Tuberculosis after HAART initiation in HIV-positive patients from five countries with a high tuberculosis burden

Maryline M.B. Bonnet[a], Loretxu L.P. Pinoges[a], Francis F.V. Varaine[b], Barbara B.O. Oberhauser[b], Daniel D.O. O'Brien[b], Yared Y.K. Kebede[b], Cathy C.H. Hewison[b], Rony R.Z. Zachariah[b] and Laurent L.F. Ferradini[a]

Background: HAART reduces tuberculosis (TB) incidence in people living with HIV/AIDS but those starting HAART may develop active TB or subclinical TB may become apparent in the immune reconstitution inflammatory syndrome.

Objective: To measure the incidence rate of notified TB in people receiving HAART in five HIV programmes occurring in low-resource countries with a high TB/HIV burden.

Methods: A retrospective review in five Médecins Sans Frontières programmes (Cambodia, Thailand, Kenya, Malawi and Cameroon) allowed incidence rates of notified TB to be calculated based on follow-up time after HAART initiation.

Results: Among 3151 patients analysed, 90% had a CD4 cell count of < 200 cells/μl. Median follow-up time ranged from 3.7 months in Thailand or Kenya to 11.1 months in Cambodia. Incidence rates were 7.6, 10.4, 17.6, 14.3 and 4.8/100 person-years for pulmonary TB and 12.7, 4.3, 6.9, 2.1 and 0/100 person-years for extra-pulmonary TB in the programmes in Cambodia, Thailand, Kenya, Malawi and Cameroon, respectively. Overall, 62.3% of pulmonary TB and 54.9% of extra-pulmonary TB were diagnosed within 3 months after HAART initiation.

Conclusion: High incidence rates of notified TB under HAART in programmes held in poor-resource countries were observed; these were likely to include both undiagnosed prevalent TB at HAART initiation and subclinical TB developing during the immune reconstitution inflammatory syndrome. This raises operational issues concerning TB diagnosis and treatment of TB/HIV-coinfected patients and prompts for urgent TB and HIV care integration.

AIDS 2006, **20**:1275–1279

Introduction

In resource-limited settings, tuberculosis (TB) is one of the main opportunistic infections and a leading cause of mortality in people living with HIV/AIDS [1–3]. HAART, through immune restoration, reduces the TB incidence [4]. However, individuals who initiate HAART may still be reported as having TB, either

From the [a]MSF Epicentre, Paris, France, and the [b]MSF Médecins Sans Frontieres.
Corrpondence to Ms M. Bonnet, Rue de Lausanne 78 CH-1211 Genève 21, Switzerland.
E-mail: maryline.bonnet@geneva.msf.org
Received: 29 October 2005; revised: 12 January 2006; accepted: 2 March 2006.

ISSN 0269-9370 © 2006 Lippincott Williams & Wilkins

because they are developing active TB because they have subclinical TB that becomes apparent in the immune reconstitution inflammatory syndrome [5]. If this syndrome occurs, it is more likely within the first 3 months after HAART initiation [6,7]. Treatment of patients already on HAART for TB is complex because of the high number of drugs administered simultaneously, which poses practical problems related to adherence and side-effects [6–10].

This study is a retrospective cohort analysis of patients notified as having TB after HAART initiation in five Médecins Sans Frontières (MSF) programmes in low-resource countries with a high TB/HIV burden.

Methods

Settings

By December 2004, MSF was running HIV/AIDS programmes in 24 countries around the world and had approximately 34 000 people enrolled who were followed while taking HAART. Among these programmes, the five included in this study offered HAART for at least 2 years. They are located in Phnom Penh (Cambodia), Surin (Thailand), Homa Bay (Kenya), Chiradzulu (Malawi) and Yaounde (Cameroon). HAART eligibility criteria were similar in all programmes and included patients classified at being at World Health Organization (WHO) clinical stage IV or at stage I, II or III with a CD4 cell count < 200 cells/μl [11].

