

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



LSHTM Research Online

Mutevedzi, PC; Lessells, RJ; Heller, T; Barnighausen, T; Cooke, GS; Newell, ML; (2010) Scale-up of a decentralized HIV treatment programme in rural KwaZulu-Natal, South Africa: does rapid expansion affect patient outcomes? *Bulletin of the World Health Organization*, 88 (8). pp. 593-600. ISSN 0042-9686 DOI: <https://doi.org/10.2471/BLT.09.069419>

Downloaded from: <http://researchonline.lshtm.ac.uk/2721/>

DOI: <https://doi.org/10.2471/BLT.09.069419>

Usage Guidelines:

Please refer to usage guidelines at <https://researchonline.lshtm.ac.uk/policies.html> or alternatively contact researchonline@lshtm.ac.uk.

Available under license: <http://creativecommons.org/licenses/by-nc-nd/2.5/>

<https://researchonline.lshtm.ac.uk>

Scale-up of a decentralized HIV treatment programme in rural KwaZulu-Natal, South Africa: does rapid expansion affect patient outcomes?

Portia C Mutevedzi,^a Richard J Lessells,^a Tom Heller,^b Till Bärnighausen,^a Graham S Cooke^a & Marie-Louise Newell^a

Objective To describe the scale-up of a decentralized HIV treatment programme delivered through the primary health care system in rural KwaZulu-Natal, South Africa, and to assess trends in baseline characteristics and outcomes in the study population.

Methods The programme started delivery of antiretroviral therapy (ART) in October 2004. Information on all patients initiated on ART was captured in the programme database and follow-up status was updated monthly. All adult patients (≥ 16 years) who initiated ART between October 2004 and September 2008 were included and stratified into 6-month groups. Clinical and sociodemographic characteristics were compared between the groups. Retention in care, mortality, loss to follow-up and virological outcomes were assessed at 12 months post-ART initiation.

Findings A total of 5719 adults initiated on ART were included (67.9% female). Median baseline CD4+ lymphocyte count was 116 cells/ μ l (interquartile range, IQR: 53–173). There was an increase in the proportion of women who initiated ART while pregnant but no change in other baseline characteristics over time. Overall retention in care at 12 months was 84.0% (95% confidence interval, CI: 82.6–85.3); 10.9% died (95% CI: 9.8–12.0); 3.7% were lost to follow-up (95% CI: 3.0–4.4). Mortality was highest in the first 3 months after ART initiation: 30.1 deaths per 100 person-years (95% CI: 26.3–34.5). At 12 months 23.0% had a detectable viral load (> 25 copies/ml) (95% CI: 19.5–25.5).

Conclusion Outcomes were not affected by rapid expansion of this decentralized HIV treatment programme. The relatively high rates of detectable viral load highlight the need for further efforts to improve the quality of services.

Une traduction en français de ce résumé figure à la fin de l'article. Al final del artículo se facilita una traducción al español. الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.

Introduction

South Africa is home to 5.7 million people living with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), or approximately 1 in 6 of the world's HIV+ population.¹ It also has the largest public-sector antiretroviral therapy (ART) programme in the world, with an estimated 460 000 individuals established on ART by December 2007. However, as 1.5 million people living with HIV/AIDS in South Africa are estimated to be in need of ART, this figure only equates to 30% coverage.² If the ambitious target set under the National Strategic Plan of universal access by 2011 is to be achieved, scale-up of ART services must be intensified.^{3,4}

There is good evidence that ART can be delivered effectively in South Africa, with individual virological and immunological responses to ART equivalent to those in high-resource settings.⁵ Most published evidence relating to ART scale-up in South Africa, however, has come from urban treatment cohorts or from provinces with primarily urban populations.^{5–9} Neighbouring countries in southern Africa have also reported programme outcomes, although again based largely on urban cohorts.^{10,11} Only the Malawi national programme has reported large-scale data on a predominantly rural population.¹² Delivery of HIV treatment and care to rural communities presents unique challenges, and current ART delivery models may significantly limit the accessibility of ART.¹³ To have the greatest impact on public health, HIV treatment programmes will have to be decentralized and

integrated into the existing primary health care system.¹⁴ Preliminary evidence from such rural programmes has demonstrated that ART provision in rural communities is feasible, given the appropriate resources and infrastructure.^{15,16}

Concern has been raised that the rapid expansion of HIV services will reduce the quality of care for individuals within the programme as capacity and resources are stretched.¹⁷ Characteristics of individuals accessing treatment may change over time, and this in itself may affect overall treatment outcomes.¹⁸ Monitoring treatment outcomes is essential to identify constraints or deficiencies in programme performance, and viral load monitoring may provide warning of adherence problems and of possible development of acquired antiretroviral resistance.¹⁹

To evaluate a decentralized model of ART delivery in a rural community, we analysed the scale-up of our programme and explored trends in the characteristics of individuals accessing treatment and their outcomes within the first year of treatment.

Methods

Setting

The Hlabisa HIV Treatment and Care Programme is a partnership between the local Department of Health and the Africa Centre for Health and Population Studies to deliver the South African Comprehensive HIV and AIDS Care, Management and Treatment Plan.²⁰ It is a decentralized programme of HIV treatment and care delivered through a network of 16 primary health

^a Africa Centre for Health and Population Studies, PO Box 198, Mtubatuba, 3935, South Africa.

^b Hlabisa Hospital, Hlabisa, KwaZulu-Natal, South Africa.

Correspondence to Portia C Mutevedzi (e-mail: pmutevedzi@afriacentre.ac.za).

(Submitted: 3 July 2009 – Revised version received: 9 December 2009 – Accepted: 11 December 2009 – Published online: 10 May 2010)

care clinics in the Hlabisa subdistrict of Umkhanyakude district in northern KwaZulu-Natal. The subdistrict covers an area of 1430 km² and has a population of approximately 220 000, mostly living in rural areas.²¹ HIV infection prevalence peaks at 50.9% among females aged 25–29 years and 43.5% among males aged 30–34 years.²² The programme employs a public health approach to ART delivery aimed at facilitating rapid scale-up of HIV treatment services.^{14,23} Support for the programme is provided by the President's Emergency Plan for AIDS Relief (PEPFAR) through the United States Agency for International Development (USAID).

