

# Maintaining wellbeing for South Africans receiving ART: The burden of pain and symptoms is greater with longer ART exposure

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**Background.** Physical and psychological symptom burden among people with HIV infection is associated with poor quality of life, poorer treatment adherence, viral rebound and risk behaviour. Symptomatology has not been investigated among outpatients in sub-Saharan Africa.

**Objective.** To measure the seven-day period prevalence, burden and correlates of pain and other physical and psychological symptoms among HIV patients receiving antiretroviral therapy (ART).

**Methods.** This was a cross-sectional self-report study. A total of 378 patients were interviewed using validated tools in three South African public sector clinics.

**Results.** The most prevalent symptoms were feeling sad (64%), feeling irritable (61.6%), worry (60.8%), numbness and tingling in hands/feet (59.8%), and sexual problems (51%). In multivariate analysis, later disease stage was associated with worse psychological symptom burden ( $\beta=0.359$ ; 95% confidence interval (CI) 0.202 - 0.516;  $p<0.001$ ), global symptom burden ( $\beta=0.365$ ; 95% CI 0.204 - 0.526;  $p<0.001$ ) and number of symptoms ( $\beta=0.308$ ; 95% CI 0.150 - 0.465;  $p<0.001$ ). Those receiving treatment for a greater number of years also reported higher burden for physical ( $\beta=0.083$ ; 95% CI 0.037 - 0.129;  $p<0.001$ ), psychological ( $\beta=0.068$ ; 95% CI 0.019 - 0.117;  $p=0.007$ ) and global symptoms ( $\beta=0.065$ ; 95% CI 0.016 - 0.115;  $p=0.010$ ), and a greater number of symptoms ( $\beta=0.081$ ; 95% CI 0.032 - 0.130;  $p=0.001$ ).

**Conclusions.** The data reveal a high symptom burden despite treatment. Detailed symptom assessment and control continues to be required in the era of treatment.

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Evidence from high-income settings has shown that HIV patients experience a high physical and psychological symptom burden in the presence of antiretroviral therapy (ART).<sup>[1,2]</sup> This symptom burden has been associated with sexual risk-taking,<sup>[3]</sup> poor adherence,<sup>[4]</sup> treatment switching<sup>[5]</sup> and viral rebound.<sup>[6]</sup>

HIV patients perceive that their symptoms remain untreated.<sup>[7,8]</sup> This perception is supported by evidence that physicians detect three-fold fewer HIV-related symptoms than their patients report.<sup>[9]</sup> Doctors tend to overlook the assessment of pain and other treatable symptoms, instead focusing on symptoms that are physically measurable such as fever and weight loss, and are more likely to ask about symptoms in HIV patients perceived to be severely ill.<sup>[10]</sup>

The World Health Organization (WHO) advocates pain and symptom control as an essential component of HIV clinical care.<sup>[11]</sup> A significant proportion of patients receiving ART experience drug toxicities such as peripheral neuropathy and gastrointestinal problems,<sup>[12]</sup> requiring drug discontinuation or treatment change within, and between, classes of ART.<sup>[13]</sup> Investigation into prevalence and correlates of HIV-related symptoms is required to inform clinical practice and thereby improve clinical outcomes and quality of life in the presence of ART.<sup>[14,15]</sup>

The vast majority of data on pain and symptom prevalence have been reported from the pre-ART era in patients in high-income countries with AIDS-defining illnesses. As there are fewer treatment options available in low- and middle-income countries, adherence must be optimised and movement between classes of drugs minimised.

Given the relationship between symptom burden, poor adherence, treatment switching and viral rebound, symptom data are urgently needed to inform patient assessment and management in Africa.

The prevalence and high burden/high frequency of symptoms for patients receiving ART and those not receiving ART have been reported previously.<sup>[16]</sup> We report the seven-day period prevalence, burden and correlates of pain, and other physical and psychological symptoms, among HIV patients receiving ART in three public sector HIV clinics in South Africa (SA).

## Methods

### Study design

The study design was cross-sectional self-report with additional clinical data extracted from patient records.

The study was approved by the Committee for Research in Human Subjects (Medical) at the University of the Witwatersrand and by the Human Research Ethics Committee of the University of Cape Town.

