diagnosed Co-infection TB/HIV (n=144)** | | **OR** | **$IC_{95\%}$ (OR)** | | $\chi^2$ | p |
|---|---|---|---|---|---|---|---|
| | Positive : n (%) | Negative: n (%) | | Lim < | Lim > | | |
| **Gender of tuberculosis patients** | | | | | | | |
| Male | 50 (72.5) | 17 (22.7) | 8.978 | 4.21 | 19.11 | 35.8 | 0.000 |
| Female | 19 (27.5) | 58 (77.3) | | | | | |

Thus, the bivariate analysis between diagnosed HIV and the gender of tuberculosis patients showed that there is a statistically significant association: p= 0.000. Therefore, gender (precisely male) would be a risk factor for TB/HIV co-infection.

The relationship between the clinical form and the final outcome of people living with HIV is presented in table 4.

**Table 4:** Relationship between the clinical form and the final fate of PLW HIV

| **Parameters** | **Clinical form (n=144)** | | | **IC$_{95\%}$ (OR)** | | $\chi^2$ | p |
|---|---|---|---|---|---|---|---|
| | Pulmonary (+) : n=85 (%) | Pulmonary (-) : n=45 (%) | Extrapulmonary n=14 (%) | Lim < | Lim > | | |
| **Final outcome** | | | | | | | |
| Deceased | 39 (45.9) | 23 (51.1) | 5 (35.7) | 0.52 | 0.68 | 1.0 | 0.47 |
| Healed | 46 (54.1) | 22 (48.9) | 9 (64.3) | | | | |

The bivariate analysis between the clinical form and the final fate of the PLHIV showed that there is no statistically significant association: p-value = 0.47. Thus, the clinical form of tuberculosis does not define the patient's fate, conversely, any form linked to HIV would result in death.

Table 5 shows the relationship between anti-tubercular drugs administered and the final fate of PLHIV.

**Table 5:** Relationship between anti-tubercular drugs and final outcome of PLHIV

| **Parameters** | **Anti-tubercular treatment (n=144)** | | **OR** | **IC$_{95\%}$ (OR)** | | $\chi^2$ | p |
|---|---|---|---|---|---|---|---|
| | RHZ: n=65 (%) | SHM: n=76 (%) | | Lim < | Lim > | | |
| **Final fate of people living with HIV** | | | | | | | |
| Deceased | 43 (63.2) | 24 (31.6) | 8.978 | 4.21 | 19.11 | 35.8 | 0.000 |
| Healed | 25 (36.8) | 52 (68.4) | | | | | |

The bivariate analysis between the anti-tubercular therapy received and the final fate of the PLHIV indicated that there is a statistically significant relationship: p-value = 0.00. Thus, the quality of management defines the fate of the patient with TB/HIV co-infection.

Table 6 shows the relationship between HIV diagnosed and the final fate of PLHIV.

**Table 6:** Relationship between HIV diagnosed and final outcome of people living with HIV

| Parameters | Diagnosed HIV (n=144) | | OR | $IC_{95\%}$ (OR) | | $\chi^2$ | p |
|---|---|---|---|---|---|---|---|
| | Positive: n=69 (%) | Negative: n=75 (%) | | Lim < | Lim > | | |
| **Final fate on PLHIV** | | | | | | | |
| Deceased | 50 (72.5) | 17 (22.7) | 8.978 | 4.21 | 19.11 | 35.8 | 0.000 |
| Healed | 19 (27.5) | 58 (77.3) | | | | | |

The bivariate analysis between the diagnosed HIV and the final fate of the PLHIV showed a perfect statistically significant relationship: p= 0.000. Thus, rather than HIV diagnosis, the sooner antiretroviral therapy is started to reduce the viral load.

### 3.3 Predictors of mortality in patients with TB/TB/HIV co-infection

Different predictive variablesof intention analyzed by regression is presented in the table below.

**Table 7:** Regression analysis for different predictive variables of intention

| Variables | β | t | ρ |
|---|---|---|---|
| Variables of model | | 3256 | |
| Clinical Form | -032 | -601 | 549 |
| TB treatment | 231 | 3152 | 002 |
| Diagnosed HIV | 448 | 6154 | 000 |
| Age of PLHIV | -054 | -764 | 446 |
| | $R^{2=}0.281$; F= (df : 4)= 2.6; *p<0.05 | | |

In the light of the analysis of multiple regression for the predicted variables of TB/HIV co-infection, it can be seen that these variables explain 28% of the variance in the association of tuberculosis and HIV with ($r^2$=0.281) followed by ANOVA of (F= (df : 4) = 2.6 ; *p0.05).

However, the findings indicate that the main predictors of TB-HIV co-infection were, in order of importance, patients diagnosed with HIV (0.448; p=0.05), patients treated with anti-tubercular drugs (0.231; p=0.05) and, on the other hand, the clinical form of tuberculosis (-0.032; p=0.05) and the age of the PLHIV (0.038; p0.05) are not significantly associated with TB-HIV co-infection.

## 4. Discussion

### 4.1. Socio-demographic parameters

Regarding the descriptive findings, it should be noted that the participants in this study were aged between 18 and 66 years and more than two thirds were female (53.5%). Essomba et al. [12] reported that the average age of

respondents was 39 ± 10 years. However, the majority were female (54.1%) with a sex ratio of 0.84. The majority had only completed secondary education (50.7%), but the aforementioned author reported that 41.0% had only completed primary education. The majority of respondents had tuberculosis in clinical pulmonary form, 59.0% of positive cases compared to 31.3% with negative cases. More than half, 48.6%, had positive bacillary microscopic diagnostic tests and only 46.5% of these participants were negative. Akksilp et al. [13] found that 56.6% of patients had positive microscopy tuberculosis. Finally, 47.9% of respondents in the radiological diagnostic examination performed showed positive congestion and 52.1% were negative. Furthermore, the majority of participants (47.2%) received RHZ treatment for tuberculosis compared to only 52.8% who were put on SHM and both combinations were not used together..

