

Original article

Impact of Isoniazid Chemo Prophylaxis on the incidence of Tuberculosis and the mortality rate in patients on antiretroviral treatment at the Reference Health Center of Commune II of Bamako from 2016 to 2020

Impact de la Chimio Prophylaxie à l'Isoniazide sur l'incidence de la Tuberculose et le taux de mortalité chez les patients sous traitement antirétroviral au Centre de Santé de Référence de la Commune II de Bamako de 2016 à 2020

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Abstract

Introduction: Tuberculosis (TB) is the leading cause of death among HIV-positive people. In Mali, the National Strategic Framework for the fight against HIV had planned to reduce mortality among people living with HIV (PLHIV) by 50% by 2017 through preventive treatment with isoniazid (IPT). The objective of this study was to assess the impact of IPT on TB incidence and mortality rates among PHAs.

Methodology: This was a retrospective cohort study carried out at the Reference Health Centre of Commune II. Concerning the monitoring data of PLHIV from 2015, our reference and those from 2016 to 2020, the period of effectiveness of the TPI. The Preventive Fraction in Expos was used to measure the effectiveness of IPT and logistic regression to determine factors associated with the occurrence of death.

Results: Among the 122 patients included between May and October 2020, the median age was 37 years,

the sex ratio 2.5 in favor of women. The IPT was 94% effective [0.76 - 0.99]. Age ($p=0.008$ [0.911 - 0.986]), and BMI ($p=0.011$ [1.046 - 1.407]) were associated with the occurrence of death among PHAs.

Conclusion: IPT has reduced deaths and reversed HIV/TB co-infection. This is why we suggest that the supervisory authority carry out a national impact assessment of the CFI.

Keywords: Impact, Isoniazid chemoprophylaxis, PLHIV, CSRef CII of Bamako, HIV/TB.

Résumé

Introduction : La tuberculose (TB) est la principale cause de mortalité chez les séropositifs. Au Mali le Cadre Stratégique National de lutte contre le VIH avait prévu de réduire de 50% la mortalité chez les personnes vivant avec le VIH (PVVIH) d'ici 2017 grâce au traitement préventif à l'Isoniazide (TPI). Cette étude avait pour objectif d'évaluer l'impact du TPI sur l'incidence de la TB et le taux de mortalité

chez les PVVIH.

Méthodologie : Il s'agissait d'une étude de cohorte rétrospective réalisée au Centre de Santé de Référence de la Commune II. Portant sur les données de suivi des PVVIH de 2015, notre référence et de celles allant de 2016 à 2020, période d'effectivité du TPI. La Fraction préventive chez les exposés a été utilisée pour mesurer l'efficacité du TPI et la régression logistique pour déterminer les facteurs associés à la survenue de décès.

Résultats : Parmi les 122 patients inclus entre mai et octobre 2020, l'âge médian était de 37 ans, le sexe ratio 2,5 en faveur des femmes. Le TPI a été efficace à 94% [0,76 - 0,99]. L'âge ($p=0,008$ [0,911 - 0,986]), et l'IMC ($p=0,011$ [1,046 - 1,407]) ont été associées à la survenue de décès chez PVVIH.

Conclusion : Le TPI a permis de réduire les décès et d'annuler la co-infection VIH/TB. C'est pourquoi nous suggérons à la tutelle de procéder à une évaluation nationale d'impact du TPI.

Mots-clés : Impact, Chimio prophylaxie à l'Isoniazide, PVVIH, CSRéf CII de Bamako, HIV/TB.

Introduction

Tuberculosis (TB) is the leading opportunistic infection and cause of death among people infected with the human immunodeficiency virus (HIV) in the world(1). According to the WHO's 2019 Global Report on Tuberculosis, there were an estimated 1.2 million TB deaths among HIV-negative people in 2018 and an additional 251,000 deaths among HIV-positive people(2). Isoniazid chemoprophylaxis (ICC) was recommended by the 2010 and 2011 WHO guidelines at the meetings of the Review Committee on Scaling Up Tuberculosis Testing in People Living with HIV (PLHIV) and Isoniazid Prophylactic Treatment(3–5). The African region is home to about four out of five HIV-positive TB cases and an equal proportion of TB deaths among HIV-positive people, according to the same report(6).

