

Assessment of antiretroviral treatment outcome in public hospitals, South Nations Nationalities and Peoples Region, Ethiopia

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Abstract

Background: The outcome of antiretroviral treatment, survival patterns and associated determining factors in public hospitals are not well known. Thus a longitudinal study is vital to understand the pattern of survival and treatment outcome.

Objective: To assess the outcome of antiretroviral treatment in rural public hospitals in South Nations, Nationalities and Peoples Region, Ethiopia.

Method: A historical retrospective cohort study design was used for patients visiting hospitals from January 1, 2005 to January 31, 2009. A total of 5,664 patient records were examined from eight randomly selected public hospitals. Kaplan-Meier models were used to estimate mortality and Cox proportional hazards models to identify predictors of mortality.

Results: The median age was 30 years and 73.6% were in the age group 25-40 while the higher HIV risk age group 14-24 covered only 12.8%. The proportion of females was 56.3%. The cumulative proportions of survivals were 92%, 90%, 88% and 86% at months 6, 12, 24 and 36 respectively. The hazard of death was higher in male (AHR: 1.632, CI: 1.309-2.034) and those who had a baseline CD4 cell count < 50 cells /ml compared to these with a count of above 200 (AHR: 3.176, CI: 2.304- 4.434). Patients with WHO stage IV at baseline had a higher risk of death compared to these with a WHO stage I (AHR: 5.603, CI: 1.753-17.905).

Conclusions: There is an indication of improvement of survival in the patient population. An advanced disease stage, Low CD4 cell count, gender and timing of ARV regimen combinations had significant contribution in determining a longer survival time. Priority should thus be given to identify HIV-infected individuals and start ART earlier in the course of their illness. [*Ethiop. J. Health Dev.* 2011;25(2):102-109]

Introduction

The Acquired Immune Deficiency Syndrome (AIDS) disease has been one of the most destructive epidemics to hit Ethiopia. There were 977,394 people living with the virus, and of these 258,264 require antiretroviral treatment (ART). Adults and adolescents account for 24% of antiretroviral (ARV) service coverage by December 2006 (1). A Federal Ministry of Health (FMoH) report showed that 95,756 patients started ART treatment in Ethiopia. Out of these 71,773 (74.95%) patients are presently on ART (2).

The national antiretroviral initiation criteria for both adults and adolescents states that, in places where CD4 cell count is available, WHO clinical stage IV, irrespective of CD4 cell count, WHO stage III and if CD4 cell count is less than 350 and all WHO stage IV and CD4 cell count is less than 50 are criteria for eligible patients to start ART. However, for places where CD4 cell count is not available, WHO stage IV and WHO stage III, irrespective of TLC, WHO stage II and if TLC is less than or equal to 1200 are eligible to initiate ART treatment. Large numbers of people, without age and

gender limitation, need to access free antiretroviral treatment and prolong survival (3).

Prevention of HIV infection, retention of patients in chronic care and retention of physicians in the public health care facilities need urgent attention for effective and sustainable HIV/AIDS health system responses in the long term (4). The widespread availability of ART has led to a substantial decline in mortality (5).

A study in South Africa concluded that scaling up ART provision was associated with reduced early mortality (6). Early mortality rates in sub-Saharan Africa are very high; between 8 to 26 % of patients die in the first year of ART with most deaths occurring in the first few months (7).

Clinical staging and BMI (body mass index) could be important screening tools to identify and target individuals who are still at high risk of early death. A study in South Africa showed that risk factors associated with mortality were WHO stage IV disease, baseline CD4 count and malnutrition (8). Mortality was high in CD4 cell count less than 50 for both experienced and

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non-experienced treating physician in comparison to CD4 cell count above 200 strata (9).

A study in northern Uganda of ART patients' showed that mortality is comparable in patients who were treated in conflict and peaceful areas and low income settings (10). An Indian experience showed that monitoring body weight during follow up emerged as an inexpensive predictors of treatment failure in a resource poor setting (11).

A better knowledge of prognostic factors would allow closer follow up and more targeted interventions to improve survival. Little information is available on a longer follow up antiretroviral treatment outcome. Hence, the objective of this study was to assess the outcomes of antiretroviral treatment and predicting factors in rural public hospitals in the South Nations, Nationalities and Peoples Region, (SNNPR) Ethiopia. It also described the pattern of CD4 cell count and body weight change at months 0, 6, 12 and 24.

Methods

The study was made in eight hospitals located in South Nations, Nationalities and Peoples Region (SNNPR). The study population were all adults age above 14 years, who started ART treatment between January 1, 2005 and January 31, 2009.

