Antiretroviral therapy and early mortality in South Africa

Andrew Boulle, a Peter Bock, b Meg Osler, c Karen Cohen, d Liezl Channing, e Katherine Hilderbrand, f Eula Mothibi, g Virginia Zweigenthal, h Neviline Slingers, i Keith Cloete j & Fareed Abdullah k

Objective To describe province-wide outcomes and temporal trends of the Western Cape Province antiretroviral treatment (ART) programme 5 years since inception, and to demonstrate the utility of the WHO monitoring system for ART.

Methods The treatment programme started in 2001 through innovator sites. Rapid scaling-up of ART provision began early in 2004, located predominantly in primary-care facilities. Data on patients starting ART were prospectively captured into facility-based registers, from which monthly cross-sectional activity and quarterly cohort reports were aggregated. Retention in care, mortality, loss to follow-up and laboratory outcomes were calculated at 6-monthly durations on ART.

Findings By the end of March 2006, 16 234 patients were in care. The cohort analysis included 12 587 adults and 1709 children. Women accounted for 70% of adults enrolled. After 4 and 3 years on ART respectively, 72.0% of adults (95% confidence interval, CI: 68.0–75.6) and 81.5% (95% CI: 75.7–86.1) of children remained in care. The percentage of adults starting ART with CD4 counts less than 50 cells/µl fell from 51.3% in 2001 to 21.5% in 2005, while mortality at 6 months fell from 12.7% to 6.6%, offset in part by an increase in loss to follow-up (reaching 4.7% at 6 months in 2005). Over 85% of adults tested had viral loads below 400 copies/ml at 6-monthly durations until 4 years on ART.

Conclusion The location of care in primary-care sites in this programme was associated with good retention in care, while the scaling-up of ART provision was associated with reduced early mortality.

Introduction

The national antiretroviral treatment (ART) programme in South Africa was launched in April 2004.1 However, for some years prior to this, demonstration projects had provided ART to HIV-infected individuals with advanced disease through government health services. Several projects were located in the Western Cape Province which, as a result, is able to report on outcomes up to 4 years after initiation of therapy. The first such project began providing ART in Khayelitsha in May 2001,2,3 followed by a project in Gugulethu in September 2002.4–6

Since inception, the clinical guidelines and approaches to monitoring used in the Western Cape Province have been in line with those recommended by WHO.7–9 The treatment setting is reflective of public sector health services in South Africa. A description of outcomes 5 years into this provincial programme, and after significant scaling-up of care, has relevance to what can be anticipated in South Africa and other similar settings in the region.

This paper demonstrates that robust and useful information can be generated using a basics-first, paper-based monitoring system, as recommended by WHO.10 There are some sites in the province that collect clinical data electronically and enhance these data for cohort surveillance and research. These are designated as sentinel sites and address particular clinical and epidemiological questions. This takes pressure off the remaining sites from having to institute complex monitoring systems and ensures that in the majority of sites only the information essential for management and programme assessment is collected.

The aim of this paper is to describe the key clinical outcomes in the Western Cape provincial ART programme, in patients on therapy for up to 4 years, and the evolution of the programme over a 5-year period. Secondary aims are to demonstrate the field utility of the WHO monitoring guidelines and the feasibility of scaling-up services through primary-care sites.

Programme description

The first project to routinely offer ART in the public sector and on a district-wide basis in South Africa was started in 2001 as a partnership between the provincial government and Médecins Sans Frontières in the Cape Town township of Khayelitsha. At that time, several local clinicians had already been involved in ART provision through clinical studies and private funding and
were able to support this and subsequent initiatives. These early sites can be considered as “innovator sites” in as far as they were able to grapple with many of the logistics of setting up services in anticipation of a more rapid scaling-up of ART services. By the time the national programme was launched in South Africa in April 2004, there were 16 discrete sites offering ART in the province, eight of which were in primary care. At this time there were 2327 patients receiving ART. By the end of March 2006, there were 16 234 patients receiving ART (87% adults) across 43 sites, the majority being treated in primary-care settings (67% in clinics and community health centres, and 13% in district hospitals). Enrolment increased steadily over this time to reach 1000 patients per month, with seasonal decreases in enrolment each December (Fig. 1 and Fig. 2). Care was first offered as part of the primary-care HIV intervention for children in 2002, with follow-up for children in this analysis extending to 3 years. Children were defined as patients starting ART under the age of 14 years.