In Mali, according to the 2015 report of the Sectoral

Unit for the Fight against AIDS of the Ministry of Health (CSLS/MS), there were 34974 patients on ARVs, including 517 co-infected TB/HIV(7). The same year, the National TB Control Program (PNLT) revealed that 13% of tuberculosis cases, all forms screened, were infected with HIV, the highest rate of co-infection being in Bamako with 15%(8). The National Strategic Framework (NSF) for the fight against HIV 2013-2017 has planned as impact results 2: the reduction of mortality among PLHIV by 50% by 2017 with the intervention strategy: isoniazid prophylaxis (INH)(9).

According to the 2015 global report of the CSRef CII's HIV care, out of 102 patients initiated to ARVs in the facility, 29 developed active tuberculosis, i.e. a TB/HIV co-infection rate of 28.4% and 10 died, i.e. a mortality rate of 9.8%(10). Thus, the ICC for six (06) months, coupled with ARVs from initiation, was established in 2016 as part of the care of PLHIV. In five (5) years of application, we have not found any evaluation report conducted in Mali concerning the contribution of this health action, hence the interest of our study.

The hypothesis of the present study was that the ICC for six (6) months had reduced tuberculosis morbidity and mortality in PLHIV followed at the CSRéf CII from June 2016 to September 2020.

The objective of the study was to assess the impact of IPC for six (6) months on TB incidence and mortality rates in PHAs.

Methodology

This was a retrospective cohort study carried out at the Reference Health Center of Commune II (CSRef CII) of the District of Bamako. The study focused on PLHIV monitoring data from 2015, our reference, and those from 2016 to 2020, the period of effectiveness of the TPI. We carried out an exhaustive sampling by purposive choice. The study was open to all PHAs initiated with ART and IPT from 2016 to 2018 and followed up until September 30, 2020, our data collection deadline. Included in our study were

the medical records of all confirmed cases of HIV, on ART and who received IPT at their initiation to ARVs at the CSRef CII, during the period covered by the data collection.

Data collected using a questionnaire from medical records, TPI and follow-up registers, ESOP-5 database; focused on the sociodemographic and clinical characteristics of patients, the treatment regimen adopted, adherence to treatment and the patient's outcome during follow-up. Data were analyzed with SPSS-25. The Preventive Fraction in Exposures was used to measure the effectiveness of IPT, and logistic regression to determine factors associated with the occurrence of death. The significance level was less than 0.05.

Ethical considerations

After obtaining the authorization of the chief physician of the CSRef CII for the use of the data of the health facility. During data collection, details related to patient identification were not collected. No physical or oral contact was made with patients. No data were disclosed throughout the study. Our study was not submitted to the ethics committee for approval, as it was carried out as part of our end-of-cycle thesis.

Results

Our study population consisted of 122 HIV-positive patients followed at the CSRef CII, the median age was 37 years with extremes of 16 and 77 years. The sex ratio was 2.5 in favour of women. The profession most affected by HIV was shopkeepers 32% (39/122), the least affected pupils/students 4.9% (6/122). Monogamous married couples were more frequently affected, 41% (50/122). HIV type 1 was the most represented with 94.3% (115/122) and three-quarters (76.1%) (70) had a CD4 count < 350 cells/mm³.

- *Frequency of active tuberculosis and death among PLHIV on ART and CUP during follow-up*

During the follow-up, 102 patients completed their six (6) months of IPT (83.6%), the compliance rate was 81.1% (99/122), five (5) reported adverse drug reactions (4.1%). Two (2) patients developed active

tuberculosis, i.e. a TB/HIV co-infection rate of 1.6%, and 19 died, i.e. a mortality rate of 15.6% in 5 years (Table I).

