SHORT REPORT

Worsening and unmasking of tuberculosis in HIV-1 infected patients after initiating highly active anti-retroviral therapy in Uganda

Joshua Baalwa,[1*] Harriet Mayanja-Kizza,[1] Moses R. Kamya,[1] Laurence John,[2] Andrew Kambugu,[1] & Robert Colebunders[3]

1. Makerere University, Infectious Diseases Institute, Kampala, Uganda,
2. Chelsea and West-minister NHS, United Kingdom,
3. Institute of Tropical Medicine, University of Antwerp, Belgium.

Abstract

Objectives: To determine the proportion of patients developing active tuberculosis (TB) versus that of patients who experience worsening of TB, after initiating highly active anti retroviral therapy (HAART).

Methods: Charts of HAART naïve patients with or without clinically active TB who consecutively commenced HAART at Mulago Hospital Infectious Diseases Institute were reviewed. Patients were assessed for worsening of TB on treatment or development of new active TB (unmasking of TB) after initiating HAART.

Results: Of 271 patients without active TB at baseline who initiated HAART, 16 (5.9%) developed active TB within 6 months (early unmasking) and 10 (2.7%) after 6 months (late unmasking). Seven of 10 late unmasking patients had a past history of treatment for a TB disease episode. Of 45 patients who commenced HAART with coexisting active TB, 13 (29%) experienced worsening of TB symptoms, signs and/or radiological features. Nine of these 45 commenced HAART during the intensive phase of TB treatment, of whom 2 (22%) experienced worsening of TB. Thirty six of 45 started HAART during the continuation phase of TB treatment of whom 11 (31%), experienced worsening of TB. The median time from initiation of HAART to worsening of TB in patients on concurrent active TB treatment was 5 weeks, and 18 weeks to unmasking of new active tuberculosis.

Conclusion: Unmasking of TB was commonest in the first 6 months of HAART and declined in the subsequent months with most in the late unmasking group being TB recurrences. Worsening of TB occurred even after HAART was delayed to the continuation phase of TB treatment.

Keywords: Immune reconstitution, tuberculosis, antiretroviral therapy

African Health Sciences 2008 8(3): 190-195

Introduction

Restoration and preservation of immune functions by highly active anti-retroviral therapy (HAART), has led to a significant risk reduction for tuberculosis (TB) and improved survival of TB-HIV co-infected patients[1-4].

However in some instances HAART induces deleterious effects, such as increased morbidity, which are attributable to immune reconstitution enhanced inflammatory responses against TB antigens. This TB related morbidity following HAART may manifest itself as paradoxical worsening of active TB undergoing successful treatment or progression of latent TB infection to active TB (unmasking), and has been termed as TB immune reconstitution inflammatory syndrome (TB-IRIS)[5-15].

[*]***Corresponding Author:***
Joshua Baalwa, Makerere University Medical School, Department of Internal Medicine, 4th Floor,
Mulago Hospital Complex, P. O Box 7072, Kampala, Uganda.
Email: jbaalwa@yahoo.com. Tel. 256-772-431-414.

Few studies have systematically highlighted the burden of TB-IRIS in Sub-Saharan Africa, despite TB and HIV co-infection being highly prevalent in this region. In this study, we characterized patients with paradoxical worsening and new onset or recurrence of active TB after initiating HAART.

Methods

Design and study population

We reviewed charts of 316 anti-retroviral therapy naïve patients who started HAART between March 2003 and September 2004 at the Infectious Diseases Institute, Makerere University Kampala, Uganda, and were still alive by March 2005. Using the HAART register, 271 charts of HAART naïve patients who commenced HAART without clinically active TB were identified and reviewed for development of new episode of active TB disease. Another 45 patients who commenced HAART during anti-TB treatment were identified using the TB and HAART registers and assessed for worsening of TB.

Patient charts were reviewed from the time they commenced HAART up to the end of March 2005. All adult patients (age e"18 years), with confirmed HIV-1 infection and eligible for HAART according to the Ugandan ART guidelines were included. Patients were excluded if they had a prior history of default or clinical failure of TB treatment, if they were on HAART prior to March 2003 or if they were not adherent to HAART during the study period. Patients on TB treatment were eligible for the study if they were adherent to their current anti-TB medication, and if the decision to commence HAART was taken after their response to TB treatment was deemed satisfactory. The primary study outcomes were; new active TB disease or worsening of TB symptomatology, after initiating HAART. New active TB cases were further categorized into early or late unmasking TB groups, if TB developed within or after 6 months of initiation of HAART respectively.

