Virological follow-up of adult patients in antiretroviral treatment programmes in sub-Saharan Africa: a systematic review

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Following large-scale roll-out of antiretroviral therapy in sub-Saharan Africa, the non-clinical efficacy of antiretroviral therapy has received little attention. We aimed to systematically review virological efficacy and drug-resistance outcomes of programmes of antiretroviral therapy in sub-Saharan Africa. 89 studies with heterogeneous design, definitions, and methods were identified. Overall, in on-treatment analysis, 10 351 (78%) of 13 288 patients showed virological suppression after 6 months of antiretroviral therapy, 7413 (76%) of 9794 after 12 months, and 3840 (67%) of 5690 after 24 months. Long-term virological data are scarce. Genotyping results were available for patients with virological failure (HIV-1 RNA greater than 1000 copies per mL). Most patients (839 of 849; 99%) were infected with a non-B HIV-1 subtype. However, drug-resistance patterns were largely similar to those in subtype B. Resistance profiles were associated with the antiretroviral drugs commonly used: the lamivudine-associated M184V mutation was most common, followed by K103N which is associated with non-nucleoside reverse transcriptase inhibitors. Thymidine-analogue mutations and the K65R mutation were less common. First-line antiretroviral therapy regimens used in sub-Saharan Africa are effective. Profiles of drug resistance suggest that a second-line treatment regimen based on protease inhibitors, with a backbone of nucleoside reverse transcriptase inhibitors, is a reasonable option for patients with HIV in sub-Saharan Africa who experience first-line treatment failure.

Lancet Infect Dis 2010; 10: 155–66

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Introduction

An estimated 33 million people worldwide are infected with HIV, most of whom live in sub-Saharan Africa. Highly active antiretroviral therapy (HAART) was introduced in 1996 in developed countries and acknowledged as the standard of care for people with HIV/AIDS ever since. When the Doha declaration was adopted in 2001, which enabled developing countries to circumvent patent rights to increase access to essential medicines, HAART became more widely accessible in resource-limited settings. Subsequently, large funds were provided by the US President's Emergency Plan for AIDS Relief (PEPFAR), which was established in 2002, and by the Global Fund for AIDS, Tuberculosis and Malaria, operating since 2003. In that same year WHO launched their 3 by 5 Initiative, aimed at providing 3 million people with antiretroviral therapy by the end of 2005. Although this goal was not met, the initiative led to a substantial increase in the roll-out of antiretroviral therapy and 2 years later, by the end of 2007, nearly 3 million people worldwide were receiving HAART. The greatest increase in the number of people receiving treatment was in sub-Saharan Africa.[1]

Early results from antiretroviral treatment programmes in African countries have been promising, showing similar results to those in developed countries.[2,3] However, long-term data are scarce; the weighted average follow-up in 32 papers included in a review[4] on retention of patients programmes in sub-Saharan Africa was less than 10 months.

Because of insufficient financial and logistical means, laboratory monitoring of patients receiving antiretroviral therapy is limited in sub-Saharan African countries. The cost of laboratory monitoring of patients has meant that HIV-RNA measurements and genotypic resistance tests are not generally recommended by WHO and are therefore not done consistently. As a substitute, recommendations have been made by WHO to define the failure of antiretroviral therapy by use of clinical criteria and CD4 T-cell counts. Several studies in African settings, however, have shown that the association between these determinants and virological failure is limited.[5–7]

Treatment switches in patients who do not experience virological failure will increase treatment costs and might limit treatment options in the future. Unnecessary loss of treatment options is especially hazardous since only one second-line antiretroviral therapy regimen is available in most sub-Saharan African countries.

Alternatively, continuation of a treatment regimen when patients experience virological failure might compromise patients' immunological and clinical status and, because of ongoing viral replication, lead to the selection of viruses with enhanced resistance to antiretroviral drugs. Resistance outcomes across programmes of antiretroviral treatment with differing intensities of virological monitoring were compared, showing how useful regular virological monitoring is in both resource-rich and resource-limited settings.[8]

In our Review, we assess the results of programmes of antiretroviral treatment in sub-Saharan Africa that reported any relevant virological outcome of first-line HAART in adults infected with HIV. We systematically analyse virological suppression (virological success) and failure as well as selection for drug resistance and discuss the possible implications of these findings on future treatment strategies in this region.

Methods

Search strategy

We systematically reviewed published work in accordance with QUORUM guidelines.[9] We searched the online databases PubMed and Embase for articles available in English before June 1, 2009, with the terms "Africa" or "Afrika" or "sub-Sahara Africa" or "sub Sahara Africa" or "southern Africa" AND "HIV" or "AIDS" or "human immunodeficiency virus" or "acquired immunodeficiency syndrome" AND "antiretroviral therapy" or "antiretroviral*" or "HAART" or "ART" or "ARV" AND "viral load" or "HIV-RNA" or "resistance" or "genotyp*" or "drug-resistance" or "drug resistance". We hand searched the abstract books from selected conferences that were held between early 2007 and June 2009: International AIDS Society Conference 2007 and 2008, and Conference on Retroviruses and Opportunistic Infections 2007, 2008, and 2009. The lists of references from articles that were retrieved and extracted were also screened for potentially relevant articles and abstracts.

Study selection

We included original research papers or abstracts of studies of adult patients infected with HIV-1 that were treated with first-line HAART, defined as a combination of three different antiretroviral drugs, in sub-Saharan Africa. In the included studies HIV-1 RNA had to be measured at least once after starting first-line HAART, and the follow-up of patients needed to be at least 3 months after the start of treatment. The studies could be randomised controlled trials, non-randomised trials, cohort studies, cross-sectional studies, or case series.

We excluded studies in which most patients were either infected with HIV-2, were children (defined as younger than 15 years), received monotherapy or dual therapy, or were on second-line HAART. We also excluded studies done outside sub-Saharan Africa and papers that did not report original data.