A retrospective historical cohort study with single stage cluster sample of unequal size was employed for the study. Assuming a homogeneous ART treatment care throughout the region, eight hospitals were randomly selected among sixteen hospitals.

The sample size was calculated to detect the difference between two proportions formula to allow comparisons using gender as a factor with the following assumptions; 5% type I error, 80% power, ratio of male to female 1:1, 19.8% and 14.4% proportion of crude death rate in males and female, adjustment of lost follow up rate of 21% of the one year follow up study in Zambia were assumed (12). Moreover, a 0.001 intra-class correlation was considered. Based on the above assumptions the minimum sample size required for the study was 2,311.

The study used secondary data collected routinely in the hospitals and entered in an ART register database. De-identified databases were backed up and merged in ART data warehouse designed by the principal investigator. As a result, the study used a sample size of 5,664 patient records out of 20,451 total patient records in the region. Since the number of records was higher than the minimum required sample size increasing the importance of the study.

The outcome variable was death and follow up time from the start of ART to one of the following event (LOST, DROP, TRANSFER OUT, STOP, DEAD) until the end

of the study which was January 31, 2009). Whichever outcome occurred first was considered. The covariates included in the Cox hazard model were sex, age, WHO stage, functional status, CD4 cell count and presence and absence of Nevirapine drug in ARV regimen at baseline.

Operational Definitions:

The following operational definitions were obtained from routine work environment.

LOST: Not seen since ≥ 1 month < 3 months.

DROP: Lost to follow up for > 3 months.

Transfer out: A patient is referred to another health facility for care.

Functional Status

- **Working:** Able to perform usual work in or out of the house.
- **Ambulatory:** Able to perform activities of daily living.
- **Bedridden:** Not able to perform activities of daily living.

Ethical clearance was obtained from the Joint Committee of School of Public Health and Faculty of Informatics, Addis Ababa University. Written permissions were obtained from SNNPR, Woreda Health Bureau and hospital administrations.

SPSS version 15 was used for data analysis. Descriptive statistics, repeated measures analysis of variance, Kaplan-Meier graphs and Cox regression models were performed. Variables with a P-value less than 5% were considered as statistically significant.

Results

Socio-demographic characteristics: 5,664 patient records were analyzed in the study of which 56.3% were female and 43.7% male (Table 1). The median age was 30 (range: 14 to 80 years). 4,111 (72.6%) were in age group 25 to 40 years. The youngest age group (between 14 and 24 years) and the older age group (>40 years) were 724 (12.8%) and 829 (14.6%) respectively.

Clinical characteristics: From 5,642 known baseline WHO stage classifications, 282 (5%) were in WHO stage I, 780 (13.8%) in stage II and 4,580 (81.5%) in stage III or IV. Of the 5,181 available CD4 cell counts measured at and three months before ART initiation, 755 (14.6%) had CD4 cell count of less than 50/ml, 2,910 (56.2%) had between 50 and 200 per μL and 1,516 (29.2%) had above 199 cells per/ml. The median CD4 cell count was 140 cells per/ml.

The mean (SD) baseline weight for 2,114 male and 3,092 female participants measured were 54 (8.4) and 47.7 (8.7), respectively. Functional status at start of ART initiation was 562 (10.4%), ambulatory 2,105 (39.0%) and working 2,725 (50.5%).

Table 1: Socio-demographic and clinical characteristics of ART patients at start of ART initiation in selected hospitals in SNNPR, January 1, 2005 to January 31, 2009.

Characteristics	Value
Sex (n =5,664)	n (%)
Male	2,477 (43.7%)
Female	3,187 (56.3%)
Age (n=5664, Mean=32.7, SD=8.6, Range= 14 - 80)	n (%)
14-24	724 (12.8%)
25-30	2,128 (37.6%)
31-40	1,983 (35.0%)
≥41	829 (14.6%)
Weight (n=5,505, mean=50.5, SD=9.2 kg)*	n (x,SD)
Male	2,413 (54.1, 8.4)
Female	3,092 (47.7, 8.7)
<60 kg	4,662 (47.7, 6.7)
≥60 kg	883 (65.1, 5.8)
CD4 cell count (n=5,181, mean=153.3, median=140, SD=99.2)*	n (%)
0-49	755 (14.6%)
50-199	2,910 (56.2%)
≥200	1,516 (29.2%)
WHO stage at entry (n=5,642)*	n (%)
Stage I	282 (5.0%)
Stage II	780 (13.8%)
Stage III	3,571 (63.3%)
Stage IV	1,009(17.9%)
Functional status at entry (n=5,392)*	n (%)
Bedridden	562 (10.4%)
Ambulatory	2,105 (39.0%)
Working	2,725 (50.5%)
Is NVP ARV in baseline regimen (n=5,664)	n (%)
Yes	3,848 (67.9%)
No	1,783 (31.7%)
Undetermined	33 (0.6%)
Baseline ARV regimen type (n=5,664)	n (%)
Ia(30)-d4t(30)-3TC-NVP	2,866 (50.60%)
Ia(40)=d4t(40)-3TC-NVP	276 (4.87%)
Ib(30)=d4t(30)-3TC-EFV	1,290 (22.78%)
Ib(40)=d4t(40)-3TC-EFV	92 (1.62%)
Ic=AZT-3TC-NVP	702 (12.39%)
Id=AZT-3TC-EFV	399 (7.04%)
4a=d4T-3TC-NVP	3 (0.05%)
4c=AZT-3TC-NVP	1 (0.02%)
4d=AZT-3TC-EFV	2 (0.045%)
Other combinations	33 (0.58%)