Case definitions

Worsening of TB was presumptively confirmed if a patient responding to adequate TB treatment, paradoxically redeveloped clinical features and new radiological signs suggestive of TB after initiating HAART and did not respond to empiric broad spectrum antibiotic therapy or had no other cause identified after clinical and laboratory evaluation.

A person with new active TB unmasking while on HAART was defined as having smear positive pulmonary TB if microscopy of their sputum revealed acid fast bacilli (AFB). Additionally, some patients with failure of B symptoms (fever, night sweats and weight loss) to respond to an antibiotic trial were presumptively diagnosed with disseminated TB if they showed clinical response to anti-TB trial therapy. Patients were presumptively diagnosed to have smear negative pulmonary TB if they had persistent B symptoms despite a trial of broad spectrum antibiotic and a chest radiograph suggestive of TB but with three or more negative sputum smears for AFB.

Tuberculous meningitis, abdominal TB, tuberculous pleural effusion, TB adenitis and TB pericarditis were diagnosed as per the Uganda National TB Treatment guidelines[16].

Results

Of the 271 HAART naïve patients without TB at baseline, 16 (5.9%) developed active TB within 6 months (early unmasking) and 10 (2.7%) after 6 months (late unmasking) after initiating HAART. The mean duration from initiation of HAART to unmasking of TB was 25 weeks, with a range of 2 to 63 weeks and median of 18 weeks. Seven of 10 (70%) late unmasking TB subjects had prior history of treatment for a TB disease episode, compared to 6 of 16 (37.5%) early unmasking TB subjects.

Thirteen (29%) of 45 patients on TB treatment experienced worsening of TB symptoms and signs after commencement of HAART. The mean duration from initiation of HAART to worsening of TB was 6 weeks, with a range of 2 to 12 weeks and median of 5 weeks. Nine of 45 commenced HAART during the intensive phase of TB treatment, of whom 2 (22%) experienced worsening of their TB, while 36 of 45 started HAART during the continuation phase of TB treatment of whom 11 (31%), experienced worsening of their TB. Table 1 and 2 below summarize the characteristics of patients who developed new active TB or worsening of TB after HAART was initiated.

Table 1: Characteristics of subjects with unmasking of TB after initiating HAART treatment

Age (Years)	Sex	Clinical Presentation	Past history of TB	Site of TB	Diagnosis of TB at unmasking	Intervalfrom initiation of HAART or unmasking of TB (Weeks)
24	F	Cough, sputum, fever & weight loss	NO	PTB	Sputum smear positive	7
33	M	Cough, sputum, dyspnoea, fever, night sweats & weight loss	NO	PTB	Sputum smear positive	62
43	M	Fever, cough & weight loss	NO	PTB	Sputum smear negative	53
31	M	Fever, cough, night sweats & weight loss	YES	PTB	Sputum smear negative	37
25	M	Cervical, axillary, & Abdominal Lymphadenopathy	YES	EP	TB adenitis by Histology	57
			NO	EP	Disseminated TB	3
34	M	Cough, dyspnoea, fever, night sweats & weight loss				
32	M	Cough, dyspnoea, fever, night sweats & weight loss	YES	PTB	Sputum smear negative	45
27	M	Fever, cough & weight loss	YES	PTB	Sputum smear negative	18
32	M	Fever, cervical Lymphadenopathy	YES	EP	TB adenitis by Histology	28
42	M	Fever, weight loss, headache, stiff neck	YES	EP	Tuberculous meningitis	63
37	M	Cough, sputum, dyspnoea, fever, night sweats & weight loss	NO	EP	Disseminated TB	61
52	M	Fever, weight loss, night sweats headache, stiff neck	YES	EP	Tuberculous meningitis	12
34	M	Fever, weight loss, Abdominal lymphadeno pathy	YES	EP	Abdominal TB	4
35	M	Pleural effusion, cough, sputum, fever & weight loss	NO	EP	TB Pleural effusion	22
39	F	Fever, weight loss, cervical lymphadenopathy	NO	EP	TB adenitis by Histology	3
36	F	Fever, cough, sputum & dyspnoea	NO	PTB	Sputum smear negative	52
40	F	Fever, weight loss, headache, stiff neck, altered mentation & cervical lymphadenopathy	NO	EP	Disseminated TB (Tuberculous meningitis and TB adenitis by Aspirate)	18
27	F	Fever, weight loss, night sweats, cough	NO	EP	Disseminated TB	8
36	F	Cough, sputum & dyspnoea	NO	PTB	Sputum smear positive	15
30	F	Fever, night sweats & weight loss	YES	EP	Disseminated TB	3
25	F	Fever, weight loss, pericarditis, cough & dyspnoea	YES	EP	Tuberculous pericarditis	32
30	F	Fever, weight loss, Cervical lymphadenopathy	NO	EP	TB adenitis by Histology	14
29	F	Fever, cervical lymphadenopathy	YES	EP	TB adenitis by Histology	18
34	F	Cough, sputum & dypnoea	NO	PTB	Sputum smear positive	20
42	F	Fever, weight loss, headache, stiff neck	YES	EP	Tuberculous meningitis	28
35	F	Fever, weight loss, headache, stiff neck	YES	EP	Tuberculous meningitis	2

