Public-Health and Individual Approaches to Antiretroviral Therapy: Township South Africa and Switzerland Compared

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Abbreviations: 3TC, lamivudine; AZT, zidovudine; CI, confidence interval; d4T, stavudine; EFV, efavirenz; HAART, highly active antiretroviral therapy; IQR, interquartile range; LPV, lopinavir; NFV, nelfinavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; TNV, tenofovir

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ABSTRACT

Background

The provision of highly active antiretroviral therapy (HAART) in resource-limited settings follows a public health approach, which is characterised by a limited number of regimens and the standardisation of clinical and laboratory monitoring. In industrialized countries doctors prescribe from the full range of available antiretroviral drugs, supported by resistance testing and frequent laboratory monitoring. We compared virologic response, changes to first-line regimens, and mortality in HIV-infected patients starting HAART in South Africa and Switzerland.

Methods and Findings

We analysed data from the Swiss HIV Cohort Study and two HAART programmes in townships of Cape Town, South Africa. We included treatment-naïve patients aged 16 y or older who had started treatment with at least three drugs since 2001, and excluded intravenous drug users. Data from a total of 2,348 patients from South Africa and 1,016 patients from the Swiss HIV Cohort Study were analysed. Median baseline $CD4^+$ T cell counts were 80 cells/μl in South Africa and 204 cells/μl in Switzerland. In South Africa, patients started with one of four first-line regimens, which was subsequently changed in 514 patients (22%). In Switzerland, 36 first-line regimens were used initially, and these were changed in 539 patients (53%). In most patients HIV-1 RNA was suppressed to 500 copies/ml or less within one year: 96% (95% confidence interval [CI] 95%–97%) in South Africa and 96% (94%–97%) in Switzerland, and 26% (22%–29%) and 27% (24%–31%), respectively, developed viral rebound within two years. Mortality was higher in South Africa than in Switzerland during the first months of HAART: adjusted hazard ratios were 5.90 (95% CI 1.81–19.2) during months 1–3 and 1.77 (0.90–3.50) during months 4–24.

Conclusions

Compared to the highly individualised approach in Switzerland, programmatic HAART in South Africa resulted in similar virologic outcomes, with relatively few changes to initial regimens. Further innovation and resources are required in South Africa to both achieve more timely access to HAART and improve the prognosis of patients who start HAART with advanced disease.

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Introduction

The introduction of highly active antiretroviral combination therapy (HAART) since 1996 has substantially improved the prognosis of HIV-infected patients in industrialized countries [1]. Only few drugs were available initially, but today over 20 approved antiretroviral drugs from four drug classes are available, including nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and fusion inhibitors. In industrialized countries doctors prescribe from the full range of available antiretroviral drugs. Resistance testing and frequent monitoring of CD4 cell counts and viral load are used to individually tailor drug regimens.

In contrast, based on the experience of treating tuberculosis, the World Health Organization (WHO) has developed a public-health approach to providing HAART in resource-limited settings. This approach takes the realities of weak health systems into account, including the level of training of health-care workers, the high patient burden, limited availability of drugs, and the experience of pilot programmes [2,3]. Key characteristics of this public-health approach include the standardisation of first-line and second-line regimens, simplified clinical decision-making, and standardised clinical and laboratory monitoring [3]. The choice of regimens in these programs is determined primarily by cost and ease of administration and can include drugs that are no longer widely used in industrialized countries. Viral load monitoring is not considered essential, and individual drug resistance testing is generally not available. A survey of national guidelines developed by 43 low- and middle-income countries showed that the public-health approach to antiretroviral therapy has been widely adopted in these countries [4]. An estimated 2 million people living with HIV/AIDS were receiving treatment in low- and middle-income countries by December 2006, representing 28% of the estimated 7.1 million people in urgent need of treatment at that time [5].

We compared the public-health and individual approach to HAART by analysing virologic response, changes to first-line regimens, and mortality in patients starting HAART in Switzerland and two townships in Cape Town, South Africa.

Methods

We analysed data from the Khayelitsha and Gugulethu HAART programmes in the Republic of South Africa, which are part of the International Epidemiological Databases to Evaluate AIDS in Southern Africa (IeDEA-SA), and made comparisons with the Swiss HIV Cohort Study (SHCS).

Khayelitsha and Gugulethu Cohorts, Cape Town, South Africa

Khayelitsha and Gugulethu are townships located within the Cape Town metropolitan area with estimated populations of 400,000 and 300,000 people, respectively. Khayelitsha had, in 1999, the first routine government-run programme for the prevention of mother-to-child transmission of HIV in South Africa. Antiretroviral treatment has been available since 2001 at three government clinics providing HIV care, supported by Médecins Sans Frontières. In Gugulethu the Usaphu Luwethu ("Our Family Clinic") antiretroviral treatment programme was initiated by the Desmond Tutu HIV Centre in September 2002. Ten primary-care HIV clinics form the patient referral base.

Enrolment into treatment programmes follows the South African government's Department of Health national guidelines, which are based on the 2002 WHO recommendations [6]. Individuals are eligible for treatment if they are in WHO stage 4 (with the exception of extrapulmonary tuberculosis, which is a stage 4–defining illness but not a criterion for starting therapy in the Western Cape) or have a CD4 count below 200 cells/μl. Data are collected prospectively using structured records completed at each consultation, including information on WHO stage-defining illnesses [7].

In Khayelitsha, viral load assessments are performed routinely before starting HAART, after 3 mo, and then every 6 mo. In Gugulethu viral load is assessed before starting HAART and every 4-mo thereafter. Plasma viral load was measured using a branch DNA hybridization technique (Bayer HIV-1 RNA 3.0 assay, Leverkusen, Germany) or nucleic acid sequence-based amplification (Nuclisens EasyQ assay, bioMérieux, Boxtel, The Netherlands). In South Africa, provincial and national guidelines recommend switching drug regimens after two consecutive viral loads above 5,000 copies/ml, but patients were not necessarily switched when they fulfilled these criteria.

