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Retention in Care among Patients Attending a Large HIV Clinic in Nigeria Who Were Treated for Tuberculosis

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Abstract

A retrospective study of 2764 patients was conducted at an HIV clinic in Nigeria to evaluate retention in care in patients treated for TB. At 6 and 12 months after commencement of TB treatment, 1842(66.6%) and 1624(58.8%) participants remained in care. Of the 922 and 1140 not in care at 6 and 12 months, 814(88.3%) and 1006(88.2%) respectively were lost to follow-up (LTFU). VL < 1000copies/ml was associated with higher odds of retention in care at 6 and 12 months (OR = 2.351 and 2.393) than VL > 1000 copies/ml. HAART use was associated with high likelihood of being in care at 12 months (OR = 3.980). CD4 counts of 200–350 and >350 cells/mm^3 were associated with increased odds of remaining in care at 12 months compared with CD4 < 200 cells/mm^3 ($p = 0.005$ and $p = 0.001$). Targeted interventions such as early HAART and close follow-up for high risk groups are likely to improve retention in care.

Keywords

retention in care, loss to follow up, TB-HIV co-infection, TB, HIV

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Introduction

Retention in care at HIV clinics in resource limited settings is influenced by variety of social, economic, logistical, and other factors.[1–4] High retention rates are essential in ensuring the effectiveness of HAART and for providing other life-saving interventions to patients living with HIV. People co-infected with HIV and Tuberculosis (TB) represent a very vulnerable subset of people living with HIV who require comprehensive care and close follow up to achieve a cure for TB and virologic suppression of HIV.[5–7] TB is the commonest opportunistic infection among HIV patients globally and requires well-coordinated management of both HIV and TB with an emphasis on timely initiation of HAART.[5,7,8] Poor retention in care at these clinics presents a major obstacle to overcoming high mortality rates in TB-HIV co-infected patients and has significant individual and public health implications.[9] Our study aims to evaluate retention in care of patients treated for TB at a large HIV clinic in Southwest Nigeria at 6 months and 12 months after the commencement of TB therapy and determine factors associated with retention in care at the clinic.

Methods

Study Design

This was a retrospective cross-sectional study of 2764 HIV positive patients aged 15 years or older who were treated for TB between September 2003 and April 2016.

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Study Setting

The study was carried out at the University College Hospital (UCH), Ibadan, Nigeria affiliated HIV clinic. The University College Hospital is the oldest teaching hospital in Nigeria and is an 800-bed multispecialty, academic, tertiary hospital. The adult HIV clinic was established in 2002 and provides counselling, testing, clinical consultation, pharmacy, and laboratory services to individuals aged 15 years and above. There was a total clinic population of 24,268 during the period studied (2003-2016) and at the time of carrying out the study in April 2017, there were about 6000 active patients. Clinical practice is guided by the Nigerian National Guidelines for treatment of HIV and Tuberculsosis.[10] Diagnosis of TB at the UCH HIV clinic was made by a combination of history, clinical findings, smear or culture of sputum or other appropriate specimen such as peritoneal fluid or lymph node tissue and chest radiograph or other appropriate radiologic investigation. After 2015, the XpertMTB/Rif® assay of sputum and other appropriate specimens was made available in addition to the aforementioned. Sputum testing is carried out at the TB reference laboratory of the National TB and Leprosy Control Programme located on the UCH campus at no cost to patients. Occasionally, the diagnosis was also made based on strong clinical suspicion from suggestive symptoms and signs (including but not limited to cough of two weeks or more, fever and weight loss) in the absence of microbiologic or XpertMTB/Rif® confirmation. This was not ideal and was only considered in the infrequent instances when available laboratory investigations were not congruent with a strong clinical suspicion for TB.