Patients

The programme adheres to the national antiretroviral treatment guidelines, which recommend initiation of ART for adults with stage IV disease as defined by the World Health Organization (WHO)²⁴ or a CD4+ lymphocyte (CD4 cell) count of < 200 cells/ μ l.²⁵ The first-line ART regimen consists of stavudine, lamivudine and either efavirenz or nevirapine. ART is initiated at primary health care clinics (or at Hlabisa hospital) by a physician after standard pre-ART evaluation and three treatment literacy sessions. Monitoring and ART dispensing are performed by nurses and counsellors at 2 weeks and 4 weeks and then at 4-weekly intervals thereafter. CD4 cell count and HIV load are measured every 6 months.

Data acquisition

Longitudinal individual patient records are maintained at primary health care clinics. After initiation of ART, clinical and demographic information is transferred to a database developed and housed at the Africa Centre for Health and Population Studies (ART Evaluation and Monitoring Information System, or AR-Temis), which is then updated monthly with follow-up status. Laboratory results (CD4 cell count and HIV load) are regularly imported into ARTemis. Demographic information is collected biannually and put into the Africa Centre Demographic Information System for approximately 90 000 individuals who are members of households within the Africa Centre Demographic Surveillance Area,²⁶ which covers about one-third of the Hlabisa health subdistrict. Information relating to socioeconomic status and household structure for individuals in ARTemis is therefore obtained through

linkage of data sets, for all of which the patient's national identity number is used. For these analyses, data were taken from the demographic surveillance period encompassing \pm 9 months from the date of ART initiation.

Data analysis

Our analyses included all adults (\geq 16 years of age) who initiated ART within the programme between 1 October 2004 and 30 September 2008. Patients already on ART (504) who transferred into the programme were excluded. Patients were categorized into 6-monthly groups on the basis of date of ART initiation and were stratified into four clinic groups: hospital-based (1 clinic); urban/periurban (2 clinics); large rural (\geq 200 patients on ART as of 30 September 2008 – 6 clinics); and small rural (< 200 patients on ART as of 30 September 2008 – 7 clinics). We assessed trends and differences in baseline characteristics across the 6-monthly and clinic strata on the basis of median tests and centile regression for continuous variables and proportions test and logistic regression for categorical variables. To assess possible selection bias associated with incomplete linkage of clinical and population data, we compared baseline and outcome variables between linked and unlinked individuals.

Outcomes (death, loss to follow-up and detectable viral load) at 12 months post-ART initiation were analysed for all patients who initiated ART up to 30 September 2007. Follow-up status was analysed at 12 months, whereas HIV load values were taken at 12 months \pm 2 months to allow for variance in collection time points. HIV load was measured at a provincial laboratory using the Nucli-Sens EasyQ[®] HIV-1 assay (bioMérieux sa, Marcy l'Etoile, France), with a lower detection limit of 25 copies/ml. Loss to follow-up was defined as having no clinic visit for 90 days or more. A total of 84 patients (2.8%) had only a baseline visit before being reported as deceased (n = 29), lost to follow-up (n = 38) or transferred out (n = 17). These patients were allocated 15 days of follow-up – the median time between the baseline visit and their next scheduled monthly clinic visit. Kaplan–Meier survival analysis was used to assess trends in time to death and detectable viral load and Cox regression to assess determinants of these two outcomes.

To account for substantial missing viral load data, independent baseline factors associated with missing data at 12 ± 2 months post-ART were determined through logistic regression at a 25% significance level. The resultant deterministic model was used to generate a propensity-to-be-missing score, defined as the probability for each patient of having a missing viral load reading.^{27,28} The Cox proportional hazard model for detectable viral load was controlled for the propensity score as a re-weighting adjustment factor. Data were analysed using Stata version 10.0 (StataCorp, College Station, United States of America).

Ethical approval

Written informed consent was obtained from all patients in the programme to allow use of anonymous clinical data in research. Ethical approval was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal and the Research Office of the KwaZulu-Natal Department of Health for linkage and use of these data.

Results

Patients

A total of 5719 adult patients were initiated on ART in the programme between 1 October 2004 and 30 September 2008 (Fig. 1); 2509 patients (43.9%) reported a physical address within the demographic surveillance area at the time of ART initiation and hence were eligible for linkage, and 1804 (72%) of them were successfully linked.

Despite a 10-fold increase in the number of patients initiating ART (Table 1), the health worker-to-patient ratio only declined by 0.5, as staff increased from 6 in the first half-year of analysis to 99 in the last half-year. The most rapid growth occurred in large rural clinics as decentralization progressed (Fig. 2).

Baseline characteristics

Females (3883) made up 67.9% of all patients initiated on ART, with no significant differences in proportion of females between clinic groups. Males initiated at a higher median age (37 years, interquartile range, IQR: 32–45) than females (34 years, IQR: 28–41) (P < 0.001) and had a lower median CD4 cell count at initiation (91 cells/ μ l, IQR: 41–156) than females (128 cells/ μ l, IQR: 66–179) (P < 0.001). A higher

proportion of males (29.6%) than females (18.2%) ($P < 0.001$) initiated with a CD4 cell count < 50 cells/ μl ($P < 0.001$). Prevalent tuberculosis at initiation was more common in males (20.4%) than females (15.6%) ($P < 0.001$).

There were no significant differences across clinic groups, except for the median CD4 cell count, which was significantly lower at the hospital clinic (99 cells/ μl) than at the urban/peri-urban (114 cells/ μl ; $P = 0.032$), large rural (128 cells/ μl ; $P < 0.001$), and small rural clinics (117.5 cells/ μl ; $P = 0.023$).

Table 1 shows overall baseline characteristics and trends over time.