*There were missing data

Sixty eight percent of the patients 3,848 (68 %) started with a Nevirapine combined regimen while 1,783 (31.7%) initiated with an Efavirenz combined regimen. The most common prescribed ARV regimen at baseline was a combination of Stavudine + Lamivudine + Nevirapine (d4t-3TC-NVP) which accounted for 55.5 % of the initiation regimens.

Survival and follow up outcome: The end point follow up status distribution showed that cumulative proportion, of patients alive, dead and dropout were 64.7%, 8.4% and 13.6% while 10.8% were transferred out to other health facilities, LOST and temporary withdrawal of medication (STOP) contributes 2.3% and 0.2% respectively by end of January 2009. Overall mean survival time was 43 months after ART initiation (Figure 1).

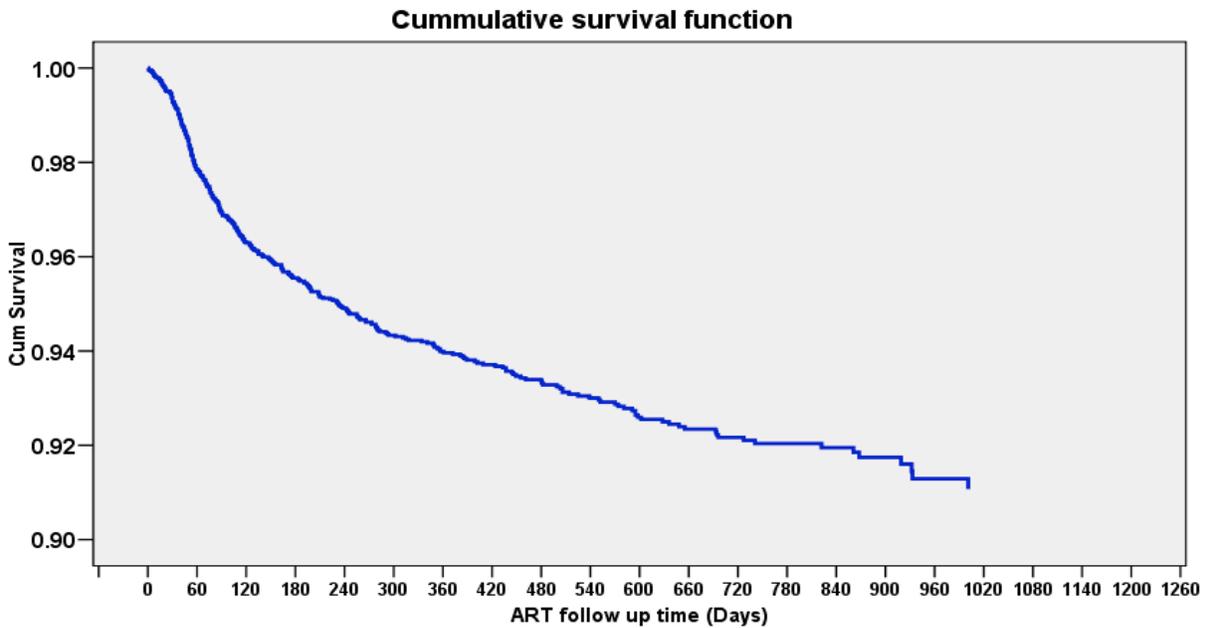


Figure 1: Cumulative survival function of ART patients in selected hospitals of SNNPR, January 1, 2005 to January 31, 2009.

