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Original article

Management of tuberculosis and HIV co-infection in Cotonou, Benin☆

Évaluation de la prise en charge de la co-infection tuberculose et VIH à Cotonou, Bénin

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Abstract

Objectives. – The authors had for aim to assess the management of tuberculosis and HIV co-infection in Cotonou, Benin.

Patients and methods. – We made a cross-sectional, retrospective, and descriptive study comparing the clinical presentation and outcome of patients with tuberculosis and HIV co-infection versus patients with tuberculosis alone, all managed at the National Pneumophtisiology Center in Cotonou, Benin, in 2009.

Results. – The rate of HIV screening in TB patients was 99%. One thousand and eighty-six TB patients were included and 259 were HIV positive. The mean age of co-infected patients was 36 years, versus 34 for TB mono-infected patients. The sex ratio among co-infected was 1.15 versus 2.25 among TB patients. Positive pulmonary sputum was less frequent with co-infection. Two hundred and fifty-seven over 259 patients were treated with cotrimoxazole. One hundred and eighty-five over 234 (79.05%) had CD4 counts < 350. Eighty-five (46%) of the 185 patients with CD4 < 350, were given antiretroviral therapy. Treatment success rate was lower for co-infected (75%) than for patients with TB alone (86%), and death rates were higher in co-infected patients (10% vs. 3%).

Conclusion. – High death rate and high rate of lost to follow-up are arguments for systematic antiretroviral treatment of co-infected patients. Early screening for TB and HIV, and reviewing the current national recommendations, as well as an increased governmental effort to provide medicines to all patients in need of ARV are mandatory.

Keywords: Co-infection; Tuberculosis; HIV; AIDS

Résumé

Objectifs. – Évaluer la prise en charge de la co-infection tuberculose et VIH à Cotonou, Bénin.

Patients et méthodes. – Étude transversale, rétrospective, à visée descriptive et analytique comparant les caractéristiques épidémiocliniques et évolutives des patients co-infectés par la tuberculose et le VIH aux patients mono-infectés par la tuberculose et pris en charge en 2009 au Centre national de pneumophtisiologie de Cotonou.

Résultats. – Le taux de dépistage du VIH chez les patients infectés par la tuberculose était de 99 %. Des 1086 patients inclus, 259 étaient co-infectés par le VIH. L'âge moyen des co-infectés était de 36 ans, versus 34 ans pour les mono-infectés. Le sex-ratio chez les co-infectés était de 1,15 versus 2,25 chez les mono-infectés. L'atteinte pulmonaire bacillifère était moins fréquente dans la co-infection.Deux cent cinquante-sept sur 259, soit 99 %, des co-infectés on été mis sous cotrimoxazole. Cent quatre-vingt-cinq sur 234 (79,05 %) des co-infectés avaient des taux de CD4 < 350. Des 185 co-infectés avec CD4 < 350, 85 (46 %) ont été mis sous anti-rétroviraux. Sur le plan évolutif, les différences entre co-infectés et mono-infectés étaient statistiquement significatives pour les taux de succès thérapeutique (75 % vs 86 %) et de décès (10 % vs 3 %).

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Conclusion. – Les taux élevés de décès et de perdus de vue observés plaident pour une mise systématique sous anti-rétroviraux des co-infectés. Le dépistage précoce, la révision des recommandations actuelles, ainsi qu'un effort accru des pouvoirs publics pour la mise à disposition des médicaments sont nécessaires.

Mots clés : Co-infection ; Tuberculose ; VIH ; SIDA

Subsaharan Africa groups close to 80% of patients presenting with a tuberculosis and HIV co-infection in the world [1]. In 2009, the average prevalence in Subsaharan Africa was 44%; the management remained difficult with a rate of cotrimoxazole chemoprophylaxis (CTM) at 77%, and rate of antiretroviral treatment (ARV) at 36% [1]. In Benin, the surveillance of HIV infection in TB patients began in 1990 at the National Pneumophtisiology Center in Cotonou, (NPCC) and was extended to all Centers for the Screening and Treatment of tuberculosis (CST) in Benin in 2006. In 2008, the co-infection management policy implemented conjointly by the National Plan against Tuberculosis (NPT) and National AIDS Prevention Program (NAPP) was clearly stated with the drafting and and the distribution of the co-infection guide [2].