Diagnosis of tuberculosis

Before HAART initiation, patients were screened for clinical suggestive signs of pulmonary or extra-pulmonary TB. In the Cameroon programme, chest X-ray was systematically performed before starting HAART.

Patients presenting with cough or any respiratory symptoms for 2 weeks or more had three sputum examinations for detection of acid-fast bacilli. Diagnosis of smear-negative cases was based on standard algorithms following WHO guidelines, which include non-response to at least one course of antibiotic targeting pneumonia, chest X-ray suggesting active pulmonary TB and clinician's decision to prescribe a full course of anti-TB therapy [12]. Diagnosis of extra-pulmonary TB included the association of clinical signs, radiological findings, biochemistry of body fluid, eventually peripheral lymph node fine needle aspiration consistent with active extra-pulmonary TB and clinician's decision to prescribe a full course of anti-TB therapy. Culture of *Mycobacterium tuberculosis* was not available in these programmes.

Inclusions and data collection

All HIV-positive individuals aged 13 years or more and receiving HAART up to December 2003 were included in the analysis. Patients taking TB therapy at the time of HAART initiation were excluded. Data were routinely collected using a standardized monitoring software for HIV patients, called FUCHIA (Follow-UP Care of HIV Infection and AIDS; Epicentre, Paris, France). Demographic data, duration of follow-up, WHO clinical stage, TB and other opportunistic infections, CD4 cell counts and HAART regimen were confidentially recorded. As CD4 cell count was not systematically measured when TB was reported, the most recent available cell count performed 2 months either side of the TB diagnosis was utilized.

Statistical analysis

Incidence rates of notified TB cases were calculated using the numbers of new reported TB cases and were expressed per 100 person-years of follow-up on HAART. The time of follow-up was defined as the interval between HAART initiation and TB diagnosis. For patients on HAART without TB diagnosis, the time of follow-up was defined as the interval between HAART initiation and the last follow-up visit recorded before the date of analysis (April 2004). For patients lost to follow-up or dead, the date of their last recorded visit was utilized. Incidence rates of notified pulmonary and extra-pulmonary TB were measured separately. Simple proportion and 95% confidence intervals were calculated. Analysis was performed using SPSS 11.5 (SPSS, Chicago, Illinois, USA).

Results

A total of 3151 HIV-positive individuals who initiated HAART between December 2001 and December 2003 were included in the analysis. The sex ratio (M/F) ranged from 0.4 in the Cameroon programme to 1.3 in the Cambodia programme. Mean age ranged from 33 years in the Thailand programme to 35 years in the Malawi and Cameroon programmes. Classification as WHO stage 4 also varied, from 26/199 patients (13.1%) in the Cameroon programme to 305/654 (46.6%) in the Kenya programme. Baseline CD4 cell count of < 200 cells/μl ranged between [146/187 (78.1%)] in the Cameroon programme and [621/631 (98.4%)] in the Cambodian programme. The predominant HAART regimen initially prescribed was the fixed drug combination of stavudine, lamuvidine and nevirapine in all programmes (46.3% to 77.8%) except the Cambodia programme, where stavudine, lamuvidine and efavirenz was mostly prescribed (78.0%) (Table 1).

The median durations of follow-up on HAART in Cambodia, Thailand, Kenya, Malawi and Cameroon programmes were 7.3 [interquartile range (IQR) 3.7–12.8], 3.7 (IQR, 1.3–8.3), 3.7 (IQR, 1.4–8.0), 6.7

Table 1. Baseline characteristics of the 3151 patients included in the analysis from the programmes in Cambodia, Thailand, Kenya, Malawi and Cameroon.