At entry into care, all patients of the UCH HIV clinic are screened for tuberculosis by history, sputum examination and/or chest radiograph; and thereafter if they develop suggestive symptoms. All ambulatory or hospitalized patients diagnosed with TB at other clinics or wards at UCH are screened for HIV infection if not previously diagnosed. Those who test positive for HIV are referred to the UCH HIV clinic for further care while anti-TB drugs are commenced once TB is diagnosed. Patients with TB who are newly diagnosed with HIV or previously diagnosed but not yet on HAART are placed on TB treatment immediately and then on HAART 2 weeks later or as soon as feasible after commencing anti-TB medications regardless of CD4 count. HAART regimens compatible with anti-TB medications (such as Efavirenz/Tenofovir/Lamivudine) were prescribed and clinical consultation and laboratory investigations were recommended as indicated by providers at the HIV clinic. Patients continue to receive their anti-TB medications at a separate clinic pharmacy and are seen by physicians at that clinic as deemed necessary by the TB program staff or physicians at the medical outpatient clinic. Of note, during the time period covered in the study, patients newly diagnosed with HIV were generally commenced on HAART at a CD4 count of less than 350 cells/mm^3 until 2007 and less than 500 cells/mm^3 thereafter. These antiretroviral medications were available to patients free of charge.

Participants

All patients enrolled in care at the UCH HIV clinic who were treated for TB between September 2003 and April 2016 were included in the study.

Variables and Outcomes

Socio-demographic, laboratory and longitudinal follow up data were obtained from the electronic records of the patients.

Variables collected include: socio-demographic variables such as age, gender, marital status and occupation. Data on sexual orientation were not available for use in the study. Clinical and laboratory variables such as CD4 count, viral load, hemoglobin and HAART treatment status were collected as well as retention in clinic at 6 and 12 months. Retention in care at 6 or 12 months is defined as having presented to the clinic for a routine visit/consultation or the clinic pharmacy for drug pick up at any time within the preceding 90 days and up to two weeks after. Scheduled clinic appointments for a TB-HIV co-infected patient managed as an out-patient usually range between 1 and 2 months, often more frequently but not less frequently than 3 months. Those who were not retained in care were classified as dead if there was documented evidence of their death in the clinic database, transferred out (if they had requested transfer to another HIV care facility and documentation had been provided by our clinic to facilitate such a transfer) and lost to follow up (if they had not presented at the clinic for consultation, laboratory visit or drug pick up in the preceding 90 days without any information as to why). In the event that anyone who reached either of the endpoints of loss to follow up or transfer out at 6 months later returned to care after the sixth month, they were censored out of the 12-month analysis and remained in the study records as having met such end points to avoid duplication.

Data Collection

Data were extracted into an excel spreadsheet using database queries by a senior data manager. The data were inspected by another one of the investigators for errors which were rectified from the source database. The data of 17 otherwise eligible patients were excluded from the study due to incompleteness

Quantitative variables were grouped according well-recognized categories for data analysis.

Statistical Methods

Descriptive statistics were used to summarize the socio-demographic variables. Chi-square test was used to assess association between socio-demographic variables, clinical and laboratory variables, ARV treatment status and retention in care at 6 and 12 months. Logistic regression was used to determine the strength of association between the variables that were found to be significant at 5% with the chi-square test. The data were analyzed using SPSS version 20 (IBM Corporation, Armonk, New York, USA).

Ethical Approval and Informed Consent

Approval for this study was given by the joint Institutional Review Board of the University of Ibadan and the University College Hospital, Ibadan (approval number-UI/IRC/04/0070).

