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Improvements in Physical Wellbeing over the First Two Years on Antiretroviral Therapy in Western Kenya

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Abstract

Improvements in physical wellbeing during the first six months on antiretroviral therapy (ART) are well known, but little is known regarding more long-term follow-up. We conducted a prospective cohort study among 222 HIV-positive adult tea plantation workers in western Kenya to assess wellbeing over their first two years on ART. Study subjects completed a standardized questionnaire during repeat ART clinic visits. A 30-day recall period was used to elicit the number of days that subjects experienced poor health and the number of days that pain made it difficult to complete usual activities at home and work. A seven-day recall period was used to assess the severity of bodily pain, nausea, fatigue and rash. Prevalence of most symptoms declined over time. A median of 7 days poor health during the first month on ART declined to 3 days in the 24th month ($p=0.043$). For pain making usual activities difficult, a median of 7 days during the first month on ART fell to 0 by 12 months ($p\leq 0.0001$) but increased to 3 days by two years. Any bodily pain (range 59-83%) and fatigue (range 51-84%) over the past 7 days were common through 2 years. However, pain and fatigue *often* over the past 7 days declined over two years (24% to 10% ($p=0.067$) and 41% to 15% ($p=0.002$)). Skin rash was rare at all times, though higher at two years (8.6%) than any other time. Initial improvements in physical wellbeing were sustained over two years, however, increased pain and skin rash at year two, may indicate problems as treatment programs mature. These improvements in physical wellbeing will be important in sustaining the long-term success of HIV treatment programs.

Keywords

HIV; antiretroviral therapy; wellbeing; Africa

Introduction

Antiretroviral therapy (ART) for HIV/AIDS has been associated with short-term improvements in quality of life in both developed (Carrieri et al., 2003; Casado et al., 2004; Burgoyne & Tan, 2008; Nieuwkerk et al., 2000; Rabkin, Ferrando, Lin, Sewell, & McElhiney, 2000; Preau et al., 2004; Jia et al., 2007) and developing countries (Booyesen, Van Rensburg,

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Bachmann, Louwagie, & Fairall, 2007; Stangl, Wamai, Mermin, Awor, & Bunnell, 2007; Jelsma, Maclean, Hughes, Tinise, & Darder, 2005; Rosen, Ketlhapile, Sanne, & Desilva, 2008; Poupard et al., 2007; Wouters, Meulemans, Van Rensburg, Heunis, & Mortelmans, 2007), with data from the developing world generally showing improvements in physical wellbeing over the first six months on ART (Beard J, Feeley F, & Rosen S, 2009). Less clear is the effect of ART on patients' physical wellbeing beyond the first 6-12 months on treatment. So far, little evidence about the longer-term consequences of ART for quality of life and physical wellbeing exists.

A growing literature exists on the relationship between quality of life (QoL) measures and both untreated and treated HIV in developed countries. A recent review of research on treatment and QoL outcomes after a decade of ART availability found modest improvement in average QoL ratings during the initial year on ART as reductions in illness are balanced with treatment side-effects (Burgoyne & Tan, 2008). One of the few long-term studies of ART on QoL found no changes in wellbeing ratings after two years, irrespective of initial disease state or prior HAART exposure (Saunders & Burgoyne, 2002). Developing country studies, where both biological and social factors may modify the effects of ART on wellbeing, are far scarcer, but those assessing changes in wellbeing over time have shown a rapid increase in physical wellbeing through one year on ART (Stangl, Wamai, Mermin, Awor, & Bunnell, 2007; Jelsma, Maclean, Hughes, Tinise, & Darder, 2005b; Booysen et al., 2007). While encouraging, additional research is needed to understand the relationship between wellbeing and ART over time. To address this we set out to measure changes in physical wellbeing over the first two years on ART in a cohort of agricultural workers in western Kenya.

Methods

Study Site and Patient Population

This analysis was conducted as part of a larger study investigating the impact of ART on work performance (Larson et al., 2008) among tea plantation workers employed by two companies in Kericho District, Rift Valley Province, Kenya. The estimated adult HIV prevalence in the area is between 6 and 14% (Foglia et al., 2008; National AIDS and STI Control Programme, 2005; National AIDS and STI Control Programme, 2008). Each company has >10,000 permanent employees and provides employees and dependents with company housing and free on-site medical care. Free HIV treatment has been provided by each site since 2004.