If the description of the study was unclear on some of the inclusion or exclusion criteria (eg, minimum length of follow-up), but there were no explicit grounds to exclude the study, the study data were extracted and included. The report was excluded if key data were missing (location of study, number of people included, treatment status of patients, HIV-RNA follow-up data). If the same group of patients was described in more than one article or abstract, the report with the most detailed virological results was included, or, if the reports were complementary, both were included and data combined.

Within the set of papers fitting the above inclusion and exclusion criteria, we identified relevant papers on presumably acquired drug resistance. Such reports were included if they reported drug-resistance mutations of patients experiencing virological failure while on first-line antiretroviral therapy. Articles or abstracts were included independently of the definition of virological failure that was used, but patients had to have detectable HIV-RNA at the time of genotypic testing.

All titles of identified reports were reviewed (exclusion step one). Of the remaining reports the abstracts were reviewed (exclusion step two). The full-length paper was retrieved if it was not an abstract-only report. These papers were checked (exclusion step three).

Validity checking and data extraction

All reports remaining after exclusion step three were independently assessed in duplicate by two authors (RB and MSvdL) according to a set format. We extracted the following key data: first author, year of publication, country (countries) of the study, period of enrolment, type of study (randomised clinical trial, other trial, cohort, cross-sectional study, patient series), number of patients, median age of patients, proportion of females, antiretroviral regimen (based on non-nucleoside reverse transcriptase inhibitors, protease-inhibitors, or other antiretroviral drugs), median or mean baseline (pretreatment) CD4-T-cell count and $\log_{10}$ HIV-RNA plasma concentration, method of analysis (intention to treat or on treatment), months of follow-up, number of patients with HIV-RNA tested at time of analysis, definition of success used in the report, proportion of patients experiencing virological success, definition of virological failure used in the report, proportion of patients experiencing virological failure, number of patients for whom the HIV-subtypes were established, and HIV-subtypes and their frequencies.

Because of the heterogeneous nature of the studies that were included, we decided not to assess the validity of the individual studies. Instead, we present the crucial study characteristics.

Data analyses

HAART was defined as a combination of three different antiretroviral drugs, irrespective of the number of drug-classes used. Definitions of virological success and failure varied between studies. All cut-off values used by investigators were accepted for inclusion in our Review and the definitions used are presented. We did several analyses to compare the results of the various studies; for this purpose we applied specific criteria to define viral suppression, and virological success and failure. For these analyses, suppression was defined as a viral load of fewer than 50 copies per mL and virological success as an HIV-1 RNA of fewer than 400 copies per mL at time of measurement. Virological failure was defined as a viral load of more than 1000 copies per mL in at least one test and at least 3 months after the start of HAART.

Reported drug resistance in adults experiencing virological failure on first-line HAART in a sub-Saharan African treatment programme was summarised. Mutations were analysed according to the International AIDS Society 2008 update of drug resistance mutations.[10] Only major mutations that are not natural polymorphisms

were included. A supplementary analysis was done on the basis of a more extensive list of mutations associated with non-nucleoside reverse transcriptase inhibitors.[11]

Because the studies differed in design (size, length of follow-up, location of study, overall quality of study, intention-to-treat or on-treatment analysis, treatment regimens), formal calculation of summary statistics for virological success and failure was not appropriate. Instead, we report the overall proportions of patients with virological success at 6, 12, or 24 months (ie, number of patients with virological success divided by all patients). Also, the median and range of the proportion of virological success across studies is provided. Similar data are provided for virological failures.

Analyses included all studies, irrespective of first-line regimen. Additionally, we did a subgroup analysis of studies in which more than 90% of patients received antiretroviral treatment based on the use of non-nucleoside reverse transcriptase inhibitors.

Results

The search strategy identified 902 potential articles and 587 potential abstracts (figure). 1199 reports were excluded after checking the titles, mainly because they dealt with obviously different issues, and the abstracts of the remaining 290 reports were reviewed consequently excluding a further 149. Of the remaining 141 reports, the full-length text (if it concerned papers rather than abstracts) were retrieved and reviewed independently in duplicate. In this process another 52 reports were excluded (figure). 89 reports were fully extracted (summarised in tables 1 and 2, and in full in the webappendix);[2,3,5,12–97] these are 69 full-text papers and 20 conference abstracts.

In total, virological data of 63 684 patients on first-line antiretroviral therapy in sub-Saharan African treatment programmes for HIV/AIDS were described. Studies from 18 countries were included, and nine multisite studies. Most of the treatment programmes were set in urban centres; only seven papers[2,3,54,55,61,85,87] and four abstracts[59,72,75,80] contained reports of patients in rural areas. Sample sizes ranged from 16 to 9060 patients; in 33 studies, fewer than 200 patients were included. Three of the included articles were published in 2002[50,79,92] and four in 2003.[32,33,52,67] All other studies had been published more recently. Length of follow-up varied substantially between the studies, ranging from 3 months to 60 months. Of all patients, 5021 (8%) participated in clinical trials.

Most patients were at an advanced disease stage when starting antiretroviral therapy. Median baseline CD4 cell counts were generally lower than 200 cells per µL, although the variation in immunological suppression between studies was substantial (range 43–387 cells per µL). HAART regimens were specified for 58 608 (92%) patients: 53 129 (91%) of these were treated with a regimen consisting of two nucleoside reverse transcriptase inhibitors and either nevirapine or efavirenz as non-nucleoside reverse transcriptase inhibitors; 3626 patients (6%) had regimens based on protease inhibitors, and 1853 (3%) were treated with other regimens such as dual therapy or triple nucleoside reverse transcriptase inhibitors.