Patients were considered eligible for ART if they had a stage IV illness (excluding extrapulmonary tuberculosis) or a CD4 count less than 200 cells/µl. The adult regimens used throughout comprised two nucleotide reverse transcriptase inhibitors (NRTIs) and one non-nucleotide reverse transcriptase inhibitor (NNRTI). Initially, the NRTI backbone in Khayelitsha comprised zidovudine and lamivudine, but was later changed to stavudine and lamivudine in line with the national programme. Paediatric regimens varied, with NNRTIs and protease inhibitors...
being variously used with the NRTI backbone.

Six-monthly CD4 counts and viral-load testing were provided in the programme, together with safety monitoring according to the specific regimens. The protocol for changing to second-line therapy was two consecutive viral loads above 5000 copies/ml. All laboratory tests were conducted by the National Health Laboratory Services. CD4 counts were performed using the panLeucogating method. Viral loads were conducted using the NucliSens HIV-1 QT® assay, and later NucliSens EasyQ® HIV-1 assay (bioMérieux, Boxtel, the Netherlands) for which the upper limit of detection is just under 400 copies/ml, hence the use of 400 copies/ml as the definition of suppression in all registers and analyses.

Data collection and analysis

The routine monitoring system

Data analysed were collected through the routine monitoring system. This system is one component of a framework for the monitoring of the ART programme in the province (Fig. 3). Other components include observational cohort studies in sentinel sites, special studies to address priority clinical research questions, and a passive-stimulated pharmacovigilance reporting system.

Patients are entered into a register in the order in which they start ART. Monthly reporting is universal across the sites and comprises cross-sectional patient and enrolment totals (Fig. 1 and 2), the essential information required by managers to keep track of resource allocation and progress against targets. Quarterly cohort reports are also universal and are provided a quarter in arrears to allow sites to complete the ascertainment of outcomes before reporting. These reports are aggregated by starting quarter, as well as by 6-monthly durations on ART, allowing for cohort outcomes to be reported. The metrics reported on quarterly include regimen (first- or second-line), CD4 count, viral load and outcome (i.e. in care, transferred out, lost to follow-up, died).

When aggregating from the registers, the measure of advanced immune suppression at baseline is determined by the proportion of adults with a baseline CD4 cell count of less than 50 cells/µl and in children a CD4 percentage of less than 15% of total lymphocytes. Immunological response during follow-up is determined by the proportion of patients tested with CD4 cell counts above 200 cells/µl or greater (20% in children) and virological response by the proportion of patients tested with viral loads below 400 copies/ml. All cohort analyses are limited to treatment-naive patients.

Data analysis

The monthly data are presented as cross-sectional monthly totals, whilst the quarterly data are presented as combined annual enrolment cohorts followed up until study closure. The monthly data cover April 2004 to March 2006, whilst the cohort data include patients enrolled between May 2001 and December 2005, followed until March 2006. Owing to the aggregate nature of the data, all data are presented as proportions with 95% binomial confidence intervals. The definition of “remaining in care” is patients who had had at least one visit in the preceding 90 days. Correspondingly, the definition of “loss to follow-up” is patients who had not had a contact with the health services for 90 days or more. The small number of patients who transferred their care to other sites are excluded in both the numerator and the denominator in the calculation of the proportions remaining in care, died and lost to follow-up. These measures
Antiretroviral therapy and early mortality

Andrew Boulle et al.