Enrollment began in February 2006. Due to post-election violence in Kenya which caused disruptions in the region, we halted interviews in January 2008. The current analysis is limited to interviews that occurred after ART initiation up to a maximum of 720 days after initiation. Eligible subjects were >18 years old, permanently employed as a tea plucker, HIV-positive and receiving care at one of the company HIV clinics and either currently on ARVs or had a CD4 count of 200-350 cells/mm³. Many enrolled well after initiating ART (median 387 days: IQR: 185-560). Subjects contributed a median of 2 visits (range 1–9), fairly evenly distributed over the two years after ART initiation.

The study was approved by the Institutional Review Boards at Boston University, the Kenya Medical Research Institute, and the Walter Reed Army Institute of Research.

Study design and data collection

At enrollment, patients gave consent to review medical records for date of initiation of ART and other baseline clinical data. Subjects were interviewed at regular clinic visits by the sites' trained study nurse who administered a structured questionnaire in a private location. The questionnaire, which was adapted from a previous study (Rosen, Ketlhapile, Sanne, & Desilva,

2008), was administered verbally in English or Kiswahili and addressed three major domains: 1) demographic characteristics of the subject and his/her household; 2) costs of obtaining medical treatment; and 3) information about recent wellbeing. At each visit, subjects were asked for how many of the past 30 days: 1) was your physical health not good? and 2) did pain make it hard for you to do your usual activities at home and work? At each interview, subjects were also asked how often over the past 7 days did the following conditions limit their ability to undertake normal daily activities: 1) bodily pain; 2) nausea; 3) feeling tired or fatigued; and 4) skin rash. Subjects were asked to select one of five response options: (a) none, (b) just once or twice, (c) three to six times, (d) at least once every day, or (e) almost all the time.

Statistical analysis

As the 30 day recall outcomes were skewed, we used medians and interquartile ranges (IQR). We used non-parametric quantile regression to estimate the evolution of these outcomes during the initial two years on ART (Koenker R & Bassett G, 1978). Quantile regression is much like ordinary least squares but allows estimation of quantiles (in this case medians) of the outcome distribution instead of means. P-values were generated using bootstrapped standard errors.

For each interview, we calculated days on ART as the interview date minus the date the subject initiated ARVs. Time on ARVs through two years on treatment was stratified into eight 90-day increments. Since changes in wellbeing may be more rapid immediately after initiating treatment, the first 90-day period was subdivided into days 0-30 and 31-90 on ART, for a total of 9 time periods.

The following explanatory variables were used in the quantile regressions: 8 of the 9 post-ART periods (with 0-30 days as the baseline), age at baseline (continuous); gender; and WHO stage at ART initiation. With baseline defined as the initial 0-30 days on ART, the estimated coefficients for the 8 post-baseline time periods show how the estimated median evolves over time compared to baseline. We also tested for interactions among sex and time, but as no significant interactions were detected we present collapsed data.

The 7-day recall outcomes are ordered categorical variables. For statistical analysis, two dichotomous outcomes were created: reporting *any* symptoms (categories b-e); and reporting a symptom *often* (categories d-e, at least once a day or all the time). For 7-day recall outcomes, crude comparisons between time periods were made using chi-squared tests. Changes over time in the probability of reporting a symptom *often* were estimated using odds ratios from logistic regression. We accounted for multiple observations per subject using generalized estimating equations, and we adjusted for age, gender, and baseline WHO stage.

For most outcomes we compared the odds of reporting the symptom *often* at each time point compared to the baseline (*i.e.* 0-30 days on ART). As no subjects reported skin rash *often* between 0-30 days, the baseline was 31-90 days. We could not estimate odds ratios for nausea as few subjects reported nausea *often* after the first 30 days.

Results

Among the 222 subjects who started ART and met our inclusion criteria, we conducted 545 interviews, each occurring during subjects' first 720 days on ART. The median interval between interviews was 2.0 months (IQR 1.0–3.3 months). While patients could enroll at any time after initiation of ART up to two years on treatment, interviews were fairly evenly dispersed over the full 0-24 month time period.

