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Impact of Antiretroviral Therapy on Health-Related Quality of Life among South African Women in the CAPRISA 002 Acute Infection Study

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Abstract

Concerns are often raised regarding potentially adverse effects of antiretroviral therapy (ART) on health-related quality of life (HRQoL), but there is limited longitudinal data to prove this. Building on our prior investigation, we examined the impact of ART on HRQoL among HIV-infected South African women with extensive follow-up in the CAPRISA 002 Acute Infection Cohort Study. Overall HRQoL and five sub-domains [physical well-being (PWB), emotional well-being (EWB), functional and global well-being (FGWB), social well-being (SWB) and cognitive functioning (CF)] were assessed using the Functional Assessment of HIV Infection (FAHI) instrument. Our analyses comparing FAHI scores between pre-ART (established infection) and ART phases using paired Wilcoxon signed-rank tests and adjusted mixed-effects regression models revealed improvements on ART in overall HRQoL, and in PWB, EWB, and SWB, but not in FGWB and CF. No long-term adverse impact of ART on HRQoL was detected, providing additional non-biomedical support to early treatment strategies.

Keywords

Health-related quality of life; South Africa; Acute HIV infection; Functional assessment of HIV infection; ART

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Introduction

Given the recent breakthroughs in the use of antiretroviral therapy (ART) for HIV prevention [1] and early treatment [2], there is a growing focus on health-related quality of life (HRQoL) of individuals living with a life-long disease for which there is currently no cure. Rapid expansion of ART coverage in South Africa [3], the nation with the highest burden of HIV infection globally [4], not only means less infections to others through a reduced individual and community HIV viral load [5, 6], and the benefits of a stronger immune system to prevent co-infections such as tuberculosis [7], but also provides an opportunity for individuals to recover or even thrive after the devastating HIV diagnosis. While reducing viral load and the number of adverse events are key endpoints in ART studies, the HRQoL outcome is an important indicator of treatment adherence [8, 9] and the quality of health care delivery [10].

Health-related quality of life, a multi-dimensional and dynamic concept [11], reflects non-biomedical perspectives of HIV treatment, incorporating important subjective assessments on wide ranging aspects of individual well-being, including physical, functional, social, emotional [12] and even spiritual well-being [13] over time. While the scale-up of ART in KwaZulu-Natal province (KZN) has led to a dramatic increase in life expectancy [14], the question of long-term HRQoL benefits of ART remains debated and has seldom been investigated [15]. Few longitudinal studies, and even less recruiting at acute HIV infection, have been conducted in sub-Saharan Africa. In our previously published report in this journal [16], we used data from the CAPRISA 002 Acute Infection Study, a cohort study with extensive follow-up to assess HRQoL of HIV-positive South African women from acute infection up to ART initiation. Building on these investigations, here, we report on the long-term impact of ART on HRQoL among HIV-infected women from the CAPRISA 002 study.

Methods

Study Population

The CAPRISA 002 Acute HIV infection study is an ongoing prospective cohort study in KZN, South Africa. The study [17], which started recruitment in 2004, enrolled a cohort of HIV uninfected women 18 years and older with the aim to investigate the natural history of HIV-1 subtype C infection. Study participants were recruited at two sites: Durban, the largest city in KZN; and Vulindlela, a rural community located north-west of Durban. Participants were followed up for up to 4 years. Those who acquired HIV were enrolled into the acute infection stage (Phase II). Women who seroconverted in other CAPRISA prevention trials [18] also entered the CAPRISA 002 study at Phase II. Acute HIV infection status of all study participants was established based on a positive HIV antibody status with a documented HIV negative antibody test within 5 months of study enrollment or by plasma HIV-1 RNA testing using Amplicor or TaqMan (Roche Diagnostics, Rotkreuz, Switzerland) prior to seroconversion. Testing procedures of the CAPRISA 002 study have been described previously in detail [19].

Participants enrolled in the acute infection study completed a baseline acute infection assessment immediately after HIV diagnosis and were then followed-up for a maximum of 9 years at the time of our analysis. The follow-up assessment phase was classified as follows: acute infection (Phase II ≤3 months, but excluding the baseline assessment), early infection (Phase III >3–12 months), established infection (Phase IV >12 months post-enrolment) and on ART (Phase V). Fifty-one of 160 participants initiated ART (referred to hereafter as the ART cohort) according to the South African Adult HIV Treatment Guidelines [20]. All participants received reimbursement for their time and travel expense for each assessment. Following diagnosis, post-HIV/sexually transmitted infection risk-reduction counselling, as well as ART treatment education, was available to study participants. Condoms were provided on request, and those requiring clinical care received it at the CAPRISA clinical research site, or at a specialist treatment centre where necessary. The Biomedical Research Ethics Committee of the University of KwaZulu-Natal approved the study.