The guide recommends a systematic screening of HIV infection for all patients presenting to prevent other opportunistic infections. ARV treatment is given according to eligibility criteria including CD4 count [2]. ARV treatment should be initiated between 2 weeks and 2 months after initiation of antituberculous treatment if it is well tolerated, when the CD4 count < 200. If this count ranges between 200 and 300, it should be initiated at the end of the 2nd months or when possible, at the end of antituberculous treatment at the 6th or 8th month according to patients, and when it is above 350, it should be initiated at the end of antituberculous treatment, if no patient is classified stage IV according to the WHO scale.

One year after implementing the co-infection management policy, we decided to assess the management of the tuberculosis and HIV co-infection in Cotonou

We had for specific goal to:

- describe the epidemiological and clinical aspects of tuberculosis and HIV co-infection;
- compare the results of treatment between co-infected and mono-infected patients;
- issue recommendations to improve the management of co-infection.

1. Study design, materials, and method

We made a cross-sectional, retrospective, descriptive, and analytic study comparing patients with tuberculosis and HIV co-infection (co-infected group) versus patients with tuberculosis alone (mono-infected group).

The patients were all managed by the National Pneumophtisiology Center in Cotonou (NPCC), Benin, a reference center for the management of tuberculosis. The NPCC is also the largest Diagnostic and Treatment Center (CST) of Benin and manages an average 33% of TB patients in the country. The study population included all patients diagnosed with TB and treated with antituberculous antibiotics between the January 2009 and December 31, 2009. The patients were all adult (> 15 years) and presented with tuberculosis disease.

1.1. Tuberculosis case definition

Pulmonary tuberculosis positive on direct microscopic examination (+DEPT) was defined as a case of pulmonary presentation with at least one sputum smear positive for acid-fast bacillus (AFB) on direct microscopic examination. This group included new cases (1st episode) and retreatment cases (2nd episode). Pulmonary tuberculosis negative on direct microscopic examination (−DEPT) was defined as a case of pulmonary tuberculosis with the association of the three following conditions:

- absence of AFB positivity after two series of three sputum smears made at least 15 days apart;
- no improvement of clinical symptoms after non-specific antibiotherapy (amoxicillin 3 g/d for 15 days) between the two series of three sputum smears;
- and radiological imaging suggesting tuberculosis.

Extrapulmonary tuberculosis (EPTB) was defined as any tuberculous presentation other than lung parenchyma. The medical diagnosis is made on clinical, biological (inflammation chronic), radiological (imaging), and therapeutic data (no improvement of symptoms after non specific antibiotherapy for 15 days).

HIV was screened for in blood with the ELISA. Positive samples were confirmed by a highly discriminating test for HIV1/2 (Genie II HIV1/HIV2®, Biorad, France).

The patients with a non-determined HIV status were excluded from study. All patients were treated by antituberculous antibiotics according to national recommendations [2]. The treatment for new cases during the initial phase included, 2 months of rifampicin, isoniazid, pyrazinamide, and ethambutol combination, and during the 4-month maintenance phase a combination of rifampicin and isoniazid (2RHZE/4RH). The retreatment protocol lasted 8 months and included three phases: an initial, an intermediate, and a maintenance phase. The initial phase lasted 2 months and combined rifampicin, isoniazid, pyrazinamid, ethambutol, and streptomycin (2RHZES); the intermediate phase lasted 1 month and combined rifampicin, isoniazid, pyrazinamid (ERHZ); the maintenance phase lasted 5 months and combined ethambutol, rifampicin, isoniazid, and pyrazinamide (5ERH), for retreatments [2 RHZES/ERZ/5 ERH]. In case of TB and HIV co-infection, the patient had to be systematically treated with cotrimoxazole (CTM) to prevent

other opportunistic infections. CD4 count was performed with a flow cytometer CYFLOW version 2. The antiretroviral treatment (ARV) combined two nucleoside analogues (stavudine or zidovudine + lamivudine and a non-nucleoside analogue (efavirenz). In case of HIV 2 infection (or HIV 1 and 2), three nucleoside analogues (stavudine + lamivudine + abacavir or zidovudine + lamivudine + abacavir) were used according to national recommendations [2].

1.2. Treatment results

Therapeutic success was any favorable outcome at the end of treatment according to clinical, biological and radiological (−DEPT and TEP), and/or bacteriological (+DEPT) data.