Death as an outcome: The cumulative mortality rate was 74.5 deaths per 1,000 PYO (473 deaths/ 6,352 person-year observation), in which 70.8% (335/473), 15.2% (72/473), 11.0% (52/473) and 2.9%(14/473) deaths occurred in the first 6 months, six to one year, one to two years, after second year of follow up respectively.

From Cox regression models, a hazard ratio of death in patients whose CD4 cell count was less than 50 cells/ml and between 50 to 199 cells/ml, relative to ones whose CD4 cell count above or equal to 200 cells/ml, were found to be 3.176 (CI: 2.304, 4.434) and 1.900 (CI: 1.405, 2.569) respectively. However, there was no

significance death rate difference between patients whose age group was 25 through 30 and 31 through 40 years.

The survival patterns of ART patients were different at the various WHO stage classifications (Figure 2). The difference in the risk of death between WHO stage II and stage I at any given time is similar (Table 2). However, the Hazards Ratio (HR) of WHO stage III and WHO stage IV compared to WHO stage I were 4.320 (CI: 1.375, 13.569) and 5.603(CI: 1.753, 17.905) respectively. The hazard of death was higher in advanced WHO stages.

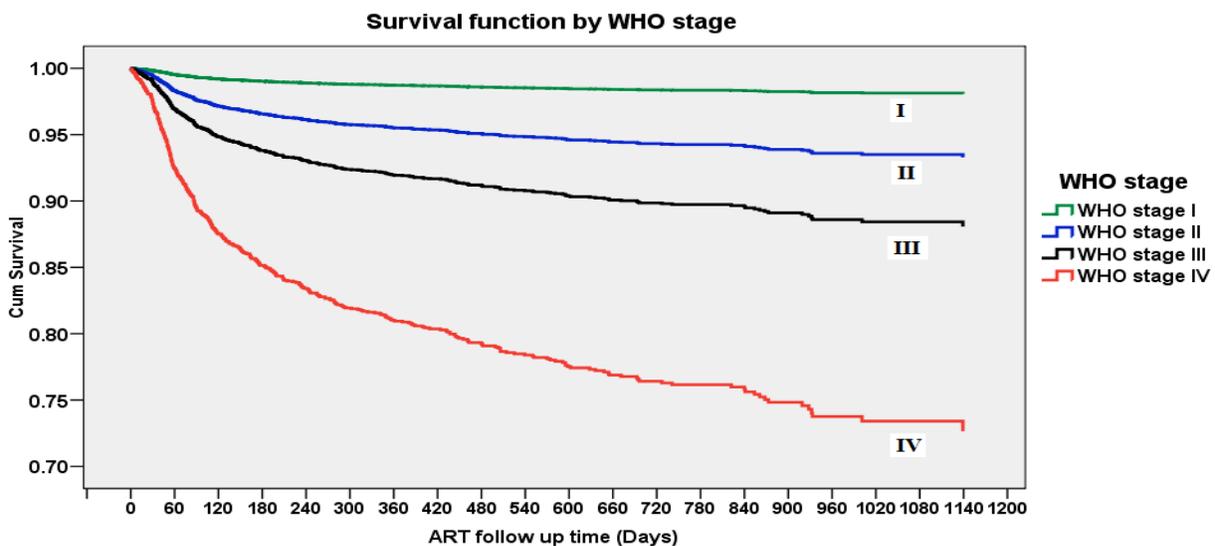


Figure 2: Survival graph by WHO stage at start of ART initiation in selected hospitals of SNNPR, January 1, 2005 to January 31, 2009.