Table 1. Sociodemographic characteristics, laboratory data and HAART treatment status

Variables		Frequency (%)
Gender (n = 2764)	Male	1069 (38.7)
	Female	1695 (61.3)
Age of respondents (n = 2764)	24 and below	167 (6.0)
	25-34	963 (34.8)
	35-44	1005 (36.4)
	45 and above	629 (22.8)
Marital status (n = 2090)	Single	299 (14.3)
	Married	1186 (56.7)
	Separated/Divorced	330 (15.8)
	Widowed	275 (13.2)
Occupation (n = 2096)	Trading	1022 (48.8)
	Teaching/Civil Servant/Professional	468 (22.3)
	Artisan	400 (19.1)
	Student/Unemployed	206 (9.8)
On HAART at time of start of TB treatment (n = 2764)	Not on HAART	934 (33.8)
	On HAART	1830 (66.2)
Body Mass Index (kg/m^2) (n = 2661)	Underweight <18.5	2269 (85.3)
	Normal 18.5-24.9	362 (13.6)
	Overweight 25-29.9	28 (1.1)
	Obese >30.0	2 (0.1)
CD4 count ($cells/mm^3$) (n = 2742)	<200	1639 (59.8)
	201-350	623 (22.7)
	>350	480 (17.5)
Viral load (copies/ml) (n = 2513)	<1000	389 (15.5)
	≥1000	2124 (84.5)
Hemoglobin (mg/dL) (n = 1675)	≤ 8	381 (22.7)
	8.1-10.9	729 (43.5)
	11-11.9	197 (11.8)
	≥12	368 (22.0)

Informed consent was not required as existing data were collected and de-identified for use in this study; no human or animal trials were conducted.

Results

The mean (SD) age of the patients was 37.8 (10.1) years, and a greater proportion of the participants were female [1695 (61.3%)]. About one-third [934 (33.8%)] of the participants were not on HAART when they commenced anti-TB medications. Majority of the study participants, 2269 (85.3%) were underweight with a BMI <18.5 kg/m^2. With regard to CD4 count, 1639 (59.8%) of them had a CD4 count of <200 $cells/mm^3$ with a large number of participants, 2124 (84.5%) having a viral load of >1000 copies/ml. Other socio-demographic and laboratory data are as listed in the Table 1.

At 6 months, 1842 (66.6%) of the study population were retained in care and by 12 months, this had declined to 1624 (58.8%) participants (Figure 1).

Among the 922 (33.4%) HIV patients that were not in care in our clinic at 6 months, 814 (88.3%) were lost to follow-up, 85 (8.6%) died, and 23 (2.5%) had transferred to other facilities. Among the 1140 HIV patients that were not in care at 12 months, 1006 (88.2%) were lost to follow-up, 97 (8.5%) had died, and 37 (3.2%) were transferred. At the 6-month mark, only 23 (1.2%) of participants who remained in care at the clinic had not commenced HAART. At 12 months, just 9 (0.6%) of those in care had not commenced HAART.

Table 2 shows the association between socio-demographic and clinico-pathological characteristics of HIV patients enrolled in TB care and their retention in care at 6 months and 12 months. Gender and occupation were not associated with retention in care at either 6 months or 12 months. Marital status was associated with retention in care at 6 months (but not at 12 months) ($p = 0.016$), with the widowed having the highest (82.9%) and the separated/divorced having the lowest (73%) retention in care at 6 months, respectively. Likewise, age was associated with retention in care at 6 months but not at 12 months ($p = 0.007$). Participants aged 15–24 years had the lowest retention rates at 6 months with 98 (58.7%) retained in care at 6 months. Retention in care at 6 and 12 months was associated with CD4 count ($p < 0.001$ and $p < 0.001$ respectively). Participants with a CD4 count >350 $cells/mm^3$ had the lowest retention rates at 6 months [261(54.4%)] and 12 months [228(47.5%)]. Being on HAART at time of commencing anti-TB medications is associated with retention in care at both 6 and 12 months ($p < 0.001$ and $p < 0.001$). Just 421 (45.1%) and 361 (38.7%) study participants who were not on HAART compared with 1421 (77.7%) and 1263 (69%) who were on HAART when they commenced anti-TB medications remained in care at 6 and 12 months, respectively.

