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Low uptake of antiretroviral therapy after admission with human immunodeficiency virus and tuberculosis in KwaZulu-Natal, South Africa

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SUMMARY

OBJECTIVES: A prospective cohort study was conducted among human immunodeficiency virus (HIV) infected in-patients with tuberculosis (TB) or other opportunistic infections (OIs) in South Africa to estimate subsequent antiretroviral therapy (ART) uptake and survival.

METHODS: Logistic regression modeling explored associations between baseline characteristics and starting ART, and ART exposure-adjusted incidence of death was estimated over 6 months of follow-up.

RESULTS: Among 49 participants enrolled, median CD4 cell count at hospital discharge was 42 cells/μl and the most common presenting OIs were TB (76%), *Pneumocystis* pneumonia (8%), chronic diarrhea (8%), cryptococcal meningitis (6%), and *Toxoplasma gondii* (4%). By 6 months, only 20 (45%) patients had initiated ART, and four (8%) were lost to follow-up. ART uptake was independently associated with previous use of traditional medicine (OR 7.2, 95%CI 1.4–55.1) and with less advanced HIV infection (baseline CD4 count per 50 cells/μl increase OR 1.4, 95%CI 0.9–2.2). A total of 14 (31%) patients died before initiating ART; the monthly incidence of death did not decrease over the 6-month interval.

CONCLUSION: The high mortality observed within the 6 months following hospitalization with TB or other acute OIs indicate that mechanisms are needed to expedite ART for patients after an acquired immune-deficiency syndrome defining illness.

KEY WORDS: co-infection; tuberculosis; antiretroviral therapy

SIGNIFICANT pre-antiretroviral therapy (ART) mortality has been documented among human immunodeficiency virus (HIV) infected out-patients awaiting initiation of ART in resource-limited settings.[1,2] In South Africa, the delay of ART until completion of tuberculosis (TB) therapy was associated with an increased risk of death among ART-eligible patients.[3] A growing evidence base suggests that patients with recent opportunistic infection (OI) may benefit from rapid ART initiation.[4] However, following discharge from hospital, HIV-infected patients with recent OI and patients in resource-limited settings face several potential barriers to timely initiation of ART, potentially placing them at increased risk for poor outcome. These barriers include the loss of functional capacity associated with hospitalization, as well as structural hurdles such as pre-ART readiness-assessment processes. A significant delay in initiating ART would be expected to adversely impact survival, estimated to be only 1.3 years after an acquired immune-deficiency syndrome (AIDS) defining illness.[5]

To improve ART uptake and reduce pre-ART mortality among ART-eligible in-patients with TB or other OI, a pilot program was initiated at McCord Hospital in Durban, South Africa, to expedite access to ART after hospitalization. In the pilot program, HIV-infected patients with TB or other OI transitioned rapidly from the in-patient ward to a step-down center for initiation of ART. Eligible patients who did not enter this pilot program and instead sought ART as out-patients were also prospectively followed, and their outcomes are presented here.

METHODS

McCord Hospital is a 166-bed general hospital in South Africa that provides in-patient care to patients from Durban townships. HIV-infected patients with

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TB or other acute OI comprise approximately half of admissions to the hospital's medical wards. As part of routine in-patient care, HIV and CD4 count testing are performed, and at discharge, HIV-infected patients with a CD4 count of <200 cells/μl are directed to enroll as out-patients for ART at the Sinikithemba Clinic at McCord Hospital (large vertical site) or at one of several other local clinics.

During the study period from December 2006 until February 2007, HIV-infected, ART-naïve patients hospitalized at McCord Hospital with TB or other acute OI were approached to enter a pilot project which consisted of immediate initiation of ART in a step-down center with stavudine, lamivudine and efavirenz. Patients were required to pay for the cost of additional days of hospitalization (median 14 days, interquartile range [IQR] 12–19) associated with the immediate ART program. Patients who did not participate in this pilot project were prospectively enrolled and followed.