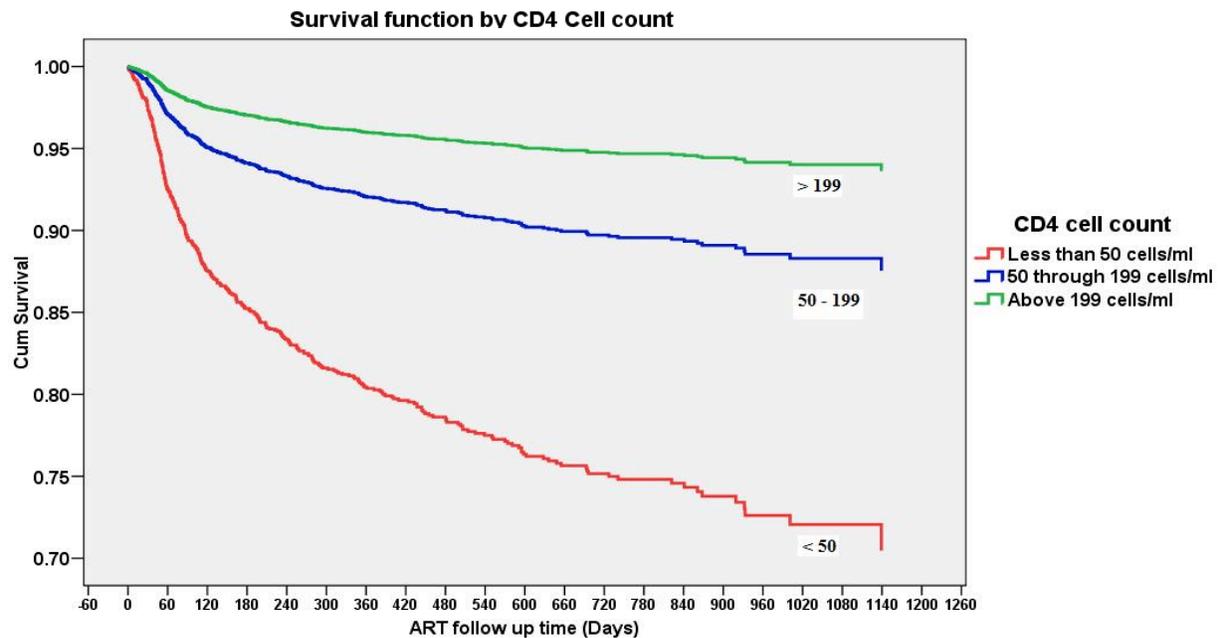


Figure 3: Survival graph by CD4 cell count at start of ART initiation in selected hospitals of SNNPR, January 1, 2005 to January 31, 2009, SNNPR

The hazard ratio of death in patients with Nevirapine combined regimen at the beginning of ART was 1.493 (CI: 1.184, 1.883) times higher than with Non-Nevirapine regimen at the beginning of ART initiation (Table 2). Similarly, a hazard ratio and 95% confidence interval for hazard of death in patients with baseline functional status ambulatory or bedridden, compared to

working status were 1.825 (CI: 1.415, 2.347) and 4.331 (CI: 3.156, 5.945) respectively.

From Cox model, gender WHO stage, baseline functional status, CD4 cell count, and Nevirapine drug as a combined baseline regimen at start of ART initiation had significant association in determining the pattern of survival and hazard of deaths in ART patients.

Table 2: Cox regression model: Factors determining the survival of ART patient in rural public health hospitals, January 1, 2005 to January 31, 2009, SNNPR.

Covariates	Death as outcome		Death or dropout as outcome	
	AHR (95% CI)	Sig.	AHR (95% CI)	Sig.
Sex				
Male	1.632 (1.309-2.034)	.001	1.362 (1.194-.552)	.001
Female	1		1	
Age				
14-24	1		1	
25-30	0.752 (0.534-1.060)	.103	.755 (.625-913)	.004
31-40	0.763 (5.38-1.083)	.130	.717 (.568-.906)	.005
≥41	0.976 (662-1.438)	.900		
WHO stage				
WHO Stage I	1		1	
WHO Stage II	3.018 (.918-9.917)	.069	.850 (.581-1.244)	.403
WHO Stage III	4.320 (1.375-3.569)	.012	1.062 (.757-1.489)	.727
WHO Stage IV	5.603 (1.753-7.905)	.004	1.386 (.959-1.975)	.083
Baseline functional status				
Working	1		1	
Ambulatory	1.825 (1.417-2.350)	.001	1.535 (1.327-.776)	.001
Bedridden	4.331 (3.156-5.945)	.001	2.999 (2.465-.648)	.001
CD4 cell count				
≥200	1		1	
50-199	1.900 (1.405-2.569)	.001	1.324 (1.129-.553)	.001
<50	3.176 (2.304-4.434)	.001	1.940 (1.604-2.345)	.001
NVP in baseline regimen				
No	1		1	
Yes	1.493 (1.184-1.883)	.001	1.181 (1.03-1.354)	.016

Death or dropout as event of outcome: Permanent discontinuation of care can be explained by a rate of retention in terms of dead and dropout patients. The effect of discontinuation of follow up rate due to death or dropout were found to be 75.7% (942/1,245), 13.7% (170/1,245), 8.4% (105/1,245) and 2.3%(28/1,245) in the first 6 months, six to one year, one to two years, after second year of follow up, respectively.