M - Male
F- Female
EP- extra-pulmonary tuberculosis
PTB - Pulmonary tuberculosis

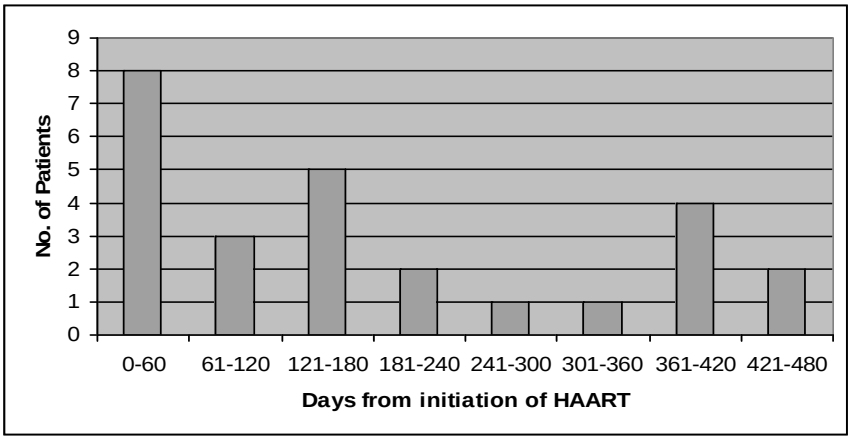
Past history of TB - History of having been treated for a TB disease prior to the current episode.
PTB - Pulmonary tuberculosis
EP - Extra-pulmonary tuberculosis

Table 2: Clinical characteristics of TB worsening after HAART was initiated

Age	Sex	Sputum smear Type of current TB episode	Previous history of TB, prior to current episode	Clinical Presentation of TB worsening	Duration from initiation of HAART to worsening of TB
30	F	POS	NO	Cough, sputum, dyspnoea & fever > 2 weeks	8.3
49	F	POS	YES	Cough, sputum, dyspnoea, fever >2 weeks	8.7
29	F	NA	NO	Fever, tender hepatosplen omegaly. USS- abdominal lymphadenopathy	2
36	F	NA	NO	Fever, CCF & pericarditis	3.6
28	F	NA	NO	USS-Retroperitoneal abdominal lymphade nopathy	5.3
27	F	NEG	NO	Fever > 2 weeks and Productive cough	2
34	M	NA	YES	Fever, cervical lympadenitis	4
31	F	NEG	YES	Fever, weight loss, hemoptysis. CXR-miliary	10
45	F	NEG	NO	Fever, chest pain, dyspnoea. CXR-miliary picture	6
34	F	NA	YES	Cervical lymphadenitis	11.9
37	M	POS	YES	Fever >2 weeks, cough and dyspnoea	4.6
28	F	NA	NO	Fever, cervical suppurative adenitis	4
25	F	NA	NO	Hepatosplenomegaly. USS-hypoechoeic infiltrates and ascites	3.3