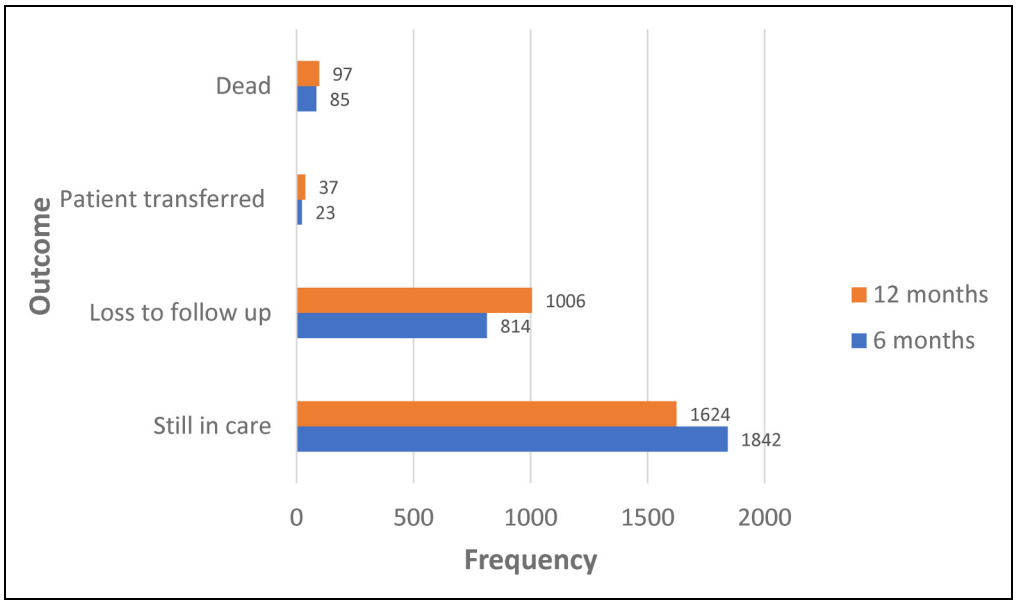

Figure 1. Status of patients treated for TB at 6 months and 12 months after commencing TB treatment at the UCH HIV Clinic in Ibadan, Nigeria.

In the multivariate analysis at 6 months, participants aged 25–34 years and 35–44 years are more likely to be retained in care than those aged 45 years or more [p = 0.032 OR (95% C.I) = 1.619 (1.043-2.5140] and [p = 0.011, OR (95% C.I) = 1.733 (1.133-2.652)] (Table 3). Participants aged 35–44 years and 45 years or more are more likely to be in care at the clinic at 12 months than those aged 24 years or less [p = 0.035, OR (95% C.I) = 1.393(1.023-1.897)] and [p = 0.041, OR (95% C.I) = 1.384 (1.014-1.890)]. In addition, participants with a viral load <1000 copies/ml are more than twice as likely to be retained in clinic at 6 months than those with viral load >1000 copies per ml [p = 0.003, OR (95% C.I) = 2.351 (1.337-4.134)], findings are similar at 12 months [p < 0.001, OR (95% C.I) = 2.393 (1.689-3.391)]. HAART use does not appear to be associated with increased likelihood of retention in care at 6 months. However, being on HAART gives almost 4 times the likelihood of being retained in clinic at 12 months [p < 0.001, OR (95% C.I) = 3.980 (3.114-5.086)] as compared with not being on HAART.

While no relationship was found between CD4 count and retention in care at 6 months, those with a CD4 count of 200–350 cells/mm^3 are 59% more likely while those with a CD4 > 350 are 86% more likely to remain in the clinic at 12 months than those with a CD4 count <200 (p = 0.005 and p = 0.001 respectively).

Discussion

This study describes the retention in care at an HIV clinic of patients treated for TB. There are little data describing retention in care at an ART clinic for patients who have been treated for TB in Nigeria which has high prevalence of both diseases. TB is a well described risk factor for poor outcomes and non-retention in care in HIV clinics in sub-Saharan Africa and other less developed settings and this study affords a focused look at this subset of patients.[11–13] Loss to follow up for chronic infections like HIV and TB often means no access to medications, worsening of both disease conditions, possible development of drug resistance, death, and a higher possibility of further transmission of either or both diseases to other individuals.

