JACOBS PUBLISHERS

OPEN ACCESS

Jacobs Journal of AIDS/HIV

Research Article

The Presence of Tuberculosis at the Initiation of Antiretroviral Therapy Predicts Retention in Care: A Retrospective Review of Patients on ART in Nigeria

Joseph Enegela*[1], Apata Jummai[2], Epoupa Flora[3], Onu Eugene[3], Olutola Ayodotun[3]

[1]*Pro Health International Nigeria, Nigeria*

[2]*Maryland Global Initiative Corporation, Nigeria*

[3]*Center for Clinical Care and Clinical Research, Nigeria*

**Corresponding author:* *Dr. Joseph Enegela, No 49 Kado district, Cadastral zone B09 Kado Abuja, Tel: +2348097323804; Email: jenegela.ihvar@gmail.com, jenegela@phint.org*

Received: 05-17-2015

Accepted: 06-02-2015

Published: 06-08-2015

Abstract

Background

Tuberculosis remains an important opportunistic infection among patients that are HIV-positive, and it continues to be a significant cause of mortality in sub-Saharan Africa. Its presence in patients with HIV determines the threshold for commencing antiretroviral therapy, and it is important in predicting long term retention in care. We aimed to determine the outcomes of patients that were co-infected with tuberculosis and HIV at the commencement of antiretroviral therapy.

Methods

For this retrospective study, we reviewed the records of adult patients across 12 comprehensive antiretroviral therapy treatment facilities in Nigeria. Eligible patients had been on antiretroviral therapy for a minimum of nine months. We collected patient data on age, sex, number of months on therapy, CD4 count at initiation of antiretroviral therapy, and the presence or absence of tuberculosis within three months before and one month after commencing antiretroviral therapy. Patients with tuberculosis at the start of therapy comprised the tuberculosis group, and patients without tuberculosis comprised the non-tuberculosis group. All patients were evaluated for the probability that the care would end. Care ended when patients were lost to follow up, died, stopped antiretroviral therapy, or transferred their care to another facility.

Results

A total of 1262 patient charts were included. Patients had an average age of 37 years, and 65.3% were female. The tuberculosis group constituted 9.73% of the patient population. The median follow up was 26 and 27 months for the tuberculosis and non-tuberculosis groups, respectively. A total of 34 (2.69%) patients had ended care at various times during therapy; 23.53% were patients in the tuberculosis group. A comparison between groups showed that the tuberculosis group had a higher risk of ending care than the non-tuberculosis group (Relative Risk [RR] = 2.849, P= 0.014, Yates Chi^2: 6.022; 95%CI: 1.204 - 6.403).

Conclusion

Patients that have tuberculosis when they start antiretroviral therapy have a higher risk of dropping out of care than those without tuberculosis. Therefore, patients with tuberculosis require close monitoring and follow up, even after completion of their anti-tuberculosis therapy.

Keywords: Tuberculosis; Attrition; ART Initiation; HIV; Opportunistic infections

Cite this article: *Enegela J. The Presence of Tuberculosis at the Initiation of Antiretroviral Therapy Predicts Retention in Care: A Retrospective Review of Patients on ART in Nigeria.J J Aids Hiv. 2015, 1(1): 004.*

Introduction

In sub Saharan Africa, tuberculosis [TB] remains a major opportunistic infection among people living with HIV/AIDS, and TB continues to be a leading cause of mortality [1, 2]. In 2013 alone, 1, 300,000 individuals died from TB, and of those, 300,000 were co-infected with HIV [2]. In patients with HIV, TB causes severe debilitation, as demonstrated in a pre HAART, 7-year, longitudinal study conducted in Malawi. In that study, only 11% of all patients co-infected with HIV and TB survived after 7 years [3]. The fact that TB remains a significant public health problem in developing countries has been accentuated by the scourge of HIV, particularly in sub Saharan Africa [4]. Although HIV services have been rapidly scaled up in the TB control programs, TB services are poorly integrated into HIV treatment facilities. Thus, the lack of available man power and training continue to stretch otherwise poorly-managed health systems in sub Saharan Africa [4]. Opportunistic infections generally impact HIV patient outcomes [5-7] particularly a chronic, debilitating infection, such as TB where evidence has demonstrated the negative effect of TB on the outcomes of patients with HIV [4, 8], and incontrovertible evidence has confirmed its impact on mortality rates in patients with HIV [4, 9, 10]. TB represents a determinant for when patients commence antiretroviral therapy [ART] [11-13], and it has become an absolute indication for the initiation of ART [14]; thus, it is important to link standalone TB clinics to comprehensive ART centers. With the evolution of HIV programs in Africa, opportunistic infections in general, and TB in particular, have clear effects on retention in care. Several studies have demonstrated that the presence of TB in patients with HIV had a negative effect on their outcome [4, 8] and consequently, their retention in HIV care programs [15]. However, there remains a paucity of published data on the prevalence of TB among patients positive for HIV in Nigeria. In this study, we aimed to determine the prevalence of TB among patients initiating ART, to review their outcome, and to determine the association between TB and attrition from HIV care.