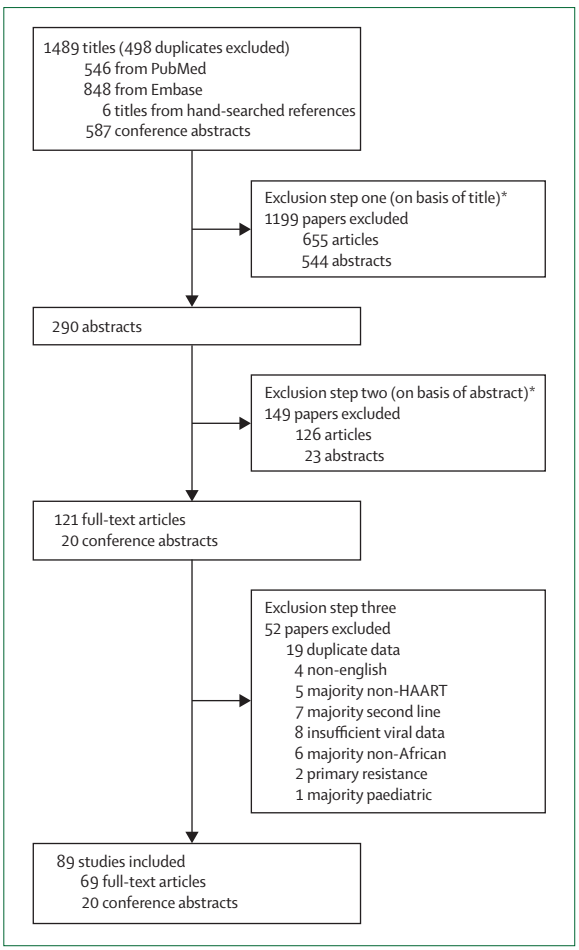

Figure: **Search strategy**
*Studies with no original or virological data, paediatric and in-vitro studies, studies outside of sub-Saharan Africa, studies of prevention of mother-to-child transmission, studies of primary resistance, studies of alternative therapies, and studies on social-science subjects.

See Online for webappendix

Virological success

Tables 1 and 2 and the webappendix show the virological outcome data of the included studies. Virological success was reported in 57 articles and 17 abstracts. 47 papers presented the proportion of patients reaching a viral load of fewer than 400 copies per mL. A cutoff point of 500 copies per mL was used in six studies,[24,27,47,50,51,97] and six additional studies had a stricter definition of either 200 copies per mL or 300 copies per mL.[20,31–34,40] Table 1 summarises data on virological success.

Short-term outcome, after antiretroviral therapy for 6 months, was reported in 25 studies. In total, virological success was achieved in 10 351 (78%) of 13 288 patients in the studies that did an on-treatment analysis. The median proportion of patients with virological success across

	Median age in years*	Proportion of women*	Treatment regimen*	Median CD4 count at baseline* (cells per µL)	Time point of analysis (months)	ITT/OT	Number of patients tested	Proportion of patients with virological success
Botswana[14-16]	33–36	60–91%	NNRTI 100%	67–199	6 12 24 36 60	OT OT OT OT OT	54 984 397 243 60	87% 79–91% 71% 90% 98%
Burkina Faso[20]†	NA	100%	NA	142	36	OT	NA	91%
Burkina Faso, Mali[24]‡	38	67%	NNRTI 84%, PI 16%	387	NA	NA	606	86%
Cameroon[26-29]‡	35–41	66–73%	NNRTI 99–100% PI 0–1%	118–150 1 study: NA	6 12 24	ITT/OT ITT/OT ITT/OT	162/108 135/381 85/247	80–90/95% 80–87/78–97% 67–82/75–90%
Côte d'Ivoire[31-34]†	34–38	5–76%	NNRTI 16–90% PI 10–80% Other 0–11%	122–253 1 study: NA	6 12 24 37	OT ITT/OT OT OT	837 NA/29 15 106	55–85% 50/51% 46% 58%
Côte d'Ivoire, Kenya, Senegal, Uganda[35]	36	62%	PI 100%	119	22	ITT/OT	206/166	52/65%
Kenya[36]	37	64%	NNRTI 100%	96–106	12	OT	137	82%
Malawi[3]	35	64%	NNRTI 99%, PI 1%	114	10	OT	397	84%
Malawi, Mozambique, Tanzania[39]	37	60%	NNRTI 100%	166	6	OT	2112	77%
Mali[40]†	35	61%	NNRTI 100%	105	7	ITT	109	76%
Mozambique[41]	36	69%	NNRTI 100%	115	23	OT	149	79%
Nigeria[43-44]	35–36	56–73%	NNRTI 100%	129–260	6 12	ITT/OT OT	NA/NA 145	72/78–92% 79–91%
Senegal[47,49-51]‡	36–42	45–58%	NNRTI 0–100% PI 0–100% Other 0–10%	109–144	6 12 24 36	ITT/OT ITT/OT OT OT	NA/NA NA/NA 79 34	71–73/78% 51–83/82% 66% 62%
South Africa[2,5,53,55,58,60-63,65,67,69,71]	31–43 Two studies: NA	4–77%, median 69% 2 studies: NA	NNRTI 33–100% (median 100%) PI 0–50% Other 0–26% 4 studies: NA	43–268 (median 106) 2 studies: NA	6 12 24 36	ITT/OT ITT/OT ITT/OT/NA OT	1601/>3961 >1784/>4009 482/1141/360 679	83/75–92% 55–77/66–90% 75/60–72/92% 61%
Tanzania[73]	41	63%	NNRTI 100%	114	12	OT	150	68
Uganda[75-80,82,84,86]	33–39	27–71%, median 66%	NNRTI 69–100% PI 0–31% 2 studies: NA	19–160 (median 99) 2 studies: NA	6–9 12 24	ITT/OT ITT/OT ITT/OT	656/>258 1013/>454 559/246	68–72/66–97% 61–75/83–86% 55/86%
Uganda, Zimbabwe[89]	38	66%	Triple NRTI 100%	101	6 12	ITT/OT ITT/OT	281/281 272/272	79/82% 72/74%
Zambia[90]	NA	52%	NNRTI 100%	115	25	OT	913	74%
Zimbabwe[91,94]	42 1 study: NA	51% 1 study: NA	NNRTI 100%	117–129	4–6 12	ITT/OT OT	NA/NA NA	85/85–96% 74%
Nine countries in southern Africa[96]	36	62%	NNRTI 97% PI <3%	146	6 12 24	OT OT OT	3912 3192 2337	69% 62% 62%
ART-LINC[97]‡	35	49%	NNRTI 57% PI 29% Other 14%	137	6	OT	1914	75%