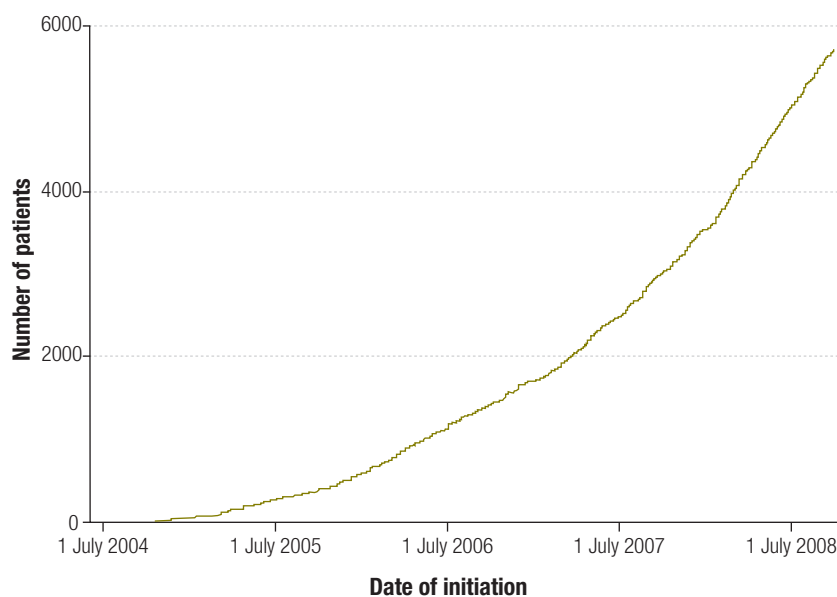
Outcomes

People who initiated treatment between October 2007 and September 2008 (2709) were excluded, leaving 3010 patients for outcomes analysis. Overall retention at 12 months was 84.0% (95% confidence interval, CI: 82.6–85.3) and mortality was 10.9% (95% CI: 9.8–12.0). The proportion with a detectable viral load declined but remained high at around 23%. Table 2 shows overall outcomes, including trends over time.

At 12 months post-initiation, the 3010 patients had accumulated 2617 person-years of follow-up, with 329 deaths: a mortality rate of 12.6 deaths per 100 person-years (95% CI: 11.3–14.0). The mortality rate peaked in the first 3 months following ART initiation at 30.1 deaths per 100 person-years (95% CI: 26.3–34.5) and fell thereafter to 6.2 deaths per 100 person-years (95% CI: 5.2–7.4). Male gender, lower weight, CD4 cell count < 50 cells/ μl , low haemoglobin, high creatinine and lack of formal education were significantly associated with mortality (Table 3). Univariably, initiation outside the hospital clinic was associated with lower mortality (with reference to the hospital clinic, hazard ratio, HR: 0.49, 0.62 and 0.51 for urban, small rural and large rural clinics, respectively; $P < 0.01$), but significance was not maintained when we adjusted for time period. There were no statistically significant differences between people with missing values and the reference group for the respective variables (Table 3).

Of 2527 people recorded as active 12 months post-initiation, 758 (30.0%) had a viral load result recorded at 12 ± 2 months following ART initiation, and 174 of those 758 patients (23.0%; 95% CI: 19.5–25.5) had detectable viral loads (≥ 25 copies/ml). The propensity

Fig. 1. Cumulative number of patients initiating antiretroviral therapy between October 2004 and September 2008 in a decentralized HIV treatment programme in rural KwaZulu-Natal, South Africa



HIV, human immunodeficiency virus.

to be missing decreased from a median probability of 0.96 in the first half-year to 0.52 in the final half-year ($P < 0.001$). The hazard of having a detectable viral load was 2.8 (95% CI: 1.05–7.85) in the last three half-year periods compared to the three preceding periods. This increased risk lost statistical significance after we adjusted for the propensity score. We found no factors that were significantly associated with having a detectable viral load in the multivariable model.

Comparison of data

The proportion of patients who died was 11.3% in the unlinked group versus 10.3% in the linked group ($P = 0.347$). The proportion retained was 83.5% versus 84.8% ($P = 0.423$) in the unlinked and linked groups, respectively, and the proportion with a detectable viral load was 22.9% versus 23.0% ($P = 0.987$). Although the proportion of females in the unlinked group (66.4%) was slightly lower than in the linked group (71.1%) ($P < 0.001$), there were no significant differences in other baseline characteristics: CD4 cell count and proportion with CD4 cell count < 50 cells/ μl , blood creatinine, blood haemoglobin, weight and age.

Discussion

To meet targets of universal access to ART, efforts to scale up HIV treatment programmes in South Africa need to

be intensified. The treatment model described here, a decentralized programme with treatment delivered through the primary health-care system, has allowed rapid scale-up, with 5719 adult patients initiated on ART in a 4-year period. The rapid growth in rural clinics is encouraging and suggests that the availability of care at the local level reduces the common barriers (travel time and cost) to ART uptake. Success in scale-up may be partly attributed to growth in the programme's financial and human resources, which increased by about 20-fold in the first 4 years as a result of PEPFAR support. Notwithstanding all efforts to scale up financial and human resources, most of the programme emphasis has been on initiating patients onto treatment. Other aspects of HIV care, such as pre-ART monitoring and long-term adherence support, have received less emphasis so far, but these will become more important as programmes mature, and additional resources will be required to maintain delivery of high-quality care.

Sustaining such programmes requires significant inputs of human and financial resources, and it may not be feasible to maintain steep increases. However, at some point a steady-state will likely be reached, and resources can then be focused on sustaining the programme. Task-shifting and reducing the number of times patients attend clinics for drug collection may enhance programme sustainability.

Table 1. Baseline characteristics of 5719 patients initiated on antiretroviral therapy in a decentralized HIV treatment programme in rural KwaZulu-Natal, South Africa, over a 4-year period, 2004–2008, stratified by half-year