Materials and Methods

The AIDS Relief program in Nigeria commenced initiating patients on ART in 2004, and care was transitioned to local implementing partners in 2011. At the time of this study, it had enrolled over 54,000 patients on ART across its 34 secondary health care facilities, which provided comprehensive care and treatment for patients with HIV across Nigeria. Patients enrolled into care at these facilities received laboratory investigations, ART medications, prophylaxis, and management for all opportunistic infections, including TB. Over the years, the Nigerian HIV/AIDS program has evolved from care domiciled in tertiary hospitals to care in secondary health facilities, and currently, it has started to decentralize ART services. However, during the period covered in this study, the country had not started decentralizing ART services to primary health care centers. In addition, some patients received supportive care, including home visits and adherence and psychosocial support. Upon initiating ART, all patients received an initial clinical evaluation, which included a screen to determine immunologic and clinical eligibility for ART, presence or absence of opportunistic infections (including TB), and patient readiness for ART. As part of the continuum of care, patient adherence to medications and appointments was monitored through pill counts and missed-appointment records, respectively; patients that missed appointments were actively tracked with an established protocol, and they either returned to care or their status was determined. When a patient's status was determined, they were either justified in not returning to care, or they were not found, and consequently, considered missing. When, despite the efforts of the tracking team, a patient did not return to care after 90 days of the missed appointment, the patient was declared lost to follow up [LTFU], and their care was ended..

The AIDS relief program conducted an annual patient level outcome [PLO] survey as part of a broad program evaluation. In this survey, patient outcome, program quality, and program performance were assessed. As part of this PLO survey, in 2011, we carried out a chart review of a representative sample of patients who had been enrolled into the ART program between 2004 and 2011 across 12 comprehensive care and treatment facilities in Nigeria. Patient charts were reviewed for age at initiation of ART, sex, date of initiation of ART, CD4 cell count at initiation of ART, presence of TB at ART initiation, and documented evidence of attrition from care. Also, active patients had their blood drawn for viral RNA measurements with the Roche Amplicor 2.0. We defined the presence of TB at the initiation of ART as a diagnosis of TB within three months prior and one month after ART initiation. We also considered patients to have ended care when they had been transferred out of the facility for any reason, had died from any cause, stopped returning for care for any reason, or were LTFU. Our viral suppression threshold was defined as any viral RNA result that was equal to or less than 1000 copies/ml.

For study inclusion, patients had to be sixteen years or older at initiation of ART, and they had to have been on ART for at least 9 months at the time of the review, without any bias to regimen type. For purposes of comparison, the patients where categorized into the TB group (all patients with TB, based on our definition) and the non-TB group (patients without a TB diagnosis).

Statistical Analyses

The representative sample of patient charts was selected with a simple random sampling method. All statistical analyses were performed with STATA version 12. The age distribution was expressed as a simple average; the sex distribution and proportions of groups were expressed as simple percentag-

es. Comparisons between groups were performed with Pearson's Chi^2 or Yate's Chi^2 analyses, as appropriate. To determine whether the presence of TB at the initiation ART had an effect on patient outcome, we used a relative risk ratio (RR) to determine the probability that the TB group would have a higher rate of ending care than the non-TB group.