	Cambodia	Thailand	Kenya	Malawi	Cameroon
No.	717	500	654	1064	216
Mean age [years (SD)]	34 (7.1)	33 (6.6.)	34 (8.9)	35 (9.1)	35 (8.4)
Sex ratio (M/F)	1.3 (409/308)	1.1 (265/235)	0.6 (248/406)	0.5 (367/666)	0.4 (62/152)
WHO stage [No. (%)]	717	498[a]	654	999[a]	199[a]
1–2	43 (6.0)	79 (15.9)	22 (3.4)	135 (13.5)	37 (18.6)
3	354 (49.4)	117 (23.5)	326 (49.8)	585 (58.6)	136 (68.3)
4	320 (44.6)	302 (60.6)	305 (46.6)	279 (27.9)	26 (13.1)
CD4 cell count [(No. (%)][b]	631	478	558	827	187
50 cells/μl	418 (66.2)	342 (71.6)	201 (36.0)	171 (20.7)	46 (24.6)
50–200 cells/μl	203 (32.2)	117 (24.5)	311 (55.7)	532 (64.3)	100 (53.5)
Antiretroviral therapy [(No. (%)]	717	500	654	1064	216
3TC/d4T/NVP	135 (18.8)	298 (59.6)	392 (59.9)	828 (77.8)	100 (46.3)
3TC/d4T/EFV	559 (78.0)	88 (17.6)	99 (15.1)	3 (0.3)	12 (5.6)
3TC/ZDV/NVP	11 (1.5)	14 (2.8)	95 (14.5)	223 (21.0)	94 (43.5)
3TC/ZDV/EFV	7 (1.0)	9 (1.8)	67 (10.2)	7 (0.6)	5 (2.3)

WHO, World Health Organization; ZDV, zidovudine; 3TC, lamivudine; d4T, stavudine; NVP, nevirapine; EFZ, efavirenz.
[a]In some cases, baseline WHO stage were not recorded.
[b]CD4 cell counts were not systematically measured for all patients.

(IQR, 3.2–15.4) and 11.1 (IQR, 3.2–19.0) months, respectively.

The incidence rates of notified TB are presented for each programme in Table 2. A total of 320 patients with notified TB was reported, including 209 with pulmonary TB (65.3%) and 111 with extra-pulmonary TB (34.7%).

The incidence rate of notified pulmonary TB ranged from 4.8/100 person-years in the Cameroon programme to 17.7/100 person-years in the Kenya programme. Pulmonary TB was reported within the first 3 months after HAART initiation for 29/38 (76.3%), 21/40 (52.5%), 27/52 (51.9%), 46/69 (66.7%) and 8/10 (80.0%) patients with notified pulmonary TB in Cambodia, Thailand, Kenya, Malawi and Cameroon programmes, respectively.

The incidence rate of extra-pulmonary TB ranged from 0/100 person-years in the Cameroon programme to 12.7/100 person-years in the Cambodia programme. Extra-pulmonary TB was reported within the first 3 months after HAART initiation in 34/62 (54.8%), 9/17 (52.9%), 14/21 (66.7%), 4/11 (36.4%) and 0 patients with notified extra-pulmonary TB in the same programmes, respectively.

CD4 cell counts were available at the time of TB diagnosis for only 84/209 (40.2%) patients with pulmonary TB. Among these, 66 (78.6%) had a CD4 cell count < 200 cells/μl and 37 (44.0%) < 50 cells/μl. Similarly, among the 41/111 (36.9%) patients with extra-pulmonary TB and available CD4 cell counts, none had a CD4 cell count > 200 cells/μl and 27 (65.8%) were < 50 cells/μl.

Discussion

Our analysis of open observational cohorts reveals high incidence rates of notified TB among individuals on HAART in five MSF programmes, particularly in the Malawi and Kenya programmes, with pulmonary TB incidence rate of 14.3/100 person-years and 17.6/100 person-years, respectively. These two countries have a very high TB burden, with an overall TB incidence estimated in 2003 of 441/100 000 inhabitants in Malawi and 610/100 000 in Kenya [13]. A lower pulmonary TB incidence rate was observed in the Cameroon programme, where the estimated overall TB incidence (180/100 000 inhabitants) is lower [13]. Even if the high incidence rates observed in programmes in countries with a high TB burden could be expected, we are fully aware

Table 2. Incidence rate of pulmonary and extrapulmonary tuberculosis in the programmes in Cambodia, Thailand, Kenya, Malawi and Cameroon.