All treatment, clinic consultations, and laboratory work are free of charge. In both sites patients receive counselling and adherence support. Patients on HAART who miss appointments are contacted where possible, and if required, traced through home visits. More details on the Khayelitsha and Gugulethu cohorts are given elsewhere [8,9].

Swiss HIV Cohort Study

Set up in 1988, the Swiss HIV Cohort Study is a national prospective cohort study of HIV-infected patients followed up at outpatient departments of five University hospitals (Basel, Bern, Geneva, Lausanne, and Zurich) and two Cantonal hospitals (Lugano and St. Gallen) in Switzerland. A comparison with official AIDS notifications and deaths indicated that about 70% of all patients living with AIDS in Switzerland participate in the study [10].

Data collection and study procedures are standardised. Detailed information on demographics, mode of HIV acquisition, risk behaviours, clinical events, laboratory results, and treatments is collected at registration and then at intervals of 6 mo. HIV-1 RNA (Roche Amplicor HIV-1 Monitor assay), CD4 counts, and other laboratory parameters are measured at least every 3 mo. Clinical AIDS diagnoses (Centers for Disease Control and Prevention [CDC] stage C) are recorded by the treating physicians on the basis of the 1993 CDC criteria [11]. The decision to change therapy was informed by the International AIDS Society-USA guidelines. All services, including antiretroviral therapy and laboratory testing, are covered by compulsory health insurance. More details on the SHCS are given elsewhere [12,13].

Eligibility Criteria and Definitions

The same eligibility criteria were applied to patients in Switzerland and South Africa. All treatment-naïve patients who started HAART at any point since 2001 (the year when HAART became available in the two South African sites), had at least one day of follow-up, and were aged 16 y or older were included. Patients from Switzerland who acquired HIV

through intravenous drug use were excluded from the analysis because they are a group that is not represented in the South African cohorts. In the South African cohorts HIV transmission information is not routinely recorded, but most patients were infected through heterosexual contacts. HAART was defined as a combination of at least three antiretroviral drugs. The type of regimen was defined as PI-based (two NRTIs and one PI), NNRTI-based (two NRTIs and one NNRTI), and other. Boosted PIs are counted as one drug. The stage of disease was classified as less advanced (CDC stage A/B, WHO stage I/II) or advanced (CDC stage C, WHO stage III/IV).

Ethical Approval and Laboratory Quality Assurance

The local ethics committees of all seven study sites that participate in the SHCS approved the study, and written informed consent was obtained from all participants. Data collection in the townships Khayelitsha and Gugulethu, South Africa, as well as participation of these studies in the Antiretroviral Treatment in Lower Income Countries Collaboration (ART-LINC) collaboration of IeDEA, were approved by the ethics committee of the University of Cape Town, which did not require informed consent. All laboratories involved in South Africa and Switzerland participate in quality assurance programmes.

Endpoints

The following endpoints were considered: time to first treatment change (overall and by reason for change), virologic suppression (defined as HIV-1 RNA $\leq$500 copies/ml), viral rebound (defined as HIV-1 RNA above 500 copies/ml) after having achieved viral suppression, CD4 response, and death from all causes. Viral rebound is usually defined as two consecutive values above a given threshold. In our analysis we used a single value, as the measurement frequency differed between settings. In a sensitivity analysis we used two consecutive values above 500 copies/ml. The threshold of 500 copies/ml was chosen because assays of different sensitivities were used during the study period. Regimen change was defined as any change to the treatment regimen, including interruption and discontinuation, but excluding dosage adjustments. The treating physician indicated the reason for regimen changes, and these reasons were classified as failure (virologic, immunologic, or clinical), toxicity, and other. Specific definitions of reasons for regimen change, including, for example, lactic acidosis, were not standardised across sites. The severity of toxicities was not assessed.

Finally, we determined the proportion of initial regimens that complied with the national South African guidelines or, in the case of Switzerland, the International AIDS Society–USA guidelines current at the time of starting HAART.

Statistical Analysis

We used an "intent-to-continue-treatment" approach and thus ignored changes to treatment, including treatment interruptions and terminations for virological endpoints and death. Time was measured from the start of HAART or from the first viral load measurement of 500 copies/ml or below to the time the outcome occurred, the time of the last follow-up visit, or 2 y after baseline, whichever came first. A patient was considered lost to follow-up if the time between the last visit of the patient and the closing date of the cohort was longer than 1 y. Only patients who potentially had 1 y of follow-up were included in the analysis of loss from follow-up.

We used Kaplan–Meier graphs and Cox proportional hazard models (for mortality and first treatment change) and logistic regression (for viral response and viral rebound) to estimate hazard ratios (HRs) and odds ratios (ORs) of endpoints occurring, in comparing the two South African cohorts with the Swiss cohort. For mortality, a separate model was fitted for the first 3 mo after starting HAART (the period with the highest mortality [14]) and for months 4–24. Since background mortality differs between the two settings, we compared expected mortality rates in Switzerland and South Africa. We obtained estimates of non-HIV-related background mortality by sex and age group from the Global Burden of Disease project [15,16], and used these rates to calculate expected numbers of deaths in the two South African cohorts. Similarly, we used rates available from the Swiss Federal Statistical Office to calculate expected deaths for the Swiss cohort.

For viral response the first viral load measurement within 6–12 mo after baseline was classified into $\leq$500 copies/ml (virologic suppression) or >500 copies/ml. We used logistic regression instead of a time-to-event approach, because the frequency and timing of viral load measurements differed between the two settings. Analyses were adjusted for baseline CD4 count, HIV-1 viral load, stage of disease, sex, and age.

We calculated the rate of changing the first treatment regimen by reason of change and time periods (1–3 mo, 4–6 mo, 7–12 mo, and 13–24 mo) by dividing the number of patients developing the event by the number of person-years at risk. We used Poisson regression to calculate confidence intervals (CIs) for rates. Cause-specific cumulative incidences were calculated applying a competing risk approach [17,18]. We used competing risk Cox regression as described by Lunn and McNeil [19] to jointly analyze treatment change due to failure, intolerance, and other reasons. This analysis was adjusted for the same variables as above.

All analyses were performed using Stata version 9.2. Results are presented as Kaplan–Meier probabilities, rates per 100 person-years, and HRs or ORs, with 95% CIs.