Measures

The outcome data were obtained by trained research nurses throughout the study. The Functional Assessment of HIV Infection (FAHI) instrument was used to measure self-reported HRQoL, and was assessed at baseline, month three and bi-annually. The FAHI was designed to assess HRQoL of individuals living with HIV/AIDS and its reliability and validity has been established [21, 22]. It contains 44 items consisting of five subscales: physical well-being (PWB) (10 items), emotional well-being (EWB) (10 items), functional and global well-being (FGWB) (13 items), social well-being (SWB) (8 items), and cognitive functioning (CF) (3 items). Each item is rated on a 5-point ordinal scale of 0 (not at all) to 4 (very much). Higher FAHI scores reflect greater HRQoL. The Cronbach alpha internal consistency coefficient for the overall FAHI of the ART cohort was 0.90. Consistency coefficients for the PWB, EWB, FGWB, SWB, as well as the CF sub-scales were 0.92, 0.80, 0.83, 0.73 and 0.60, respectively.

The main exposure of our study is ART treatment initiation. The date of ART treatment initiation was obtained through patient chart review (with the permission of the participant). The study also assessed HIV knowledge, frequency of unprotected sexual practices, and the number of casual partners, irrespective of marital status at each visit via self-report. For unprotected sexual practices, risky sexual behavior was dichotomized as either high risk if the study participant self-reported sex without the use of a condom every time, or no/low risk for having no sex or sex with a condom being used every time. While we recognize that many study participants might utilize condoms sometimes, its consistent use is not only part of recommended practice by the US Center for Disease Control and Prevention [23], but also shown to substantially reduce HIV infection according to a meta-analysis [24]. In addition to face-to-face interviews, measurements for body mass index (BMI) and blood tests, including viral load and CD4, were obtained during the routine clinical assessments at every study visit.

Data Analysis

Descriptive statistics were used to summarize the demographic characteristics of the ART cohort. The differences in baseline demographic characteristics between the ART and non-

ART cohort was assessed using either Chi square (χ^2), student's *t* test or Wilcoxon rank-sum test. To assess associations between ART and HRQoL, FAHI scores pre-ART during established infection were compared to FAHI scores on ART using paired Wilcoxon signed-rank tests. The proportion of study participants above the minimally important differences (MID) threshold was calculated using the standard deviation (SD) method [25]. Under this method, the threshold is half the SD of the baseline score, which is defined as the closest FAHI score prior to ART initation in our study context. The last observed FAHI score during the ART phase was the end point in this analysis. Therefore, a study participant was considered to have achieved minimally important improvement when the end point FAHI score was greater than the threshold. Linear mixed effects regression models were fitted to longitudinal FAHI scores to assess trends over time since ART referral, adjusting for demographic, HIV behavioral risk and clinical factors. Separate regression models were fitted for overall FAHI and five different sub-domains. To avoid over-adjustment bias related to controlling for intermediate variables on the causal pathway [26], viral load and CD4 were not included in the models (referred to hereafter as main models). Separate analyses were conducted to assess whether CD4 and viral load were effect modifiers in the relationship between ART and overall FAHI and five different sub-domains outcomes. All analyses were conducted using STATA version 13 (StataCorp, College Station, TX, USA).

Results

Characteristics of ART Cohort at Enrolment

All participants (Table 1) were black South African women (n = 51) with a mean age of 25.9 years (range 18–43). Approximately 75 % were married or had a stable partnership, and over half (54.9 %) reported having completed grades 11 or 12 of schooling. Thirty-one women (60.8 %) had at least one child who was financially dependent, and seven (13.7 %) disclosed being engaged in sex work. The majority of participants (82.4 %) had knowledge of HIV transmission and over half (54.9 %) were considered to be overweight/obese based on BMI measurement. The mean CD4 count was 488 cells/mm^3 (range 229–1,358), and median log viral load was 4.7 copies/ml (IQR 4.2–5.1) at enrollment. The median number of days between baseline and referral for ART initiation was 638 days.

The group comparison assessment of baseline characteristics indicates that marital status ($\chi^2 = 6.78$, $p = 0.03$), presence of casual partners ($\chi^2 = 7.64$, $p < 0.01$) and educational attainment ($\chi^2 = 10.49$, $p = 0.01$) were significantly associated with ART initiation status. Lower baseline CD4 ($t = 3.18$, $p < 0.01$) and higher log viral load ($p < 0.01$) were detected among the ART-cohort compared (n = 51) to non-ART cohort (n = 109).