Fig. 4. Estimates of retention in care for treatment-naive adults

<table>
<thead>
<tr>
<th>Duration on ART (months)</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>42</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total adults starting ART</td>
<td>12 587</td>
<td>8 341</td>
<td>4 726</td>
<td>2 167</td>
<td>852</td>
<td>561</td>
<td>328</td>
<td>189</td>
<td>80</td>
</tr>
<tr>
<td>Deaths since start a,b</td>
<td>545 (6.7)</td>
<td>397 (8.8)</td>
<td>239 (11.6)</td>
<td>131 (15.8)</td>
<td>96 (17.6)</td>
<td>60 (18.9)</td>
<td>36 (19.7)</td>
<td>18 (23.1)</td>
<td></td>
</tr>
<tr>
<td>Lost to follow-up since start a,b</td>
<td>340 (4.2)</td>
<td>286 (6.3)</td>
<td>148 (7.2)</td>
<td>27 (3.3)</td>
<td>18 (3.3)</td>
<td>13 (4.1)</td>
<td>5 (2.7)</td>
<td>1 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Transfers out since start a,b</td>
<td>223 (2.7)</td>
<td>214 (4.5)</td>
<td>98 (4.5)</td>
<td>23 (2.7)</td>
<td>16 (2.9)</td>
<td>10 (3.0)</td>
<td>6 (3.2)</td>
<td>2 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Remaining in care – absolute a,b</td>
<td>89.1 (88.4–90.8)</td>
<td>84.9 (83.8–85.9)</td>
<td>81.3 (79.5–83.0)</td>
<td>80.9 (78.1–83.6)</td>
<td>79.1 (75.4–82.4)</td>
<td>77.0 (72.0–81.6)</td>
<td>77.6 (70.9–83.4)</td>
<td>75.6 (64.6–84.7)</td>
<td></td>
</tr>
<tr>
<td>Remaining in care – cumulative a,b</td>
<td>89.5 (88.9–90.1)</td>
<td>85.3 (84.5–86.1)</td>
<td>82.1 (80.9–83.1)</td>
<td>80.0 (78.5–81.4)</td>
<td>77.8 (75.9–79.6)</td>
<td>74.8 (72.1–77.2)</td>
<td>73.2 (70.0–76.1)</td>
<td>72.0 (68.0–75.6)</td>
<td></td>
</tr>
</tbody>
</table>

ART, antiretroviral therapy.

a Deaths since start = deaths / (total - transfers out).

b Values in parentheses are percentages.

c Lost to follow-up since start = losses to follow-up / (total - transfers out).

d Transfers out since start = transfers out / total.

e Remaining in care – absolute = (total - losses to follow-up - deaths - transfers out) / (total - transfers out).

f Values in parentheses are exact binomial confidence intervals.

g Weighted Kaplan–Meier estimate.
h Values in parentheses are Greenwood point-wise confidence intervals.

are limited to those patients followed up for at least the full duration under analysis. In addition, the proportion of patients remaining in care is further described as Kaplan–Meier estimates based on weighted survival data derived from the count data. All analyses were performed using Stata statistical software version 9.0 (StataCorp. LP, College Station, TX, United States of America).

Results

Overall, 12 587 adults and 1709 children were included in this cohort report, totalling 14 296 treatment-naive patients. This is a near-complete representation of all public-sector patients started on ART in the Western Cape Province by the end of 2005. Follow-up for the oldest quarterly cohorts extends to 4 years on treatment. A further 2.4% of patients were treatment experienced before starting ART, and were not included in this analysis.

The percentage of men starting ART has remained around 30% over the 5 years of enrolment in the province, with a very slight increase over time. The gender breakdown of children is not routinely recorded but reviews of paediatric sentinel site data reveal that the gender breakdown of children starting ART is roughly even. Overall, 22.7% of adults began ART with a CD4 count below 50 cells/µl while 45% of children started ART with a CD4 count below 15% of total lymphocytes.