	Pulmonary tuberculosis ($n = 209$)			Extrapulmonary tuberculosis ($n = 111$)		
	No.	Person-years	IR (95% CI)	No.	Person-years	IR (95% CI)
Cambodia	38	501.9	7.6 (5.2–10.0)	62	489.6	12.7 (9.5–15.8)
Thailand	40	382.8	10.4 (7.2–13.6)	17	396.1	4.3 (2.3–6.3)
Kenya	52	295.3	17.6 (12.8–22.4)	21	304.7	6.9 (3.9–9.8)
Malawi	69	482.8	14.3 (10.9–17.7)	11	520.0	2.1 (0.8–3.3)
Cameroon	10	210.2	4.8 (1.8–7.8)	0	217.5	0

IR, incidence rate (per 100 person-years); CI, confidence interval.

that under routine programme conditions with no access to *M. tuberculosis* culture, presumptive TB instead of confirmed TB was likely to be reported. In addition, the limited availability of diagnostic tools would make it impossible to distinguish between immune reconstitution inflammatory syndrome and undiagnosed prevalent tuberculosis; this is a common problem in such resource-poor settings. Indeed, since 90% of analysed patients had baseline CD4 cell count < 200 cells/μl, it is possible that some of those with notified TB were in fact suffering from immune reconstitution inflammatory syndrome, which is known to be more common in severely immunocompromised patients initiating antiretroviral therapy [14–19]. Consequently, notified TB cases are likely to be a mixture of true incident diseases, subclinical TB becoming apparent during immune reconstitution inflammatory syndrome and undiagnosed prevalent tuberculosis. Another reason that could lead to overestimation of the number of TB notified cases is the short follow-up of analysed patients (range, 3.7–11.1 months), which also explains the high proportion (60%) of notified cases during the first 3 months after HAART initiation. These limitations might explain why our results are apparently in contrast with those reported in two recent studies conducted in South Africa (incidence rate, 2/100 person-years) and in Ivory Coast (incidence rate, 4/100 person-years), which were both prospective cohort studies with high clinical acumen, full access to *M. tuberculosis* culturing and histology and longer follow-up (medians 16.8 and 26 months in South Africa and Ivory Coast, respectively) [14,15].

In spite of this, our data illustrate the limitations of TB diagnosis in HIV/TB-coinfected patients in resource-poor settings and the urgent need to develop more effective and rapid tests. Indeed, direct sputum microscopy only detects up to 50% of pulmonary TB in HIV-positive patients and a recent prospective study evaluating the prevalence of active TB in HIV-infected patients with a CD4 cell count of > 200 cells/μl reported that 29% of those with culture-confirmed pulmonary TB had normal radiography and clinical examination [20,21]. This study outlined the intrinsic limitations of classical diagnostic tools in HIV-positive patients even when performed in optimal conditions, and the situation is likely to be even worse in more severely immunocompromised patients. Despite such limitations, there is an urgent need to make radiography and other diagnostic tools more widely available and affordable [22]. For instance, fluorescence microscopy, which is more sensitive than the Ziehl–Neelsen method for detecting *M. tuberculosis* and reduces laboratory workload significantly, could be used in many settings [23]. *M. tuberculosis* culture, particularly rapid methods, should also be encouraged in some specific settings [24]. In spite of its lower sensitivity in severely immunocompromised patients, the tuberculin skin test could be assessed for a potential role in improving TB exclusion before HAART initiation, as could the newly introduced interferon-γ assay, but these clearly need further investigation [25].

A direct consequence of TB diagnosis in HIV-positive patients is the need to switch from a nevirapine-based fixed drug combination to an efavirenz-based regimen according to current WHO recommendations [26]. Indeed, interactions between coadministrated rifampicin and nevirapine could increase the risk of hepatotoxicity and potentially impair the efficiency of virological control. Similarly, the replacement of rifampicin by rifabutin is not a realistic alternative for low-income countries because of the high cost of rifabutin. Regardless of the drug chosen, using either efavirenz or rifabutin in HIV/TB-coinfected patients results in discontinuation of the fixed drug combination therapy in HIV or TB treatment, leading to potential deleterious impacts on treatment adherence and disease control. The potential overestimation of TB notified cases in HIV-treatment programmes might lead to poorer individual and programme HIV outcomes by increasing the number of inappropriate treatment changes.