- *Comparison of Active TB Frequency and Mortality Rate among PHAs before IPT in 2015 to those of 2020 after IPT*

The incidence of active TB disease and the mortality rate in 2015 (the period before the introduction of IPT among PHAs) were 28.4% and 9.8%, respectively. On the other hand, those of 2020, corresponding to the fifth year of implementation of the TPI, were 0% and 1.7% respectively. This demonstrates the impact of IPT on the survival of HIV-positive people (Figure).

- *Measuring the effectiveness of IPT in PHA (Table II)*

Patients who received IPT were 94 times less likely to develop active TB during their follow-up compared to those who did not (RR= 0.06 [0.01-0.24]). In other words, the implementation of IPT prevented the occurrence of 94% more cases of active TB in PLHIV from 2016 to 2020 (eFP= 94% [0.76 - 0.99]).

- *Factors associated with mortality in PLHIV on ARV treatment and receiving Isoniazid Chemo Prophylaxis for six (6) months at CSRef CII.*

After adjusting for other independent variables (sex, weight, height, occupation, education level, marital status, nutritional status, tuberculosis history, HIV type, WHO clinical stage at initiation, baseline CD4 count, baseline hemoglobin level, baseline viral load, treatment line at initiation, Cotrimoxazole prophylaxis, adherence to treatment, outcome and the occurrence of drug-related side effects) found that the variables Age (p = 0.008 [0.911 - 0.986]), and BMI (p = 0.011 [1.046 - 1.407]) were significantly associated with the occurrence of death in PLHIV on ARV+IPT (Table III).

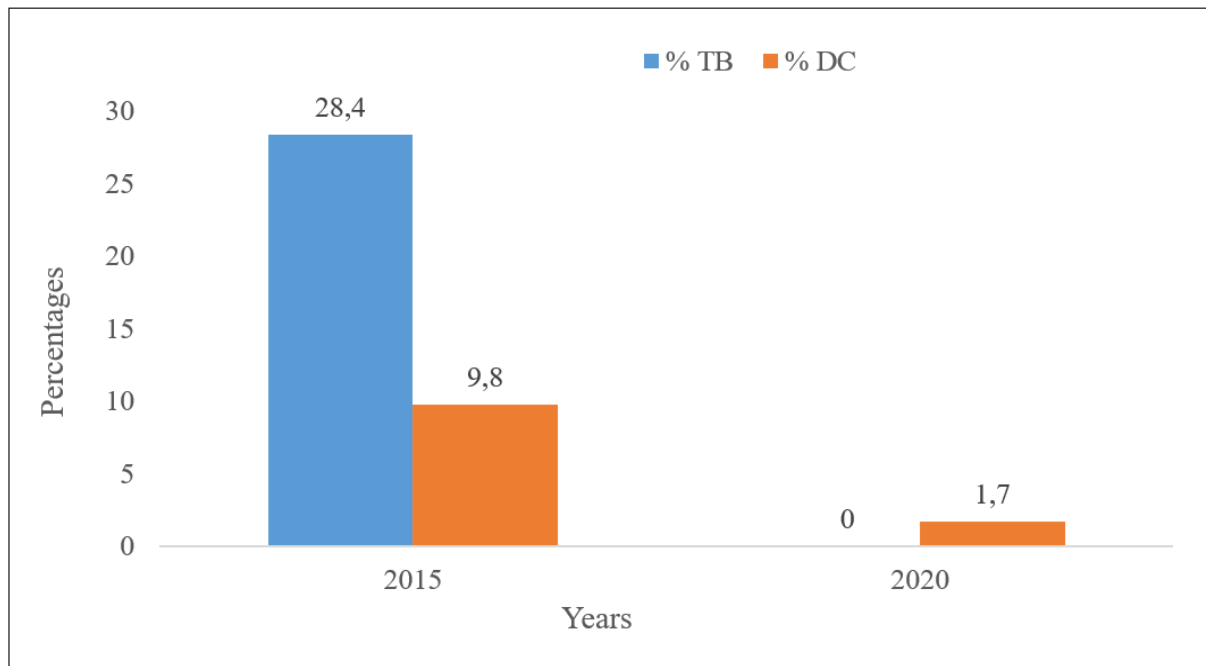


Figure 1: Comparison of the incidence of active TB disease and the mortality rate among PHA before IPT in 2015 to those of 2020 after IPT was introduced