Treatment was considered as having failed if a +DEPT patient still had a positive direct microscopic examination at the end of the 5th or 6th month of treatment for new cases or at the end of the 8th month for retreated patients. Death occurring at any time during antituberculous treatment was reported in the study. Patients were considered as lost to follow-up when absent for at least 2 months during treatment, or absent for the cohort analysis. Patients were classified as transferred when a patient was transferred to another site of management during treatment and whose treatment result was not documented.

1.2.1. Data collection and processing

The study data was collected in the tuberculosis and co-infection registers and in the medical files of included patients. A questionnaire was used to assess the management, with question on the epidemiological and clinical aspects as well as on the outcome of treatment, to collect individual data for all included patients. The epidemiological and clinical aspects to be documented were: sociodemographic data, clinical presentations: +DEPT, −DEPT, TEP, screening for HIV in tuberculous patients, CD4 count at diagnosis, CTM and ARV treatment or not. Treatment outcome was documented for co-infected and mono-infected patients and compared. The data was collected then processed with the EPI Data Analysis software, version 2.0. The Chi-test^2 was used for comparisons. The statistical threshold of significance was set at 5% ($p < 0.05$). The CI was 95% for the prevalence of co-infection in all included patients.

1.3. Results

One thousand and ninety-nine cases of tuberculosis in adults were recorded during the study period, 1087 were tested for HIV (99%). One patient was excluded because his HIV status was not determined, thus 1086 patients were finally included in the study.

2. Epidemiological and clinical data

2.1. Sociodemographic data

The seroprevalence of HIV among patients presenting with tuberculosis was 24% in our study (IC95%: 21.4–26.5%). The

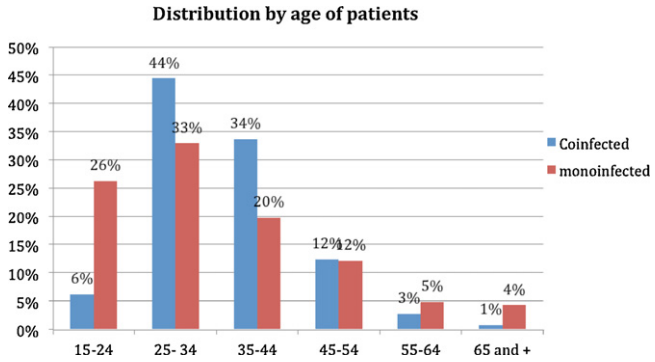

Fig. 1. Distribution by age of patients.
Répartition suivant l'âge des patients.

average age of patients was 36 years (15–72 years) for co-infected and 34 years (15–90 years) for mono-infected patients, and 35 years (15–90 years) for the whole study population. The male/female sex ratio was 1.14 for co-infected versus 2.25 for mono-infected patients. Most co-infected patients were young adults between 25 and 44 years of age (Fig. 1).

2.2. Prevalence of clinical tuberculosis presentations in co-infected patients

Bacilliferous presentations were significantly les frequent in co-infected patients contrary to −DEPT and of the TEP (Table 1). For TEP, the most frequent localizations were: pleural 55 cases (46%), lymph nodes 24 cases (20%), vertebral 19 cases (16%), peritoneal 18 cases (15%), pericardial three cases (2%), ENT three cases (2%), and neuromeningeal two cases (1.6%).

2.2.1. CD4 count at diagnosis

Two hundred and fifty-nine patients were co-infected, 234 (90%) had a CD4 count at initiation of antituberculous treatment.

One hundred and eighty-five over 234 (79.05%) of co-infected patients had a CD4 count < 350 (Table 2)

2.2.2. Rate of CTM chemoprophylaxis

Two hundred and fifty-seven over 259, 99%, of the co-infected patients were treated with CTM

2.2.3. Rate of ARV treatment

One hundred and eighty-five co-infected patients had a CD4 count < 350. 85 (46%) were treated with ARV.

Table 1
Clinical forms of tuberculosis in the co-infection.
Formes cliniques de tuberculose au sein de la co-infection.