Overall and Subscale FAHI Score Comparisons Between Established Infection and ART Phase

Comparison of FAHI scores between pre-ART (established infection) and ART phases using paired Wilcoxon signed-rank tests (Table 2) showed that overall ($z = -3.6$, $p < 0.01$), PWB ($z = -3.0$, $p < 0.01$), EWB ($z = -3.8$, $p < 0.01$), and SWB ($z = -2.8$, $p < 0.01$) were significantly higher on ART compared to the established infection phase. No significant difference between phases was detected in FGWB and CF. The proportion of study

participants meeting meaningful HRQoL improvements in overall, PWB, EWB, FGWB, SWB and CF were 39, 30, 30, 20, 36 and 32 %, respectively (Table 2).

Health-Related Quality of Life Ratings Over Time from ART Referral

The adjusted linear mixed effects regression models (Table 3), similar to the Wilcoxon signed-rank tests, showed that ART was associated with higher levels of overall HRQoL (β = 12.31, p <0.01), and of PWB (β = 2.73, p = 0.03), EWB (β = 2.72, p = 0.03), and SWB sub-domains (β = 3.81, p <0.01). Stable partnership, as compared to multiple partnerships, was also a significant positive predictor of various aspects of HRQoL [overall (β = 14.13, p = 0.03), PWB (β = 6.20, p = 0.01), FGWB (β = 4.28, p = 0.03) and CF (β = 1.88, p = 0.04)]. The assessment of the time trend variable from the same regression models indicated that overall and FAHI sub-scale remained stable since ART referral. The assessment of the interaction term in separate models indicated that CD4 was an effect modifier of the relationship between ART and EWB (β = 0.81, p = 0.04), as well as CF (β = −0.48, p <0.01) outcomes, but not in other sub-domains. The exposure to ART was an independent predictor of (only) CF after adjusting for interaction terms (β = 3.74, p <0.01).

Discussion

Our study found an improvement in overall HRQoL, PWB, EWB, and SWB on ART and no negative impact on FGWB and CF. Approximately one-third of participants showed meaningful long-term HRQoL improvements from the time of ART referral. No adverse impact of ART on HRQoL was detected.

While our findings are consistent with other quality of life studies that detected positive treatment outcomes in physical [27–30], emotional/mental [27, 29, 31–33], and social well-being [29, 32, 34], some studies raise concerns over potential negative consequences of ART on HRQoL, including possible short-term adverse drug reactions [35], which may explain the decline in well-being domains in certain studies [33, 36]. In addition, fear of stigma and social discrimination [37–41] associated with ART treatment disclosure may negatively influence the quality of social relationships and general well-being. While adverse effects and stigma are major concerns in HIV treatment, medical interventions as well as perceptions of the disease evolve over time with education and public awareness. Our study did not detect any detrimental impact of ART, and it is possible, that newer ART regimens are better tolerated, which may account for the lack of decline in PWB in our study, although the role and availability of post-HIV counselling and ART clinical treatment guidance for our participants cannot be discounted.

Notably, a South African qualitative study of ART-related stigma indicated a positive life outlook facilitated by treatment literacy courses and treatment support groups involving patient, peers and family members at clinics [42]. These networks provided supportive environments and lessened the experiences of isolation, fear and stress among study participants. Thus, the counseling and treatment advice available in the study may partially account for observed improvements in social relations. While disclosure of ART may lower the quality of social relations and induce stigma, based on our findings, we generally concur

with the World Health Organization's [43] statement that attitudes towards HIV can change, and stigma can be reduced given that the disease is preventable and treatable with ART.

While our study did not detect ART-related improvements in FGWB and CF from the time of ART referral, this finding should be interpreted with some caution. Cognitive decline is known to accompany HIV progression, a finding detected in our previous investigation of the natural history of HIV 1 subtype C infection in ART-naïve women with extensive follow-up after acute infection [16]. In our current study, however, CF exhibited a non-monotonic shape, indicating initial stabilization and later rebounding, a finding consistent with a systematic review suggesting only partial improvement in neurocognitive function due to ART [44]. Lastly, FGWB, measuring performance of normal activities and overall feelings of well-being, (including hope and outlook for the future), remained stable from the time of ART referral. This may signal uncertainty towards the future among those on ART, and it justifies the need for supportive environments accompanying any ART scale-up initiatives. The overall ART-related improvement or stabilization on HRQoL warrants strengthening and further improvement of access to such life-saving services.