This study shows that vast majority of patients who are not retained in this large HIV clinic in sub-Saharan Africa are lost to follow up and not confirmed to be dead or transferred out to other facilities. While death registry data exist, they may not be linked to the HIV clinics. Families of patients who die at home outside of the umbrella healthcare system of our HIV clinic may not disclose their HIV status in the process of registering their death to avoid stigmatization of the surviving family. In addition, our clinic also serves as a regional referral center and many patients return to their place of domicile after initial entry into TB and/or HIV care without initiating a proper transfer out to another facility. There are linkages of data between HIV clinics who are supported by the same HIV program implementing partners that capture transfers into such clinics from ours. Such patients have been accounted for as transferred out in our study. It highlights the huge gap in knowledge regarding the exact outcomes of these patients. It also shows that the loss to follow up occurs mostly in the first 6 months of TB treatment in this subset of HIV patients. There are data to suggest that much of the early loss to follow up in resource limited settings occur because of death.[8,11,14–16] This is however not confirmed in this cohort due to lacking data but clearly highlights the need for close follow up of co-infected patients especially within the first 6 months.

Patients aged less than 25 also need special attention as it has been shown here and elsewhere that they have lower

Table 2. Association between socio demographic and clinico-pathological variables and retention in care at 6 months and 12 months

	At 6 months			At 12 months		
Socio demographics	Not in care n (%)	In care n (%)	P value	Not in care n (%)	In care n (%)	P value
Sex						
Male	375 (35.1)	694 (64.9)	0.127	461 (43.1)	608 (56.9)	0.111
Female	547 (32.3)	1148 (67.7)		679 (40.1)	1016 (59.9)	
Marital status						
Single	65 (21.7)	234 (78.3)	**0.016**	90 (30.1)	209 (69.9)	0.268
Married	238 (20.1)	948 (79.9)		334 (28.2)	852 (71.8)	
Separated/Divorced	89 (27.0)	241 (73.0)		111 (33.6)	219 (66.4)	
Widowed	47 (17.1)	228 (82.9)		78 (28.4)	197 (71.6)	
Age of participants (years)						
15- 24	69 (41.3)	98 (58.7)	**0.007**	79 (47.3)	88 (52.7)	0.063
25-34	306 (31.8)	657 (68.2)		381 (39.6)	582 (60.4)	
35-44	313 (31.1)	692 (68.9)		400 (39.8)	605 (60.2)	
45 and above	234 (37.2)	395 (62.8)		280 (44.5)	349 (55.5)	
Occupation						
Trading	195 (19.1)	827 (80.9)	0.187	280 (27.4)	742 (72.6)	0.192
Teaching/Civil Servant/Professional	109 (23.3)	359 (76.7)		147 (31.4)	321 (68.6)	
Artisan	92 (23.0)	308 (77.0)		130 (32.5)	270 (67.5)	
Student/Unemployed	45 (21.8)	161 (78.2)		60 (29.1)	146 (70.9)	
BMI (kg/m^2)						
Underweight	754 (33.2)	1515 (66.8)	**<0.001**	950 (41.9)	1319 (58.1)	**<0.001**
Normal	73 (20.2)	289 (79.8)		93 (25.7)	269 (74.3)	
Overweight	7 (25.0)	21 (75.0)		8 (28.6)	20 (71.4)	
Obese	1(50.0)	1 (50.0)		1 (50.0)	1 (50.0)	
CD4 (cells/mm^3)						
<200	515 (31.4)	1124 (68.6)	**<0.001**	652 (39.8)	987 (60.2)	**<0.001**
200-350	168 (27.0)	455 (73.0)		215 (34.5)	408 (65.5)	
>350	219 (45.6)	261(54.4)		252 (52.5)	228 (47.5)	
Viral load (n = 2513)						
<1000	75 (19.3)	314 (80.7)	**<0.001**	106 (27.2)	283 (72.8)	**<0.001**
≥1000	671 (31.6)	1453 (68.4)		821 (38.7)	1303 (61.3)	
Hemoglobin (g/dl)						
≤ 8	156 (40.9)	225 (59.1)	**<0.001**	185 (48.6	196 (51.4)	**<0.001**
8.1-10.9	232 (31.8)	497 (68.2)		303 (41.6)	426 (58.4)	
11-11.9	39 (19.8)	158 (80.2)		55 (27.9)	142 (72.1)	
≥ 12	79 (21.5)	289 (78.5)		108 (29.3)	260 (70.7)	
HAART at time of starting TB treatment						
Not on HAART	513 (54.9)	421 (45.1)	**<0.001**	573 (61.3)	361 (38.7)	**<0.001**
On HAART	409 (22.3)	1421 (77.7)		567 (31.0)	1263 (69.0)	