Virological success defined as HIV-RNA <400 copies per mL. NNRTI=non-nucleoside reverse transcriptase inhibitor. OT=on-treatment analysis. NA=data not available or applicable. PI=protease inhibitor. ITT=intention-to-treat analysis. ART-LINC=several countries in Africa, Latin America and Asia. *If more than one study is included, the ranges between studies is provided. †A stricter cut-off value of HIV-RNA <200/<300 copies per mL was used by some studies. ‡A more lenient cut-off value of HIV-RNA <500 copies per mL was used by some studies.

Table 1: **Summary of virological success data of sub-Saharan African antiretroviral therapy programmes**

studies was 82% (range 54–97%). In six studies with on-treatment analyses,[43,44,71,75,80,94] the proportion of patients with virological success after 6 months of antiretroviral therapy was reported, but the number of people who received an HIV-RNA test was not; in these studies, the proportion with virological success was much the same as that in other studies (range 78–92%). Virological success was reported for 2257 (79%) of 2856 patients in intention-to-treat analyses (median across studies 78%, range 71–90%).

Response data for 1 year were reported in 29 studies. On-treatment data were similar to those at 6 months, 7413 (76%) of 9794 patients had virological success (median across studies 82%, range 51–97%). 2233 (69%) of the 3236 patients for whom an intention-to-treat

	Median age in years*	Proportion of women*	Treatment regimen*	Median CD4 count at baseline* (cells per μL)	Time point of analysis (months)	ITT/OT	Number of patients tested	Proportion of patients with virological suppression
Burkina Faso, Mali[24,25]	38 1 study: NA	67 1 study: NA	NNRTI 84%, PI 16% 1 study: NA	387 1 study: NA	6 NA	OT NA	798 606	75% 77%
Cameroon[28,29]	35	68	NNRTI 100%	118	6 12 24	ITT ITT/OT ITT/OT	60 60/48 60/42	65% 68/79% 48/64%
Côte d'Ivoire, Kenya, Senegal, Uganda[35]	36	62	PI 100%	119	22	ITT/OT	99/82	48/59%
Malawi[3]†	35	64	NNRTI 99%, PI 1%	114	10	OT	397	69%
Mozambique[41]	36	69	NNRTI 100%	115	23	OT	149	72%
Senegal[47,49]	36-37	50-58	NNRTI 100%	126-133	6 12 24	ITT ITT ITT	NA NA NA	50% 43–73% 78%
South Africa[2,53,56,68]	33-41 1 study: NA	5-72 1 study: NA	NNRTI 100%	67–158	4–6 12 24	OT ITT/OT OT	>1909 609/1607 454	63–83% 46/63–70% 65%
Tanzania[72]†	34	73	NNRTI 100%	NA	12	OT	97	85%
Uganda[81]	NA	NA	NNRTI 50% Other 50%	99	12	ITT	600	62–77%
Uganda, Zimbabwe[89]	38	66	Triple NRTI 100%	101	6 12	ITT/OT ITT/OT	281/281 272/272	59/63% 61/62%
Zimbabwe[91]	42	51	NNRTI 100%	117	4–6	ITT/OT	NA/NA	77/87%

Virological suppression defined as HIV-RNA <50 copies per mL. *If more than one study is included, ranges between studies are provided. †A cut-off value of HIV-RNA <40 copies per mL was used by some studies. NNRTI=non-nucleoside reverse transcriptase inhibitor. NA=data not available or applicable. OT=on-treatment analysis. ITT=intention-to-treat analysis. PI=protease inhibitor.

Table 2: **Summary of virological suppression data of sub-Saharan African antiretroviral therapy programmes**

analysis was done had virological success; the median proportion was 74% (range 51–87%). Similar response rates (on treatment 74–85%, intention to treat 50–83%) were reported in the seven studies[32,47,49,69,71,80,94] that did not report the absolute number of patients tested.

On-treatment data at 24 months (range 22–25 months) for 3353 patients reported by 14 studies[15,26,27,29,33,35,41,51,53,60,62,77,90,96] showed virological success in 3840 (67%) of 5690 patients. However, virological success ranged from 46% to 90% (median 72%) in individual studies. Intention-to-treat data after 2 years were available in few studies; the proportion with virological success was lower overall than in on-treatment analysis (837 [63%] of 1332 patients)[26,29,35,63,82] and the median across studies was 67% (range 52–82%).

Long-term data (more than 2 years of follow-up) were scarce. Five studies[14,20,34,51,62] reported on-treatment data after 3 years of treatment, with virological success achieved in 712 (67%) of 1062 patients.

If analyses were done including only studies in which more than 90% of patients received antiretroviral therapy based on non-nucleoside reverse transcriptase inhibitors, results were similar to those in the main analyses (data not shown).

19 papers[2,3,24,25,28,29,35,38,41,47,49,53,56,59,68,72,81,89,91] reported viral suppression with lower cut-off values for success (HIV-RNA of fewer than 40 copies per mL or 50 copies per mL), as is the standard in developed countries. By this stricter criterion in on-treatment analysis, 67% of patients had viral suppression at 6 months (2352 patients) and 12 months (2421 patients) and 66% at 24 months (727 patients). Intention-to-treat data were less favourable, with viral suppression in 60% (341 patients) at 6 months, 59% (1541) at 12 months, and 48% (159) at 24 months. Table 2 summarises reported data on virological suppression.