Nevertheless, the study had some limitations. Firstly, the relatively small sample of the ART cohort warrants some caution with regards to the interpretation. In particular, the observed association between ART and CF, may not be generalizable, requiring further studies with a larger cohort size of patients on ART. Secondly, the study was limited by not systematically measuring adherence to ART. While improvements in HRQoL are believed to be correlated with treatment adherence, it is possible that there is a delayed effect. The lack of adherence data, such as pill count, did not permit us to employ regression models to better capture causal inference between ART and HRQoL. Despite of these limitations, our results suggest that HRQoL among HIV-infected women either improved or stabilized on ART. Given that we did not detect a negative impact of ART on quality of life, this study provides additional non-biomedical support to early treatment strategies.

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Table 1

Baseline characteristics of ART cohort in the CAPRISA 002 study at enrolment (n = 160)

Variable	Category/unit	ART cohort (n = 51)		ART not-initiated (n = 109)		Statistics, *p*
		n	%	n	%	
Age groups	18–20	11	21.6 %	17	15.6 %	χ^2 = 8.81, 0.07
	21–24	17	33.3 %	44	40.4 %	
	25–29	10	19.6 %	31	28.4 %	
	30–39	12	23.5 %	10	9.2 %	
	40–59	1	2.0 %	7	6.4 %	
Race	Black	51	100.0 %	108	99.1 %	χ^2 = 0.47, 0.49
Marital status	Married[b]/stable partnership[c]	38	74.5 %	82	75.2 %	χ^2 = 6.78, 0.03
	Many partners	7	13.7 %	4	3.7 %	
	No partner—single	6	11.8 %	23	21.1 %	
Presence of casual partners	Yes	14	27.5 %	11	10.3 %	χ^2 = 7.64, < 0.01
Highest completed education	Less than high school < 8th grade	2	3.9 %	5	4.6 %	χ^2 = 10.49, < 0.01
	High school up to 10th grade	21	41.2 %	19	17.4 %	
	At least Grade 11/12	28	54.9 %	85	78.0 %	
Contraception use	Yes	36	70.6 %	91	83.5 %	χ^2 = 3.53, 0.06
Knowledge of HIV	Yes	42	82.4 %	99	90.8 %	χ^2 = 2.38, 0.12
Sex work	Yes	9	17.7 %	11	10.1 %	χ^2 = 1.81, 0.18
BMI	Underweight	2	3.9 %	2	1.8 %	p = 0.39[d]
	Normal	21	41.2 %	37	33.9 %	
	Overweight/obese	28	54.9 %	70	64.2 %	
CD4 count[a]	Cells per mm^3	M = 488.02	SD = 203.2	M = 606.89	SD = 219.4	t = 3.18, < 0.01
Log viral load[a]	Copies/mL	Mdn = 4.7	IQR = 4.2–5.1	Mdn = 4.1	IQR = 3.3–4.8	p <0.01[e]

[a] 3-month post infection

[b] Marriage based on customary, religious or civil marriage/union

[c] Stable partneship defined as having one regular partner but not necessary falling under solemnization category of customary, religious or civil marriage/ union

[d] Based on Fisher's exact test

[e] Based on rank-sum test

Table 2

Pre- and post-ART HRQoL rating and minimally important difference (MID)

Domains	Established infection phase	ART phase	Phase comparison		MID score	Number of participants meeting threshold $T_2 > T_1$
	Median score	Median score	*z*	*p*	T_1	
Overall (0–176)	160.5	168.8	−3.6	< 0.001	14.6	17 (38.6%)
Physical well-being (0–40)	38.5	39.9	−3.0	< 0.01	4.8	13 (29.6%)
Emotional well-being (0–40)	35	37.3	−3.8	< 0.001	4.7	13 (29.6%)
Functional/global well-being (0–52)	51	51	−0.6	0.52	4.6	9 (20.5%)
Social well-being (0–32)	28	30	−2.8	< 0.01	3.8	16 (36.4%)
Cognitive functioning (0–12)	11	11.6	−1.9	0.06	1.4	14 (31.8%)

z and *p* value based on Wilcoxon sign-rank pair for phase comparisons

MID minimally importance difference

T_2 FAHI score prior to ART phase—last FAHI score during ART phase

Table 3

Trend analysis for overall FAHI and sub-scale outcomes using adjusted mixed-effects models since the time of ART referral