Tuberculosis presentation	Co-infected patients		Mono-infected patients		p
	n	%	n	%	
+DEPT	178	69	696	84	< 0.01
−DEPT	44	17	40	5	0.21
TEP	37	14	91	11	0.92
Total	259	100	827	100	–

Table 2
CD4 count at diagnosis of tuberculosis.
Taux de CD4 au moment du diagnostic de la tuberculose.

CD4	*n*	%
< 200	121	52
200–350	64	27
≥ 350	49	21
Total	234	100

Table 3
Results of treatment.
Résultats du traitement.

Results of treatment	Co-infected patients		Mono-infected patients		*p*
	n	%	*n*	%	
Success	195	75	712	86	< 0.01
Failure	3	1	31	4	0.04
Dead	27	10	26	3	< 0.01
LFU	28	11	48	6	0.80
Transferred	6	2	10	1	0.23
Total	259	100	827	100	–

One hundred and twenty-one had a CD4 count < 200. 80 (66%) were treated with ARV. Eight (16%) of the 49 co-infected patients with CD4 > 350 were treated with ARV.

2.3. Outcome data

The observed differences were statistically significant for success, failure, and death rates. The rate of lost to follow-up (LFU) was higher in co-infected patients (Table 3).

The failure rate was higher in mono-infected patients.

Twenty-seven co-infected patients died: 24 (89%) had a CD4 count < 350. 8 (30%) had been treated with ARV.

Among the 28 LFU: 24 (85.71%) had a CD4 count < 350. Seven (25%) had been treated with ARV.

Some differences were observed for success, failure, and death rates in co-infected patients (pNS) between those treated with ARV and those without ARV (Table 4).

The results of treatment for co-infected patients with CD4 < 350 were better than for those not treated with ARV (Table 5), whereas for co-infected patients with CD4 > 350, no significant difference was observed for the death rate (Table 6)

Table 4
Results of treatment for co-infected patients with CD4 > 350 (*n* = 49).
Résultats du traitement des co-infectés avec CD4 > 350 (n = 49).

Results of treatment	Co-infected patients with ARV		Co-infected patients without ARV		*p*
	n	%	*n*	%	
Success	6	75	31	76	0.63
Failure	0	0	1	2	–
Dead	0	0	2	5	–
LFU	1	12.5	6	15	0.12
Transferred	1	12.5	1	2	–
Total	8	100	41	100	–

Table 5
Results of treatment for co-infected patients with CD4 < 350 (*n* = 85).
Résultats du traitement des co-infectés avec CD4< 350 (n = 85).

Results of treatment	Co-infected patients with ARV		Co-infected patients without ARV		*p*
	n	%	*n*	%	
Success	70	82	68	68	0.33
Failure	1	2	1	1	1.00
Dead	9	10	16	16	1.00
LFU	4	5	12	12	0.11
Transferred	1	2	3	3	0.63
Total	85	100	100	100	

Table 6
Results of treatment for co-infected patients with CD4 > 350 (*n* = 49).
Résultats du traitement des co-infectés avec CD4 > 350 (n = 49).

Results of treatment	Co-infected patients with ARV		Co-infected patients without ARV		*p*
	n	%	*n*	%	
Success	6	75	31	76	0.63
Failure	0	0	1	2	–
Dead	0	0	2	5	–
LFU	1	12.5	6	15	0.12
Transferred	1	12.5	1	2	–
Total	8	100	41	100	–

3. Discussion

We assessed the management of co-infection by analyzing the epidemiological and clinical aspects as well as the outcome of co-infection 1 year after implementing the conjoint recommendations of the national plan against tuberculosis and national plan against AIDS in Benin. Our study could have limitations due to its retrospective aspect and related to data collection. Nevertheless, the management of tuberculosis is standardized and data is usually collected routinely in the same fashion; so if there was any bias, it would not have been very important. Thus, this study allowed assessing routine practice. Most co-infected patients were young adults between 25 and 44 years of age, the most active part of our population, whether economically or sexually. The average age of 36 years in this Cotonou population was similar to the average 35 years of age reported in Lome, Togo by Dagnra et al. [3]. Tosi et al. [4] had reported an average age of 31 years a few years earlier in N'djamena, Chad. This young age is thus common to most capitals of Subsaharan Africa.

The great difference in sex-ratio between mono and co-infected patients could be due to the feminization of the HIV epidemic in our country; indeed the prevalence is 1.2% in the global population, and 1.5% for women versus 0.8% for men. [5]. This vulnerability of women could be due to the difficult condition of women in our country.