Results and Discussions

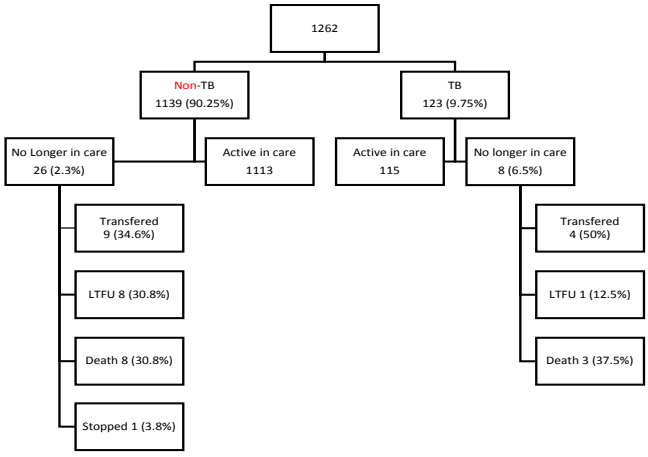
The 1262 included patients (Figure 1) were predominantly female (65.3%), with an average age of 37 years. Of these, 1139 (90.25%) did not have TB (non-TB group) at the initiation of ART, and 123 (9.75%) had a TB diagnosis (TB group); 118 had only pulmonary TB, 3 had extra pulmonary TB, and 2 had a combination of both. The median follow up periods for the TB and non-TB groups were 26 and 27 months, respectively. Only 1218 (96.5%) patients had a documented baseline CD4 cell count; of these, 495 (40.64%) had baseline CD4 cell counts between 201-400 cells/mm^3 (Table 1).

Table 1. Distribution of baseline CD4 cell counts among patients with available data.

CD 4 Cell count (cells/mm^3)	Frequency	Percentage (%)
<200	165	13.55
201-400	495	40.64
401-600	323	26.52
601-800	160	13.14
>800	75	6.16
Total	**1,218**	**100**

The overall attrition rate of the group of patients was 2.9% (N=34; Figure 1). Of these, 76.5% (N=26) were in the non-TB group and 23.5% (N=8) were in the TB group (Table 2). However, individual group attrition rate was higher in the TB group (6.5%) than in the non-TB group (2.3%). There was a statistically significant relationship between the presence of TB and the probability of attrition (Chi2 = 7.5460, P = 0.006; Table 2). A closer look at the causes of attrition showed that, in the TB group, 50% were due to transfers, 12.5% were LTFU, and 37.5% were due to death. In the non-TB group, transfers, LTFU, and death were responsible for 34.6%, 30.8%, and 30.8% of attritions, respectively [Figure 1].

Figure 1. Patient flow cascade.



LTFU: Lost to follow up; Stopped: Follow stopped with justification; Transfer: care transferred to another facility

Table 2. Association between patients TB status at initiation of ART and attrition from care.

	Active in care (%)	Not in care (%)	Total
Non-TB group	1,113 (90.64)	26 (76.47)	1139 (90.25)
TB group	115 (9.36)	8 (23.53)	123 (9.75)
Total	1,228 (100)	34 (100)	1,262 (100)

Pearson's Chi^2 = 7.5460, P= 0.006

A total of 1115 patients remained in active care and underwent blood draws for viral load estimations. Of these, 92.3% in the non-TB group and 91.1% in the TB group were virologically suppressed. We found no association between the presence of TB and viral suppression (Pearson's Chi^2 = 0.1896, P = 0.663; Table 3).

Table 3. Association between patients TB status at initiation of ART and Virologic outcome.

	Not suppressed	Suppressed	Total
Non-TB group	78	936	1,014
TB group	9	92	101
Total	87	1,028	1,115

Pearson's Chi^2 = 0.1896, P=0.663

There was no association between the baseline CD4 cell count and the attrition rate (Pearson's Chi^2 = 2.552, P = 0.635; Table 4). The TB group showed a higher risk of dropping out of care compared to the non-TB group (RR = 2.849, P= 0.014, Yates Chi^2 6.022, 95%CI: 1.204 – 6.403).

Table 4. Distributions of baseline CD4 cell counts in groups currently in care or no longer in care for HIV.

Baseline CD4 cell count (cells/mm3)	Still in Care	Not Active	Total
<200	160	5	165
	13.36%	25%	13.55%
201-400	488	7	495
	40.73%	35%	40.64%
401-600	319	4	323
	26.63%	20.00%	26.52%
601-800	157	3	160
	13.11%	15.00%	13.14%
>800	74	1	75
	6.18%	5.00%	6.16%
TOTAL	**1,198**	**20**	**1,218**
	100%	**100%**	**100%**