Legend for Table 2:
CCF-Congestive cardiac failure
CXR-Chest radiograph
F-Female
M-Male
NA-Data not available
NEG-Smear negative
YES-History of previous tuberculosis disease episode
NO-No previous history of tuberculosis disease episode
POS –Smear positive
TB -Tuberculosis
USS-Abdominal ultra-sound scan

Figure 1: Bi-modal peak of TB unmasking after initiation of HAART



Between 0 to 180 days (first peak) of initiating HAART the majority of unmasking cases were first TB disease episodes, while in the second peak most unmasking TB cases were recurrences.

Discussion

Overall, this study reveals that a substantial proportion of patients develop active TB within weeks to months of initiating HAART or worsening of TB while on concurrent anti-TB and HAART medications. Our study limitations included the unavailability of CD4 count and viral load results at the time of TB worsening, and the diagnosis of active TB not being corroborated by positive culture results. Despite this, the study was similar in design to those reported elsewhere [7, 8,11, 16] and our findings provide vital baseline statistics regarding TB-IRIS in East Africa where HIV-1 clades A and D infections predominate.[17] Moreover, all patients meeting the criteria of our study end points, had their records further scrutinized by the study team, composed of a panel of clinicians with considerable experience in HIV/TB treatment.

This study also reaffirms what earlier studies had found, that despite significant reduction in the risk of TB acquisition during HAART treatment, a small proportion of patients remains at risk for TB disease especially those from TB endemic areas who might harbor undetected latent TB infection[6, 18]. In a study by Bonnet M.B. et al, conducted in 5 high TB burden countries, the risk for pulmonary TB after initiation of HAART ranged between 7.6 and 17.6% per 100 person years.[19] In less TB endemic areas, unmasking of TB has been shown to occur in high proportions among immigrants from TB endemic areas and black populations who initiate HAART without concurrent active TB disease.[7] Notably, our study found that the majority of patients (70%) who developed active TB six months after initiating HAART (late unmasking) were TB recurrences, while those who developed active TB within 6 months of initiating HAART (63%) were experiencing their first active TB episode. This finding apparently reveals a limitation in the protective effects of HAART against TB recurrence and arguably reiterates the need to consider TB chemoprophylaxis as a supplement to HAART in reducing TB incidence among HIV-1 infected populations in TB endemic areas[20]. Alternatively, studies are required to determine if earlier initiation of HAART, when CD4 counts fall $< 350/mm^3$, is superior in reducing TB incidence compared to what is conventionally practiced in Uganda and other developing countries today.

In the past, some reports have suggested that delaying HAART may significantly reduce the risk for TB-IRIS.[16, 21] However, this was not the case with our study since more than 80% of TB-IRIS cases occurred when HAART was initiated during the continuation phase of TB treatment. Thus, considering the remarkable survival benefit of HAART particularly in TB patients with advanced AIDS,[4] we propose that the decision to delay HAART should mainly be based on the likelihood of overlapping toxicities and high pill burden other than the anticipation for IRIS, pending systematic observations from large prospective studies.

Acknowledgements: This work was supported supported by a grant from the National Institutes of Health-Forgaty International Center (FIC) to TB-HIV Clinical Operational and Health Services Research (COHRE) project based at the Joint Clinical Research Center (JCRC), Kampala, Uganda. We thank Prof.

Nelson K. Sewankambo, Prof. Elly Katabira, Prof. Peter Mugyenyi and Prof. Allan Ronald for their input; Regina Namirembe and Nelson Kakande of the COHRE secretariat at JCRC for their logistical support and Shuyi Wang for graphics and manuscript preparation.