Characteristic	Total	Oct 04–Mar 05	Apr 05–Sep 05	Oct 05–Mar 06	Apr 06–Sep 06	Oct 06–Mar 07	Apr 07–Sep 07	Oct 07–Mar 08	Apr 08–Sep 08	Total	P
Total initiated on ART, no. (%)	5719	139 (2.4)	242 (4.2)	501 (8.8)	524 (9.2)	646 (11.3)	958 (16.8)	1253 (21.9)	1456 (25.5)	5719 (100)	0.001
Female sex, no. (%)	5719	94 (67.6)	169 (69.8)	345 (68.9)	355 (67.8)	432 (66.9)	642 (67.0)	848 (67.7)	998 (68.5)	3883 (67.9)	0.824
CD4 count (cells/ μ l), median (IQR)	5338	103 (48–155)	115 (61–177)	123 (60–170)	122 (63–178)	110 (45.5–172)	120 (54–177)	111.5 (54.5–168)	119 (60–175)	116 (53–173)	0.123
CD4 count (< 50 cells/ μ l), no. (%)	5338	26 (25.5)	41 (21.6)	88 (21.3)	91 (19.7)	161 (26.7)	214 (23.1)	274 (22.4)	275 (19.5)	1170 (21.9)	0.141
WHO stage 3 or 4 ^a , no. (%)	3056	83 (84.7)	115 (78.2)	204 (80.6)	184 (75.1)	307 (81.0)	477 (78.6)	576 (85.1)	584 (89.9)	2530 (82.8)	0.125
TB at initiation, no. (%)	5692	28 (20.1)	50 (20.7)	87 (17.4)	52 (9.9)	129 (20.0)	136 (14.2)	248 (19.9)	301 (20.9)	1031 (18.1)	0.855
Pregnant at initiation ^b , no. (%)	3554	0 (0)	2 (1.3)	3 (0.9)	9 (2.8)	1 (0.2)	31 (5.3)	50 (6.5)	88 (9.7)	184 (5.2)	<0.001
Linked data, no. (%)	2509 ^c	49 (84.5)	78 (68.4)	196 (84.1)	196 (81.7)	239 (72.2)	327 (72.3)	358 (66.8)	361 (66.2)	1804 (71.9)	0.001
Employed, no. (%)	1724	46 (95.8)	68 (87.2)	151 (80.3)	74 (39.8)	81 (35.8)	48 (15.3)	38 (11.2)	55 (15.9)	561 (32.5)	<0.001
Education, no. (%)	1408										
Secondary		20 (54.1)	41 (67.2)	80 (56.3)	89 (57.1)	117 (63.2)	140 (52.8)	156 (57.1)	186 (64.4)	829 (58.9)	0.221
Primary		14 (37.8)	13 (21.3)	43 (30.3)	48 (30.8)	48 (26.0)	90 (34.0)	74 (27.1)	70 (24.2)	400 (28.4)	0.075
None		3 (8.1)	7 (11.5)	19 (13.4)	19 (12.2)	20 (10.8)	35 (13.2)	43 (15.8)	33 (11.4)	179 (12.7)	0.545
Household members, no. (%)	1456										
1–5		13 (34.2)	20 (30.3)	59 (37.6)	36 (21.3)	51 (26.0)	70 (28.2)	75 (25.9)	101 (34.6)	425 (29.2)	0.963
6–10		15 (39.5)	24 (36.4)	47 (29.9)	68 (40.2)	83 (42.4)	111 (44.8)	114 (39.3)	92 (31.5)	554 (38.1)	0.324
> 10		10 (26.3)	22 (33.3)	51 (32.5)	65 (38.5)	62 (31.6)	67 (27.0)	101 (34.8)	99 (33.9)	477 (32.8)	0.350

ART, antiretroviral therapy; HIV, human immunodeficiency virus; TB, tuberculosis; WHO, World Health Organization.

^a Staging category at time of ART initiation in accordance with WHO staging criteria.²⁴

^b Expressed as a percentage of the total number of women of reproductive age (16–49 years of age) initiating in that half year.

^c Total number of people eligible for matching (on treatment and member of household within the demographic survey area).

Table 2. Outcomes from a 3-year cohort of 3010 patients at 12 months following initiation antiretroviral therapy in a decentralized HIV treatment programme in rural KwaZulu-Natal, South Africa, 2004–2007

Outcome	Oct 04–Mar 05		Apr 05–Sep 05		Oct 05–Mar 06		Apr 06–Sep 06		Oct 06–Mar 07		Apr 07–Sep 07		Total		P
	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	Total	95% CI	
On treatment	79.1	72.3–85.9	90.9	87.2–94.5	85.6	82.6–88.7	86.8	83.9–89.7	83.3	80.4–86.2	80.9	78.4–83.4	84.0	82.6–85.3	0.623
Death	19.4	12.8–26.0	7.9	4.5–11.3	10.4	7.7–13.1	8.0	5.7–10.3	11.5	9.0–13.9	12.0	9.9–14.1	10.9	9.8–12.0	0.015
Lost to follow-up	0.7	0–2.0	0.8	0–2.0	3.6	2.0–5.2	4.2	2.5–5.9	4.0	2.5–5.5	4.5	3.2–5.8	3.7	3.0–4.4	0.034
Transferred out	0.7	0–2.1	0.4	0–1.2	0.4	0–1.0	1.0	0.1–1.8	1.2	0.4–2.1	2.6	1.6–3.6	1.4	1.0–1.8	0.171
Detectable viral load	41.4	28.5–54.2	41.5	32.1–50.9	28.8	23.4–34.1	23.0	18.6–27.3	16.5	13.1–19.8	21.5	18.4–24.5	23.3	21.4–25.1	0.001

CI, confidence interval; HIV, human immunodeficiency virus.

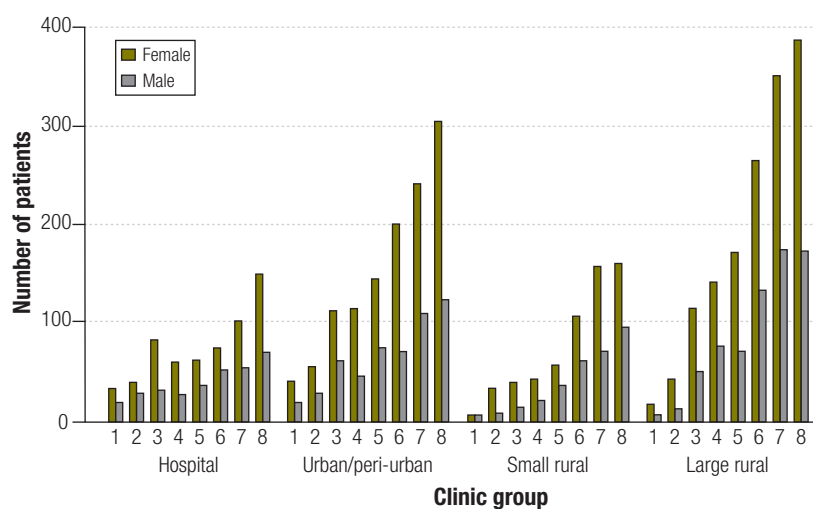
Further integration of primary health care systems and HIV treatment and care delivery services will also facilitate programme continuity.