Table 1 shows demographic and social characteristics of the cohort at enrollment. A large proportion of subjects were married (61%), 30-49 years old (86%) and from the Luo (49%) or

Kisii (30%) tribes. Subjects were fairly even distributed between men and women. At enrollment subjects had been on ART an average of 312 days and were more likely to be WHO stage III/IV (74%) at ART initiation.

Results for 30 day recall outcomes

For both 30-day recall outcomes, crude and adjusted medians showed substantial improvements in wellbeing over time (Table 2, Figure 1). Subjects reported a crude median of 7 days of health not being good in the first month on ART; this declined to 3 days per month by the end of two years ($p=0.0282$), with some variation over the two years. After adjusting for age, sex, and WHO stage, patients still showed a decline in the median number of days reporting poor health at all time points compared to the first 30 days on ART (a reduction of between 3.0 and 6.5 days, $p<0.05$).

The unadjusted median number of days in which pain made usual activities hard also declined significantly, from 7 days in the first month on ART to 3 days in the period 31-90 days on ART and remained between 0 and 3 days through the end of two years ($p=0.0003$). After adjusting for age, sex, and WHO stage, patients again showed substantial declines in median days with pain compared to baseline (a reduction of between 3 and 6 days, $p<0.0001$ at all points compared to baseline). The median of 3 days at the end of two years on ART was up from 0 – 2 days at earlier time points; increases between several earlier time points and the last time period are statistically significant.

Results for 7 day recall outcomes

Table 3 and Figure 2 show 7-day recall outcomes. Unadjusted reports of *any* bodily pain over the past 7 days were common throughout the 2-year period ($>50\%$ at all time points); *any* bodily pain was most common in the first month on ART (83%) and declined to only 72% by two years ($p=0.177$). When limited to reporting pain *often* (daily or all the time), the proportion declined more substantially from 24% to 10% over the two years ($p=0.038$). After adjustment, odds ratios comparing the proportion reporting daily bodily pain at each time point to baseline (0-30 days on ART) were significantly reduced for 4 of the 8 post-baseline time points.

Unadjusted reports of *any* fatigue in the past seven days were also common (range 51%-84% over two years). At baseline 41% of subjects reported fatigue *often*. Declines from baseline were dramatic, dropping to 15% over the two years ($p=0.002$). After adjustment, compared to baseline all time points show significant reductions ($p<0.05$) in the proportion of subjects reporting fatigue *often*.

In crude analyses, reports of *any* nausea and skin rash were less common (range 12-44% and 27%-35% respectively). Unadjusted reports of nausea showed statistically significant declines over two years both in terms of reporting *any* nausea (from 44% to 21%, $p=0.0104$) and in terms of reporting nausea *often* (from 16% to 4%, $p=0.0175$). Because no patients reported nausea *often* at many time points, adjusted odds ratios could not be estimated.

Reports of *any* skin rash were fairly stable over time. Unadjusted reports of the occurrence of rash *often* were very uncommon at any time, though were highest at two years (8.6%, $p<0.05$ compared to all other time points in unadjusted analyses). After adjusting for age, sex, and WHO stage, we found no differences in the proportion of subjects reporting skin rash *often* at any time point compared to baseline.

Discussion

The current study extends earlier findings of short-term improvements in physical wellbeing among HIV-positive tea plantation workers after initiating ART in western Kenya (Larson et

al., 2008). We have demonstrated that initial improvements in physical wellbeing among 222 individuals were sustained over two years on ART even after adjustment for confounding. We noted substantial declines in reports of most negative symptoms of physical wellbeing over two years. In some cases the declines were dramatic, from approximately 41% of subjects reporting fatigue often at ART initiation to about 15% at two years. These gains in physical wellbeing are encouraging and should be recognized as part of the overall benefit of ART.

Our results are consistent with previous findings in this cohort which showed that initiating ART coincided with substantial increases in days worked compared to their pre-ART working patterns, and to levels similar, though somewhat lower than the general population (Larson et al., 2008). The current study demonstrates that these productivity gains are accompanied by improvements in physical wellbeing. We cannot distinguish the direction of the effects from our data—that is, whether ART improves physical wellbeing which leads to an improved ability to work, or ART improves the ability to work, which then leads to improvements in physical wellbeing. We speculate, however, that the first relationship is more likely.