Another challenge encountered in HIV/AIDS programmes is the difficulties in documenting correctly the notified TB cases, because such cases are diagnosed by, or referred to, existing parallel TB programmes. Indeed, notified TB was difficult to document in our programmes because TB was only reported as 'any other opportunistic infection' using our routine monitoring system and detailed TB-related data were only collected under the TB programme conditions. Our results clearly illustrate the urgent need for active integration of TB and HIV/AIDS care, as already stressed strongly by the international community, in order to improve data collection, diagnosis and treatment of TB in HIV-positive patients in resource-poor settings [27].

Our study of observational HIV-positive patient cohorts clearly illustrates the challenges faced by resource-poor countries in TB diagnosis, HIV/TB cotreatment and care integration for TB and HIV. Such challenges will become even more prominent in countries who are scaling up their HAART treatment programmes and adapting their TB protocol from 8 months (with only 2 months rifampicin) to 6 months of a rifampicin-containing regimen [28]. Further research is clearly needed in both TB diagnosis and in devising creative solutions for TB/HIV integrated care in order to improve prognosis of TB/HIV-coinfected patients in developing countries.

Acknowledgements

The authors are grateful to all the medical officers of the programmes in Phnom Penh, Surin, Homa Bay, Chiradzulu and Yaounde.

Sponsorship: This study was supported by the French, Belgium, Swiss and Holland sections of Médecins Sans Frontières.