Enrollment criteria

HIV-infected, ART-naïve patients aged ⩾18 years with a CD4 cell count of <200 cells/μl (or with World Health Organization Stage IV disease) were prospectively enrolled. Patients were excluded if they did not indicate both a readiness to initiate ART after discharge and a willingness to be contacted after 6 months for follow-up.

Data collection

Clinical, demographic and laboratory data were collected during admission, and clinical outcomes were collected at month 6. Data collected at admission included age, sex, education, prior OI history, date of HIV diagnosis, use of traditional medicines, body mass index (BMI), presence of thrush, CD4 cell count, albumin, alanine aminotransferase (ALT), creatinine and hemoglobin. Six months after hospital discharge, data collected included current medications, date and location of current ART clinic (if enrolled), new clinical events (hospitalizations and OI), and vital status (obtained from emergency contact, if necessary). At that time, patients were also offered a clinic visit at McCord Hospital if they had not seen a physician in the last month.

Study design

We conducted an observational, non-randomized prospective cohort study. The primary outcomes were ART initiation within 6 months of hospital discharge, and death within 6 months of hospital discharge.

Statistical analysis

Multivariable logistic regression modeling explored the associations between baseline (i.e., pre-hospital discharge) characteristics and ART initiation at 6 months. Covariates included in the modeling process were age, sex, education, use of traditional medicines, use of cotrimoxazole, date of HIV diagnosis (concurrent with current OI vs. prior), BMI, presence of thrush, TB (vs. other OI), CD4 cell count, percentage of lymphocytes, ALT, hemoglobin, creatinine and albumin. All covariates were initially fit alone (univariate models), and only those suggestive of an association were fit in a multivariable model. Logistic regression analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC, USA). All tests of statistical significance were 2-sided, without adjustment for multiple testing.

Summaries of survival used ART exposure stratified and interval-specific incidence rate estimation. Both the incidence point estimate and a 95% confidence interval (CI) on the estimate are presented. To estimate survival by ART exposure, if and when individuals started ART, their subsequent follow-up survival time contributed to the post-ART initiation stratum. Incidence estimation was performed using STATA software, version 8.2 (Stata Corp, College Station, TX, USA).

Ethical approval

The study was approved by the McCord Hospital Research Ethics Committee in Durban, South Africa.

RESULTS

Forty-nine patients with HIV and TB or other acute OI requiring hospitalization were prospectively enrolled between December 2006 and February 2007 (Figure 1). The reasons cited for declining participation in the immediate ART program were cost of hospitalization (74%), family or employment obligations (19%) or other (7%).

Baseline characteristics at admission with tuberculosis or other acute OI

At admission, the median age was 34 (IQR 28–40), 49% were female and the median CD4 cell count was 42 cells/μl (IQR 14–106; Table 1). The median time since initial HIV diagnosis was 2.9 months (IQR 1.1–3.9) and, for 67% of patients, the current admission was the first OI. The admission OIs were pulmonary TB 28%, extra-pulmonary TB (including TB meningitis) 38%, *Pneumocystis* pneumonia 8%, chronic diarrhea (>30 days) 8%, cryptococcal meningitis 6%, *Toxoplasma gondii* 4% and unknown 8%. More than one third (37%) of patients had a low BMI of <18.5 kg/m^2, and the median admission albumin, creatinine and hemoglobin were respectively 2.65 g/dl, 1.05 mg/dl and 10.5 g/dl.