Virological failure

36 articles and six abstracts reported virological failure (webappendix). The duration of follow-up and the definitions of failure varied substantially. Most studies used a cross-sectional approach, establishing HIV-RNA and genotypic resistance at one point in time. At time of analysis patients had been on antiretroviral therapy for 3–48 months.

In most studies, virological failure was defined as an HIV-RNA rebound of greater than 1000 copies per mL. The proportion of patients in whom there were virological failures according to this definition was presented in 19 papers;[2,3,12,27,29,41,42,46,51,52,54,68,72,73,84,87–89,95] the overall proportion was 15%. The median proportion of patients experiencing virological failure across studies was 14% (range 0–43 %, data derived from 17 of 19 studies). The highest proportion of virological failure was seen in a Rwandan cohort (43%).[46] Patients in this study started antiretroviral therapy before 2003, 233 (9%) of whom received monotherapy or dual therapy instead of HAART.

More lenient definitions of virological failure were described in nine studies: HIV-RNA greater than

	Number of patients in whom HIV subtype was established (subtype)
Angola[12]	23 (four A, four CRF01_AE, three C, two B, two F, two G, two H, two CFR14_BG, one CRF02_AG, one CRF13/CRF11)
Botswana[17]	16 (C)
Botswana[18]	24 (23 C, one CRF11_cpx)
Burkina Faso[21]	6 (three CRF02, two CRF06, one CRF09)
Burkina Faso[23]	75 (36 CRF06_cpx, 30 CRF02_AG, 6 Unclear, one A, one B, one CRF09_cpx)
Burkina Faso, Mali[25]	46 (26 CRF02_AG, 12 CRF_AGK/K, eight Other)
Cameroon[27]	72 (44 CRF02_AG, nine A, seven D, four F, three CRF11_cpx, two G, two CRF13_cpx, one CRF01_AE)
Cameroon[39]	35 (22 CRF02_AG, three F2, 2xCRF01_AE, two CRF02_AG/F, two CRF11_cpx, two D, one CRF13_cpx, one A)
Malawi[3]	50 (C)
Mali[40]	22 (22 CRF_02 AG)
Mozambique[41]	12 (eight C, four CRF08)
Rwanda[46]	22 (11 A, eight C, three Other)
Senegal[50]	39 (23 CFR02_AG, two O, two A, three B, four C, two G, two ?/K, one G/K)
Senegal[52]	47 (25 CRF02_AG, five A, five C, three B, three CRF06, two O, two G, one D, one UK)
South Africa[54]	21 (C)
South Africa[64]	112 (112 C, one A, one B, one C/J)
South Africa[70]	100 (97 C, three Other)
Tanzania[73]	27 (ten A, ten D, seven C)
Uganda[80]	NA (A [49%], D [43%], C [5%], Other [3%])
Uganda[86]	36 (16 A, 15 D, three A/D, two A/E)
Uganda, Zimbabwe[89]	20 (eight C, six A, five D, one D/A)
Zimbabwe[92]	21 (C)
Zimbabwe[93]	20 (C)

CRF=circulating recombinant form. NA=not available.

Table 3: **HIV subtypes in sub-Saharan African antiretroviral treatment programmes**

5000 copies per mL or 10 000 copies per mL and two consecutive measurements of high HIV-RNA titres. Between 2% and 54% of patients had virological failure, with a median across studies of 10%. Stricter definitions (viral loads greater than 40–500 copies per mL) were used in the remaining studies, resulting in higher proportions failing (overall 1131 [19%] of 5942 patients; median across studies 22%, range 6–42%).

In most studies, duration of antiretroviral therapy at time of failure was undefined and solely on-treatment analyses were done.

Subtype analysis and drug-resistance development

HIV-1 subtypes were reported in 849 patients in 22 studies in whom treatment failed (table 3). The most prevalent was subtype C, noted in 399 (47%) patients. The recombinant form CRF-02_AG was found in 195 patients (23%), subtype A in 66 patients (8%), and subtype D in 40 patients (5%). Subtype B, which is predominant in developed countries, was only detected ten times (1%). The remaining 136 patients (16%) were infected with various other subtypes, mosaic, and recombinant forms of HIV-1.

29 studies reported genotypic resistance data. The frequency of specific mutations was provided in 27 of those studies, including 734 patients with virological failure. HIV-RNA genotypic tests were done with commercial assays in all but two studies, in which in-house assays were used. All patients had been exposed to nucleoside reverse transcriptase inhibitors at time of failure. 600 patients (82%) had also been treated with non-nucleoside reverse transcriptase inhibitors. 116 (16%) had received protease inhibitors. The antiretroviral drugs taken by the remaining 18 patients (2%) were not specified.

A summary of the drug-resistance mutations shows that major mutations happened at 40 different codons (table 4). All 16 mutations associated with nucleoside reverse transcriptase inhibitors listed in the drug-resistance list of the International AIDS Society were recorded.[10] The most prevalent drug-resistance mutation was the M184V mutation conferring resistance to lamivudine and emtricitabine, which was recorded in 478 patients (65%). The various thymidine analogue mutations (M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E) were seen in 540 patients (5–20%) and the K65R mutation in 36 (5%).

11 major mutations associated with non-nucleoside reverse transcriptase inhibitors were reported. The K103N mutation, conferring resistance to nevirapine and efavirenz, was found in 310 patients (52%) exposed to non-nucleoside reverse transcriptase inhibitors. Other common mutations associated with non-nucleoside reverse transcriptase inhibitors included Y181C found in 103 patients (17%), G190A in 100 (17%), and V106A/M in 79 (13%).