The characteristics of individuals accessing ART through the programme have changed little over time. Unlike the situation in other programmes in South Africa that started before the national roll-out of ART⁵⁻⁷, the median baseline CD4 cell count of patients served by our programme has remained relatively high since inception in 2004, although it is similar to that reported for other programmes in sub-Saharan Africa in 2005–2006.¹⁸ A high proportion of patients continue to start treatment with very advanced disease: 1 in 3 male patients have CD4 cell counts of <50 cells/ μ l when they initiate ART. The higher proportion and younger age of females in the programme are consistent with local prevalence data and with other cohorts in South Africa.^{5-7,22} However, the difference in median baseline CD4 cell count between females and males (37 cells/ μ l) is even greater than the mean difference reported for other sub-Saharan Africa programmes participating in the Antiretroviral Therapy in Lower Income Countries (ART-LINC) Collaboration (22 cells/ μ l).¹⁸ The finding that male sex was also independently associated with mortality highlights the need for strategies to engage men in HIV care before the onset of advanced disease.

The overall mortality rate in our programme (12.6 deaths per 100 person-years) is high but still comparable to the rates found in other cohorts in southern Africa.^{8,29-32} Most deaths occur in the first 3 months after ART initiation, as seen in other cohorts, largely as a result of people presenting with late-stage disease, although our rate of 30.1 deaths per 100 person-years during the first 3 months of ART is much higher than reported elsewhere. The contribution of immune reconstitution inflammatory syndrome (IRIS) and/or the lack of routine physician follow-up to this early mortality cannot be ascertained from our data. Linkage with our demographic surveillance data has revealed that lack of education is significantly associated with death among patients on ART. This relationship has been described elsewhere and may indicate a group that requires enhanced support both before and after initiating ART.³³

We show relatively low rates of loss to follow-up. This is likely explained in part

Fig. 2. Number of patients initiated on antiretroviral therapy from October 2004 to September 2008 in a decentralized HIV treatment programme in rural KwaZulu-Natal, South Africa, by sex and clinic group



HIV, human immunodeficiency virus.

by the active tracking system within the programme, which includes phone contact by clinic staff, followed, if necessary, by a home visit from a tracker nurse. Our figures for mortality and loss to follow-up might thus reflect the true situation better than those from other programmes in which patients are not actively tracked and where up to half of those lost to follow-up may have died.^{34,35} It is possible that the decentralized model, with treatment provided closer to patients' homes, also contributes to this low rate of loss to follow-up. It is encouraging that there is no sign of a consistent increase in loss to follow-up rates despite the rapid scale-up of the programme.

One troubling aspect of our data is the relatively high rate of detectable viral load among patients on ART. There were many missing results, which is likely to be related to several factors: samples not taken at appropriate time points, results not returned from the provincial reference laboratory and faults in data capture. However, by using propensity score reweighting, we have shown that almost 1 in 4 people on ART had a detectable viral load at around 12 months. We used a strict cut-off (<25 copies/ml), as we believe that this will alert us to deficiencies within the programme, although this approach makes comparison with other programmes using different criteria difficult. Primary drug resistance should not be a significant factor in lack of virological suppression, as levels of primary resistance were low in our setting at the time of the analysis.³⁶ There have been no significant stock-outs of ART in our programme, and the high rate of unsuppressed

viral load may therefore suggest suboptimal adherence. We are researching this question in more detail and are learning how to translate successful models of adherence support from neighbouring programmes.³⁷

The similarity between the unlinked and linked groups is as expected, given that most of the lack of linkage in those eligible arose as a result of typographical errors in entering identity numbers into patient records, failure to match the identity number to other personal identifiers, or the fact that patients presented at clinics without identity documents. Since these occurrences probably occurred at similar rates in all groups, we do not believe they influenced outcomes or their associated factors.

Our study had certain limitations. Data collected from routine programme evaluation are limited by operational constraints that might not hamper formal research cohorts. Our description of scale-up and outcomes is limited by a lack of information on individuals enrolled in the programme but not initiated on ART. Data from other programmes suggest that mortality is extremely high in the period after enrolment but before initiation of ART.^{29,30} It would be extremely useful to evaluate whether our decentralized model based on primary health care improves access to treatment and reduces pre-initiation mortality but increases early post-initiation mortality. By exploring outcomes at 12 months only we may have missed trends in longer-term outcomes, particularly retention and viral suppression.

Table 3. Risk factors for death within 12 months in patients initiated on antiretroviral therapy from October 2004 to September 2007 in a decentralized HIV treatment programme in rural KwaZulu-Natal, South Africa

Variable	HR	95% CI	AHR	95% CI
Sex				
Male	1.62	1.49–1.77	1.33	1.06–1.67
Weight^a				
1-kg increase	0.95	0.94–0.96	0.96	0.94–0.99
CD4 count (cells/μl)				
>200	1			
150–200	0.74	0.44–1.24	0.70	0.42–1.16
100–149	1.02	0.63–1.67	0.84	0.52–1.36
50–99	1.82	1.16–2.86	1.42	0.91–2.21
<50	3.17	2.08–4.84	2.02	1.33–3.08
Missing	1.20	0.69–2.06	0.92	0.53–1.60
WHO clinical stage^b				
1 or 2	1			
3 or 4	3.25	1.98–5.34	2.13	1.29–3.51
Missing	1.68	1.01–2.82	1.44	0.86–2.42
Haemoglobin (g/dL)				
≥8	1			
<8	4.10	3.12–5.37	2.72	2.03–3.63
Missing	1.31	0.96–1.77	1.04	0.67–1.59
Creatinine (μmol/L)				
≤120	1			
121–240	2.72	1.86–3.98	1.66	1.13–2.44
>240	9.24	4.74–17.99	2.88	1.42–5.81
Missing	1.27	0.93–1.73	1.28	0.84–1.97
Education				
Secondary	1			
Primary	1.36	0.84–2.20	1.14	0.71–1.86
None	1.74	1.05–2.87	1.81	1.10–2.99
Missing	0.78	0.35–1.75	0.63	0.28–1.50
Not matched	1.39	0.99–1.94	1.30	0.93–1.83
Half-year of initiation				
Oct 04–Mar 05	1			
Apr 05–Sep 05	0.40	0.22–0.72	0.39	0.21–0.70
Oct 05–Mar 06	0.56	0.35–0.88	0.53	0.33–0.84
Apr 06–Sep 06	0.40	0.25–0.65	0.46	0.28–0.75
Oct 06–Mar 07	0.57	0.37–0.90	0.53	0.34–0.83
Apr 07–Sep 07	0.61	0.40–0.93	0.61	0.40–0.95

AHR, adjusted hazards ratio; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazards ratio.

^a Weight assessed as a time-varying covariate.