While we estimated substantial reductions in the frequency of having symptoms *often* overtime, we did not detect significant continual improvements over time. For example, outcomes after one year on ART were not statistically different from two years on ART. Future research in larger cohorts is needed to determine if gains on ART continue to increase over time.

Our findings are also consistent with earlier evidence from a clinical trial in Uganda (Stangl, Wamai, Mermin, Awor, & Bunnell, 2007) and data from South Africa (Jelsma, Maclean, Hughes, Tinise, & Darder, 2005c) which showed significant decreases in reports of negative symptoms after one year on ART. Our findings extend these earlier results by showing that gains are largely sustained over the second year on ART.

We did note, however, some increased reporting of bodily pain and skin rash at two years compared to levels reported at earlier time points. It is encouraging to note that in all cases levels of these symptoms at two years were still below what was observed at ART initiation. If real, however, these increases are troubling and may warn of problems as treatment programs mature, particularly if these increases are markers for ART treatment failure. Two-year attrition rates from ART programs have been shown to be as high as 40% (Rosen, Fox, & Gill, 2007), and attrition is likely affected by patients experiencing symptoms while on ART. Long-term monitoring of patient welfare will therefore be needed to ensure that treatment programs continue to generate benefits for patients and families. If these late upward trends are substantiated or continue to increase after two years, program resources will likely need to be targeted at dealing with negative changes in wellbeing.

Our study should be considered in light of several limitations. First, because our study was nested within a larger cohort study, our data do not come from patients all enrolled at the time of ART initiation. Many patients were already on ART at enrollment and we therefore have no pre-ART baseline comparison. However, assuming subjects do represent a random sample of all ART patients in the program, the medians and proportions calculated over time will still be valid estimates of the impact of ART.

Second, there may be some selection bias in our study. Sicker patients would be more likely to leave care before study enrollment began. Sicker patients might also have been less likely to enroll if experiencing significant problems during their clinic visits. Thus, the tea pluckers enrolled were likely to be healthier than the general population of tea pluckers on ART during enrollment. Once enrolled in the overall study, however, productivity records show that study subjects continued to be employed and experienced substantial improvements in work outcomes after one year on ART. Thus the results presented here may underestimate the

average population level improvements from ART if patients remain in care. Our findings should be interpreted as being conditional on remaining in care for two years.

Although this study is being conducted in a plantation setting, plucking tea is physically demanding outdoor work like much agricultural work in Africa. Pluckers walk substantial distances to fields, stand for hours, carry heavy packs to weighing stations, and are constantly reaching, plucking, and tossing tea leaf in their basket. Many of the characteristics of tea plucking are thus similar to other types of labor commonly found in rural Kenya, such as family labor on one's own farm.

Third, our measures of physical wellbeing were based on self-report and reflect subjects' recall ability over the previous seven or thirty days. Recall bias is possible, particularly if symptoms are more likely to be remembered by patients who have been on treatment for shorter or longer periods of time. If time since treatment initiation leads to a decrease in reports of symptoms, rather than an actual decrease, then the declines we observed will overestimate the impact of ART on wellbeing.

Fourth, tea pluckers are generally not as poor as the surrounding rural population and generally have good access to high quality health care. Barriers to accessing and adhering to ART within this setting are probably as low as possible. Cash transportation costs to the ART clinic are zero (the company provides transportation) and travel times are modest. If long term adherence to ART is substantially worse among the general rural population, the potential positive socio-economic impacts of ART among rural populations will be muted.

Finally, we had no data on treatment adherence, and thus were not able to adjust for differences in adherence over time. If patients were not adhering to their medications, symptoms might be observed that are not directly related to medication, but rather to the underlying illness. This increase in symptoms would likely occur well after the initiation of treatment as patients either began experiencing side effects or treatment fatigue. This may explain why reports of symptoms increase approaching two years, though our data cannot discern this.

In conclusion, we found substantial improvements in physical wellbeing over the two years since ARV initiation. Improvements were largest in the first few months after initiating treatment but were generally sustained over two years. These gains are important in sustaining long-term adherence to ART and as such the long-term success of HIV treatment programs, but future research should be targeted at determining predictors of wellbeing on ART. We did note some increases in reports of negative symptoms near two years on treatment and these changes will need to be monitored to make sure improvements in wellbeing are not reversed with long-term care.