After 4 years on ART, 76% of adults remained in care (Fig. 4 and Table 1). For each duration on ART, this absolute estimate was based only on the data for those patients who started that number of months previously. Using the weighted survival data, the Kaplan–Meier estimate of retention in care was 72.0% at 4 years on ART with a narrower confidence interval (95% confidence interval, CI: 68.0–75.6). A similar analysis of paediatric outcomes (Fig. 5 and Table 2) revealed 81.5% (95% CI: 75.7–86.1) of
Table 2. Estimates of retention in care for treatment-naive children

<table>
<thead>
<tr>
<th>Duration on ART (months)</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total children starting ART</td>
<td>1709</td>
<td>1216</td>
<td>770</td>
<td>371</td>
<td>72</td>
<td>51</td>
<td>35</td>
</tr>
<tr>
<td>Deaths since start</td>
<td>84 (7.4)</td>
<td>68 (9.8)</td>
<td>32 (9.3)</td>
<td>4 (5.7)</td>
<td>4 (8.2)</td>
<td>4 (11.8)</td>
<td></td>
</tr>
<tr>
<td>Lost to follow-up since start</td>
<td>22 (1.9)</td>
<td>23 (3.3)</td>
<td>19 (5.5)</td>
<td>4 (6.7)</td>
<td>3 (6.1)</td>
<td>2 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Transfers out since start</td>
<td>84 (6.9)</td>
<td>77 (10.0)</td>
<td>27 (7.3)</td>
<td>2 (2.8)</td>
<td>2 (3.9)</td>
<td>1 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Remaining in care – absolute</td>
<td>90.6 (88.8–92.3)</td>
<td>86.9 (84.1–89.3)</td>
<td>85.2 (81.0–88.8)</td>
<td>88.6 (78.7–94.9)</td>
<td>85.7 (72.8–94.1)</td>
<td>82.4 (65.5–93.2)</td>
<td></td>
</tr>
<tr>
<td>Remaining in care – cumulative</td>
<td>90.9 (89.3–92.4)</td>
<td>88.5 (86.5–90.2)</td>
<td>84.8 (81.9–87.2)</td>
<td>83.5 (79.4–86.8)</td>
<td>81.5 (75.7–86.1)</td>
<td>81.5 (75.7–86.1)</td>
<td></td>
</tr>
</tbody>
</table>

ART, antiretroviral therapy.  
\[a\] Deaths since start = deaths / (total - transfers out).  
\[b\] Values in parentheses are percentages.  
\[c\] Lost to follow-up since start = losses to follow-up / (total - transfers out).  
\[d\] Transfers out since start = transfers out / total.  
\[e\] Remaining in care = (total - losses to follow-up - deaths - transfers out) / (total - transfers out).  
\[f\] Values in parentheses are exact binomial confidence intervals.  
\[g\] Weighted Kaplan–Meier estimate.  
\[h\] Values in parentheses are Greenwood point-wise confidence intervals.

children remained in care after 3 years. If looking only at those children who had been in care for the entire 3 years, the estimate is comparable (82.4%). In both adults and children starting ART, mortality was highest in the first 6 months on therapy. The first laboratory metric reported on is the proportion of tests that are done when they should be done. This is a proxy for quality of care. Results were received in the cohort system for four out of five patients who should have received these tests (Table 3). There is currently a slight drop-off in the test completion proportion as the duration on ART increases.

Fig. 5. Estimates of retention in care for treatment-naive children

Looking at adult laboratory outcomes, of those tested, 90.6% of adults achieved virological suppression by 6 months on ART (Table 3). Although the proportion of patients on second-line regimens increases with duration on ART, and the data system does not distinguish which viral loads are done in patients on first-line versus those on second-line, for all patients combined this percentage remained at 85% or above until 4 years on ART. At 2 years on ART, 3.7% of adults were on second-line, rising to 17.9% at 4 years on ART. Combining all adult patients together, irrespective of the duration on ART, 1.3% of patients were reported to be on second-line regimens at the end of 2005. At the end of the first year on treatment, 74.7% of adult patients had attained a CD4 count above 200 cells/µl or greater, rising to 86.0% at 2 years on ART and 95.3% at 4 years on ART.