Results

Patient characteristics

A total of 3,364 patients—2,348 from Khayelitsha and Gugulethu and 1,016 from the Swiss HIV Cohort Study—were observed for 2,362 and 1,564 person-years, respectively. The median observation time (taking censoring after 2 y into account) was 0.7 y (interquartile range [IQR] 0.3–1.3 y) for Gugulethu, 1.0 years (0.5–1.5 y) for Khayelitsha and 2.0 y (1.1–2.0 y) for the Swiss cohort. Table 1 shows the characteristics of patients at the time of treatment initiation. The patients in the South African cohorts were younger, more likely to be female, and in more advanced stages of the infection: the median baseline CD4 count was 80 cells/μl compared to 204 cells/μl in the Swiss cohort, and 2,126 (90.6%) and 188 (18.5%), respectively, were in CDC stage C or WHO stage III/IV. In South Africa the number of patients starting HAART almost doubled every year from 79 in 2001 to 509 in 2003, whereas in Switzerland the number of patients starting HAART remained fairly constant since 2001.

Table 1. Baseline Characteristics of Patients Starting HAART in Khayelitsha and Gugulethu, South Africa and the Swiss HIV Cohort Study

Category	Subcategory	South African Cohorts	Swiss HIV Cohort
Patients, *n*	—	2,348	1,016
	Females, *n* (%)	1,663 (71%)	333 (33%)
Age, y, median (IQR)	—	32.7 (28.5–38.2)	38.3 (31.7–46.1)
CD4 cell count, cells/μl, median (IQR)	—	80 (30–138)	204 (122–291)
CD4 cell count, number missing (%)	—	123 (5.2%)	50 (4.9%)
HIV-1 viral load, $\log_{10}$ copies/ml, median (IQR)	—	5.1 (4.6–5.5)	5.0 (4.5–5.5)
HIV-1 viral load, number missing (%)	—	288 (12.3%)	53 (5.2%)
Clinical stage: CDC stage C, WHO stage III/IV, *n* (%)	—	2,126 (90.6%)	188 (18.5%)
Duration of follow-up (years)[a], median (IQR)	—	0.9 (0.5–1.5)	2.0 (1.1–2.0)
Number of patients starting HAART in year, *n* (%)	2001	79 (3.4%)	179 (17.6%)
	2002	246 (10.5%)	204 (20.1%)
	2003	509 (21.7%)	185 (18.2%)
	2004–2006[b]	1,514 (64.5%)	448 (44.1%)
Initial HAART regimen, *n* (%)	2 NRTIs + 1 NNRTI	2,339 (99.7%)	470 (46.3%)
	2 NRTIs + 1 PI	9 (0.4%)	449 (44.2%)
	Other	0	97 (9.6%)
Four most commonly used initial HAART regimens, *n* (%)	3TC D4T EFV	918 (39.1%)	—
	3TC D4T NVP	780 (33.2%)	—
	3TC AZT EFV	425 (18.1%)	—
	3TC AZT NVP	216 (9.2%)	—
	3TC AZT EFV	—	304 (29.9%)
	3TC AZT LPV/r	—	202 (19.9%)
	3TC AZT NFV	—	99 (9.7%)
	3TC TNV EFV	—	65 (6.4%)
Initial HAART regimens used to treat 95% of patients, *n*	—	4	36
Patients using initial HAART regimens recommended by guidelines, %	—	95.1	99.6

[a]Censored after 2 y.
[b]Recruitment not completed for the years 2005/06.
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In Khayelitsha and Gugulethu over 95% of patients were treated with one of four NNRTI-based first-line regimens whereas in Switzerland 36 different regimens were used (Table 1). The most commonly used regimens in South Africa were stavudine/lamivudine (d4T/3TC) in combination with efavirenz (EFV) (39.1%) or nevirapine (NVP) (33.2%). In Switzerland the most frequent regimens were zidovudine/lamivudine (AZT/3TC) in combination with either EFV ($n = 304$, 29.9%) or boosted lopinavir (LPV) ($n = 202$, 19.9%) or nelfinavir (NFV) ($n = 99$, 9.7%). Stavudine (d4T) was used in 35 patients (3.4%) only. In South Africa 2,339 (99.6%) of patients started with a regimen that was in accordance with guidelines, compared to 966 (95.1%) of patients in Switzerland. In Switzerland 45 patients (4.5%) received regimens that may have been chosen because of primary resistance or as part of a study, and five patients (0.5%) received regimens that clearly violated guidelines.

Changes to First-Line Regimens

Changes to the initial regimen during the first 2 y of HAART were considerably more frequent in Switzerland than in South Africa: 539 patients (53.1%) compared to 514 patients (21.9%) experienced at least one change during the first 2 y of HAART. Substitutions of one drug were the most frequent change both in Switzerland (274, 50.8%) and South Africa (328, 63.8%). Figure 1 shows rates of any type of change during months 1–3, 4–6, 7–12, and 13–24 along with the estimated cumulative probability of change, by reason for changing regimens: toxicity, failure, or other reasons. The cumulative probability of change at 2 y due to toxicity was 23.8% (95% CI 21.0%–26.7%) in Switzerland compared to 11.7% (95% CI 10.0%–13.5%) in Khayelitsha and Gugulethu. In contrast, the probability of changes due to failure was similar in Switzerland and South Africa: 5.1% (95% CI 3.7%–6.8%) and 3.9% (2.5%–5.6%), respectively. In patients who were switched for failure, the median $\log_{10}$ HIV viral load values at the time of treatment switch due to failure was 4.4 $\log_{10}$ copies/ml in South Africa ($n = 31$) and 3.4 $\log_{10}$ copies/ml in Switzerland ($n = 39$) ($p < 0.001$ for difference). In South Africa all patients who switched for failure had detectable viral loads, whereas in Switzerland ten patients (29%) had viral loads $\leq$500 copies/ml. An estimated 30.9% (95% CI 27.7%–34.1%) of patients had changed regimens for other reasons in Switzerland compared to 14.1% (12.1%–16.3%) in South Africa.