	Overall FAHI			PWB			EWB			FGWB			SWB			CF		
	β	**SE**	***p***	***β***	**SE**	***p***	***β***	**SE**	***p***	***β***	**SE**	***p***	***β***	**SE**	***p***	***β***	**SE**	***p***
ART	12.31	3.35	< 0.01	2.73	1.23	0.03	2.72	1.24	0.03	1.36	1.03	0.19	3.81	1.12	< 0.01	0.68	0.43	0.12
Days since ART referral	< −0.01	< 0.01	0.67	< −0.01	< 0.01	0.72	< 0.01	< 0.01	0.74	< −0.01	< 0.01	0.70	< −0.01	< 0.01	0.71	< 0.01	< 0.01	0.78
Age category																		
21–24	−0.92	3.95	0.82	−0.54	1.44	0.71	−0.41	1.68	0.81	2.09	1.20	0.08	−3.82	1.41	0.01	−0.49	0.64	0.45
25–29	3.58	4.99	0.47	1.32	1.80	0.47	1.87	2.02	0.36	2.21	1.51	0.14	−2.97	1.71	0.08	−0.28	0.66	0.67
30–39	9.25	5.42	0.09	3.74	1.96	0.06	2.85	2.18	0.19	2.83	1.63	0.08	−2.26	1.87	0.23	0.19	0.72	0.80
40–59	−4.23	9.40	0.65	0.25	3.49	0.94	3.83	3.73	0.31	−0.64	2.84	0.82	−10.58	3.36	0.00	−1.80	1.41	0.20
Education																		
School grade < 8	−12.76	8.51	0.13	−3.55	3.08	0.25	0.26	3.41	0.94	−5.00	2.57	0.05	−1.30	2.88	0.65	−0.43	1.14	0.71
School 8–10	−2.80	3.13	0.37	1.20	1.05	0.25	−2.06	1.30	0.11	−0.83	0.88	0.35	−0.49	1.08	0.65	0.10	0.38	0.80
Marital status																		
Married/stable partner	14.13	6.60	0.03	6.20	2.39	0.01	2.41	2.70	0.37	4.28	1.99	0.03	−0.65	2.23	0.77	1.88	0.89	0.04
Single	17.34	5.30	< 0.01	3.34	1.92	0.08	4.39	2.19	0.05	3.29	1.59	0.04	3.35	1.82	0.07	1.59	0.71	0.03
Knowledge of HIV																		
Yes	−1.24	4.27	0.77	0.76	1.56	0.63	2.23	1.71	0.19	−0.33	1.29	0.80	−2.18	1.44	0.13	−0.70	0.58	0.22
Sex worker status																		
Yes	4.26	3.90	0.27	−0.63	1.40	0.65	1.15	1.66	0.49	1.63	1.17	0.17	1.13	1.36	0.41	−0.68	0.54	0.20
Casual partner																		
Present	0.14	6.47	0.98	1.82	2.33	0.43	−0.29	2.35	0.90	0.40	1.94	0.84	−3.25	2.18	0.14	1.06	0.83	0.20
BMI																		
Underweight	−9.94	15.14	0.51	−4.59	5.46	0.40	−1.66	5.46	0.76	−2.55	4.57	0.58	0.44	5.06	0.93	1.45	1.92	0.45
Overweight/obese	−1.97	3.00	0.51	0.89	1.11	0.42	−1.70	1.19	0.15	0.15	0.94	0.87	0.00	1.00	1.00	0.79	0.39	0.05
Peno-vaginal sex act[a]																		
High risk	−3.32	4.98	0.51	−0.06	1.80	0.97	0.46	1.80	0.80	0.21	1.50	0.89	−3.64	1.68	0.03	−0.58	0.64	0.37
Oral sex act[a]																		
High risk	11.31	10.69	0.29	2.08	3.85	0.59	−0.32	3.79	0.93	2.05	3.22	0.52	4.84	3.66	0.19	−0.14	1.36	0.92
Sex act under influence of alcohol[a]																		

	Overall FAHI			PWB			EWB			FGWB			SWB			CF		
	β	**SE**	***p***	***β***	**SE**	***p***	***β***	**SE**	***p***	***β***	**SE**	***p***	***β***	**SE**	***p***	***β***	**SE**	***p***
High risk	12.50	8.11	0.12	1.57	2.93	0.59	2.92	2.97	0.33	2.60	2.44	0.29	4.38	2.74	0.11	−0.14	1.05	0.89

[a]Time covariant. Reference category: Age [18–20], education [grade>10], marital status [many partners], BMI [normal], and sex (peno-vaginal, oral and under influence of alcohol) act [no or low risk since condoms used]

ββ estimate, *SE* standard error, *PWB* physical well-being, *EWB* emotional well-being, *FGWB* functional/global well-being, *SWB* social well-being, *CF* cognitive functioning