References

1. Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC, *et al*. **The growing burden of tuberculosis. Global trends and Interactions with the HIV epidemic.** *Arch Intern Med* 2003; **163**:1009–1021.
2. Badri M, Ehrilch R, Wood R, Pulerwitz T, Maartens G. **Association between tuberculosis and HIV disease progression in a high tuberculosis prevalence area.** *Int J Tuber Lung Dis* 2001; **5**:225–232.
3. Whalen C, Nsubuga P, Okwera A, Johnson JL, Hom D, Michael NL, *et al*. **Impact of pulmonary tuberculosis on survival of HIV-infected adults: a prospective study in Uganda.** *AIDS* 2000; **14**:1219–1228.
4. Santoro-Lopes G, Felix de Pinho AM, Harrison LH, Schechter M. **Reduced risk of tuberculosis among Brazilian patients with advanced human immunodeficiency virus infection treated with highly active antiretroviral therapy.** *Clin Infect Dis* 2002; **34**:543–546.
5. Lwan SD, Bekker L, Wood R. **How effectively does HAART restore immune responses to *Mycobacterium tuberculosis*? Implications for tuberculosis control.** *AIDS* 2005; **19**:113–124.
6. French MA, Price P, Stone SF. **Immune restoration disease after antiretroviral therapy.** *AIDS* 2004; **18**:1615–1627.
7. Sungkanuparph S, Vibhagool A, Mootsikapun P, Chetchtisakd P, Tansuphaswaswadikul S, Bowonwatanuwong C. **Opportunistic infections after the initiation of highly active antiretroviral therapy in advanced AIDS patients in an area with a high prevalence of tuberculosis.** *AIDS* 2003; **17**:2129–2131.
8. Mackie NE, Fidler S, Tamm N, Clarke JR, Back D, Weber JN, *et al*. **Clinical implications of stopping nevirapine-based antiretroviral therapy: relative pharmacokinetics and avoidance of drug resistance.** *HIV Med* 2004; **5**:180–184.
9. Ribera E, Pou L, Lopez RM, Crespo M, Falco V, Ocana I, *et al*. **Pharmacokinetic interaction between nevirapine and rifampicin in HIV-infected patients with tuberculosis.** *J AIDS* 2001; **28**:450–453.
10. Joint United Nation Programs on HIV/AIDSUNAIDS. ***Report on the Global HIV/AIDS Epidemic: 4th Global Report.*** Geneva: UNAIDS; 2004.
11. World Health Organization. ***Scaling up Antiretroviral Therapy in Resource-limited Settings: Treatment Guideline for a Public Health Approach.*** Geneva: World Health Organization; 2004.
12. World Health Organization. ***Treatment of Tuberculosis: Guidelines for National Programs.*** Geneva: World Health Organization; 2003.
13. World Health Organization. ***Global Tuberculosis Control: Surveillance, Planning, Financing.*** Geneva: World Health Organization; 2005.
14. Badri M, Wilson D, Wood R. **Effect of highly active antiretroviral therapy on incidence of tuberculosis in South Africa: a cohort study.** *Lancet* 2002; **359**:2059–2064.
15. Seyler C, Toure S, Messou E, Bonard D, Gabillard D, Anglaret X. **Risk factors for active tuberculosis after antiretrovital treatment initiation in Abidjan.** *Am J Respir Crit Care Med* 2005; **172**:123–127.
16. Kirk O, Gatell JM, Mocroft A, Pedersen C, Proenca R, Brettle RP, *et al*. **Infections with *Mycobacterium tuberculosis* and *Mycobacterium avium* among HIV-infected patients after the introduction of highly active antiretroviral therapy.** *Am J Respir Crit Care Med* 2000; **162**:865–872.
17. Girardi E, Antonucci G, Vanacore P, Libanore M, Errante I, Matteelli A, *et al*. **Impact of combination antiretroviral therapy on the risk of tuberculosis among persons with HIV infection.** *AIDS* 2000; **14**:1085–1091.
18. Lawn SD, Bekker LG, Miller RF. **Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals.** *Lancet Infect Dis* 2005; **5**:361–373.
19. Breen RAM, Smith CJ, Cropley I, Johnson MA, Lipman MCI. **Does immune reconstitution syndrome promote active tuberculosis in patients receiving highly active antiretroviral therapy?** *AIDS* 2005; **19**:1201–1206.
20. Harries AD, Maher D, Nunn P. **An approach to the problems of diagnosing and treating adult smear-negative pulmonary tuberculosis in high HIV-prevalence settings in sub-Saharan Africa.** *Bull World Health Organ* 1998; **76**:651–662.
21. Mtei L, Matee M, Herfort O, Bakari M, Horsburgh R, Wadell R, *et al*. **High rates of clinical and subclinical tuberculosis HIV-infected patients ambulatory subjects in Tanzania.** *Clin Infect Dis* 2005; **40**:1500–1507.
22. van Cleef MRA, Kivihya-Ndugga LE, Meme H, Odhiambo JA, klatser PR. **The role and performance of chest X-ray for the diagnosis of tuberculosis: A cost-effective analysis in Nairobi, Kenya.** *BMC Infect Dis* 2005; **5**:111.
23. Kivihya-Ndugga LA, van Cleeff MRA, Githui WA, Nganga LW, Kibuga DK, Odhiambo JA. **A comprehensive comparision of Ziehl–Neelsen and fluorescence microscopy for the diagnosis of tuberculosis in a resource-poor urban setting.** *Int J Tuberc Lung Dis* 2003; **7**:1163–1171.
24. Perkins MD, Kritski AL. **Diagnosis testing in the control of tuberculosis.** *Bull World Health Organ* 2002; **80**:512–513.
25. Pai M, Riley LW, Colford JM Jr. **Interferon-γ assays in the immunodiagnosis of tuberculosis: a systematic review.** *Lancet Infect Dis* 2004; **4**:761–776.
26. Harries A, Maher D, Graham S. ***TB/HIV: A Clinical Manual*, 2nd edn.** Geneva: World Health Organization; 2004:153–154.
27. World Health Organization. ***Interim Policy on Collaborative TB/HIV Activities.*** Geneva: World Health Organization; 2004.
28. Jindani A, Nunn AJ, Enarson DA. **Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial.** *Lancet* 2004; **364**:1244–1251.