In both settings toxicity was the dominant reason for treatment change in the first 3 mo, but rates were considerably higher in Switzerland than in South Africa: 53 per 100 person-years (95% CI 44–63) compared to 21 per 100 person-years (17–25). Other reasons dominated from month 4 onwards, again with higher rates of change in Switzerland. Treatment failure as reason for drug changes was rare in both settings. Table 2 compares reasons for regimen change in more detail. For toxicity the most notable difference relates to elevated lactate levels and lactic acidosis: in Khayelitsha and Gugulethu 32 (13.4%) of all regimen changes due to toxicities were due to lactic acidosis (associated with d4T in 31 patients). In the Swiss study no patient changed the initial regimen due to elevated lactate levels. Treatment changes due to abdominal and gastrointestinal toxicity, including liver toxicity, were more common in Switzerland than in South

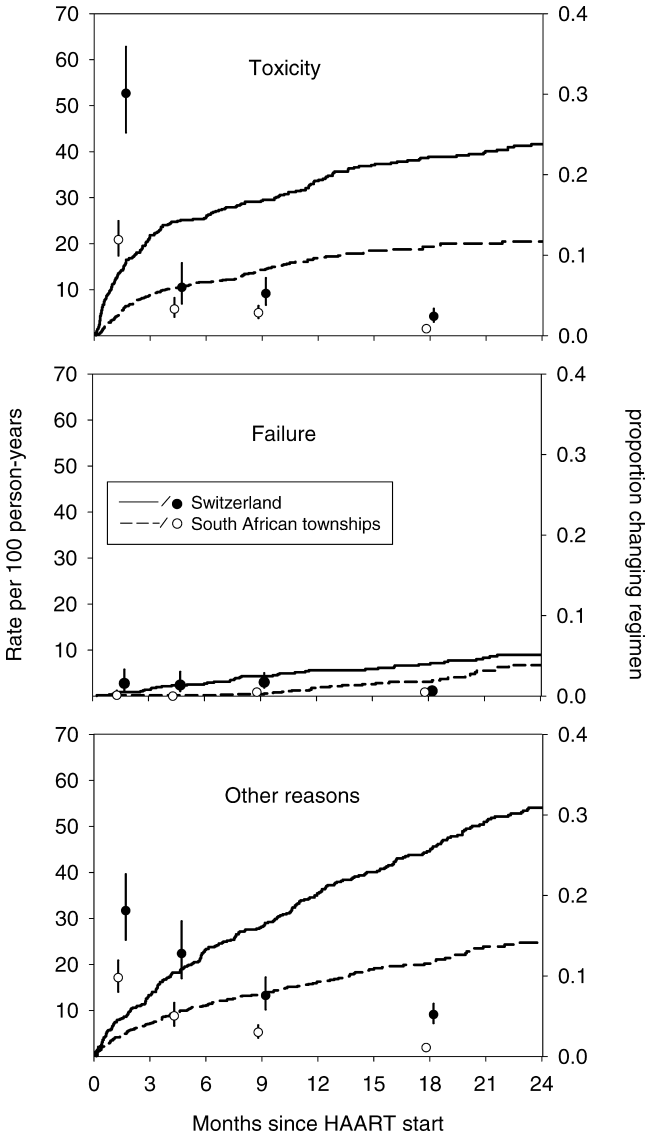

Figure 1. Rates and Kaplan-Meier Plots of First Treatment Change Due to Toxicity, Failure, and Other Reasons in Khayelitsha and Gugulethu, South Africa and the Swiss HIV Cohort Study

Dots indicate rates during months 1–3, 4–6, 7–12, and 13–24 with 95% CIs; lines indicate the estimated proportion of patients changing their first-line regimen. "Other reasons" (bottom graph) include mainly treatment changes due to tuberculosis and pregnancy in South Africa and changes due to patients' wishes or physicians' decisions in Switzerland.

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Africa. Changes due to other reasons were also more frequent in Switzerland. The predominant other reasons for changing first-line regimens in South Africa were pregnancy and tuberculosis. In Switzerland changes due to patient requests were common.

Virologic Response, Rebound, CD4 Response, and Mortality

The frequency of HIV-1 RNA measurements differed in the two settings (Figure 2). The median time to the first HIV-1 RNA determination was 3.1 mo (interquartile range [IQR] 2.8–3.7 mo) in Khayelitsha and Gugulethu compared to 1.0 mo (0.7–1.5 mo) in the Swiss study. During follow-up HIV-1 RNA was measured at regular time intervals in South Africa (median 3.9 mo, IQR 3.2–6.0 mo) whereas in Switzerland the time intervals were not well defined (2.9 mo, 1.9–3.4 mo). A similar picture was evident for CD4 counts (unpublished data). Kaplan-Meier plots show that in both settings most patients suppressed HIV-1 RNA to 500 copies/ml or less (Figure 3, top graph) within one year: 96.0% (95% CI 95.1%–96.9%) of patients in the townships and 95.5% (94.0%–96.7%) in the Swiss cohort. The proportion of patients with viral load values ≤500 copies/ml at different time points was around 90% up to 2 y in both Switzerland and South Africa.

Among the 2,644 patients who suppressed viral replication to ≤500 copies/ml (1,716 in South Africa and 928 in Switzerland), the probability of a viral rebound at 2 y after suppression was 25.5% (95% CI 22.1%–29.3%) in South Africa and 27.1% (23.9%–30.7%) in Switzerland (Figure 3, middle graph). When analyses were repeated with two consecutive measurements above 500 copies/ml, the rate of viral rebound was slightly higher in Switzerland than in South Africa, which is expected considering the higher measurement frequency in Switzerland. During the 2 y the median CD4 count increased from 80 cells/μl at baseline (IQR 30–138) to 372 cells/μl (260–497) in South Africa and from 204 cells/μl (122–291) to 449 (310–607) in Switzerland. Patients starting HAART with lower CD4 cell counts tended to have lower values throughout the study period, both in South Africa and Switzerland.