ART initiation within 6 months of hospital discharge

Follow-up at 6 months following hospital discharge was available for 45 of the 49 (92%) patients (Table 2). By this time, 20/45 (45%) patients had initiated ART. Among those who initiated ART, the observed time from discharge until start of ART was a median

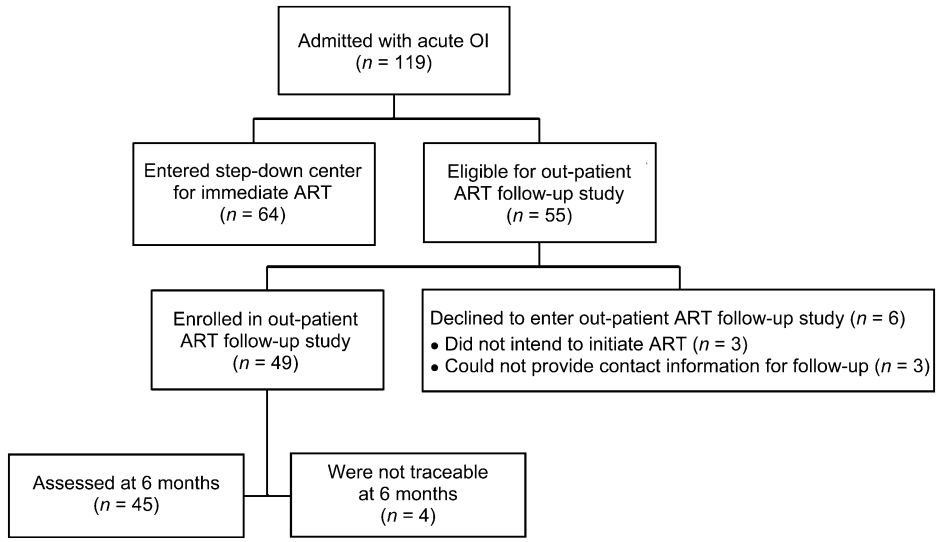

Figure Inclusion of patients in a prospective study of ART uptake and mortality after hospitalization with acute OI at McCord Hospital in Durban, South Africa, December 2006–February 2007. OI = opportunistic infection; ART = antiretroviral therapy.

Table 1 Baseline characteristics of patients at hospital admission with acute OI in South Africa

Characteristics (N = 49)	n (%)
Median age, years [IQR]	34 [28–40]
Women	24 (49)
Educational level less than secondary school	26 (53)
Median time since initial HIV diagnosis, months [IQR]	2.9 [1.1–3.9]
On an ART waiting list at admission	10 (20)
Alternative medicine use in the last 3 months	
Product sold as 'immune booster'	14 (29)
Traditional medicine	10 (20)
History of prior OI	16 (33)
Opportunistic infection at admission	
Pulmonary TB	14 (28)
Extra-pulmonary TB, including TB meningitis	18 (38)
Pneumocystis pneumonia	4 (8)
Chronic diarrhea*	4 (8)
Cryptococcal meningitis	3 (6)
Toxoplasma gondii	2 (4)
Other	4 (8)
Median weight, kg [IQR]	57.3 [50–62]
Median body mass index, kg/m^2 [IQR]	20.3 [17.6–25.4]
Body mass index <18.5 kg/m^{2†}	18 (37)
Median CD4 count, cells/μl [IQR]	42 [14–106]
CD4 cell count category, cells/μl	
⩽50	27 (55)
51–199	18 (36)
⩾200	3 (6)
Biochemical parameters	
Albumin, median, g/dl‡	2.65
Creatinine, median, mg/dl	1.05
Hemoglobin, median, g/dl	10.5
ALT, median, IU/l‡	25.5

*⩾30 days.
†i.e., underweight.
‡Fifteen patients did not have a baseline albumin and ALT measurement.
OI = opportunistic infection; IQR = interquartile range; HIV = human immunodeficiency virus; ART = antiretroviral therapy; TB = tuberculosis; ALT = alanine aminotransferase; IU = international unit.