A follow up failure rate ratio of patients with baseline functional status, ambulatory and bedridden, compared to working were 1.535 (CI: 1.327, 1.776) and 2.999 (CI: 2.465, 3.648), respectively. In addition, patients with CD4 cell count of less than 50 cells/ml and between 50 to 199 cells/ml, relative to the ones whose CD4 cell count was above or equal to 200 cells/ml, were found to be 1.940 (CI: 1.604, 2.345) and 1.324 (CI: 1.129, 1.553), respectively (Table 2).

The hazard of discontinuing follow up rate was higher in Nevirapine combined regimen than Efavirenz at baseline 1.181(CI: 1.031, 1.354).

Baseline functional status, sex, CD4 cell count, and Nevirapine as a combined baseline regimen at start of ART initiation were strong predictors of permanent discontinuation of ART follow up.

CD4 cell count and body weight: Mean CD4 cell count and body weight change patterns differ significantly across time. There were significance difference of mean CD4 cell count at baseline, month 6, 12 and 24, with an increasing pattern. The mean (SD) CD4 cell count result for 172 patients were 149.8 (80.8), 278.7 (124.1), 302.2 (124.6) and 330.5 (137.4) at baseline, month 6, 12 and 24 respectively (Figure 4).

The estimated marginal mean (SD) of body weight for 1,221 patients were 50.7(8.7), 55.5(8.7), 56.7(8.8) and 56.0(8.7) at baseline, month 6, month 12 and month 24 respectively. There were significant difference of mean body weight at baseline, month 6, month 12 and month 24. However, weight gain decreased at month 24.

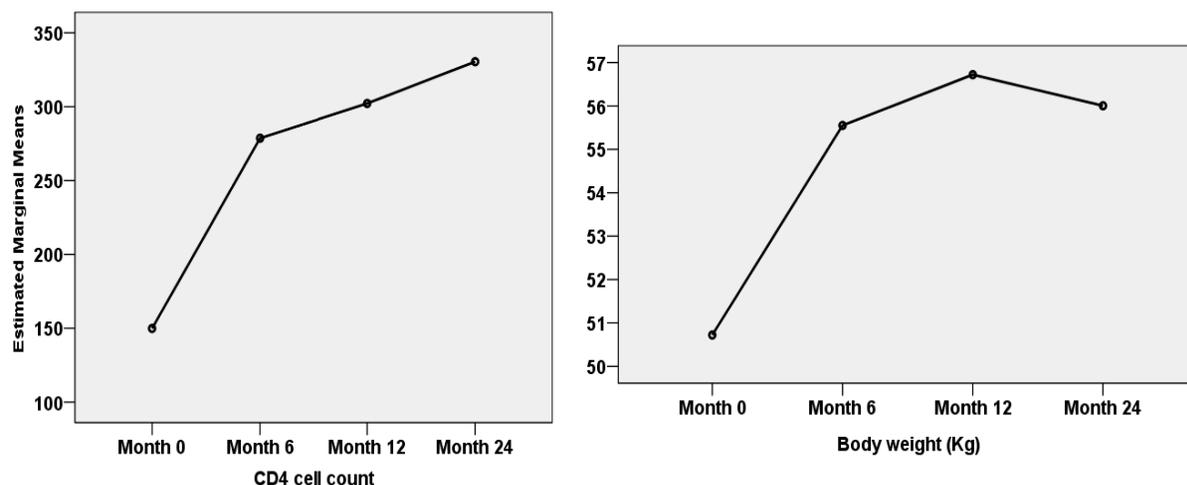


Figure 4: Profile plot of estimated marginal means of CD4 cell count and body weight change pattern of ART patients in SNNPR, January 1, 2005 to January 31, 2009, SNNPR.

Discussion

In this study the socio-demographic characteristics like proportion of females, age distribution and WHO classification in ART service delivery program was comparable with two Zambia studies (12, 13). A community bases South Africa study showed that a median age of ART initiation without tuberculosis infection was 31 years in the Nevirapine (NVP) group and 34 years in the Efavirine (EFV) group with 80% and 57% of female enrolment, respectively (14).

A significant increase of CD4 cell count was observed throughout follow up time. However, the increment is not as much as in a similar retrospective cohort study in western Kenya which showed a mean CD4 cell count increase of 109,160 and 225 at month 0, month 12 and month 24 (15).

In this study, males were in a higher risk of death compared to females. Similarly, in multi-centric observational study in resource-poor settings also indicated that being male and CD4 cell count were significantly associated with death (16).