Table I: Characteristics of the follow-up of the 122 PLHIV who received ART+TPI

Characteristics	Frequency	Percentage
Treatment adherence		
Good	99	81,1
Bad	23	18,9
Adverse drug reaction		
Yes	5	4,1
No	117	95,9
Patient fate		
6 months of TPI completed	102	83,6
Lost from sight	19	15,6
Transferred	1	0,8
Active tuberculosis that occurred		
Yes	2	1,6
No	120	98,4
Death of the patient		
Yes	19	15,6
No	103	84,4

Table II: Evaluation of the impact of ART+TPI in our study population

Exhibition	TB+	TB-	Total	P	Inc.	RR [95% CI]	FPe [95% CI]	Fpp
TPI+	2	120	122	54,46	0,02	0,06	0,94	51,32
TPI-	29	73	102	45,54	0,28	[0,01- 0,24]	[0,76 - 0,99]	
Total			224	100				

TB+: presence of active tuberculosis; TB-: absence of active tuberculosis; IPT+: subject to preventive treatment with isoniazid; PTPI+: proportion of subjects who have benefited from IPT; PTPI-: proportion of subjects who did not benefit from the IPT; Inc. TPI+: the number of cases among the exposed; Inc. TPI-: the

number of cases among the unexposed; RR: the relative risk, risk ratio for the exposed and the non-exposed; [95% CI]: 95% confidence interval; FPe ($FPe=1-RR$): the preventive fraction of the risk in the exposed; FPP ($FPP = FPe * P$): The preventive fraction in the population, it also tells us about the effectiveness and coverage rate of the intervention.

Table III : Factors associated with the occurrence of death in PHA who received ART+IPT

Factors	B	H.E.	Wald	ddl	GIS.	Exp(B)	I C 95% de EXP(B)
							Inf. U.
Age	-0,054	0,02	7,074	1	0,008	0,948	0,911 0,986
BMI	0,193	0,076	6,511	1	0,011	1,213	1,046 1,407
Constant	-0,168	1,642	0,01	1	0,919	0,846	

B: slope, SE: standard error, Wald: the value of the statistical test, ddl: degree of freedom, Sig.: statistical significance, EXP(B): odds ratio, BMI: body mass index

Discussion

• *Challenges and limitations of the study*

The relatively short time of six (06) months, led us to restrict our period concerned by the collection, from 2016 to 2018, which we would have liked to extend until the end of September 2020. In addition, the study could be subject to information bias because the dates of death of our patients, most of whom are notified by telephone to the head of the HIV care unit during the active search for those lost to follow-up for more than 3 months.

• *Discussion of the main results of the study*

Our study population of 122 HIV-positive patients followed at the CSRef CII, had a median age of 37 years with extremes of 16 and 77 years. This result is similar to that of Golub JE. et al., 2007 who, in their study carried out in Rio de Janeiro on the impact of ART+IPT, found a median age of 35 years(11); and superior to that of Yirdaw KD. et al., 2014 in their cohort study on the beneficial effects of IPT on TB incidence among PLHIV in Ethiopia who report a median age of 30 years(12). This result could be explained by the fact that the population is mostly young in commune II, also because it is the segment of society that is more sexually active, better informed and aware, and above all more autonomous in terms of decisions concerning the use of care.

The sex ratio was 2.5 in favour of women. This result is higher than those found by Yirdaw KD. et al., 2014 who reported a sex ratio of 1.23% in favour of women; as well as that of Coulibaly MY., 2011 during its study on HIV/BK co-infection at the Reference Health Center of Commune I of the District of Bamako, which found a sex ratio of 1.67 in favor of women(13). This result shows that women are more affected by HIV than men, this can be explained by the fact that anatomically the contact surface in women is larger than for men, socially by the fact that we are in a society with a polygamous majority in which men tend to neglect themselves by making less use of health care.