Mortality was substantially higher in South Africa than in Switzerland during the first months of HAART (Figure 3, bottom graph). Cumulative mortality at 6 mo was 8.6% (95% CI 7.5%–9.8%) and 0.9% (0.5%–1.8%), respectively. The proportion of patients lost to follow-up was similar: by 1 y, 3.5% (95% CI 2.5%–4.7%) of patients in Khayelitsha and Gugulethu and 3.2% (2.2%–4.7%) of patients in the Swiss cohort were lost to follow-up.

Univariable and Multivariable Analyses

The results from univariable and multivariable logistic and Cox models comparing the South African cohorts with the Swiss cohort are presented in Table 3. For the three endpoints change from first-line regimen, virologic response and viral rebound, adjusting the models for sex and age, CD4 cell count, HIV-1 RNA, and stage of disease at baseline had only modest effects on HRs and ORs. The adjusted HRs comparing South Africa with Switzerland for treatment change due to failure, intolerance, and other reasons were 0.25 (95% CI 0.12–0.50), 0.44 (0.32–0.60), and 0.30 (0.22–0.40) respectively, but there was little evidence for a difference in virologic response and viral rebound (Table 3). In contrast, HRs for the mortality endpoints were attenuated considerably in multivariable analysis: the adjusted HRs were 5.90 (95% CI 1.81–19.21) during months 1–3 and 1.77 (0.90–3.50) during months 4–24. The expected non-HIV-related mortality rate was 28.1 per 10,000 person-years in the South African cohorts compared to 13.3 in the Swiss cohort, for a rate ratio of 2.11 (95% CI 1.10–4.06).

Discussion

This comparative study of patients starting HAART in South Africa and Switzerland found that the initial virologic response was similar, despite profound differences in patient

Table 2. Reasons for Change of the First HAART Regimen in the First Two Years of Treatment in Khayelitsha and Gugulethu, South Africa and the Swiss HIV Cohort Study

Reason	Details	South African Cohorts ($n = 514$)	Swiss Cohort ($n = 539$)
		Patients, *n* (%)	Patients, *n* (%)
Toxicity	Any	238 (46.3%)	220 (40.8%)
	Peripheral neuropathy	46 (8.9%)	53 (9.8%)
	Gastrointestinal, including liver	37 (7.2%)	64 (11.9%)
	Haematological	36 (7.0%)	20 (3.7%)
	Lactic acidosis	32 (6.2%)	0 (0%)
	Hypersensitivity[a]	30 (5.8%)	34 (6.3%)
	Lipodystrophy	6 (1.2%)	12 (2.2%)
	Dislipidaemia	4 (0.8%)	5 (0.9%)
	Nephrological	0 (0%)	7 (1.3%)
	Not specified	47 (9.1%)	25 (4.6%)
Failure	Virologic, immunologic, or clinical	31 (6.0%)	39 (7.2%)
Other	—[b]	244 (47.5%)	257 (47.7%)
Unknown	—	1 (0.2%)	23 (4.3%)

[a]Any type of hypersensitivity in Switzerland, rash in South Africa.
[b]In South Africa "other" reasons mainly included contraindications related to tuberculosis or pregnancy (167 patients); in Switzerland physician decisions (including contraindications, changes in guidelines, etc.; 107 patients) and patient requests (85 patients).
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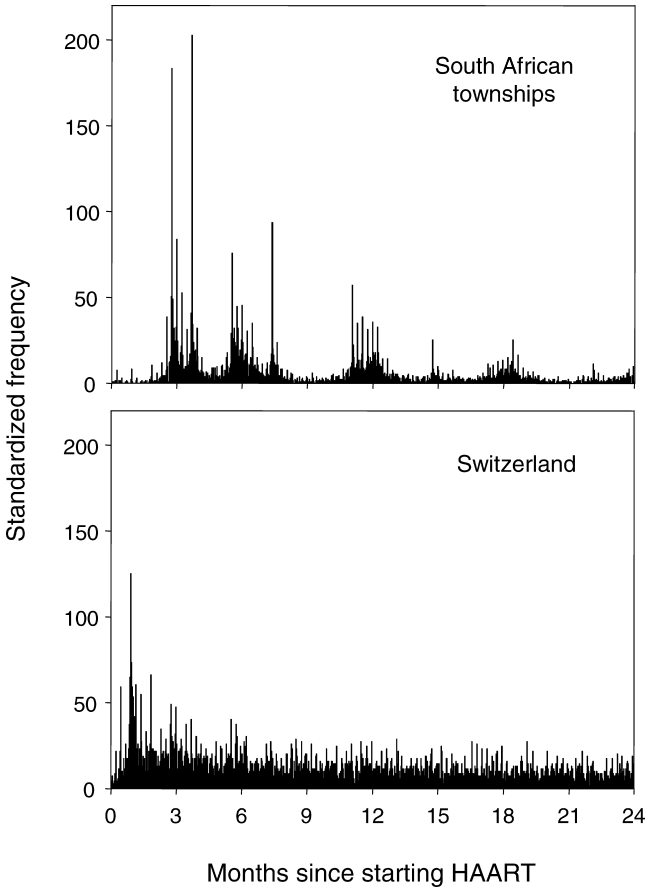

Figure 2. Frequency of Viral Load Measurements in Khayelitsha and Gugulethu, South Africa and the Swiss HIV Cohort Study

The frequency was standardized to the total number of measurements in each setting.
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characteristics and the approach to antiretroviral therapy, and different viral strains causing the epidemics in the two countries. Compared to South Africa, about twice as many changes to the treatment regimen were recorded in Switzerland during the first two years. Mortality was higher in South Africa than in Switzerland, particularly during the first three months of HAART.

Public Health and Individualised Approaches to HAART

In South Africa, where the prevalence of HIV-1 subtype C infection in the general population is estimated at 19%, the Department of Health published detailed treatment guidelines for adults and children in 2004 [6], with the objective of providing access to all patients in need. All patients start a regimen consisting of a recommended NRTI backbone and either EFV or NVP. In December 2006, an estimated 1,000,000 people in South Africa needed HAART, and 325,000 were receiving it [5]. In contrast, in Switzerland the prevalence of HIV-1 is below 1% and mainly of subtype B, HAART is covered by the compulsory basic health insurance package, and access is therefore universal. Care is highly individualised and delivered by specialists in HIV medicine. The choice of the initial regimen is influenced by several factors, including convenience, viral resistance to treatment, potential side effects, and physician and patient preferences. In both countries the provision of HAART has been found to be cost-effective from a health services and societal perspective [20–22].