Close to 80% of patients were diagnosed with a CD4 count < 350. This explains the lower frequency of bacilliferous +DEPT presentations and the predominance of -DEPT. Indeed, cellular immunodepression prevents the granulomas

which usually become necrotic to create the cavity with as clinical consequence, the expulsion of BK in sputum [6]. This cellular immunodepression is also responsible for lymph node extension and spreading of BK to all the body, which accounts for the high frequency of extra-pulmonary localizations [7]. This was reported previously by Malawi by Teck et al. [8] who had concluded that, at diagnosis of co-infection, nine patients out of ten also presented an indication for ARV treatment.

Systematic screening for HIV (99%) in patients with tuberculosis, as well as CTM treatment, seems to be well-anchored habits with 99% of CTM treatment. The rate of ARV treatment for co-infected patients in Cotonou should still be improved. This low rate of ARV treatment was also reported by other African authors. Kumwenda et al. reported a rate of 38% in Zomba, Malawi [9]; Takarinda et al. reported a rate of 15% in Chitangwiza, Zimbabwe [10]. The difficulty to organize and support the assessment of eligibility seem common to all. Indeed, in our study, 10% of co-infected patients had not had a CD4 count. Even though CD4 count is a free assessment, accessibility to this examination is not systematic; indeed Cyflow breakdowns are not uncommon. This explains the delay before initiation of ARV treatment. Furthermore, when CD4 counts are available, and when they range between 200 and 350, recommendations are not explicit enough on when to initiate antiretroviral treatment. Thus, it is difficult to clearly determine the responsibility of prescribers in case of non-observance of eligibility criteria for ARV treatment for these patients. And when the counts < 200, ARV treatment should be initiated in every case before the end of the initial phase of antituberculous treatment [2]. ARV treatment was initiated for 66% of patients at the end of antituberculous treatment in our study. This could be due to a weak involvement of prescribers since there were no formal contraindications noted in the patients' files. The reasons for a high rate of LFU (11% versus 6%) are not documented in this study, but it is reasonable to think that advanced HIV infection and its burden of opportunistic diseases may discourage patients, with as unavoidable consequence death. In any case, the reported death rate was significantly higher (10% versus 3%,) in co-infection.

The higher rate of failure for mono-infection vs. co-infection does not correlate to frequently reported situations [11,12]. The failure issue of antituberculous treatment is bacteriological. It may be observed only for +DEPT cases. Hence, the significant predominance of bacilliferous presentations (84% versus 69%) among co-infected patients could explain this. The other reason, just as important and associated to the previously mentioned one, could be the difference in sex ratio between co-infected and mono-infected patients. Indeed, several authors, African or not [13–16], have reported the better observance of antituberculous treatment in women. Thus it was not surprising that more failures are observed in mono-infected patients for whom the male/female sex ratio was twice higher than for co-infected patients.

One year after implementing the new conjoint NPT-NAPP recommendations, the impact of HIV on the outcome of antituberculous treatment must still be improved in Cotonou. It may be difficult to organize and support the assessment of eligibility, but it is also important to trigger more involvement in prescribers for an aggressive management of co-infection. The clinical benefit of a rapid ARV treatment initiation, without waiting for the end of the antituberculous treatment, is well documented and decreases mortality by more than 50% [17,18]. The differences observed between co-infected patients treated with ARV and co-infected patients without ARV with CD4 counts < 350, even if non statistically significant, and the high death rate in patients with CD4 counts > 350 without ARV, could confirm this. This is why it is mandatory to choose an early introduction of ARV at diagnosis of co-infection, according to international recommendations [19,20]. This entails reviewing the national management strategy of tuberculosis co-infection for ARV treatment. This means a greater effort of public administration for the availability of drugs. ARV will allow reducing the death rate in co-infection [21], but also reducing the incidence of tuberculosis in patients infected by HIV [22,23].

4. Conclusion

Tuberculosis and HIV co-infection in Cotonou is typically observed in a young population and the diagnosis is late. The subsequent high rate of LFU and death are arguments for systematic ARV treatment of co-infected patients. It is equally important to promote the education and awareness of young people, as well as early screening of HIV and tuberculosis.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article and that this study did not benefit from any financial help.

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