The profession most affected by HIV was shopkeepers 32% (39/122), the least affected pupils/students 4.9% (6/122). This result is different from that of Coulibaly MY., 2011, who found that traders represent 25% and pupils/students 6.3% of HIV-positive people. These results express a possible relationship between the level of education and the risk of contracting HIV, because in the Malian context most traders are not in school.

Monogamous married couples were more frequently affected, 41% (50/122). This result is lower than that of Coulibaly MY., 2011 who found that married couples were the most affected and represented 56.2% of patients; This difference could be explained by the

fact that he did not distinguish between the categories of bride and groom. This is due to the fact that monogamists are less likely to use HIV prevention measures such as fidelity, abstinence and condom use. HIV type 1 was the most represented with 94.3% (115/122). This result is in line with that of COULIBALY MY., 2011 which found 96.9% HIV-1. This is normal because HIV-1 is very widespread throughout the world. It is the cause of the AIDS pandemic and poses a major public health problem in all continents. On the other hand, HIV-2 has a much more limited spread. It is mainly present in West Africa, in particular in Guinea-Bissau, Gambia, Senegal, Côte d'Ivoire and Burkina Faso(14).

The rate of completion of the assessment to determine the CD4 count at baseline was 75.4% (92/122), of these, three-quarters or 76.1% (70/92) had a low CD4 count (less than 350 cells/mm³). This result is similar to that of Yirdaw KD. et al., 2014 who report a baseline CD4 count < 350 cells/mm³ in 77% of cases. We understand from this result that T-DC4 lymphocyte testing is strongly performed in common II, but that sensitization efforts must be made so that PLHIV can start ART before having a low CD4 count.

- *Frequency of active tuberculosis and death among PLHIV on ART and CUP during follow-up*

During follow-up, two (2) patients developed active tuberculosis, i.e. a TB/HIV co-infection rate of 1.6% and 19 died i.e. a mortality rate of 15.6% in 5 years.

- *Measuring the effectiveness of IPT in PHA*

Patients who received IPT were 94 times less likely to develop active TB during their follow-up compared to those who did not (RR= 0.06 [0.01-0.24]). This result is similar to that of Golub JE. et al., 2007 who find RR= 0.24 (0.11–0.53).

- *Factors associated with mortality in PLHIV on ARV treatment and receiving Isoniazid Chemo Prophylaxis for six (6) months at the CSRef de la Commune II*

After adjusting for other independent variables: sociodemographic, clinical, and follow-up; Age variables (p = 0.008 [0.911 - 0.986]), and BMI (p = 0.011 [1.046 - 1.407]) were significantly associated

with the occurrence of death in PLHIV on ARV+IPT. A one-unit increase in the patient's BMI value was associated with a 19.3% increase in the patient's risk of death. This result could be explained by the fact that our study population is mostly young and age does not have a normal distribution. It is in contradiction with that of Adambounou TAS. et al., 2015 in their study on Factors associated with the death of TB/HIV co-infected patients in Togo, reporting a 92% reduction in the risk of death in coinfecting patients whose weight status had improved compared to those who had remained thin(15). This discrepancy could be explained by their type of study, case-control and the fact that they used the evolution of weight status from the beginning and at six (6) months, while we used only the weight status at the initiation of ART+TPI.

Conclusion

Our study found that preventive treatment with isoniazid for six (6) months from initiation of ART in PHAs significantly reduced the rate of HIV-related deaths from 2016 to 2020 and almost eliminated HIV/TB co-infection. However, efforts remain to be made in the context of the monitoring and evaluation of activities. This is why we suggest that the supervisory authority take into account the results of this study, which can be used as a reference to implement an assessment of the impact of IPT among PLHIV at the national level.

Authors' contributions:

- The manuscript was initiated by Doctor Adama TRAORE
- The other authors, Dr. Bakary DIARRA, Dr. Tite DEMBELE, Dr. Cheick Abou COULIBALY and Prof. Hamadoun SANGHO, have read and corrected the drafts up to this stage.

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