### Setting

The research was conducted in the outpatient adult HIV treatment clinics within three academic hospitals in Johannesburg, SA, which adhere to the most recent SA national ART guidelines. At the time of data collection, the clinics had implemented the recent change in the national guidelines to initiate ART in patients with a CD4<sup>+</sup> count <200 cells/ $\mu$ l, regardless of stage; those with a CD4<sup>+</sup> count <350 cells/ $\mu$ l and pregnant or co-infected with tuberculosis (TB);

those who are WHO stage 4 regardless of CD4<sup>+</sup> count and all patients with drug-resistant TB.<sup>[17]</sup>

### Recruitment

Inclusion criteria accounted for HIV outpatients aged 18 years or older receiving ART and able to give informed consent to participate in data collection in one of the three most common languages: English, isiZulu and Sesotho. Simple random sampling was used by inviting every fifth patient attending the clinic to participate, on days selected at random over an eight-month period in 2009 - 2010. Informed consent was obtained from participants.

### Data collection

Data were collected using self-report (demographics, symptom prevalence and burden) and extraction of data from files (CD4<sup>+</sup> count at treatment initiation, time since treatment initiation, most recent CD4<sup>+</sup> count, most recent viral load, whether the patient had switched treatment, WHO disease stage). The seven-day period prevalence and associated burden of symptoms was measured using the Memorial Symptom Assessment Scale Short Form (MSAS-SF).<sup>[18]</sup> The MSAS-SF measures 28 physical and four psychological symptoms and provides three subscale indices of Physical Symptom Distress (MSAS-Phys), Psychological Symptom Distress (MSAS-Psych) and Global Distress Index (MSAS-GDI).<sup>[14]</sup> Each of these three subscales has a possible score range of 0 - 4. The MSAS-SF has been widely used in HIV populations.<sup>[1,2,19,20]</sup> Finally, the research nurse scored the patient on the Karnofsky Performance Scale, which is a measure of physical performance scored from 0 (dead) to 100 (normal) in bands of 10<sup>[21]</sup> and is a commonly used measure of performance in HIV populations.<sup>[22]</sup>

Owing to potential literacy limitations in the population sampled, a research nurse read aloud each self-reported question and recorded the response to reduce any potential bias through mixed self-completion and researcher-administered questionnaires. Information and consent forms and the questionnaire were translated from English into isiZulu and Sesotho by forward and back translation and the interview was conducted in the patient's language of choice.

### Analysis

Descriptive data were generated for the sample characteristics. The most common symptoms have been previously reported.<sup>[16]</sup> The MSAS-SF subscales and total number of symptoms were calculated. Subsequently, the following analyses were conducted. Univariate linear regression analyses were conducted to test the association of independent covariates with the following four dependent variables: (i) MSAS-Phys; (ii) MSAS-Psych; (iii) MSAS-GDI; and (iv) total symptom burden. Each of these four dependent variables formed a separate model in the subsequent multivariate analyses described below. As the burden scores were not normally distributed (data plotting showing a left-skew), they were transformed into tertiles.

Independent variables entered in univariate analysis were: age (continuous); gender (two levels of male/female); WHO stage (three levels of stage 1, 2, 3 or 4); CD4<sup>+</sup> count at ART initiation transformed into quartiles; whether the patient had switched ART regimen (two levels: yes/no); current viral load (two levels: detectable/not detectable); current CD4<sup>+</sup> count (continuous); and time receiving ART (years).

Following each univariate regression, multivariate regressions models were constructed. Independent variables from the univariate analyses above were entered into the multivariate model if significant

at the 25% level.<sup>[23]</sup> For each independent variable, the unstandardised  $\beta$  coefficient and the 95% confidence interval (CI) were calculated. For each multivariate model, the *F*-value for the model and the *r*<sup>2</sup> were calculated. Cases with missing data were excluded from the multivariate models. All analyses were conducted using SPSS (version 19).

## Results

### Sample characteristics

A total of 378 patients participated (Table 1). The mean age of the patients was 40.3 years, the majority were female (76.2%) and of black ethnicity (98.1%). Participants had been receiving treatment for an average of three years and had a current average CD4<sup>+</sup> count of 355.85 cells/ $\mu$ l (standard deviation (SD)  $\pm$ 219.26). According to the latest results available in the participants' records, around one-quarter of the sample (*n*=99; 28.6%) did not have viral suppression, and almost half (*n*=172; 45.5%) had switched ART regimen.