^b Staging category at time of ART initiation in accordance with WHO staging criteria.²⁴

In summary, we have shown that rapid scale-up of ART delivery through a decentralized primary health care programme is feasible and produces outcomes comparable to those reported elsewhere in southern Africa. The relatively high rates of detectable viral load in patients on ART are troubling, and further scale-up poses significant challenges and will require considerable commitment if we are to reach the goal of universal access. ■

Acknowledgements

We would like to thank Colin Newell for development of and assistance with the database, Samukelisiwe Dube for assistance with data-cleaning, the monitoring and evaluation team at the Africa Centre for data collection, and the Department of Health. We would particularly like to thank all the clinic staff whose dedicated work in the face of so many challenges is an inspiration to us all.

Funding: The HIV treatment and care programme has received generous support from the United States Agency for International Development (USAID) and the President's Emergency Plan for AIDS Relief (PEPFAR) under the terms of award no. 674-A-00-08-0001-00. The opinions expressed herein are those of the authors and do not necessarily reflect the views of USAID or the United States Government. Tom Heller and Till Bärnighausen are supported by the Centre for International Migration and Development, Gesellschaft für Technische Zusammenarbeit (GTZ), Federal Ministry of Economic Cooperation and Development, Germany. The Africa Centre is supported by a core grant from the Wellcome Trust.

Competing interests: None declared.

الملخص

برنامج الارتقاء بالمعالجة اللامركزية للمصابين بفيروس الإيدز في ريف كوازولو ناتال، في جنوب أفريقيا: هل يؤثر التوسع السريع على نتائج المرضى؟

المرضى الذين استهلوا هذه المعالجة في قاعدة البيانات الخاصة بالبرنامج، وكان يجري تحديثها شهرياً بالأوضاع الملاحظة الناجمة عن المتابعة. وقد أدخل في قاعدة البيانات هذه جميع المرضى البالغين (16 عاماً) الذين بدأوا المعالجة في ما بين تشرين الأول/أكتوبر 2004 و أيلول/سبتمبر 2008، وتم ترتيبهم إلى مجموعات تخضع للدراسة لمدة ستة أشهر. وأجريت مقارنات للسمات السريرية والاجتماعية والسكانية بين هذه المجموعات، كما تم تقييم استبقاء

الغرض وُصف برنامج الارتقاء بالمعالجة اللامركزية للمصابين بفيروس الإيدز والذي يُقدم من خلال نظام الرعاية الصحية الأولية في المناطق الريفية من كوازولو ناتال بجنوب أفريقيا، وتقييم اتجاهات الصفات القاعدية والنتائج في الجمهرة السكانية التي خضعت للدراسة. الطرق بدأ البرنامج في تقديم المعالجة بمضادات الفيروسات القهقرية في تشرين الأول/أكتوبر من عام 2004. وقد أدخلت كافة المعلومات الخاصة بجميع

وغاب 3.7% عن المتابعة (فاصلة الثقة 95%: 3.0-4.4). وكانت الوفيات أكثر خلال الثلاثة أشهر الأولى التي تلت بدء المعالجة بمضادات الفيروسات القهقرية: 30.1 وفاة لكل مئة مريض في العام الواحد (فاصلة الثقة 95%: 26.3-34.5). وفي الشهر الثاني عشر اكتشفت نسبة بلغت 23.0% من العبء الفيروسي (أكثر من 25 نسخة لكل مليلتر) (فاصلة الثقة 95%: 19.5-25.5). الاستنتاج لم تتأثر النتائج بالتوسع السريع لهذا البرنامج الهادف إلى لامركزية معالجة فيروس الإيدز، أما المعدلات العالية نسبياً المكتشفة من العبء الفيروسي فأوضحت الحاجة إلى بذل المزيد من الجهود لتحسين جودة الخدمات.

الحالات في الرعاية، والوفيات، وغيابهم عن المتابعة، والنتائج الفيروسية وذلك بعد مرور 12 شهراً من بدء المعالجة بمضادات الفيروسات القهقرية. **الموجودات** اشتملت الدراسة على عدد إجمالي بلغ 5719 بالغاً بدأوا المعالجة بمضادات الفيروسات القهقرية (67.9% منهم كن إنثاءً). وكان الخط القاعدي الوسطي لتعداد الخلايا للمفاوية CD4+ هو 116 خلية لكل مكروتر (وكان المدى بين الشريحتين الربيعيتين: 53 - 173). وكانت هناك زيادة في نسبة النساء اللاتي بدأن المعالجة بمضادات الفيروسات القهقرية وكن حوامل، ولم تطرأ أية تغيرات على الصفات القاعدية الأخرى مع مرور الوقت. وكانت نسبة الاستبقاء تحت الرعاية لمدة 12 شهراً، 84.0% (فاصلة ثقة 95%: 82.6-85.3)؛ مع نسبة وفيات بلغت 10.9% (فاصلة الثقة 95%: 9.8-12.0).

Résumé

Mise en place élargie d'un programme décentralisé de traitement du VIH dans le KwaZulu-Natal rural, Afrique du Sud : une expansion rapide affecte-elle les résultats des patients?

Objectif Décrire le passage à l'échelle supérieure d'un programme décentralisé de traitement du VIH délivré au travers du système de soins de santé primaires au KwaZulu-Natal rural, Afrique du Sud, et évaluer les tendances des caractéristiques de ligne de base et les résultats sur la population étudiée.

Méthodes Le programme a commencé la distribution d'une thérapie antirétrovirale (TAR) en octobre 2004. Les informations concernant l'ensemble des patients entamant un traitement TAR ont été recueillies dans une base de données informatisée et le suivi de leur état a été actualisé chaque mois. Tous les patients adultes (≥ 16 ans) ayant commencé la TAR entre octobre 2004 et septembre 2008 ont été inclus et stratifiés en groupes de 6 mois. Les caractéristiques cliniques et sociodémographiques ont été comparées entre les groupes. Les taux de rétention sous traitement et de mortalité, ainsi que les nombres de perdus pour le suivi et les résultats virologiques ont été évalués 12 mois après le début de la TAR.