Antiretroviral Anarchy?

There has been concern that unregulated use of antiretroviral drugs, interruptions in drug supplies, and the lack of monitoring of treatment response in sub-Saharan Africa might lead to "antiretroviral anarchy" and the emergence of viral resistance [23]. For example, in Abidjan, Côte d'Ivoire, 39 (57%) of 68 patients who had relied on friends or relatives in Europe or the United States for antiretroviral drugs before a HAART programme was established had mutations in their

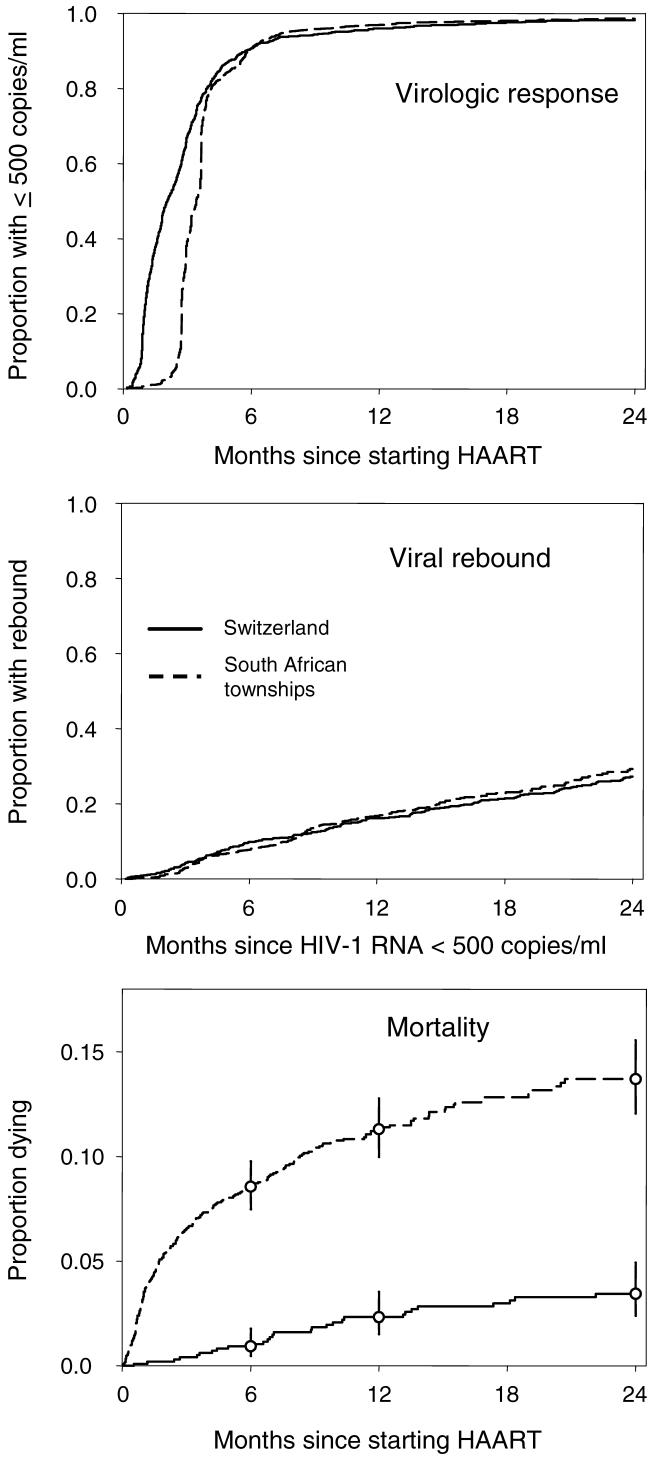

Figure 3. Kaplan Meier Plots of Virologic Response, Viral Rebound, and Mortality in Khayelitsha and Gugulethu, South Africa and the Swiss HIV Cohort Study

Viral rebound is defined as having a HIV-1 RNA >500 copies/ml after a viral load ≤500 copies/ml.

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virus associated with resistance to at least one drug [24]. Similar data were reported from Libreville, Gabon [25]. The development of resistance is closely linked to incomplete adherence to therapy, and several studies have shown that good adherence can be achieved in resource-limited settings [26–28]. The overall virologic response observed in this study suggests that adherence was good in the two South African townships (the delay in reaching viral load values below 500 copies/ml in South Africa is probably explained by the less-frequent viral load determinations in the township cohorts compared to Switzerland). Therefore, our results indicate that antiretroviral anarchy has been prevented in township ART programmes in South Africa.

In industrialized settings, a substantial proportion of new infections now involve strains resistant to one or more drugs [29]. Viral resistance is rare in South Africa at present [30], but is bound to increase in the future. WHO monitors drug resistance at sentinel sites in South Africa and elsewhere [3]. The use of single-dose NVP to prevent mother-to-child transmission of HIV may increase resistance levels, but the implications for treatment are a matter of debate and the subject of ongoing studies [31].

Considering the large number of first-line regimens used in Switzerland, and the high rate of changes to these regimens, one might argue that antiretroviral anarchy may in fact be more prevalent in Switzerland than in South Africa. However, we found that 95% of patients used regimens that were in accordance with the International AIDS Society–USA guidelines in place during this period. Few regimens violated the current guidelines. Nevertheless, a more standardised approach to the choice of the first-line regimen and monitoring of viral load could probably reduce costs in Switzerland without compromising the effectiveness of HAART.