Discussion

TB was a significant opportunistic infection in this cohort of patients with HIV infections. We found a 9.75% prevalence, which was similar to findings from a previous study that showed Northern Nigeria had prevalence 10.5% [16]. However, these estimates differed significantly from rates of up to 32.8% [17] reported elsewhere in Nigeria, and the pooled estimates of a meta-analysis, which reported rates of 31.25% for African countries [18]. We believe that the rates based on our records may have been higher if current diagnostic methods had been available during the study period represented by our records (2004-2011). Furthermore, the wide variation in rates may be affected by the suspicion index of the care givers and by the various levels of diagnostic tools available to them [18]. During the study period represented by our records, the primary tool for making a TB diagnosis was the acid fast bacilli (AFB) test, which used light microscopy, supported by x-rays and clinical exam whenever the AFB test was not conclusive. The population dynamics of our patients, including the proportion of females (65.3%) and the average age (37 years), were also consistent with findings elsewhere. In the present study, the mortality rates for both groups were relatively low (0.7% and 2.4% in the nonTB and TB groups, respectively) compared to mortality rates documented elsewhere [3, 19, 20]. This discrepancy could be due to a misclassification; that is, patients considered LTFU may have been deceased, but they were misclassified due to the inability to determine actual status. We must also bear in mind that, during the period under review, the guidelines for managing patients co-infected with HIV/TB were found to have shortcomings, and the recommendations in use evolved over time [11, 13, 14, 21]; without this evolution in management, we may have detected a higher mortality rate in the TB group.

The overall attrition rate in our cohort of patients was somewhat lower than those reported for other cohorts in sub Saharan Africa [19]. Although we found higher attrition rates in the TB group than in the non-TB group, neither rate was comparable to the rates found in other cohorts [19]. For example, a previous meta-analysis estimated 2 year retention rates of 60% and 70% (22). However, our finding of a relatively higher risk of attrition from care in the TB group compared to the non-TB group (RR 2.849, p = 0.014) was consistent with other studies in sub Saharan Africa, which demonstrated an association between patients with HIV/TB co-infections and the rate of attrition from care [19, 20, 23, 24]. This data underlines the need for adequate, appropriate follow up of patients with HIV/TB co-infections, regardless of the stage of anti-TB therapy.

Another significant finding was the disproportionately higher percentage of attrition attributed to transfers in the TB group (50%) compared to the non-TB group (35%). Contextually, in the Nigerian TB program, TB is diagnosed at secondary health facilities, known as microscopic centers while treatment is administered at Directly Observed Treatment (DOT) centers. These treatment centers may include comprehensive HIV care and treatment facilities (CCT), but in most instances, they are primary health centers (PHCs). During the period under review, the national ART program had not started to decentralize ART services to make them available at PHCs. Therefore, when patients resided at a distance from the CCT, their anti-TB treatment was generally transferred to a DOT center close to their homes, to facilitate continued daily treatment. However, these individuals continued to receive ART at the CCT. Thus, some patients with HIV/TB co-infections may have been required to receive TB and HIV management at separate health centers. This possibility raised some key questions for our study. For example, did these patients request a transfer, or were they transferred, based on care giver advice? We did not have any documentation on the reason for transfer, nor was there evidence of completed transfers (i.e., the patient reaching the receiving facility). Thus, we could only speculate that the patients remained in care after the transfer. This possibility may lend further support to the endeavor to decentralize ART to provide services at PHCs, because this endeavor will both increase coverage and enable patients with TB/HIV co-infections to be managed at a single health center.

Conclusion

In conclusion, we have demonstrated that patients co-infected with HIV and TB at the initiation of ART had a higher risk of attrition from ART. However, a significant proportion of patients that left the reviewed program were transferred to other facilities. With the continued geographic expansion of the HIV treatment program and its adoption of international best practices and standards, there is an increasing need for more robust TB control. Through the integration of synergistic programs in Nigeria, care-givers can learn from each other, heighten their

awareness of the risk of attrition, and provide improved monitoring and follow up for patients with HIV.

Acknowledgement

This publication has been supported by an unrestricted grant from Gilead Sciences Europe Ltd, for the data presentation at ICASA conference, Cape Town, December 2013.

References

1. Straetemans M, Bierrenbach AL, Nagelkerke N, Glaziou P, van der Werf MJ. The Effect of Tuberculosis on Mortality in HIV Positive People: A Meta-Analysis. PLoS One. 2010, 5(12):e15241.

2. Global Tuberculosis Report 2013.

3. Kang'ombe CT, Harries AD, Ito K, Clark T, Nyirenda TE et al: Long-term outcome in patients registered with tuberculosis in Zomba, Malawi: mortality at 7 years according to initial HIV status and type of TB. Int J Tuberc Lung Dis. 2004, 8(7): 829–836.