Simple laboratory and clinical data independently predicted mortality in Durban-South Africa and Northern Province of Cameroon studies (17, 18). The present study pointed out that CD4 cell count and advanced WHO stage were highly associated with mortality. Many studies also have indicated similar findings. WHO stage II, III and IV patients at start of ART initiation are more likely to die earlier than WHO stage I (19, 20). Early mortality among adults taking antiretroviral treatment in sub-Saharan countries, Meta results from 18 studies, concludes that 26% of deaths occur in the first year of follow up and early mortality is associated with CD4 cell

count and advanced disease stage (21). A two-year outcome study in South Africa concluded that ART can be provided in resource-limited settings with good patient retention and clinical outcome (22).

Higher proportion (68%) of initial regimen prescribed at baseline included Nevirapine as a combination. A d4t-3TC-NVP regimen covered (56%) and d4t-3TC-EFV regimen covered 24% of the total prescribed antiretroviral regimen. A study in Cote D'Ivoire shows that outcome of antiretroviral treatment is not significantly associated with initiation of on NVP-based regimen, compared to other first line regimens (23). However, this study shows that Nevirapine-based initiation of regimen has a higher risk of death compared to an Efavirenz-based one.

This study indicated that proportions of alive and in care at month 6, 12, 24 and 36 were 87.4%, 84.6%, 81.1% and 77.2%, respectively with cumulative proportion of death (8.4%). In Malawi, 74% remained alive and in care, while cumulatively 10% were estimated to have died by one year. In South Africa and Senegal, cumulative mortality estimated at longer durations was 16.9% and 24.6% by 5 years (24).

The present study showed that patient weight gain at start of ART initiation but the increment was not significant at month 24. A Quality care assessment studies conducted in the Armed Force General Hospital and Oromiya region showed that there were a significant body weight gain at month six (25, 26). Another study in two developing countries, Cambodia and Kenya, also concluded that weight gain at three months is strongly associated with survival (27).

This study used routinely collected data and estimation of mortality can be under estimated as there are many deaths at home. A study in Uganda showed that 29% of lost follow up patients were found to be actually deaths. The cumulative incidence of death at one, two and three years were 1.7%, 2.1% and 2.3%, respectively. However, after tracking sampled lost follow up patients, the corrected incidence of death at 1, 2, and 3 years were 7.5%, 10.3% and 12.2% (28). The combined result of mortality and discontinuation of follow up rate implies that the pattern of death and permanent withdrawal are occurring at the same time and pattern. Hence, the reason for high rate of withdrawal in the first six months needs to be investigated.

This study concluded that gender, WHO stage, CD4 cell count, functional status and the existence of NVP-ARV drug as a combined regimen at base-line have significant effect on determining the mortality and permanent discontinuation of treatment in a longer follow up period. The authors recommend that priority should be given to identify HIV-infected individuals to start ART initiation earlier to advanced disease stage, to investigate high mortality and permanent discontinuation of follow up

rate in the first six months, to determine proportion of deaths out of the dropouts, and to explore weight loss at two years need to be investigated.

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References

1. FMOH. Aids in Ethiopia: Sixth Report, National HIV/AIDS Prevention and Control Program in Ethiopia. Addis Ababa, 2007.
2. FMOH. Health and health related indicators of 1999 E.C/2008, FMOH. Addis Ababa, 2008.
3. FMOH. Guideline for antiretroviral treatment in adults and adolescents. Addis Ababa, 2007.
4. Assefa Y, Jerene D, Lulseged S, Ooms G, Van Damme W. Rapid scale up of antiretroviral treatment in Ethiopia: Success and System wide effects, PLoS Med Vol. 6, issue 4, 6(4): e1000056. doi: 10.1371/journal.pmed.1000056.
5. Abraham J, Graham S, Till B, Angeliq K, Frank T, Marie-Louise N. Adult mortality and antiretroviral treatment roll-out in rural KwaZulu-Natal, South Africa. Geneva: WHO; 2009; 87: 754-762. doi: 10.247/BLT.08.058982.
6. Andrew B, Peter B, Meg O, Karen C, Liezl C, Katherine H, et al: Antiretroviral therapy and early mortality in South Africa. Bulletin of WHO, September 2008;86(9).
7. Stephen D, Anthony D, Xavier A, Landon M, Robin W. Early mortality among adults accessing antiretroviral treatment programs in sub-Saharan Africa. AIDS 2008; 22:1897-1908.
8. Zachariah R, Fitzgerald M, Massaquoi M, Pasulani O, Arnould L, Makombe S, Harries AD. Risk factors for high early mortality in patients on antiretroviral treatment in a rural district of Malawi. AIDS 2006; 20: 2355-2360.
9. Evan W, Robert S, Benita Y, Richard H, Michael V. Julio SG. Is there a baseline CD4 cell count that precludes a survival response to modern antiretroviral therapy. AIDS 2003; 17:711-720.
10. Paul J, Samuel M, Raymond M, Catherine S, Gideon R, Robert D, et al. Assessment of a pilot antiretroviral drug therapy program in Uganda: Patients' response, survival and drug resistance. The Lancet 2002;360(9326):34-40.