retention rates.[17,18] While this study demonstrates that younger patients have lower odds than older age groups of retention in care at 6 months in the unadjusted analysis, it however shows, that individuals aged between 25 and 44 years have higher odds of remaining in care at 6 months than those above 45 years of age in the adjusted analysis. The adjusted findings are different at 12 months; individuals aged above 35 years have higher odds of remaining in care than those aged 24 years or less. Studies in Ethiopia and India have shown that older patients have worse TB treatment outcomes than younger ones.[19–21] Possible explanations for this could be immunosenescence or higher prevalence of co-morbid conditions seen more frequently with advancing age; both of which would negatively impact clinical outcomes and by extension retention in care. A 2015 study in our clinic showed a higher prevalence of opportunistic infections in patients above 50 years of age compared with those less than 50 years of age.[22] The underweight were poorly retained in our clinic and this might signify the advanced stage of disease at which they present which may be responsible for poor outcomes. This is congruent with what has been previously described about BMI and TB treatment success.[23] However, weight was not shown to be statistically significant in the adjusted analysis. Of note, those with CD4 counts above 200 cells/mm^3 are more likely to remain in care than those with lower CD4 counts at 12 months. Patients, with viral load >1000 copies/ml and hemoglobin <11.0gm/dl have lower odds of being in care at 6 and 12 months. Both features suggest more advanced disease and have both been described to lead to poor outcomes (and possibly loss to follow up) in

Table 3. Correlates of retention in care at 6 months and 12 months.

Variables		Odds Ratio (95%CI)	p-value
Variables at 6 months			
Marital status	Single	0.730 (0.368-1.449)	0.368
	Married	0.800 (0.470-1.365)	0.413
	Separated/ Divorced	0.628 (0.338-1.166)	0.141
	Widowed	1	
Age of participants	24 or less	2.133 (0.922-4.934)	0.773
	25-34	1.619 (1.043-2.514)	**0.032**
	35-44	1.733 (1.133-2.652)	**0.011**
	45 or more	1	
BMI	<18.5	0.408 (0.051-3.529)	0.398
	18.5-24.9	0.791 (0.093-6.704)	0.830
	25-29.9	1	
CD4	<200	0.605 (0.320-1.145)	0.122
	200-350	0.830 (0.405-1.698)	0.610
	>350	1	
Viral Load	<1000	2.351 (1.337-4.134)	**0.003**
	≥1000	1	
Hemoglobin	8 or less	1	
	8.1-10.9	1.148 (0.776-1.697)	0.490
	11-11.9	2.685 (1.328-5.431)	**0.006**
	12 or more	1.935 (1.180-3.175)	**0.009**
On HAART	No	1	
	Yes	1.080 (0.731-1.597)	0.699
Variables at 12 months			
Age of participants	24 or less	1	
	25-34	1.191 (0.723-1.962)	0.492
	35-44	1.393 (1.023-1.897)	**0.035**
	45 or more	1.384 (1.014-1.890)	**0.041**
BMI	<18.5	0.214 (0.044-1.040)	0.056
	18.5-24.9	0.414 (0.083-2.071)	0.283
	25-29.9	1	
CD4	<200	1	
	200-350	1.590 (1.149-2.202)	**0.005**
	>350	1.859 (1.278-2.704)	**0.001**
Viral Load	<1000	2.393 (1.689-3.391)	**<0.001**
	≥1000	1	
Hemoglobin	≤8	1	
	8.1-10.9	1.204 (0.896-1.619)	0.218
	11-11.9	2.180 (1.412-3.365)	**<0.001**
	≥12	2.214 (1.542-3.179)	**<0.001**
On HAART	Yes	3.980 (3.114-5.086)	**<0.001**
	No	1	