Treatment Changes

Treatment changes that were reported to be due to toxicity in the first 3 mo of treatment were more frequent in Switzerland than in South Africa, despite the fact that in Switzerland more drugs, and more drugs with a more favourable adverse effects profile, are available. The type of toxicities leading to treatment changes were fairly similar in the two settings, with the exception of symptomatic hyperlactataemia or lactic acidosis, which was recorded in 32 patients in South Africa but not observed in Switzerland. This difference is not surprising in light of the widespread use of stavudine in South Africa but not in Switzerland. In South Africa few patients switched because of lipodystrophy, despite the widespread use of stavudine, possibly because follow-up was relatively short. Indeed, a previous analysis of the Khayelitsha and Gugulethu cohorts showed that drug substitutions due to lipodystrophy occurred mainly after the first year of treatment [32]. We stress that our analysis was restricted to treatment changes attributed to toxicities: we did not assess the overall incidence of toxicities nor the severity of adverse events.

Early Mortality

Patients in South Africa started therapy with much more pronounced immunodeficiency than did those in Switzerland, reflecting the large number of patients in great need of treatment during the scale-up of HAART in South Africa. In line with a previous collaborative analysis [14], the higher mortality in the South African townships was probably only partly explained by lower CD4 cell counts and more advanced clinical stage at treatment initiation. It seems likely that specific comorbidities, including invasive bacterial and fungal infections, are important in this context. For example, an

Table 3. Unadjusted and Adjusted HRs and ORs for Study Endpoints, Comparing Khayelitsha and Gugulethu, South Africa, with the Swiss HIV Cohort Study

Study Endpoints	Number of Patients, South Africa/Switzerland	Number of Events, South Africa/Switzerland	Unadjusted HRs or ORs (95% CI)	*p*-Value	Adjusted[a] HRs or ORs (95% CI)	*p*-Value
First treatment changed	1,972/959	514/539	—	—	—	—
First treatment change due to failure	—	31/39	0.33 (0.20–0.53)	<0.001	0.25 (0.12–0.50)	<0.001
First treatment change due to intolerance	—	238/220	0.43 (0.36–0.52)	<0.001	0.44 (0.32–0.60)	<0.001
First treatment change due to other reasons	—	244/257	0.37 (0.31–0.45)	<0.001	0.30 (0.22–0.40)	<0.001
Viral suppression[b]	1,175/810	1,074/735	1.09 (0.79–1.48)	0.61	1.14 (0.67–1.93)	0.63
Viral rebound	862/783	74/52	1.32 (0.91–1.91)	0.14	1.26 (0.68–2.31)	0.46
Mortality (months 1–3)	1,972/959	118/4	14.60 (5.39–39.54)	<0.001	5.90 (1.81–19.21)	0.003
Mortality (months 4–24)	1,823/912	85/23	2.61 (1.64–4.15)	<0.001	1.77 (0.90–3.50)	0.10

HRs are given for mortality and treatment change, ORs for initial viral response and viral rebound. The difference in the number of patients included in these analyses compared to the total number of patients shown in Table 1 is explained by missing values in key variables.
[a]Analyses were adjusted for sex, age, baseline CD4 cell count, baseline HIV viral load and stage of disease.
[b]HIV-1 RNA ≤500 copies/ml.
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earlier analysis of the Gugulethu data showed that six (27%) of the 22 deaths that occurred during the first 3 mo were due to cryptococcal disease, with a clinical course suggestive of immune reconstitution disease [33].

Unfortunately, causes of death are not recorded systematically in the South African cohorts. A study from rural Uganda showed that a positive serum cryptococcal antigen was associated with substantially increased early mortality (adjusted relative risk 6.6; 95% CI 1.9–12.6) [34]. The corresponding relative risk for active tuberculosis was 4.4 (95% CI 1.2–15.4) [34]. Clinical trials in South Africa and elsewhere will help identify strategies to reduce mortality, including, for example, trials of HAART initiation in HIV–TB coinfected patients [35] and isoniazid preventive therapy in patients receiving HAART [36]. Limited access to diagnostic tests, procedures, and drugs to diagnose and treat opportunistic illnesses, including access to intensive care, may also have contributed to the higher mortality in the South African townships.

After the first few months of HAART, mortality was low in both the South African and Swiss cohorts. The higher mortality in South Africa during this period probably reflects a higher (non-HIV-related) background mortality in South Africa. This interpretation is supported by our comparison of mortality in Switzerland with non-HIV-related mortality in South Africa. South African national HAART programme still bases its treatment guidelines on the 2002 WHO guidelines, which recommend HAART only for patients with WHO stage IV disease or a CD4 cell count of less than 200 cells/μl [37]. These recommendations were revised in 2003 and now state that in patients with WHO stage III disease, treatment should be considered when the CD4 count is below 350 cells/μl and initiated before the CD4 count drops to below 200 cells/μl [38]. Recent analyses from Cape Town showed high mortality before HAART is started or before a formal AIDS diagnosis is made [39–41]. Taken together, there is strong evidence that public health strategies to increase access in South Africa should be further promoted. A recent analysis of the Swiss cohort showed that in Switzerland, late presentation is the reason for late initiation of HAART: once the diagnosis is made, uptake of HAART is fast [42].

Strengths and Limitations of the Study

All patients in this study were treatment-naïve at the start of HAART, and results are therefore not affected by previous antiretroviral therapy.

The two South African township programmes were part of the first public HAART programmes in Southern Africa and are typical of many sites involved in the scale-up of HAART in this region. Scale-up is reflected in the rapid increase in the number of patients starting therapy during the study period. Our study did not, however, include the private sector in South Africa, and no comparison has been made between the overall quality of medical care to support HAART and HIV disease management that is likely to have an important impact on mortality. The SHCS was one of the first HIV cohort studies worldwide [12], and it includes all major HIV outpatient clinics as well as a number of large private practices. It is estimated that about 40% of all patients with HIV and about 70% of patients with AIDS are included [10].

A limitation of our study is that although the reasons for changes in therapy were assessed prospectively, this was not done using the same, standardised instrument and definitions in South Africa and Switzerland. The attribution of the causes for treatment change is further complicated by the fact that causes are not independent: a patient might want to change therapy due to side effects, or side effects can cause problems with adherence, which then leads to treatment failure.

The rate of loss to follow-up was low: in both settings patients who missed appointments were contacted and, if required, traced. However, follow-up information for the South African sites is limited due to the continuous scale-up: i.e., the majority of patients were registered only recently and were thus followed only over a short period of time. These patients will, by definition, not be lost to follow-up. Continued follow-up of patients in South Africa is needed to allow comparisons of treatment responses over longer periods of time.