In some studies, additional mutations associated with non-nucleoside reverse transcriptase inhibitors were reported.[11] K101E was detected in 38 patients (6%), M230L in 16 (3%), and V179E in 15 (3%). Other mutations (L101Q, K103S, E138G, V179I/G/V, H221Y, F227L, P236L, and K238N) were reported in less than 1% of patients with treatment failure.

Among patients with exposure to protease inhibitors, seven different major mutations associated with protease inhibitors were noted. The L90M and the V82A/F/T/S mutations were seen most common, both found in 18 patients (16%).

Discussion

We identified 69 peer-reviewed papers and 20 abstracts that provided information on virological outcome of antiretroviral treatment programmes in sub-Saharan Africa.

Short-term results are promising. The proportions of patients with on-treatment success after 6–24 months of first-line therapy are comparable to those from developed countries, but intention-to-treat data are less optimistic.

In guidance published by WHO, a list of targets for antiretroviral therapy programmes in resource-limited countries is provided. A virological suppression rate of over 70% at 1 year after starting antiretroviral therapy is one of these goals.[98] Assuming that this advice is on the

	Number of patients (%)
NRTI-associated mutations (total 734)	
M41L	86 (12)
A62V	13 (2)
K65R	36 (5)
D67N	118 (16)
D67K/N	1 (<1)
D67GN	1 (<1)
T69A	4 (<1)
T69D	8 (1)
T69I	3 (<1)
T69S	4 (1)
T69A/E	1 (<1)
T69N	5 (1)
K70E	1 (<1)
K70R	78 (11)
K70R/E	19 (3)
L74V	9 (1)
V75I	9 (1)
F77L	3 (<1)
Y115F	10 (1)
F116Y	5 (1)
Q151M	10 (1)
M184I	4 (1)
M184V	478 (65)
M184V/I	1 (<1)
M184G/V	1 (<1)
L210W	38 (5)
T215F	28 (4)
T215Y	85 (12)
T215Y/F	37 (5)
T215N	1 (<1)
K219E	19 (3)
K219Q	17 (2)
K219Q/E/N/R	13 (2)
(Continues in next column)	

	Number of patients (%)
(Continued from previous column)	
NNRTI-associated mutations (total 600)	
A98G	14 (2)
L100I	10 (2)
K101E	38 (6)
K101KP	1 (<1)
K103N	310 (52)
V106A	12 (2)
V106M	61 (10)
V106A/M	6 (1)
V108I	40 (7)
V179D	2 (<1)
V179F/V	1 (<1)
Y181C	92 (15)
Y181I	2 (<1)
Y181C/I	11 (2)
Y188C	2 (<1)
Y188L	18 (3)
Y188C/L/H	12 (2)
Y188H	2 (<1)
G190A	81 (14)
G190S	5 (1)
G190A/S	19 (3)
G190S/E	1 (<1)
P225H	29 (5)
PI-associated mutations (total 116)	
D30N	2 (2)
L33F	1 (1)
M46I	3 (3)
M46L	3 (3)
M46I/L	3 (3)
I47V	2 (2)
V82A	8 (8)
V82F	3 (3)
V82T	4 (4)
V82A/T	2 (2)
V82A/T/F/S	1 (1)
I84V	11 (11)
L90M	18 (16)

NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor. PI=protease inhibitor.

Table 4: **Reported major drug-resistance mutations in 734 patients who experienced treatment failure**

basis of an HIV-RNA cut-off value of 400 copies per mL, 80% of programmes with on-treatment analysis and 63% with intention-to-treat achieved this target. This is an impressive accomplishment given the difficulties associated with treatment roll-out in areas where HIV prevalence is high but resources are limited.

Studies on treatment efficacy after the first years of HAART in developed countries, in which similar viral load cut-off values were used to those implemented in the African treatment programmes (ie, HIV-RNA less than 400 copies per mL), reported virological success in 57–75% of patients (intention-to-treat) after 6–12 months of HAART based on non-nucleoside reverse transcriptase inhibitors.[99–101] These results are comparable to those seen in cohorts in sub-Saharan Africa. However, in the reports from developed countries, many patients were pretreated with suboptimum regimens. More recent data on the efficacy of antiretroviral therapy in developed countries are better, in particular for patients who were truly treatment naive who were immediately started on a three-drug regimen. A review[102] of both clinical trial and non-trial studies, for example, showed virological success after 48 weeks of follow-up in 73% (intention to treat) of patients taking a first line HAART regimen based on non-nucleoside reverse transcriptase inhibitors. One recent trial[103] even reported viral suppression in 89% of patients at week 96 (intention to treat).

The proportions of patients with virological failure in the treatment programmes in sub-Saharan Africa were generally comparable to those for on-treatment failure in patients receiving first-line HAART in the European EuroSIDA cohort[100] if a cut-off of HIV-RNA greater than 1000 copies per mL was used to define failure.

Genotypic-resistance analysis to establish resistance to antiretroviral drugs is not usually available and therefore the selection of drugs upon switches is generally empirical. However, apart from counselling to improve treatment adherence, insight into the level and consequences of drug resistance in the treated population is important to identify the best second-line treatment regimens and achieve maximum treatment efficacy.

Most knowledge on drug resistance of HIV-1 has been derived from studies in developed countries, where subtype B is the predominant subtype. Drug-resistance profiles might differ between B and non-B HIV-1 subtypes. However, recent data suggest that the overall drug-resistance profiles in HIV-1 subtype B and non-subtype B viruses are generally similar for known resistance-related positions,[10] suggesting that the subtype-B-based algorithms to interpret the consequences of resistance mutations for drug activity, can also be applied on non-B subtypes. Nevertheless, the possibility remains that some subtype-specific mutations have not yet been identified because few well-documented resistance studies in non-B subtypes have been done.