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Figure 1.

Crude medians of self-reported number of days over the past 30 experiencing symptoms among 222 HIV-positive patients on antiretroviral therapy in western Kenya

Figure 2.

Crude proportion of reports of a) any report of symptoms and b) daily or more report of symptoms over the past 7 days among 222 HIV-positive patients on antiretroviral therapy in western Kenya

Table 1

Demographic and social characteristics of a cohort of 222 subjects on ARVs in western Kenya

Factor	Level	Site 1	Site 2	Total
Education	Never attended school	22 (17.1%)	7 (7.5%)	29 (13.1%)
	Some primary school	56 (43.4%)	47 (50.5%)	103 (46.4%)
	Completed primary school	44 (34.1%)	31 (33.3%)	75 (33.8%)
	Completed secondary school	7 (5.4%)	8 (8.6%)	15 (6.8%)
Ability to read	I can read very well	24 (18.6%)	18 (19.4%)	42 (18.9%)
	I can read somewhat	70 (54.3%)	51 (54.8%)	121 (54.5%)
	I cannot read	35 (27.1%)	24 (25.8%)	59 (26.6%)
Language at home	kiSwahili	14 (10.9%)	18 (19.4%)	32 (14.4%)
	Mother tongue	115 (89.1%)	75 (80.6%)	190 (85.6%)
Tribe	Luo	67 (51.9%)	42 (45.2%)	109 (49.1%)
	Luhya	4 (3.1%)	11 (11.8%)	15 (6.8%)
	Kisii	40 (31%)	27 (29%)	67 (30.2%)
	Kipsigis	3 (2.3%)	8 (8.6%)	11 (5%)
	Kalenjin	10 (7.8%)	0 (0%)	10 (4.5%)
	Other	5 (3.9%)	5 (5.4%)	10 (4.5%)
Marital status	Single	3 (2.3%)	10 (10.8%)	13 (5.9%)
	Married	73 (56.6%)	62 (66.7%)	135 (60.8%)
	Divorced or separated	26 (20.2%)	12 (12.9%)	38 (17.1%)
	Widowed	27 (20.9%)	9 (9.7%)	36 (16.2%)
Age group at enrollment	<20	0 (0%)	1 (1.1%)	1 (0.5%)
	20-29	4 (3.1%)	5 (5.4%)	9 (4.1%)
	30-39	52 (40.3%)	39 (41.9%)	91 (41%)
	40-49	60 (46.5%)	39 (41.9%)	99 (44.6%)
	50-59	12 (9.3%)	9 (9.7%)	21 (9.5%)
	60+	1 (0.8%)	0 (0%)	1 (0.5%)
Days on ART at enrollment	0-30 days	26 (20.2%)	10 (10.8%)	36 (16.2%)
	31-90 days	7 (5.4%)	7 (7.5%)	14 (6.3%)
	91-180 days	18 (14%)	11 (11.8%)	29 (13.1%)
	181-270 days	16 (12.4%)	6 (6.5%)	22 (9.9%)
	271-360 days	14 (10.9%)	15 (16.1%)	29 (13.1%)
	361-450 days	7 (5.4%)	13 (14%)	20 (9%)
	451-540 days	13 (10.1%)	14 (15.1%)	27 (12.2%)
	541-630 days	13 (10.1%)	5 (5.4%)	18 (8.1%)
	631-720 days	15 (11.6%)	12 (12.9%)	27 (12.2%)
Sex	Female	73 (56.6%)	34 (36.6%)	107 (48.2%)
	Male	56 (43.4%)	59 (63.4%)	115 (51.8%)
WHO stage at start of ART	1	7 (6%)	10 (11.5%)	17 (8.4%)
	2	21 (18.1%)	14 (16.1%)	35 (17.2%)
	3	84 (72.4%)	47 (54%)	131 (64.5%)
	4	4 (3.4%)	16 (18.4%)	20 (9.9%)

Factor	Level	Site 1	Site 2	Total
		MEAN (STD) N		
Days on ART		294.8 (230.2) 129	337.7 (214.9) 93	