patients with HIV treated for TB.[24] A study by Isanaka *et al* showed that anemia (specifically iron deficiency anemia) is associated with 2–3-fold increased risk of death in TB patients.[24] As expected, use of HAART was significantly associated with retention in clinic at 12 months (although not at 6 months). This finding at 6 months might be related to not having achieved virologic suppression by 6 months. HAART use and linkage to HIV care is clearly linked with better outcomes in TB/HIV co-infected patients.[8,25–27]

Another possibility for patients lost to follow up in our cohort is the fact that they might be in care in another HIV clinic either within the same locality or elsewhere in the country. This is a real problem in a tertiary referral setting such as ours, where patients are often referred from elsewhere and may opt to transfer care to other facilities close to their homes for convenience without duly informing the clinic staff. Patients whose portal of entry to the HIV clinic was via referral from the TB clinic might view the TB clinic as their primary source of care and while they might present at the HIV clinic at least once might find it challenging to attend two clinics and hence remain in care at the TB clinic but not the HIV clinic. It has been reported that regular follow up for HIV patients at an HIV clinic during treatment for TB reduces loss to follow up.[25]

The HIV and TB clinics within the UCH system are run as separate entities and require separate visits to different providers at different clinics for consultation and medication refills. This might be an undue burden to patients who may find multiple visits inconvenient due to poor health or inability to obtain time away from work or their businesses as well as childcare responsibilities. Such programmatic, logistic, social and other reasons have been well documented as reasons for loss to follow up.[3,28] Integration of TB and HIV services at our clinic would improve retention in care and other outcomes as has been described elsewhere.[29,30] Facility-specific interventions such as co-location and full integration of TB/HIV services should be put in place to improve the ease of access to comprehensive care.

This study has some limitations. This is a single center study which affects the generalizability of the findings. Standard treatment outcomes for TB such as cure, treatment failure, relapse and so on have not been studied here even for patients that remained in care. In addition, clinical parameters of the TB disease episode, prescribed regimens, adverse events, or drug-related toxicity which could have a significant effect on retention in care were not explored in this study. These could have provided some insight into the outcomes of patients who did not remain in care in the clinic. As such, we do not have clear information on the reasons for loss to follow up which would be vital in developing targeted interventions aimed at increasing retention rates. Direct interventions to trace and track patients who are lost to follow up have been shown to be effective and could be explored in our clinic so as to provide information on the true status of those considered to be lost to follow up.[31] Patient counseling at entry into care should ensure that patients and their relatives understand the importance of remaining in care and informing the clinic in the event of transfer or death.

Conclusion

This study gives a locally relevant picture of the magnitude and correlates of retention in care of patients treated for TB at a large HIV clinic which could form the basis of development of context specific solutions for this and other similarly situated clinics.

Retention in HIV clinics is low for patients treated for TB. Up to 12 months but particularly in the first 6 months after treatment of TB in HIV patients, patients under 25 and over 45 years, those with advanced immunosuppression, low hemoglobin and high

viral load should be prioritized for close follow up and specific interventions to address these issues.

Large studies should be undertaken in the current era of test and treat to determine if there has been any impact of this policy on retention in care in HIV patients who are treated for TB.

Declaration of Conflicting Interests

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