These findings meet those found by the WHO [14], which stipulate that all their study participants were on anti-tuberculosis drugs, 89% were on ARVs containing efavirenz and 81.2% had cotrimoxazole prophylaxis. In addition, 47.9% of our participants tested positive for HIV. Unfortunately, 46.5% of participants died from TB-HIV co-infection compared to only 53.5% who recovered. The WHO, [14] in a study on TB-HIV co-infection noted that 67.3% of subjects were reported cured of TB and 15.7% died. According to Kharsany and Karim [3], nearly 33% (12 to 15 million) of people living with HIV1 are co-infected with TB. However, in some parts of sub-Saharan Africa, up to 70% of patients with TB also have HIV. In addition, 33% of AIDS-related deaths worldwide are directly attributable to TB. In sub-Saharan Africa, this proportion rises to 50%.

### 4.2. Therapeutic profiles, risk factors and mortality

The results of this study reveal the influence of the diagnosed HIV association and the gender of tuberculosis patients: p-value = 0.00 at df= 1. Thus, the gender would be a risk factor for TB/HIV co-infection and therefore of the high mortality rate whereby women constitute the majority. Thuy et al. [5] in their study on risk factors for TB, they found the average age of participants to be 39 ± 10 years. Indeed, the majority were women (54.1%) with a sex ratio of 0.84.

This study did not note the clinical form of tuberculosis in the final fate of PLHIV with a non-significant association: p-value = 0.47. So, the clinical form of tuberculosis does not define the patient's fate, conversely, any form linked to HIV would result in death. Dagnra et al. [15] pointed out that the cure rate for TB/HIV co-infection in this group was 47.8 versus 84.4% in the group of HIV-positive patients with CD4 levels above 200/µl. In addition, there was no statistically significant difference between the cure rates for TB/HIV patients and TB/HIV patients with CD4 levels above 200/µl considering the negative impact of HIV on TB.

In Kinshasa, the anti-tubercular therapy received has a perfect relationship with the final fate of PLHIV: p= 0.00. Therefore, the quality of the management allows to predict the final fate of the patient having this co-infection. In Cameroon, Essomba et al, [12] reported that, regardless of the therapeutic status of patients or of the rural residence ($p < 0.0001$), co-infection with tuberculosis ($p < 0.0001$), hepatitis C ($p = 0.02$), history of toxoplasmosis ($p <$

0.008), lack of cotrimoxazole prophylaxis ($p < 0.0001$), poor compliance ($p < 0.0001$), weight at ` M0 < 50 kg ($p < 0.0001$), CD4 at M0 < 50 /mm$^3$ ($p < 0.0001$) were associated with high mortality.

It has been observed that HIV diagnosed in tuberculosis patients determines the fate of the PLHIV (death) with a statistically significant relationship: p-value = 0.00. Thus, earlierthe diagnosis of HIV associated with tuberculosis, the sooner the antiretroviral treatment will be started. Kwan and Ernst [16] reported that people whose immune systems are weakened (by poor general health or other infections such as HIV) can develop active TB, which is often fatal if left untreated. In addition, an HIV-negative person with latent TB infection has a 10% chance of developing active TB during her lifetime, while an HIV-positive person has a 10% chance of developing it each year. It has been shown that HIV serves as a driver of TB at the population level and most of them are due the reactivation of latent TB.

### 4.3. Predictors of mortality in patients with TB/HIV co-infection

In the light of the analysis of multiple regressionon the predicted risk variables of mortality from TB/HIV co-infection, the findings that these variables explain 28% of the variance of the association between tuberculosis and HIV with ($R^2$=0.281) followed by ANOVA of (F= (df : 4)= 2.6 ; *p0.05). According to the WHO [8] and Raviglione & Sulis [17], TB and HIV cause more than 4 million deaths per year. TB is one of the common infections that threaten PLHIV in the developing world. Of the 1.7 million TB-related deaths in 2008, nearly one-third were people with HIV co-infection.

However, the findings indicate that the main predictors of mortality from TB/HIV co-infection were, in order of importance, patients diagnosed with HIV (0.448; p0.05), patients treated with antitubercular drugs (0.231; p0.05) and, on the other hand, the clinical form of TB (-0.032; p0.05) and the age of the PLHIV (0.038; p=0.05) are not significantly related to TB/HIV co-infection. In Cameroon, Essomba et al. [12] found that hepatitis B (p<0.0009), lack of cotrimoxazole prophylaxis (p<0.005), poor compliance (p<0.0001), CD4 <50 (p<0.0001) were risk factors for mortality.

## 5. Conclusion

The cure of patients co-infected with TB/HIV remains low, and the mortality still remains high at the Kinshasa General Provincial Reference Hospital. However, the diagnosis of HIV infection in tuberculosis patients in the absence of anti-tuberculin prophylaxis, followed by the clinical form of tuberculosis coupled with poor compliance and significant immunosuppression are the major risk factors for mortality. On the other hand, early use of ARVs and cotrimoxazole prophylaxis, as well as compliance aids, should reduce the high mortality observed.

## Conflict of Interest

The author declare no conflict of interest exists.

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