The proportion of children achieving virological suppression ranged between 70% and 80% during the 3 years’ duration of follow-up (Table 3), while 7.4% had been changed to second-line by 3 years on ART. By 2 years on ART, 85.7% of children had achieved a CD4 greater than 20% of lymphocytes. As the rate of enrolment increased in the province (Fig. 1 and Fig. 2), the severity of illness in patients starting ART decreased, evidenced by the lower proportion with CD4 cell counts below 50 cells/µl at ART initiation. In 2001 and 2002, half the adult patients starting ART had a CD4 count below 50 cells/µl, whereas this fell to 21.5% in 2005. This, coupled with the expansion of the programme into different...
Table 3. Laboratory outcomes in treatment-naive adults and children on ART

<table>
<thead>
<tr>
<th>Duration on ART (months)</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>42</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults in care and on ART</td>
<td>7,100</td>
<td>3,738</td>
<td>1,640</td>
<td>651</td>
<td>414</td>
<td>237</td>
<td>139</td>
<td>56</td>
</tr>
<tr>
<td>On second-line (%)</td>
<td>0.5</td>
<td>1.8</td>
<td>3.3</td>
<td>3.7</td>
<td>4.8</td>
<td>9.7</td>
<td>10.8</td>
<td>17.9</td>
</tr>
<tr>
<td>Viral loads done</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completion (%)</td>
<td>84.2</td>
<td>89.1</td>
<td>85.4</td>
<td>88.0</td>
<td>82.9</td>
<td>72.2</td>
<td>66.9</td>
<td>78.6</td>
</tr>
<tr>
<td>&lt; 400 copies/ml (%)</td>
<td>90.6</td>
<td>89.0</td>
<td>88.1</td>
<td>88.3</td>
<td>88.0</td>
<td>86.0</td>
<td>84.9</td>
<td>90.9</td>
</tr>
<tr>
<td>95% CI</td>
<td>89.8–91.3</td>
<td>87.9–90.0</td>
<td>86.3–89.7</td>
<td>85.4–90.8</td>
<td>84.1–91.3</td>
<td>79.8–90.8</td>
<td>76.0–91.5</td>
<td>78.3–97.5</td>
</tr>
<tr>
<td>CD4 counts done</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completion (%)</td>
<td>84.1</td>
<td>89.2</td>
<td>84.1</td>
<td>86.6</td>
<td>80.0</td>
<td>70.9</td>
<td>68.3</td>
<td>76.8</td>
</tr>
<tr>
<td>≥ 200 cells/µl (%)</td>
<td>62.2</td>
<td>74.7</td>
<td>82.0</td>
<td>86.0</td>
<td>90.9</td>
<td>88.1</td>
<td>88.4</td>
<td>95.3</td>
</tr>
<tr>
<td>95% CI</td>
<td>60.9–63.4</td>
<td>73.2–76.2</td>
<td>79.9–84.0</td>
<td>82.9–88.8</td>
<td>87.3–93.8</td>
<td>82.2–92.6</td>
<td>80.2–94.1</td>
<td>84.2–99.4</td>
</tr>
</tbody>
</table>

| Children in care and on ART |       |       |       |       |       |       |       |       |
| On second-line (%)          | 0.1   | 0.7   | 2.0   | 4.8   | 4.9   | 7.4   | –     | –     |
| Viral loads done            | 822   | 531   | 245   | 53    | 28    | 20    | –     | –     |
| Completion (%)              | 80.7  | 88.9  | 83.6  | 85.5  | 68.3  | 74.1  | –     | –     |
| < 400 copies/ml (%)         | 72.7  | 72.3  | 74.7  | 77.4  | 78.6  | 75.0  | –     | –     |
| 95% CI                      | 69.6–75.8 | 68.3–76.1 | 68.8–80.0 | 63.8–87.7 | 59.0–91.7 | 50.9–91.3 | –     | –     |
| CD4 counts done             | 807   | 499   | 219   | 35    | 17    | 6     | –     | –     |
| Completion (%)              | 79.2  | 83.6  | 74.7  | 56.5  | 41.5  | 22.2  | –     | –     |
| > 20% lymphocytes (%)       | 57.5  | 71.5  | 74.9  | 85.7  | 88.2  | 83.3  | –     | –     |
| 95% CI                      | 54.0–60.9 | 67.4–75.5 | 66.6–80.5 | 69.7–95.2 | 63.6–98.5 | 35.9–99.6 | –     | –     |

ART, antiretroviral therapy; CI, confidence interval.