of 83 days (IQR 34.5–119.5). Four participants started ART within 1 month of discharge, 2 between 1 and 2 months, 6 between 2 and 3 months, 3 between 3 and 4 months, and the remaining 5 between 4 and 5 months. Pre-discharge covariate associations with initiating ART were estimated (Table 3). Use of traditional medicine at baseline was associated with higher odds of 6-month ART initiation: 78% of patients using traditional medicine at baseline initiated ART by 6 months compared to 36% among patients who denied recent use of traditional medicines (P = 0.04). Furthermore, patients with a higher CD4 cell count at baseline of >50 cells/μl had an increased odds of initiating ART by 6 months compared to

Table 2 Outcomes over 24 weeks following discharge with acute OI in KwaZulu-Natal, South Africa

	Patients (n = 45)*
Overall incidence of death after discharge, per 100 person/years (95%CI)	0.19 (0.11–0.32)
Incidence of death prior to ART initiation	0.24 (0.14–0.42)
Incidence of death following ART initiation	0.05 (0.0–0.37)
Initiation of ART by 24 weeks	
Initiated ART, n (%)	20 (46)
Observed days from admission to ART initiation, median [IQR]†	83 [34.5–119.5]
Mortality at 24 weeks	
Died before initiating ART, n (%)	13 (29)
Died after initiating ART, n (%)	1 (2)
Observed days from discharge to death, median [IQR]‡	98.5 [51–149]

*Among 49 patients enrolled, four patients were not traceable with the contact information provided.
†n = 20.
‡n = 14.
OI = opportunistic infection; CI = confidence interval; ART = antiretroviral therapy; IQR = interquartile range.

Table 3 Factors associated with initiation of ART after acute OI in KwaZulu-Natal, South Africa

	n	ART initiated %	Univariate OR (95%CI)	Multivariate OR (95%CI)
All subjects	45	44		
Sex				
Male	23	39		
Female	22	50	1.6 (0.5–5.1)	
Age, years				
0–29	15	47		
⩾30	30	43	0.9 (0.3–3.0)	
Baseline traditional medicine use in past 3 months				
None	36	36		
Traditional medicine use in past 2 months	9	78	6.2 (1.1–34.3)	7.2 (1.4–55.1)
Diagnosed with HIV simultaneously with OI admission				
No	25	48		
Yes	20	40	0.9 (0.8–1.0)	
OIs				
Pulmonary or extra-pulmonary TB	29	45		
OI other than TB	16	44	1.1 (0.3–3.6)	
Initial CD4 cell count, cells/μl				
0–49	25	32		
⩾50	20	60	3.6 (1.04–12.8)	1.4 (0.9–2.2)
Baseline BMI, kg/m^2				
⩾18.5	27	41		
<18.5	18	50	1.5 (0.4–4.8)	
Hemoglobin baseline				
⩾9	35	43		
<9	10	50	1.3 (0.3–5.5)	
Baseline albumin, mg/dl*				
⩾2.5	21	38		
<2.5	13	46	1.4 (0.3–6.5)	

*Fifteen patients did not have a baseline albumin measurement.
ART = antiretroviral therapy; OI = opportunistic infection; OR = odds ratio; CI = confidence interval; HIV = human immunodeficiency virus; TB = tuberculosis; BMI = body mass index.

those with a CD4 cell count of ⩽50 cells/μl (odds ratio [OR] 3.6, 95%CI 1.04–12.8). This observation was partially explained by an increased mortality among patients with baseline CD4 count of <50 cells/μl (10/25 participants with CD4 <50 cells/μl later died compared to 4/19 participants with CD4 ⩾50 cells/μl, Fisher's exact test $P = 0.2$). In univariate analysis, there was not a significant association identified between ART initiation and other baseline factors including education, date of HIV diagnosis (concurrent with hospitalization vs. prior), BMI, baseline TB (vs. other OI), ALT, hemoglobin, creatinine and albumin.

In multivariate analysis, only recent use of traditional medicines remained associated with increased odds of initiating ART by 6 months (OR 7.2, 95%CI 1.4–55.1, $P = 0.03$, Table 3) and CD4 cell count at baseline of >50 cells/μl showed a borderline association with an increased odds of initiating ART (OR 1.4, 95%CI 0.9–2.2, $P = 0.14$).