11. Sikhamani R, Lakshmanan J, Sundaraj V, Chandrahasan G, Krishnaraj R. Predictor of failure of first line antiretroviral therapy in HIV infected adults: India experience. *AIDS* 2007; 21(Suppl 4):S47-S53.
12. Jeffrey SA, Isaac Z, Jens L, Elizabeth M, Albert M, Benjamin HC, et al. Rapid scale-up of antiretroviral therapy at primary care sites in Zambia, feasibility and early outcome. *JAMA* 2006; 296(7): 782-793.
13. Benjamin H Chi, Ronald A, Issac Z, Lloyd B, Jens W, Bushimbwa C, Stewart R, et al. Adherence to first line antiretroviral therapy affects non-virologic outcomes among patients on treatment for more than 12 months in Lusaka, Zambia. *International Journal of Epidemiology* 2009, 38:746-756.
14. Andrew B, Gilles VC, Karen C, Katherine H, Shaheed M, Musaed A, et al. Outcomes of Nevirapine – and Efavirenz- based antiretroviral therapy when co-administered with Rifampicin-based anti-tubercular therapy. *JAMA* 2008; 300(5)530-539.
15. Kara W, Silvester K, Lameck D, Abraham S, John S, Constantin T, et al. Viability and effectiveness of large-scale initiatives in sub-Saharan Africa: experience from western Kenya. *AIDS* 2006;20:41-48.
16. Alexandra C, Lorextu P, Elisabeth S, Elisabeth S, Rony Z, Nathan F, et al. Generic fixed combination antiretroviral treatment in resource-poor settings: Multi-centric observational cohort. *AIDS* 2006; 20: 1163-1169.
17. Bisola O, Hui Z, Rochelle P, Zhigang L, Elena L, Janet G, et al. Predictors of mortality in patients initiating antiretroviral therapy in Durban, South Africa, NIH manuscript. *S Afr Med J* 2008;98(3):204-208.
18. Isidore S, Mohamadou S, Anne-Marie S, Joris M, Marleen B, et al. Determinants of survival in AIDS patients on antiretroviral therapy in a rural centre in the Far-North province, Cameroon. *Tropical Medicine and International Health* 2009; 14(1): 36-43.
19. Jerene D, Endale A, Hailu Y, Bernt L. Predictors of early death in a cohort of Ethiopia patients treated with HAART, Arba Minch Hospital, Ethiopia *BMC infectious Disease, Bio Med Central* 2006;6:136.
20. Jerene D. HIV Antiretroviral therapy in Ethiopia overcoming implementation challenges, thesis as a partial fulfillment for of Phd degree at the University of Bergen, Norway, 2007.
21. Stephen D, Anthony D, Xavier A, Landon M. Early mortality among adults accessing antiretroviral treatment programs in sub-Saharan Africa. *AIDS* 2008; 22:1897-1908.
22. David C, Katherine H, Andrew B, Gary M, Francoise L, Veliswa L, et al. Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa. *AIDS* 2004;18:887-895.
23. Siaka T, Bertin K, Catherine S, Moussa T, Nicole D, Julien D, et al. Rapid scaling-up of antiretroviral therapy in 10,000 adults in Cote D'Ivoire: 2-year outcomes and determinants, *AIDS* 2008;22:873-882.
24. Boulle A, Ford N. Scaling up antiretroviral therapy in developing countries: What are the benefits and challenges?, *Post Graduate Medical Journal* 2008;84:225-227.
25. Molla M. Assessment of quality of antiretroviral therapy (ART) services in the defense hospitals in Addis Ababa and Debrezeit. Masters thesis, AAU, 2008.
26. Awel M. Antiretroviral treatment adherence and its determinants among people living with HIV AIDS on highly active antiretroviral therapy at two hospitals in Oromiya Regional State. Masters thesis, AAU, 2007.
27. Yoann M, Elisabeth S, Christine G, Laurent F, Suna B, Mar P, et al. Weight gain at 3 months of antiretroviral therapy is strongly associated with survival: Evidence from two developing countries. *AIDS* 2009; 23:853-861.
28. Elvin H, Nneka E, Mwebesa B, David V. Sampling-based approach to determine outcomes of patients lost to follow up in antiretroviral therapy scale up program in Africa. *JAMA* 2008; 300(5):506-507.