Conclusions

A public-health approach to HAART provision using a limited repertoire of drugs and relatively few viral load measurements resulted in virologic treatment outcomes in townships in South Africa that were similar to outcomes in Switzerland. Our study also shows that many patients would benefit from earlier initiation of therapy, particularly in South Africa.

Supporting Information

Alternative Language Abstract S1. The Abstract Translated into French by Claire Graber

Found at doi:10.1371/journal.pmed.0050148.sd001 (26 KB DOC).

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Author contributions. OK, ME, and AB designed the study. CO, RW, HF, GvC, and AB collected data for the study and enrolled patients. OK wrote the first draft of the paper, which was subsequently revised by CO and ME. All authors contributed to the final version of the paper. CO collected and entered all the data from the South African Gugulethu site. ME, MWGB, BL, and AB advised on the statistical analyses, which were done by OK. GvC represents the Khayelitsha cohort collaboration team, which includes staff from Médecins Sans Frontières, the Infectious Disease Epidemiology Unit, and the Provincial Government of the Western Cape.

Competing Interests: HF has participated in advisory boards of GlaxoSmithKline (GSK), Bristol-Myers Squibb (BMS), Gilead, Merck Sharp & Dohme-Chibret (MSD) and Boehringer-Ingelheim. The institution of HF has received unrestricted educational grants from Abbott, GSK, BMS, Roche, Gilead, MSD, Boehringer-Ingelheim, and Essex. The other authors declare that they have no competing interests.

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Editors' Summary

Background. Acquired immunodeficiency syndrome (AIDS) has killed more than 25 million people since the first reported case in 1981, and more than 30 million people are now infected with the human immunodeficiency virus (HIV), which causes AIDS. HIV destroys immune system cells (including CD4 cells, a type of lymphocyte), leaving infected individuals susceptible to other infections. Early in the AIDS epidemic, most HIV-infected people died within 10 years of becoming infected. Then, in 1996, highly active antiretroviral therapy (HAART)—a combination of several antiretroviral drugs—was developed. Now, in resource-rich countries, clinicians provide individually tailored care for HIV-infected people by prescribing combinations of antiretroviral drugs chosen from more than 20 approved medicines. The approach to treatment of HIV in developed countries typically also includes frequent monitoring of the amount of virus in patients' blood (viral load), viral resistance testing (to see whether any viruses are resistant to specific antiretroviral drugs), and regular CD4 cell counts (an indication of immune-system health). Since the implementation of these interventions, the health and life expectancy of people with HIV has improved dramatically in these countries.

Why Was This Study Done? The history of HIV care in resource-poor countries has been very different. Initially, these countries could not afford to provide HAART for their populations. In 2003, however, governments, international agencies, and funding bodies began to implement plans to increase HAART coverage in developing countries. By December 2006, more than a quarter of the HIV-infected people in low- and middle-income countries who urgently needed treatment were receiving HAART. However, instead of individualized treatment, HAART programs in developing countries follow a public-health approach developed by the World Health Organization. That is, drug regimens, clinical decision-making, and clinical and laboratory monitoring are all standardized. This public-health approach takes into account the realities of under-resourced health systems, but is it as effective as the individualized approach? The researchers addressed this question by comparing virologic responses (the effect of treatment on the viral load), changes to first-line (initial) therapy, and deaths in patients receiving HAART in South Africa (public-health approach) and in Switzerland (individualized approach).

What Did the Researchers Do and Find? The researchers analyzed data collected since 2001 from more than 2,000 patients enrolled in HAART programs in two townships (Gugulethu and Khayelitsha) in Cape Town, South Africa, and from more than 1,000 patients enrolled in the Swiss HIV Cohort Study, a nationwide study of HIV-infected people. The patients in South Africa, who had a lower starting CD4 cell count and were more likely to have advanced AIDS than the patients in Switzerland, started their treatment for HIV infection with one of four first-line therapies, and about a quarter changed to a second-line therapy during the study. By contrast, 36 first-line regimens were used in Switzerland and half the patients changed to a different regimen. Despite these differences, the viral load was greatly reduced within a year in virtually all the patients and viral rebound (an increased viral load after a low measurement) developed within 2 years in a quarter of the patients in both countries. However, more patients died in South Africa than in Switzerland, particularly during the first 3 months of therapy.

What Do These Findings Mean? These findings suggest that the public-health approach to HAART practiced in South Africa is as effective in terms of virologic outcomes as the individualized approach practiced in Switzerland. This is reassuring because it suggests that "antiretroviral anarchy" (the unregulated use of antiretroviral drugs, interruptions in drug supplies, and the lack of treatment monitoring), which is likely to lead to the emergence of viral resistance, is not happening in South Africa as some experts feared it might. Thus, these findings support the continued rollout of the public-health approach to HAART in resource-poor countries. Conversely, they also suggest that a more standardized approach to HAART could be taken in Switzerland (and in other industrialized countries) without compromising its effectiveness. Finally, the higher mortality in South Africa than in Switzerland, which partly reflects the many patients in South Africa in desperate need of HAART and their more advanced disease at the start of therapy, suggests that HIV-infected patients in South Africa and in other resource-limited countries would benefit from earlier initiation of therapy.

Additional Information. Please access these Web sites via the online version of this summary at http://dx.doi.org/10.1371/journal.pmed.0050148.

- The World Health Organization provides information about universal access to HIV treatment (in several languages) and on its recommendations for a public-health approach to antiretroviral therapy for HIV infection
- More details on the Swiss HIV Cohort Study and on the studies in Gugulethu and Khayelitsha are available
- Information is available from the US National Institute of Allergy and Infectious Diseases on HIV infection and AIDS
- HIV InSite has comprehensive information on all aspects of HIV/AIDS, including detailed information about antiretroviral therapy and links to treatment guidelines for various countries
- Information is available from Avert, an international AIDS charity, on HIV and AIDS around the world and on providing AIDS drug treatment for millions