### Symptomatology

The mean number of symptoms (of a possible total of 32) was 10.05 (SD  $\pm$ 5.66; range 1 - 28). The symptom prevalence and burden are presented in descending order of prevalence in Table 2. Three of the four psychological symptoms (sad, irritable and worrying) were among the ten most prevalent symptoms. The ten symptoms with the highest burden (i.e. scored using the worst two response categories) were: numbness and tingling in the hands/feet (37% of whole sample); feeling irritable (36.8%); problems with sexual interest or function (35.1%); worry (34.4%); not looking like myself (34.4%); feeling sad (30.7%); pain (29.1%); weight loss (24.8%); sweats (22.7%); and feeling nervous (20.6%).

**Table 1. Sample characteristics (N=378)**

Age (years), mean ( $\pm$ SD)	40.34 ( $\pm$ 9.16)
Female gender, <i>n</i> (%)	288 (76.2)
Ethnicity, <i>n</i> (%)	
Black	371 (98.1)
Mixed ancestry	5 (1.3)
White	2 (0.5)
WHO stage, <i>n</i> (%)	
Stage 1	98 (25.9)
Stage 2	246 (65.1)
Stage 3	29 (7.7)
Stage 4	5 (1.3)
KPS, median (IQR)	90 (90 - 90)*
CD4 <sup>+</sup> count (cells/ml)	
Pre-ART, median (IQR)	93 (40.5 - 158.25)
Current, mean ( $\pm$ SD)	355.85 ( $\pm$ 219.26)
Years receiving ART, mean ( $\pm$ SD)	3.04 ( $\pm$ 1.83)
Patients with undetectable VL, <i>n</i> (%)	279 (71.4) <sup>†</sup>
Current VL for those detectable (copies/ml), median (IQR)	2500 (142 - 67 000)
Switched ART regimen (no), <i>n</i> (%)	206 (54.5)

WHO = World Health Organization; KPS = Karnofsky Performance Scale; IQR = interquartile range; ART = antiretroviral therapy; VL = viral load.

\*Data missing for 4 patients.

<sup>†</sup>Data missing for 33 patients.