Mutations recorded in the African cohorts were associated with commonly prescribed treatment regimens. Two-thirds of patients experiencing virological failure and tested for resistance had the M184V mutation. Assuming that patients who were not tested for resistance despite virological failure show a similar mutation frequency and assuming that patients without failure do not harbour this mutation, virus in an estimated 10% of all patients starting antiretroviral therapy in sub-Saharan Africa will develop the M184V mutation within a few years. This mutation causes high-level resistance to lamivudine and emtricitabine, but increases the susceptibility of viruses with initial mutations associated with tenofovir, zidovudine, and stavudine, thereby delaying the emergence of high-level resistance to these drugs. This increased susceptibility is thought to explain the lower frequency of thymidine analogue mutations[104,105] and the lower rate of acquisition of the K65R mutation. Tenofovir, and less frequently stavudine, can cause selection of this mutation. Although in-vitro research suggested a more rapid development of the K65R mutation for subtype C in the absence of M184V,[106] we did not find many patients harbouring this mutation in our Review. The low K65R prevalence in studies where 399 patients (47%) were infected with subtype C, might be explained by the limited use of tenofovir in antiretroviral therapy programmes in Africa. The K103N mutation was detected in most patients exposed to non-nucleoside reverse transcriptase inhibitors. Various other mutations associated with non-nucleoside reverse transcriptase inhibitors were reported, some of which have not yet been included in the International AIDS Society-USA list of drug-resistance mutations because they are also natural polymorphisms. Not all studies that included genotyping tests might have included these additional mutations in their analyses. Therefore, the prevalence of mutations associated with non-nucleoside reverse transcriptase inhibitors might be higher than reported here. Indeed, in one study[54] that did report on such additional mutations, mutations associated with non-nucleoside reverse transcriptase inhibitors accumulated within patients. Such accumulation might limit future treatment options with second-line non-nucleoside reverse transcriptase inhibitor drugs even further.

Since only a few patients received protease inhibitors, data on resistance mutations associated with this drug class were scarce. Second-line regimens based on protease inhibitors therefore seem to be an appropriate empirical choice for patients experiencing treatment failure in sub-Saharan Africa. On the basis of the published resistance data, the commonly available fixed-dose combination of lamivudine and zidovudine seems to be a reasonable nucleoside reverse transcriptase inhibitors backbone treatment for patients given a high genetic barrier protease inhibitor. By retaining the M184V mutation, the selection of resistance against thymidine analogues will be delayed. Even in patients who harbour virus with the K65R mutation, a zidovudine-containing salvage regimen might be appropriate because this mutation increases viral susceptibility to zidovudine. However, in settings in which treatment switches are solely on the basis of clinical failure and long-term virological failure at time of antiretroviral-therapy change is probable, thymidine-analogue mutations will be more prevalent. In the presence of thymidine-analogue mutations, the potency of a lamivudine and zidovudine containing backbone might be impaired to an extent that its use can no longer be recommended.

There are some limitations to this Review. First, studies included were rather heterogeneous in their design, the definitions used to establish virological success and failure, and the methodology of data analysis. Second, even though the reported data on virological efficacy for antiretroviral treatment programmes in sub-Saharan Africa are promising, long-term data are still scarce and in most cases result from on-treatment analyses. Because retention of patients in antiretroviral therapy programmes in sub-Saharan Africa is about 60% after 2 years,[4] results from intention-to-treat analyses would clearly be lower. Furthermore, caution is warranted when comparing results from sub-Saharan Africa with those from developed countries, because some important differences might exist between cohorts from both settings. African cohorts typically have high early mortality and large numbers of patients lost to follow-up soon after starting antiretroviral therapy. This pattern is attributed to the advanced disease stages and low counts of CD4 T cell at start of treatment in

many patients. Most patients in African treatment programmes are women, whereas men are predominant in settings in developed countries. This probably does not influence virological treatment outcomes,[107] but other, often unreported, differences, such as comorbidities, dietary intake, socioeconomic status, drug stock outs, and distance to the hospital might exist, which could have an effect on the overall treatment success rate. Last, most data on genotypic resistance come from treatment programmes in which virological monitoring is available. In programmes in which such monitoring is not feasible, patients are at greater risk of continuing a failing treatment regimen, possibly causing an accumulation of resistance mutations. As a result, the actual frequency of drug-resistance mutations might be higher as reported here.

Conclusion

Achieving similar response rates in sub-Saharan Africa with those seen in developed countries is a substantial accomplishment considering the rate at which programme expansions have taken place since 2003 and the substantial limitations in patient monitoring. However, results from intention-to-treat analyses showed decreased response compared with on-treatment analyses, probably caused by a more advanced stage of infection at start of treatment in African patients. Therefore, efforts should be made for earlier detection and treatment of infections with HIV in sub-Saharan Africa.

The resistance profiles in the included studies, which all had some viral monitoring, mainly show reduced susceptibility to lamivudine and non-nucleoside reverse transcriptase inhibitors. This reduction of susceptibility suggests that in the absence of thymidine-analogue mutations, second-line boosted regimens based on protease inhibitors can still be complemented with a backbone of nucleoside reverse transcriptase inhibitors.

The continued massive roll-out of treatment and the absence of regular laboratory monitoring might result in many patients experiencing (long-term) virological failure without notice. The continued replication of HIV-1 in these patients might further comprise treatment options. Therefore, serious efforts should be made to make newer antiretroviral drug classes available in sub-Saharan Africa, in conjunction with regular virological monitoring of all patients on antiretroviral therapy.

Contributors

RB did the initial search of published work, checked all full-text articles and extracted data from the full reports and conference abstracts. RB conceived and coordinated the analyses and wrote the first draft of the paper. MSvdL also checked all full-text articles and abstracts and independently extracted data, as a second reviewer. MSvdL checked and corrected the epidemiological analyses. RS and AH supervised the reviewing process and participated in discussion of the results. AW initiated the review. AW was available as a third reviewer in case of conflicting results after data extraction. RB, MSvdL, RS, AH, and AW all participated in writing of the final paper. All authors have seen and approved the final version of the paper.