Mortality within 6 months following discharge with tuberculosis or other acute OI

Overall, by 6 months follow-up, 14 (31%) of 45 patients with follow-up information available had died (Table 2). Thirteen of the deaths occurred prior to initiation of ART and one occurred 5 days following ART initiation. Two deaths occurred within the first month following discharge, 3 between 2 and 3 months, 5 (including 1 following ART initiation) occurred between 3 and 4 months, and 2 in each of the intervals of 4–5 and 5–6 months following discharge.

This cohort had a total of 20 years of person-time follow-up; the overall incidence of death was 0.19 per 100 person-years (py; 95%CI 0.11–0.32; Table 2). The overall incidence of death following initiation of ART (with a total of 5.23 years of follow-up available) was 0.05 (95%CI 0.01–0.37); the overall incidence rate of death before starting ART was 0.24 (95%CI 0.14–0.42). Before initiating ART, the monthly incidence rate (per 100 py) of death was as follows: 0.16 (0 to 1 month following discharge), 0.29 (2 to 3 months), 0.54 (3 to 4 months), 0.45 (4 to 5 months) and 0.692 (5 to 6 months).

DISCUSSION

After discharge, patients with TB and other OI enter a dangerous clinical trajectory in South Africa that includes poor ART access and high early mortality.

Six months after discharge, more than half of HIV-infected patients with TB (or other OI) had not initiated ART. During the 6 months after discharge, the incidence of death remained high for those not initiating ART. Patients with the most advanced disease (CD4 count of <50 cells/μl) appear to have been less likely to initiate ART after admission (32% initiated) compared to patients with less advanced HIV disease (60% initiated). The overall high mortality in this cohort—and the observation that the incidence of mortality prior to starting ART did not fall over time—suggests that, in South Africa, mechanisms are urgently needed to expedite ART access for patients with advanced HIV disease after OI. This subgroup does not appear to have received adequate attention in an ART roll-out which has been oriented towards the out-patient sector.

Although acute admission with AIDS-defining illness continues to be an important initial presentation of HIV in southern Africa, in-patients have not been a major focus of the ART roll-out. After in-patient admission in South Africa, patients with HIV infection qualifying for ART must queue with out-patients (often with less advanced disease), and participate in the same pre-ART readiness-assessment process. As this study demonstrates, the current model may impose significant barriers for this vulnerable patient group. To improve continuity of care after in-patient admission, new treatment models are required for HIV-infected patients presenting to in-patient wards. These could include the use of an in-patient ART initiation model or out-patient 'fast-track' mechanisms that could triage patients with TB or other OI to out-patient ART initiation within weeks, and not months, with less stringent preparation and training requirements.

A significant association was found between the baseline use of traditional medicine and an increased odds of ART initiation by 6 months. The use of traditional medicines may be a marker for health-seeking behavior.

The study has important limitations. The small sample size makes it difficult to model multiple baseline factors in a single model to predict the primary outcome of ART initiation after OI, and the study therefore had power to detect only large associations with this outcome. The findings presented in this report cannot be generalized to all settings in South Africa. The site of the study (McCord Hospital) includes a hospital and an ART clinic with adequate human resources. It is likely that the outcomes described among HIV-infected patients with TB and other acute OI in this report, compared to the public hospital sector in KwaZulu-Natal, represent a best-case scenario. A potential source of bias relates to the inclusion criteria for this study: participants were patients with acute OI who were eligible but elected not to participate in an ongoing in-patient ART initiation program that required an additional 2 weeks of hospitalization with associated costs.

Despite an initial intention by all patients to commence out-patient ART, less than half had succeeded by 6 months. To meet the needs of this patient group, creative and pragmatic new care models are needed. Researchers must initiate high quality patient-oriented research to meet this gap and urgently communicate results from ongoing programs focusing on this vulnerable patient group.