**Table 2. Seven-day period prevalence and burden of symptoms (N=378)**

Physical symptoms	Prevalence	Distress, n (%*)					
		N/A	None	A little bit	Somewhat	Quite a bit	Very much
Numbness/tingling in hands and feet	226 (59.8)	152 (40.2)	16 (4.5)	28 (7.4)	42 (11.1)	36 (9.5)	104 (27.5)
Problems with sexual interest or activity	196 (51.9)	182 (48.1)	14 (3.7)	18 (4.5)	31 (8.2)	27 (7.1)	106 (28)
Pain	190 (50.3)	188 (49.7)	15 (4.0)	29 (7.7)	36 (9.5)	27 (7.1)	83 (22)
'I don't look like myself'	182 (48.1)	196 (51.9)	6 (1.6)	17 (4.8)	29 (7.7)	20 (5.3)	110 (29.1)
Lack of energy	151 (39.9)	227 (60.1)	8 (2.1)	25 (6.6)	45 (11.9)	20 (5.3)	53 (14.0)
Sweats	148 (39.2)	230 (60.8)	7 (1.9)	22 (5.8)	32 (8.5)	27 (7.1)	60 (15.6)
Weight loss	144 (38.1)	234 (61.9)	6 (1.6)	24 (6.3)	24 (6.3)	17 (4.5)	73 (19.3)
Feeling bloated	143 (37.8)	235 (62.2)	10 (2.6)	38 (10.1)	24 (6.3)	35 (9.3)	36 (9.5)
Feeling drowsy	135 (35.7)	243 (64.3)	15 (4.0)	41 (10.8)	20 (5.6)	23 (6.1)	6 (9.5)
Changes in skin	132 (34.9)	246 (65.1)	13 (3.4)	27 (7.1)	26 (6.9)	14 (3.7)	52 (13.8)
Difficulty concentrating	128 (33.9)	250 (66.1)	9 (2.4)	30 (7.9)	28 (7.4)	22 (5.8)	40 (10.6)
Constipation	118 (31.2)	260 (68.8)	9 (2.4)	29 (7.7)	27 (7.1)	222 (6.1)	31 (8.2)
Itching	111 (29.4)	267 (70.6)	8 (2.1)	24 (6.6)	24 (6.3)	21 (5.6)	34 (9.0)
Lack of appetite	95 (25.1)	283 (74.9)	6 (1.6)	12 (3.2)	21 (5.6)	19 (5.0)	37 (9.8)
Cough	94 (24.9)	284 (75.1)	21 (5.6)	29 (7.7)	15 (4)	8 (2.1)	21 (5.6)
Dizziness	91 (24.1)	287 (75.9)	8 (2.1)	24 (6.3)	16 (4.2)	12 (3.2)	31 (8.2)
Swelling of arms or legs	88 (23.3)	290 (76.7)	4 (1.1)	21 (5.6)	21 (5.6)	11 (2.9)	31 (8.2)
Difficulty sleeping	86 (22.8)	292 (77.2)	8 (1.9)	13 (3.4)	12 (3.2)	14 (3.4)	39 (10.3)
Dry mouth	83 (22.0)	295 (78.0)	9 (2.4)	19 (5.0)	14 (3.0)	17 (4.8)	24 (6.3)
Shortness of breath	68 (17.7)	310 (82.3)	3 (0.8)	12 (3.2)	13 (3.4)	13 (3.2)	27 (7.1)
Nausea	64 (16.9)	314 (83.1)	6 (1.6)	22 (5.8)	11 (2.9)	7 (1.9)	18 (4.8)
Diarrhoea	58 (15.3)	320 (84.7)	8 (1.9)	16 (4.2)	10 (2.6)	10 (2.6)	14 (3.7)
Problems with urination	54 (14.3)	324 (85.7)	0 (0)	12 (3.2)	11 (2.9)	8 (2.1)	23 (6.1)
Mouth sores	52 (13.8)	327 (86.2)	20 (5.0)	19 (5.0)	14 (3.7)	4 (1.1)	14 (3.7)
Change in the way food tastes	49 (13.0)	329 (87.0)	5 (1.3)	8 (2.1)	5 (1.3)	11 (2.9)	20 (5.3)
Hair loss	35 (9.3)	343 (90.7)	4 (1.1)	8 (2.1)	5 (1.3)	3 (0.8)	15 (4.0)
Vomiting	23 (6.1)	355 (93.9)	4 (1.1)	11 (2.9)	1 (0.3)	3 (0.8)	4 (1.1)
Difficulty swallowing	15 (4.0)	363 (96.0)	1 (0.3)	5 (1.3)	1 (0.3)	4 (1.1)	4 (1.1)
Psychological symptoms	Prevalence	N/A	Rarely	Occasionally	Frequently	Almost constantly	
Feeling sad	242 (64.0)	136 (36.0)	61 (16.1)	65 (17.2)	31 (8.2)	85 (22.5)	
Feeling irritable	233 (61.6)	145 (38.4)	39 (10.3)	55 (14.3)	40 (10.6)	99 (26.2)	
Worrying	231 (60.8)	147 (39.2)	55 (14.8)	46 (12.2)	37 (9.8)	93 (24.6)	
Feeling nervous	149 (39.5)	229 (60.5)	38 (10.6)	32 (8.5)	22 (5.8)	56 (14.8)	

N/A = not present.  
\*Do not all add to 100% due to rounding.

**Regression analyses: Associations with symptom burden indices**

The univariate analysis is presented in Table 3. In multivariate analysis (Table 4), for the first model (MSAS-Phys;  $F=4.878$ ;  $p<0.001$ ;  $r^2=8\%$ ) the following independent associations were identified. Higher physical symptom distress was associated with greater age ( $\beta=0.009$ ; 95% CI 0.001 - 0.018;  $p=0.036$ ); female gender ( $\beta=-0.207$ ; 95% CI -0.399 - -0.016;  $p=0.034$ ); and greater number of years receiving ART ( $\beta=0.083$ ; 95% CI 0.037 - 0.129;  $p\leq 0.001$ ). For the second model (MSAS-Psych;  $F=6.967$ ;  $p<0.001$ ;  $r^2=9\%$ ), higher psychological distress was associated with later WHO stage