Table 2

Median differences from baseline in self-reported 30 day recall outcomes (number of days over the past 30 experiencing symptom) among 222 HIV-positive patients on antiretroviral therapy in western Kenya

Days on ART	Health not good				Pain made usual activities hard			
	N	Crude Median (IQR) *	Adjusted change from 0-30 ***	adjusted p-val **	N	Crude Median (IQR) *	Adjusted change from 0-30 ***	adjusted p-val **
0-30	32	7 (3 - 14)	ref		37	7 (3 - 14)	ref	
31-90	33	5 (1 - 14)	-3.0	0.221	34	3 (0 - 14)	-3.0	0.0305
91-180	53	3 (0 - 7)	-5.0	0.010	55	1 (0 - 4)	-6.0	<.0001
181-270	52	3 (0 - 7)	-4.5	0.031	54	1 (0 - 3)	-6.0	<.0001
271-360	60	3 (0 - 7)	-4.5	0.034	63	0 (0 - 4)	-6.0	<.0001
361-450	61	3 (0 - 7)	-4.0	0.054	67	2 (0 - 4)	-4.0	<.0001
451-540	74	3 (0 - 7)	-4.0	0.035	75	2 (0 - 5)	-4.0	<.0001
541-630	67	0 (0 - 7)	-6.5	0.001	67	0 (0 - 4)	-6.0	<.0001
631-720	78	3 (1 - 7)	-4.0	0.043	79	3 (0 - 5)	-4.0	<.0001

* IQR = Interquartile range

** Adjusted for age, sex, WHO stage at baseline using quantile regression and bootstrapped p-values

*** Estimated using quantile regression

Crude proportions and adjusted odds ratios compared to baseline for degree of a) any report of symptoms and b) report of symptoms often (daily or more) over the past 7 days among 222 HIV-positive patients on antiretroviral therapy in western Kenya

Table 3

Days on ART	Bodily Pain					Nausea**					Fatigued					Skin Rash				
	Crude			Adjusted		Crude			Crude			Crude			Crude			Crude		
	N	Any	Often	OR*	p-val	N	Any	Often	N	Any	Often	OR*	p-val	N	Any	Often	OR***	p-val		
0-30	36	83.0%	24.3%	ref		36	44.0%	16.2%	37	84.0%	40.5%	ref		37	35.0%	0.0%				
31-90	36	81.0%	16.7%	0.80	0.7431	36	28.0%	0.0%	36	78.0%	13.9%	0.17	0.0209	36	42.0%	5.6%	ref			
91-180	57	63.0%	1.8%	0.06	0.0030	57	11.0%	0.0%	57	53.0%	7.0%	0.10	0.0011	57	33.0%	3.5%	1.10	0.6228		
181-270	59	71.0%	6.8%	0.07	0.0050	58	12.0%	0.0%	59	64.0%	6.8%	0.05	0.0002	59	42.0%	3.4%	1.05	0.7785		
271-360	63	59.0%	7.9%	0.36	0.1513	63	19.0%	0.0%	63	65.0%	6.3%	0.12	0.0022	63	40.0%	4.8%	1.13	0.8526		
361-450	66	71.0%	7.5%	0.36	0.1415	66	11.0%	0.0%	66	56.0%	6.0%	0.05	0.0003	66	27.0%	0.0%				
451-540	75	65.0%	5.3%	0.19	0.0123	75	20.0%	1.3%	75	51.0%	8.0%	0.12	0.0002	75	33.0%	2.7%	1.05	0.2523		
541-630	70	63.0%	4.3%	0.17	0.0208	70	24.0%	1.4%	70	63.0%	4.3%	0.04	<.0001	70	27.0%	1.4%	1.12	0.2548		
631-720	81	72.0%	9.9%	0.33	0.0671	80	21.0%	3.7%	81	69.0%	14.8%	0.19	0.0022	80	36.0%	8.6%	1.04	0.6643		

* Odds ratios compare odds of outcome being reporting at each time point to the odds of the outcome being reported between 0-30 days on ART adjusted for age, sex and baseline WHO stage using GEE to account for repeated observations

** OR not estimable because most reported no nausea

*** Comparison was to 31-90 days and 361-450 and 451-540 days were collapsed