Résultats Au total 5 719 patients ayant initié un traitement TAR ont été inclus (67,9 % de femmes). Le nombre moyen de lymphocytes CD4+ à la ligne de base était de 116 cellules/ μ L (intervalle interquartile, IQR: 53-173). Une augmentation de la proportion de femmes ayant entamé un traitement TAR alors qu'elles étaient enceintes a été notée, mais aucun changement n'a été observé dans le temps pour les autres caractéristiques à la ligne de base. Le taux global de rétention sous traitement à 12 mois était de 84,0 % (intervalle de confiance à 95 %, IC: 82,6-85,3); 10,9 % sont décédés (IC à 95 %: 9,8-12,0); 3,7 % ont été perdus pour le suivi (IC à 95 %: 3,0-4,4). La mortalité a été plus élevée durant les 3 premiers mois qui ont suivi le début de TAR : 30,1 décès pour 100 personnes-ans (IC à 95 %: 26,3-34,5). À 12 mois, 23,0 % présentaient une charge virale détectable (> 25 copies/ml) (IC à 95 %: 19,5-25,5).

Conclusion Les résultats n'ont pas été affectés par la rapide expansion de ce programme de traitement du VIH décentralisé. Les taux relativement élevés de charge virale détectable mettent en évidence la nécessité de futurs efforts à mettre en place pour améliorer la qualité des services.

Resumen

Ampliación de un programa descentralizado de tratamiento del VIH en zonas rurales de KwaZulu-Natal, Sudáfrica: ¿afecta su rápida expansión a los resultados de pacientes?

Objetivos Describir la ampliación de un programa descentralizado de tratamiento del VIH a través del sistema sanitario de atención primaria en zonas rurales de KwaZulu-Natal, Sudáfrica, y evaluar las tendencias de las características iniciales y los resultados de la población en estudio.

Métodos El programa comenzó con la administración de un tratamiento antirretroviral (ARV) en octubre de 2004. La información de todos los pacientes que comenzaron el tratamiento ARV se recopiló en la base de datos del programa y el seguimiento se actualizó mensualmente. Todos los pacientes adultos (≥ 16 años) que iniciaron el tratamiento ARV entre octubre de 2004 y septiembre de 2008 se incluyeron y estratificaron en grupos de seis meses. Se compararon las características clínicas y sociodemográficas intergrupales. A los 12 meses del inicio del tratamiento ARV se evaluó la continuidad asistencial, la pérdida para el seguimiento y los resultados virológicos.

Resultados Se incluyó a un total de 5719 adultos que habían iniciado el tratamiento ARV, de los que el 67,9% eran mujeres. El recuento medio

inicial de linfocitos CD4 fue de 116 células/ μ l (amplitud intercuartil, AIC: 53 - 173). El porcentaje de mujeres que iniciaron el tratamiento ARV durante el embarazo aumentó, si bien no se produjo ningún cambio en otras características iniciales a lo largo del tiempo. La continuidad asistencial general a los 12 meses fue del 84,0% (intervalo de confianza del 95%, CI: 82; 6 - 85,3); el 10,9% falleció (CI del 95%: 9; 8 - 12,0); el 3,7% se perdió para el seguimiento (CI del 95%: 3,0 - 4,4). La mortalidad fue más elevada en los primeros tres meses posteriores al inicio del tratamiento ARV: 30,1 fallecimientos por cada 100 años-personas (CI del 95%: 26,3 - 34,5). El 23,0% tenía una carga viral detectable a los 12 meses (> 25 réplicas/ml) (CI del 95%: 19,5 - 25,5).

Conclusión Los resultados no se vieron afectados por la rápida expansión de este programa descentralizado de tratamiento del VIH. Los índices relativamente altos de la carga vírica detectable ponen en evidencia la necesidad de dedicar un mayor esfuerzo en la mejora de la calidad de los servicios.