( $\beta=0.359$ ; 95% CI 0.202 - 0.516;  $p\leq 0.001$ ) and greater number of years receiving treatment ( $\beta=0.068$ ; 95% CI 0.019 - 0.117;  $p=0.007$ ). For the third model (MSAS-GDI;  $F=5.152$ ;  $p<0.001$ ;  $r^2=10\%$ ), higher global symptom distress was associated with later WHO stage ( $\beta=0.365$ ; 95% CI 0.204 - 0.526;  $p<0.001$ ) and greater number of years receiving ART ( $\beta=0.065$ ; 95% CI 0.016 - 0.115;  $p=0.010$ ). For the fourth model (total symptom distress, model  $F=6.407$ ;  $p<0.001$ ;  $r^2=10\%$ ), higher total symptom distress was associated with later WHO stage ( $\beta=0.308$ ; 96% CI 0.150 - 0.465;  $p<0.001$ ) and greater number of years receiving ART ( $\beta=0.081$ ; 95% CI 0.032 - 0.130;  $p=0.001$ ).

**Table 3. Associations of covariates with symptom indices: Univariate analysis**

Dependent variable	Independent variables							
	Age	Gender	WHO stage	CD4 <sup>+</sup> count pre-ART	Years receiving ART	Current CD4 <sup>+</sup> count	Detectable VL	ART regimen switched
Model 1: MSAS-Phys (N=335)								
$\beta$	0.009	-0.238	0.157	0.047	0.087	0.000	-0.110	0.115
95% CI	0.001 - 0.018	-0.425 - 0.051	0.017 - 0.298	-0.026 - 0.119	0.044 - 0.131	-0.001 - 0.000	-0.315 - 0.095	-0.046 - 0.276
p-value	0.036*	0.013*	0.029*	0.206*	0.014*	0.463	0.291	0.160*
Model 2: MSAS-Psych (N=335)								
$\beta$	0.003	-0.195	-0.373	0.023	-0.116	<0.001	-0.206	0.102
95% CI	-0.006 - 0.012	-0.39 - 0.00	0.231 - 0.515	-0.052 - 0.097	-0.078 - 0.31	0.000 - 0.001	-0.416 - 0.005	-0.065 - 0.269
p-value	0.567	0.050*	≤0.001*	0.553	0.240*	0.420	0.055*	0.229*
Model 3: MSAS-GDI (N=335)								
$\beta$	<0.001	-0.194	0.365	0.046	0.065	-	-0.112	0.102
95% CI	-0.010 - 0.009	-0.402 - -0.014	0.204 - 0.526	-0.032 - 0.123	0.016 - 0.115	-	-0.328 - 0.104	-0.168 - 0.192
p-value	0.951	0.067	<0.001*	0.245	≤0.010*	-	0.308	0.895
Model 4: Total symptom burden (N=335)								
$\beta$	0.012	-0.173	0.362	-	0.101	-	-0.154	0.198
95% CI	0.003 - 0.021	-0.368 - 0.022	0.220 - 0.504	-	0.056 - 0.146	-	-0.366 - 0.058	0.032 - 0.364
p-value	0.010*	0.081*	≤0.001*	-	≤0.001*	-	0.153*	0.019*

WHO = World Health Organization; ART = antiretroviral therapy; VL = viral load; MSAS = Memorial Symptom Assessment Scale; MSAS-Phys = MSAS Physical Symptom Distress Index; MSAS-Psych = MSAS Psychological Symptom Distress Index; MSAS-GDI = MSAS Global Distress Index; CI = confidence interval.  
\*Entered into multivariate model.