Antiretroviral therapy and early mortality

Andrew Boulle et al.

This analysis, based on routine data from a paper-based monitoring system, has demonstrated good cohort retention at 4 and 3 years in adults and children respectively, combined with favourable immunological and virological responses to therapy. As fewer patients start ART in 2005, 4.7% had been lost to follow-up 6 months after starting ART.

Discussion

This analysis, based on routine data from a paper-based monitoring system, has demonstrated good cohort retention at 4 and 3 years in adults and children respectively, combined with favourable immunological and virological responses to therapy. As fewer patients start ART in 2005, 4.7% had been lost to follow-up 6 months after starting ART.

The antiretroviral services in the Western Cape Province are representative of the national programme in South Africa, with the prior experience of innovator sites providing the opportunity to anticipate clinical outcomes and challenges that will be faced in the national programme.

The accumulated experience of these sites enabled the province to rapidly scale-up treatment in terms of both sites and patients around the time that the national programme became a reality. It is estimated that, in the final year under review in this paper, half of those newly in need of antiretroviral therapy were able to access it in the province.

The concurrent halving in early mortality at 6 months on ART, which accompanied the improved immunological status of adults starting ART, suggests that the high early mortality that is characteristic of programmes in the region is in part mediated by the extreme disease advancement at enrolment. This concurs with studies that have been able to stratify outcomes based on CD4 count categories. Measures of the baseline CD4 count on enrolment may prove to be an extremely useful barometer of the extent to which programmes have caught up with the backlog in treatment in instances where the need for ART cannot be easily assessed.

A key limitation of this analysis, and all analyses of aggregate data, is the inability to stratify outcomes by individual baseline measures of disease severity. It is not possible from this analysis to determine if the decline over time in early mortality is fully mediated by measured improvements in the baseline clinical status of patients starting therapy.

Increasingly, patients lost to follow-up are outnumbering patients who are known to have died in developing country cohorts. For this reason we believe that retention in care is the most useful metric for reporting on programme effectiveness. Retention in care in this analysis at 3 and 4 years on ART demonstrates unequivocally the huge survival benefit conferred by...
the intervention. Most of the current simulation models that anticipate either patient numbers or the costs associated with ART have assumed a median of between 6 and 7 years survival on ART.\textsuperscript{13} The current data at 4 years, where 7 out of 10 adult patients are still in care, suggest that these estimates are not overoptimistic, especially since many of the patients lost to care may well subsequently return to care, given the very tight definition of loss to follow-up.

Using 90 days without a clinical visit as the definition of loss to follow-up enables programmes to rapidly identify changes in this parameter and respond appropriately. It also fits in very well with the quarterly cohort reporting ensuring that, when reporting one quarter in arrears, all outcomes can be fully ascertained. On the other hand, many analyses have used longer durations (up to 1 year) without contact with the services to define loss to follow-up.\textsuperscript{13}

Notwithstanding the definition used, a higher proportion of patients were lost to follow-up in the first 6 months on ART in 2005 compared to previously. It is probable that clinic patient loads exceeding manageable numbers in some clinics are affecting this. It is clear that retaining patients in constant care will become increasingly difficult as the service continues to expand, highlighting the importance of adherence promotion extending beyond the health services to the national and local media, political, social and religious platforms, as well as through community interventions. Decentralization of care to more facilities, and the appropriate resourcing of services, are key to ensuring that services at individual facilities remain of a manageable size and are able to appropriately retain patients in care.