4. Corbett EL, Marston B, Churchyard GJ, De Cock KM. Tuberculosis in sub-Saharan Africa: opportunities, challenges, and change in the era of antiretroviral treatment. The Lancet. 2006, 367 (9514):926-937.

5. Park BJ, Wannemuehler KA, Marston BJ, Govender N, Pappas PG et al. Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. AIDS. 2009, 23(4):525-530.

6. Lubeck DP, Bennett CL, Mazonson PD, Fifer SK, Fries JF. Quality of Life and Health Service Use Among HIV-Infected Patients with Chronic Diarrhea. J Acquir Immune Defic Syndr. 1993, 6(5):478-484.

7. Deribew A, Tesfaye M, Hailmichael Y, Nebiyu Negussu, Shallo Daba et al. Tuberculosis and HIV co-infection: its impact on quality of life. Health Qual Life Outcomes. 2009; 7: 105.

8. Badri M, Ehrlich R, Wood R, Pulerwitz T, Maartens G. Association between tuberculosis and HIV disease progression in a high tuberculosis prevalence area. Int J Tuberc Lung Dis. 2001. 5(3):225-232.

9. Wong EB, Omar T, Setlhako GJ, Osih R, Feldman C et al. Causes of death on antiretroviral therapy: A post mortem study from South Africa. PLoS One. 2012:7(10): e47542.

10. Harries AD, Dye C. Tuberculosis. Ann Trop Med Parasitol. 2006, 100 (5-6): 415-431.

11. Abdool Karim SS, Naidoo K, Grobler A , Nesri Padayatchi, Cheryl Baxter et al. Integration of Antiretroviral Therapy with Tuberculosis Treatment. N Engl J Med. 2011, 365: 1492-1501.

12. Blanc FX, Sok T, Laureillard D, Borand L, Rekacewicz C et al : Earlier versus Later Start of Antiretroviral Therapy in HIV-Infected Adults with Tuberculosis. N Engl J Med. 2011, 365(16): 1471-1481.

13. Havlir DV, Kendall MA, Ive P, Kumwenda J, Swindells S et al : Timing of Antiretroviral Therapy for HIV-1 Infection and Tuberculosis. N Engl J Med. 2011, 365(16):1482-1491.

14. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva World Health Organization 2013.

15. Nansera D, Bajunirwe F, Elyanu P, Asiimwe C, Amanyire G et al. Mortality and loss to follow-up among tuberculosis and HIV co-infected patients in rural southwestern Uganda. Int J Tuberc Lung Dis. 2012, 16(10):1371-1376.

16. Iliyasu Z, Babashani M. Prevalence and predictors of tuberculosis Co-infection among HIV-seropositive patients attending the Aminu Kano teaching hospital, Northern Nigeria. J Epidemiol. 2009, 19(2):81-87.

17. Awoyemi OB, Ige OM, Onadeko BO. Prevalence of active pulmonary tuberculosis in human immunodeficiency virus seropositive adult patients in University College Hospital, Ibadan, Nigeria. Afr J Med Sci. 2002, 31(4): 329–332.

18. Gao J, Zheng P, Fu H. Prevalence of TB/HIV Co-Infection in Countries except China: A Systematic Review and Meta-Analysis. PLoS One. 2013, 8(5): e64915.

19. Rosen S, Fox MP, Gill CJ. Patient Retention in Antiretroviral Therapy Programs in Sub-Saharan Africa: A Systematic Review. PLoS Med. 2007 4(10): e298.

20. Lawn SD, Myer L, Harling G, Orrell C, Bekker LG et al. Determinants of Mortality and Non death Losses from an Antiretroviral Treatment Service in South Africa: Implications for Program Evaluation. Clin Infect Dis. 2006. 43 (6): 770-776.

21. National Guidelines for HIV and AIDs Treatment and Care in Adolescents and Adults. FEDERAL MINISTRY OF HEALTH ABUJA – NIGERIA MAY 2007

22. Fox MP, Rosen S. Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007–2009: systematic review. Tropical Med Int Health. 2010, 15(Suppl 1):1–16.

23. Lawn SD, Myer L, Bekker LG, Wood R. Burden of tuberculosis in an antiretroviral treatment program in sub-Saharan Africa: impact on treatment outcomes and implications for tuberculosis control. AIDS. 2006 20 (12):1605–1612.

24. MacPherson P, Moshabela M, Martinson N, Pronyk P. Mortality and loss to follow-up among HAART initiators in rural South Africa. Trans R Soc Trop Med Hyg. 2009, 103 (6): 588-593.