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RÉSUMÉ

OBJECTIFS : On a mené une étude prospective de cohorte parmi les patients hospitalisés pour tuberculose (TB) ou d'autres infections opportunistes (OI) et infectés par le virus de l'immunodéficience humaine (VIH) en Afrique du Sud pour estimer le recours ultérieur à un traitement antirétroviral (ART) et la survie.

MÉTHODES : On a exploré par les modèles de régression logistique les associations entre les caractéristiques du début et la mise en route de l'ART ainsi que l'incidence de décès ajustée pour l'ART au cours d'un suivi de 6 mois.

RÉSULTATS : Parmi les 49 participants enrôlés, le décompte médian des cellules CD4 à la sortie de l'hôpital a été de 42 cellules/μl et les OI les plus couramment

observées ont été la TB (76%), la pneumonie à *Pneumocystis* (8%), la diarrhée chronique (8%), la méningite à cryptocoques (6%) et la toxoplasmose (*Toxoplasma gondii* ; 4%). A 6 mois, 20 sujets seulement avaient commencé l'ART (45%) et quatre (8%) ont été perdus de vue. La mise en route de l'ART est en association indépendante avec le recours antérieur à la médecine traditionnelle (OR 7,2 ; IC95% 1,4–55,1), ainsi qu'avec une infection VIH moins avancée (décompte de CD4 au départ OR 1,4 ; IC95% 0,9–2,2 par augmentation de 50 cellules/μl). Au total, il y a eu 14 décès (31%) avant la mise en route de l'ART et l'incidence mensuelle de décès n'a pas diminué au cours du suivi de 6 mois.

CONCLUSION : La mortalité élevée observée au cours des 6 mois suivant l'hospitalisation pour TB ou autre OI aiguë plaide en faveur de la nécessité de mécanismes d'accélération de la mise en route de l'ART chez les patients atteints d'une maladie entrant dans la définition du syndrome d'immunodéficience acquise.

RESUMEN

OBJETIVOS: Se llevó a cabo un estudio prospectivo de cohortes en pacientes hospitalizados con infección por el virus de la inmunodeficiencia humana (VIH) y tuberculosis (TB) u otra infección oportunista (OI) en Sudáfrica, con el fin de calcular la proporción de pacientes que aceptan luego el tratamiento antirretrovírico (ART) y su supervivencia.

MÉTODOS: Mediante un modelo de regresión logística se analizó la asociación entre las características iniciales de los pacientes, el comienzo del ART y la mortalidad ajustada a la exposición a este tratamiento, en un seguimiento de 6 meses de duración.

RESULTADOS: En los 49 participantes del estudio, la mediana del recuento de células CD4 en el momento del alta hospitalaria fue 42 células/μl y las infecciones oportunistas más frecuentes fueron la TB (76%), la neumonía por *Pneumocystis* (8%), la diarrea crónica (8%), la meningitis por criptococo (6%) y el parasitismo por *Toxoplasma gondii* (4%). A los 6 meses, solo 20 pacientes (45%) habían iniciado el ART y cuatro (8%) se perdieron durante el seguimiento. La aceptación de este tratamiento se asoció en forma independiente con una experiencia previa con la medicina tradicional (OR 7,2; IC95% 1,4–55,1) y con una infección por el VIH menos avanzada (recuento inicial de CD4, por cada 50 células/μl un aumento del OR de 1,4; IC95% 0,9–2,2). Catorce pacientes (31%) fallecieron antes de comenzar el ART; la mortalidad mensual no disminuyó durante el intervalo de 6 meses.

CONCLUSIÓN: La alta mortalidad observada en los primeros 6 meses posteriores a una hospitalización por TB u otra OI es un argumento en favor de la introducción de un mecanismo que acelere la administración del ART en los pacientes que presentan una enfermedad que define la aparición del síndrome de inmunodeficiencia adquirida.