Even though most services retained some capacity to actively follow up patients lost to care during the period under review, it is probable that there remains residual under-ascertainment of mortality in the latter years as loss to follow-up increased.\textsuperscript{16} It is further unknown to what extent in future the increased loss to follow-up will result in intermittent care and consequently increased virological resistance due to repeated treatment interruptions (which are known to be strongly associated with resistance).\textsuperscript{17}

The slower increase over time in the numbers of children on ART compared to adults is entirely anticipated and does not imply that children are being underprovided for. Whereas the number of adults newly needing ART increases year on year, the number of children is decreasing due to successful implementation of a prevention of mother-to-child transmission programme.\textsuperscript{18,19}

The virological outcomes are encouraging and suggest that at a population level the rates of viral rebound have not been alarming and are not undermining overall programme success. Nevertheless, with up to one in five patients requiring second-line therapy by 5 years on ART, it is clear that the higher cost of second-line drugs will impact on total programme costs as programmes mature.\textsuperscript{20}

There have been many lessons learned in implementing the WHO monitoring approach. This system, based on registers and regular cohort analyses, shares many attributes with systems that have been in use for many years for monitoring tuberculosis programmes. Worth noting is the value of differentiating sentinel from routine

---

### Table 4. Temporal trends in baseline CD4 count survival and loss to follow-up at 6 months in adults starting ART

<table>
<thead>
<tr>
<th>Number of adults\textsuperscript{a}</th>
<th>80</th>
<th>248</th>
<th>524</th>
<th>3981</th>
<th>3508</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year started on ART</td>
<td>2001</td>
<td>2002</td>
<td>2003</td>
<td>2004</td>
<td>2005</td>
</tr>
<tr>
<td>CD4 &lt; 50 cells/µl\textsuperscript{b,c,d}</td>
<td>51.3 (39.8–62.6)</td>
<td>50.4 (44.0–56.6)</td>
<td>36.8 (32.7–41.1)</td>
<td>24.4 (23.1–25.8)</td>
<td>21.5 (18.8–20.6)</td>
</tr>
<tr>
<td>Mortality\textsuperscript{b,c,d}</td>
<td>12.7 (6.2–21.8)</td>
<td>11.7 (8.0–16.4)</td>
<td>9.6 (7.2–12.4)</td>
<td>6.0 (5.1–6.6)</td>
<td>6.6 (5.6–7.3)</td>
</tr>
<tr>
<td>Loss to follow-up\textsuperscript{c,d}</td>
<td>0.0 (0.0–4.5)</td>
<td>0.0 (0.0–2.2)</td>
<td>1.7 (0.8–3.2)</td>
<td>4.4 (3.7–4.9)</td>
<td>4.7 (3.9–5.3)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} ART, antiretroviral therapy; CI, confidence interval.
\textsuperscript{b} Number starting in year and reaching 6 months of follow-up.
\textsuperscript{c} Proportion in starting cohort with CD4 counts < 50 cells/µl.
\textsuperscript{d} Values in parentheses are exact binomial confidence intervals.
\textsuperscript{e} Mortality = deaths by 6 months / (total in cohort - transfers out by 6 months).
\textsuperscript{f} Loss to follow-up = losses to follow-up by 6 months / (total in cohort - transfers out by 6 months).
sites,21 liberating the majority of sites from onerous data-collection procedures that are designed for clinical research rather than for supporting routine care. It has been our experience that, with viral loads being available, managers have paid little attention to CD4 count outcomes in assessing programme performance. We have also found that presenting the completion proportions for laboratory outcomes is an invaluable metric over and above the outcomes themselves in the subset of patients for whom results are available. Finally, one of the major challenges emerging as models of care evolve is the large number of patients moving between facilities, who, once transferred out, are censored in the cohort analyses.