References

1. Report on the global HIV/AIDS epidemic 2008. Geneva: Joint United Nations Programme on HIV/AIDS; 2008.
2. Towards universal access: scaling up priority HIV/AIDS interventions in the health sector. Geneva: World Health Organization; 2008.
3. HIV & AIDS and STI national strategic plan 2007–2011. Pretoria: South African Department of Health; 2007.
4. Walensky RP, Wood R, Weinstein MC, Martinson NA, Losina E, Fofana MO et al. Scaling up antiretroviral therapy in South Africa: the impact of speed on survival. *J Infect Dis* 2008;197:1324–32. doi:10.1086/587184 PMID:18422445
5. Keiser O, Orrell C, Egger M, Wood R, Brinkhof MW, Furrer H et al. Public-health and individual approaches to antiretroviral therapy: township South Africa and Switzerland compared. *PLoS Med* 2008;5:e148. doi:10.1371/journal.pmed.0050148 PMID:18613745
6. Bekker LG, Myer L, Orrell C, Lawn S, Wood R. Rapid scale-up of a community-based HIV treatment service: programme performance over 3 consecutive years in Guguletu, South Africa. *S Afr Med J* 2006;96:315–20. PMID:16670804
7. Coetzee D, Hildebrand K, Boule A, Maartens G, Louis F, Labatala V et al. Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa. *AIDS* 2004;18:887–95. doi:10.1097/00002030-200404090-00006 PMID:15060436
8. Boule A, Bock P, Osler M, Cohen K, Channing L, Hilderbrand K et al. Antiretroviral therapy and early mortality in South Africa. *Bull World Health Organ* 2008;86:678–87. doi:10.2471/BLT.07.045294 PMID:18797643
9. Fairall LR, Bachmann MO, Louqagie GM, van Vuuren C, Chikobvu P, Steyn D et al. Effectiveness of antiretroviral treatment in a South African program: a cohort study. *Arch Intern Med* 2008;168:86–93. doi:10.1001/archinternmed.2007.10 PMID:18195200
10. Stringer JSA, Zulu I, Levy J, Stringer EM, Mwango A, Chi BH et al. Rapid scale-up of antiretroviral therapy at primary care sites in Zambia. Feasibility and early outcomes. *JAMA* 2006;296:782–93. doi:10.1001/jama.296.7.782 PMID:16905784
11. Bussmann H, Wester CW, Ndwapi N, Grundmann N, Gaolathe T, Puvimanasinghe J et al. Five-year outcomes of initial patients treated in Botswana's national antiretroviral treatment program. *AIDS* 2008;22:2303–11. doi:10.1097/QAD.0b013e3283129db0 PMID:18981769
12. Lowrance DW, Makombe S, Harries AD, Shiraishi RW, Hochgesang M, Aberle-Grasse J et al. A public health approach to rapid scale-up of antiretroviral treatment in Malawi during 2004–2006. *J Acquir Immune Defic Syndr* 2008;49:287–93. doi:10.1097/QAI.0b013e3181893ef0 PMID:18845953
13. Wilson DP, Blower S. How far will we need to go to reach HIV-infected people in rural South Africa? *BMC Med* 2007;5:16. doi:10.1186/1741-7015-5-16 PMID:17577418
14. Gilks CF, Crowley S, Ekpini R, Gove S, Perriens J, Souteyrand Y et al. The WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings. *Lancet* 2006;368:505–10. doi:10.1016/S0140-6736(06)69158-7 PMID:16890837
15. Bedelu M, Ford N, Hilderbrand K, Reuter H. Implementing antiretroviral therapy in rural communities: the Lusikisiki model of decentralized HIV/AIDS care. *J Infect Dis* 2007;196(Suppl 3):S464–8. doi:10.1086/521114 PMID:18181695
16. Fredlund VG, Nash J. How far should they walk? Increasing antiretroviral therapy access in a rural community in northern KwaZulu-Natal, South Africa. *J Infect Dis* 2007;196(Suppl 3):S469–73. doi:10.1086/521115 PMID:18181696
17. Boule A, Ford N. Scaling up antiretroviral therapy in developing countries: what are the benefits and challenges? *Postgrad Med J* 2008;84:225–7. doi:10.1136/sti.2007.027748 PMID:18508978
18. Keiser O, Anastos K, Schechter M, Balestre E, Myer L, Boule A et al. Antiretroviral therapy in resource-limited settings 1996 to 2006: patient characteristics, treatment regimens and monitoring in sub-Saharan Africa, Asia and Latin America. *Trop Med Int Health* 2008;13:870–9. PMID:18373510
19. Calmy A, Ford N, Hirschel B, Reynolds SJ, Lynen L, Goemaere E et al. HIV viral load monitoring in resource-limited regions: optional or necessary? *Clin Infect Dis* 2007;44:128–34. doi:10.1086/510073 PMID:17143828
20. Operational plan for comprehensive HIV and AIDS care, management and treatment for South Africa. Pretoria: South African Department of Health; 2003.
21. Tanser F. Methodology for optimising location of new primary health care facilities in rural communities: a case study in KwaZulu-Natal, South Africa. *J Epidemiol Community Health* 2006;60:846–50. doi:10.1136/jech.2005.043265 PMID:16973529
22. Welz T, Hosegood V, Jaffar S, Bätzing-Feigenbaum J, Herbst K, Newell ML. Continued very high prevalence of HIV infection in rural KwaZulu-Natal, South Africa: a population-based longitudinal study. *AIDS* 2007;21:1467–72. doi:10.1097/QAD.0b013e3280ef6af2 PMID:17589193
23. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach, 2006 revision. Geneva: World Health Organization; 2006.
24. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. Geneva: World Health Organization; 2007.
25. National antiretroviral treatment guidelines. Pretoria: South African Department of Health; 2004.
26. Tanser F, Hosegood V, Barnighausen T, Herbst K, Nyirenda M, Muhwava W et al. Cohort profile: Africa Centre Demographic Information System (ACDIS) and population-based HIV survey. *Int J Epidemiol* 2008;37:956–62. doi:10.1093/ije/dym211 PMID:17998242
27. Baker SG, Fitzmaurice GM, Freedman LS, Kramer BS. Simple adjustments for randomized trials with nonrandomly missing or censored outcomes arising from informative covariates. *Biostatistics* 2006;7:29–40. doi:10.1093/biostatistics/kxi038 PMID:15923407
28. Moss RR, Humphries KH, Gao M, Thompson CR, Abel JG, Fradet G et al. Outcome of mitral valve repair or replacement: a comparison by propensity score analysis. *Circulation* 2003;108(Suppl 1):II-90–7. PMID:12970215 doi:10.1161/01.cir.0000089182.44963.bb
29. Lawn SD, Myer L, Orrell C, Bekker LG, Wood R. Early mortality among adults accessing a community-based antiretroviral service in South Africa: implications for programme design. *AIDS* 2005;19:2141–8. doi:10.1097/01.aids.0000194802.89540.e1 PMID:16284464
30. Lawn SD, Myer L, Harling G, Orrell C, Bekker LG, Wood R. Determinants of mortality and nondeath losses from an antiretroviral treatment service in South Africa: implications for program evaluation. *AIDS* 2006;43:770–6. PMID: 16912954doi:10.1086/507095.
31. Braitstein P, Brinkhof MWG, Dabis F, Schechter M, Boule A, Miotti P et al. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. *Lancet* 2006;367:817–24. doi:10.1016/S0140-6736(06)68337-2 PMID:16530575
32. Lawn SD, Harries AD, Anglaret X, Myer L, Wood R. Early mortality among adults accessing antiretroviral treatment programmes in sub-Saharan Africa. *AIDS* 2008;22:1897–908. doi:10.1097/QAD.0b013e32830007cd PMID:18784453
33. Aabaasa AM, Todd J, Ekoru K, Kalyango JN, Levin J, Odeke E et al. Good adherence to HAART and improved survival in a community HIV/AIDS treatment and care programme: the experience of The AIDS Support Organization (TASO), Kampala, Uganda. *BMC Health Serv Res* 2008;8:241. doi:10.1186/1472-6963-8-241 PMID:19021908
34. Dalal RP, MacPhail C, Mqhayi M, Wing J, Feldman C, Chersich MF et al. Characteristics and outcomes of adult patients lost to follow-up at an antiretroviral treatment clinic in Johannesburg, South Africa. *J Acquir Immune Defic Syndr* 2008;47:101–7. doi:10.1097/QAI.0b013e31815b833a PMID:17971708
35. Yu JK, Chen SC, Wang KY, Chang CS, Makombe SD, Schouten EJ et al. True outcomes for patients on antiretroviral therapy who are "lost to follow-up" in Malawi. *Bull World Health Organ* 2007;85:550–4. doi:10.2471/BLT.06.037739 PMID:17768504
36. Hamers RL, Derdelinckx I, van Vugt M, Stevens W, Rinke de With TF, Schuurman R. The status of HIV-1 resistance to antiretroviral drugs in sub-Saharan Africa. *Antivir Ther* 2008;13:625–39. PMID:18771046
37. Orrell C, Harling G, Lawn SD, Kaplan R, McNally M, Bekker LG et al. Conservation of first-line antiretroviral treatment regimen where therapeutic options are limited. *Antivir Ther* 2007;12:83–8. PMID:17503751