REFERENCES

1. Badri M., Wilson D., Wood R. Effect of HAART on the incidence of TB in South Africa: a cohort study. Lancet. 2002, 359(9323):2059-2064.
2. Jones J.L., Hanson D.L., Dworkin M.S., DeCock K.M. HIV-associated TB in the era of HAART The Adult/ Adolescent Spectrum of HIV Disease Group. Int J Tuberc Lung Dis. 2000, 4(11):1026-1031.
3. Santoro-Lopes G., de Pinho A.M., Harrison L.H., Schechter M. Reduced risk of TB among Brazilian patients with advanced HIV infection treated with HAART. Clin Infect dis. 2002, 34(4):543-546.
4. Dean G.L., Edwards S.G., Ives N.J. et al. Treatment of tuberculosis in HIV-infected persons in the era of highly active antiretroviral therapy. AIDS 2002, 16(11):1569-1570.
5. Narita M, Ashkin D, Hollender ES, Pitchenik AE. Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. Am J Respir Crit Care Med. 1998, 158(1):157-161.
6. Sungkanuparph S., Vibhagool A., Mootsikapun P., Chetchotisakd 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(14):2129-2131.
7. Breen R.A., Smith C.J., Cropley I., Johnson M.A., Lipman M.C. Does immune reconstitution syndrome promote active tuberculosis in patients receiving highly active antiretroviral therapy? AIDS. 2005, 19(11):1201-1206.
8. Breen R.A., Smith C.J., Bettinson H. et al. Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection. Thorax. 2004, 59(8):704-707.
9. Buckingham S.J., Haddow L.J., Shaw P.J., Miller R.F. Immune reconstitution inflammatory syndrome in HIV-infected patients with mycobacterial infections starting highly active anti-retroviral therapy. Clin Radiol. 2004, 59(6):505-513.
10. Wendel K.A., Alwood K.S., Gachuhi R., Chaisson R.E., Bishai W.R., Sterling T.R. Paradoxical worsening of tuberculosis in HIV-infected persons. Chest. 2001, 120(1):193-197.
11. Kumarasamy N., Chaguturu S., Mayer K.H. et al. Incidence of Immune Reconstitution Syndrome in HIV/Tuberculosis-Coinfected Patients After Initiation of Generic Antiretroviral Therapy in India. J Acquir Immune Defic Syndr. 2004, 37(5):1574-1576.
12. Orlovic D., Smego R.A. Jr. Paradoxical tuberculous reactions in HIV-infected patients. Int J Tuberc Lung Dis. 2001, 5(4):370-375.
13. Furrer H., Malinverni R. Systemic inflammatory reaction after starting highly active antiretroviral therapy in AIDS patients treated for extra pulmonary tuberculosis. Am J Med. 1999, 106(3):371-372.
14. Fishman J.E., Saraf-Lavi E., Narita M., Hollender E.S., Ramsinghani R., Ashkin D. Pulmonary tuberculosis in AIDS patients: transient chest radiographic worsening after initiation of antiretroviral therapy. AJR Am J Roentgenol. 2000, 174(1):43-49.
15. Chien J.W., Johnson J.L. Paradoxical reactions in HIV and pulmonary TB. Chest. 1998, 114(3):933-936.
16. National Tuberculosis and Leprosy Programme. Tuberculosis control and community-based DOTS as an essential component of district health systems. Reference manual. Kampala: Uganda Ministry of Health; 2001
17. Shelburne S.A., Visnegarwala F., Darcourt J et al. Incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy. AIDS. 2005, 19(4):399-406.
18. Rayfield M.A., Downing R.G., Baggs J. et al. A molecular epidemiologic survey of HIV in Uganda. AIDS. 1998, 12:521-527.
19. Wan B.K., Pyoeng G.C., Jae H.J. et al. Tuberculosis manifested by immune reconstitution inflammatory syndrome during HAART. AIDS, 2007: 21; 875-877.
20. Bonnet M.B., Pinoges L.P., Zachariah R.Z. et al. Incidence of tuberculosis in people living with HIV and AIDS receiving antiretroviral therapy in 5 high TB burden countries. 36th International Union Against tuberculosis and lung disease conference, Paris, France. October, 2005.
21. Zar H.J., Cotton M.F., Strauss S. et al. Effect of isoniazid prophylaxis on mortality and incidence of tuberculosis in children with HIV: randomised controlled trial. BMJ. 2007, 334(7585): 136.
22. Burman W.J., Jones B.E. Treatment of HIV-related tuberculosis in the era of effective antiretroviral therapy. Am J Respir Crit Care Med. 2001, 164(1):7-12.