The ability to report on cohort outcomes without electronic systems underscores the value of implementing a basics-first approach to routine monitoring. This does not mean that there is no role for the progressive and measured development of electronic systems22 but rather that the basic building blocks that are required for a paper-based system are the same measures that will make electronic systems a success.23

Perhaps the most important lesson from the first 5 years of this programme is that implementing an ART programme in primary-care facilities from the outset is feasible and can achieve excellent clinical results. It is probable that the location of care in community clinics is one of the key factors contributing to the retention of patients in care.24

Looking to the future, if the Western Cape Province is to come close to the stated target of treating 80% of patients newly in need of therapy each year over the coming years, the annual number of patients enrolling in care will need to double while the total number of patients in care quadruples over a 5-year period. This will require even further task-shifting and expansion of the service platform, given that enrolment is already threatened by capacity constraints in the existing service platform.25

In conclusion, this paper has demonstrated excellent clinical outcomes 5 years after the Western Cape Province began offering ART in the public sector, validating the decision to make this a primary-care intervention from the outset. The WHO monitoring system has enabled the province to keep track of the intervention and of the performance of individual sites, while allowing space for more complex and durable solutions to be developed for the larger sites.

Funding: The following organizations have provided support in whole or in part to various of the authors during the study period: the Provincial Government of the Western Cape; Médecins Sans Frontières; the Global Fund to fight AIDS, Tuberculosis and Malaria; NIH grant U01 AI069924-01.

Competing interests: None declared.
الواقعية مضمون الفيروسات القُرَبَية والوفيات المبكرة في جنوب أفريقيا

الهدف: توضيح النتائج على مستوى الم��نة، والاتجاهات الرئيسية لبرنامج المعالجة بالأدوية للمرضى الذين ي отказوا من الرعاية، وزيادة نسب الاستمرار في الرعاية، في الوقت نفسه فإن الارتقاء وضع الرعاية في مواقع الرعاية الأولية في هذا البرنامج يصاحب معالجة بمضادات الفيروسات القعرية حتى مرور أربع سنوات، إذ تراوح معدل نسبة الاستمرار تحت الرعاية بالنسبة للأطفال الذين يتلقون المعالجة السنوية، والنشاط الشري. وتم احتساب معدلات استبقاء المرضى تحت الرعاية، والوفيات، والقدرة أو السرطان في المرة الأولى، والتراجع الشري. كل استمرار أثر في الحالات المضادات الفيروسات القعرية.

المتولِّدان: بدأ برنامج المعالجة بالأدوية في جنوب أفريقيا في مطلع عام 2004، وهو برنامج يهدف إلى تقديم مخاطرات بمضادات الفيروسات القعرية في حالات الرعاية الأولية، وذلك على أنخفضت الوفيات خلال ستة أشهر بين 85% من الحالات المضادات الفيروسات القعرية. التحليل: إن وضع الرعاية في مواقع الرعاية الأولية في هذا البرنامج يصاحب معدلات حذف لاستجابة المرضى في المرة الأولى، وفي الوقت نفسه فإن الارتقاء بتقديم المعالجة الأولية مضادات الفيروسات القعرية يصاحبه تقليل معدلات الفيروسات القعرية.

الاستنتاج: تبين تعدد النتائج على مستوى الم��نة، والاتجاهات الرئيسية لبرنامج المعالجة بالأدوية للمرضى الذين ي отказوا من الرعاية، وزيادة نسب الاستمرار في الرعاية، في الوقت نفسه فإن الارتقاء وضع الرعاية في مواقع الرعاية الأولية في هذا البرنامج يصاحب معالجة بمضادات الفيروسات القعرية حتى مرور أربع سنوات، إذ تراوح معدل نسبة الاستمرار تحت الرعاية بالنسبة للأطفال الذين يتلقون المعالجة السنوية، والنشاط الشري. وتم احتساب معدلات استبقاء المرضى تحت الرعاية، والوفيات، والقدرة أو السرطان في المرة الأولى، والتراجع الشري. كل استمرار أثر في الحالات المضادات الفيروسات القعرية.

References
doi:10.1007/s10020-00303-20040690-00006
doi:10.1007/s10020-0040603-00006
doi:10.1002/ cyt.10068
doi:10.1001/ jama.296.7.782

Research Antiretroviral therapy and early mortality
Andrew Boulle et al.
Andrew Boulle et al.