**Table 4. Associations of covariates with symptom indices: Multivariate analysis**

Dependent variable	Independent variables							
	Age	Gender	WHO stage	CD4 <sup>+</sup> count pre-ART	Years receiving ART	Current CD4 <sup>+</sup> count	Detectable VL	ART regimen switched
Model 1: MSAS-Phys (N=376)								
$\beta$	0.009	-0.207	0.111	0.041	0.083	-	-	-0.041
95% CI	0.001 - 0.018	-0.399 - -0.016	-0.033 - 0.255	-0.031 - 0.113	0.037 - 0.129	-	-	-0.210 - 0.129
p-value	0.036*	0.034*	0.131	0.263	≤0.001 <sup>‡</sup>	-	-	0.637
Model 2: MSAS-Psych (N=377)								
$\beta$	-	-0.160	0.359	-	0.068	-	-0.121	0.051
95% CI	-	-0.362 - 0.042	0.202 - 0.516	-	0.019 - 0.117	-	-0.327 - 0.086	-0.227 - 0.125
p-value	-	0.121	≤0.001 <sup>‡</sup>	-	0.007 <sup>†</sup>	-	0.252	0.567
Model 3: MSAS-GDI (N=376)								
$\beta$	<0.001	-0.194	0.365	0.046	0.065	-	-0.112	0.102
95% CI	-0.010 - 0.009	-0.402 - -0.014	0.204 - 0.526	-0.032 - 0.123	0.016 - 0.115	-	-0.328 - -0.104	-0.168 - 0.192
p-value	0.951	0.067	<0.001 <sup>‡</sup>	0.245	≤0.010 <sup>†</sup>	-	0.308	0.895
Model 4: Total symptom burden (N=375)								
$\beta$	0.008	-0.174	0.308	-	0.081	-	-0.032	0.037
95% CI	-0.001 - 0.018	-0.378 - 0.030	0.150 - 0.465	-	0.032 - 0.130	-	-0.244 - 0.180	0.140 - 0.214
p-value	0.087	0.095	≤0.001 <sup>‡</sup>	-	0.001 <sup>‡</sup>	-	0.767	0.679

WHO = World Health Organization; ART = antiretroviral therapy; VL = viral load; MSAS = Memorial Symptom Assessment Scale; MSAS-Phys = MSAS Physical Symptom Distress Index; MSAS-Psych = MSAS Psychological Symptom Distress Index; MSAS-GDI = MSAS Global Distress Index; CI = confidence interval.

\*Significant at p<0.05.  
<sup>†</sup>Significant at p<0.01.  
<sup>‡</sup>Significant at p<0.001.

## Discussion

These data reveal a high prevalence and burden of symptoms among HIV patients receiving ART in SA, which persists despite relatively good physical function and the majority having been receiving treatment for several years. Seven symptoms were scored in the worst two categories of burden by around one-third of the sample, and these symptoms were psychological and physical, including a symptom indicative of peripheral neuropathy as well as other pain and sexual dysfunction.

There were a number of associations with symptom burden. Although greater age and female gender were associated with physical symptom distress, a consistent relationship was identified between worse symptom indices and greater number of years receiving ART. This may be related to the greater number of years of having HIV infection, and to the toxicity of treatment. In addition to clinician monitoring of patient wellbeing when beginning treatment, these data suggest that those who are treatment-experienced should have their symptom burden assessed alongside measurement of virological efficacy. Although there was a high symptom burden for the whole sample, the data also suggest that those with more advanced disease (as measured by WHO staging) may experience a greater burden.

A systematic review has demonstrated that palliative care can effectively control these burdensome problems in HIV populations.<sup>[24]</sup> It is essential that clinical medicine takes account of patient self-reported problems to improve quality of care.<sup>[25]</sup> Our data on pain and symptom prevalence, and associated distress, support the Joint United Nations Programme on HIV/AIDS (UNAIDS) and WHO policy that palliative care is necessary throughout the HIV disease trajectory alongside ART.<sup>[11,26]</sup> In light of the data suggesting that uncontrolled symptoms adversely affect quality of life<sup>[8,27]</sup> and are associated with poor adherence,<sup>[4]</sup> sexual risk-taking,<sup>[3]</sup> treatment switching<sup>[5]</sup> and viral rebound,<sup>[6]</sup> we recommend that clinicians regularly assess their patients' physical and psychological self-reported symptoms.

## Study limitations

There were a number of methodological limitations to our study. Firstly, the cross-sectional nature of the design meant that we could not draw causal relationships to symptom burden. Second, the reliance on file data, rather than collecting new primary data on clinical outcomes, may have introduced some inaccuracy.

## Conclusion

Within Africa, symptom prevalence data have been reported in newly diagnosed HIV patients preparing for treatment,<sup>[19]</sup> and among patients with advanced disease.<sup>[1,20]</sup> Our study has built on the small body of prior evidence on prevalence and correlates of symptom burden in African patients<sup>[28-30]</sup> and supports prior findings that symptoms persist despite ART. Our data indicate that, alongside treatment to prolong life, clinical care should include detailed assessment and control of pain and symptoms to maximise quality of life and treatment benefit. In particular, our data suggest that although all patients should have their symptoms assessed regularly and controlled, those who have spent a longer time receiving ART, and those with more advanced disease, may require greater attention.

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