Conflicts of interest

We declare that we have no conflicts of interest.

References

1 WHO. Towards universal access: scaling up priority HIV/AIDS interventions in the health sector. Geneva: World Health Organization, 2008.

2 Barth RE, van der Meer JT, Hoepelman AI, et al. Effectiveness of highly active antiretroviral therapy administered by general practitioners in rural South Africa. *Eur J Clin Microbiol Infect Dis* 2008; **27:** 977–84.

3 Ferradini L, Jeannin A, Pinoges L, et al. Scaling up of highly active antiretroviral therapy in a rural district of Malawi: an effectiveness assessment. *Lancet* 2006; **367:** 1335–42.

4 Rosen S, Fox MP, Gill CJ. Patient retention in antiretroviral therapy programs in sub-Saharan Africa: a systematic review. *PLoS Med* 2007; **4:** e298.

5 Badri M, Lawn SD, Wood R. Utility of CD4 cell counts for early prediction of virological failure during antiretroviral therapy in a resource-limited setting. *BMC Infect Dis* 2008; **8:** 89.

6 Mee P, Fielding KL, Charalambous S, Churchyard GJ, Grant AD. Evaluation of the WHO criteria for antiretroviral treatment failure among adults in South Africa. *AIDS* 2008; **22:** 1971–77.

7 Messou E, Gabillard D, Moh R, et al. Anthropometric and immunological success of antiretroviral therapy and prediction of virological success in west African adults. *Bull World Health Organ* 2008; **86:** 435–42.

8 Gupta RK, Hill A, Sawyer AW, et al. Virological monitoring and resistance to first-line highly active antiretroviral therapy in adults infected with HIV-1 treated under WHO guidelines: a systematic review and meta-analysis. *Lancet Infect Dis* 2009; **9:** 409–17.

9 Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement—Quality of Reporting of Meta-analyses. *Lancet* 1999; **354:** 1896–900.

10 Johnson VA, Brun-Vezinet F, Clotet B, et al. Update of the drug resistance mutations in HIV-1: spring 2008. *Top HIV Med* 2008; **16:** 62–68.

11 Rimsky L, Tambuyzer L, Vingerhoets J, Azijn H, Staes M, Picchio G. Compilation of mutations associated with resistance to NNRTIs deduced from clinical samples in-vitro analyses, and bibliographical studies. 16th International HIV Drug Resistance Workshop; Bridgetown, Barbados; June 12–16, 2007. Poster 63.

12 Garrido C, Zahonero N, Fernandes D, et al. Subtype variability, virological response and drug resistance assessed on dried blood spots collected from HIV patients on antiretroviral therapy in Angola. *J Antimicrob Chemother* 2008; **61:** 694–98.

13 Bisson GP, Frank I, Gross R, et al. Out-of-pocket costs of HAART limit HIV treatment responses in Botswana's private sector. *AIDS* 2006; **20:** 1333–36.

14 Bussmann H, Wester CW, Ndwapi N, et al. Five-year outcomes of initial patients treated in Botswana's National Antiretroviral Treatment Program. *AIDS* 2008; **22:** 2303–11.

15 Bussmann H, Wester CW, Thomas A, et al. Response to zidovudine/didanosine-containing combination antiretroviral therapy among HIV-1 subtype C-infected adults in Botswana: two-year outcomes from a randomized clinical trial. *J Acquir Immune Defic Syndr* 2009; **51:** 37–46.

16 Wester W, Bussmann H, Thomas A, et al. NNRTI outcomes among HIV-1C-infected adults receiving first-line HAART in Botswana: results from a randomized clinical trial. 16th Conference on Retroviruses and Opportunistic Infections; Montreal, Canada; Feb 8–11, 2009. Abstract 595.

17 Doualla-Bell F, Gaseitsiwe S, Ndungu T, et al. Mutations and polymorphisms associated with antiretroviral drugs in HIV-1C-infected African patients. *Antivir Chem Chemother* 2004; **15:** 189–200.

18 Novitsky V, Wester CW, DeGruttola V, et al. The reverse transcriptase 67N 70R 215Y genotype is the predominant TAM pathway associated with virologic failure among HIV type 1C-infected adults treated with ZDV/ddI-containing HAART in southern Africa. *AIDS Res Hum Retroviruses* 2007; **23:** 868–78.

19 Wester CW, Kim S, Bussmann H, et al. Initial response to highly active antiretroviral therapy in HIV-1C-infected adults in a public sector treatment program in Botswana. *J Acquir Immune Defic Syndr* 2005; **40:** 336–43.

20 Huet C, Ouedraogo A, Konate I, et al. Feasibility and efficacy of HAART among hard-to-reach high-risk women in Burkina Faso. 17th International AIDS Conference 2008; Mexico City, Mexico; Aug 3–8, 2008. Abstract MOPE0058.

21 Nadembega WM, Giannella S, Simpore J, et al. Characterization of drug-resistance mutations in HIV-1 isolates from non-HAART and HAART treated patients in Burkina Faso. *J Med Virol* 2006; **78:** 1385–91.

22 Perreve B, Jacomet C, Sawadogo A, Raguin G, Drabo J. Effectiveness and tolerance of two antiretroviral (ARV) strategies in naive patients in Yalgado Ouedraogo, University Teaching Hospital, Ouagadougou BF. 17th International AIDS Conference 2008; Mexico City, Mexico; Aug 3–8, 2008. Abstract CDB0228.

23 Tebit DM, Sangare L, Makamtse A, et al. HIV drug resistance pattern among HAART-exposed patients with suboptimal virological response in Ouagadougou, Burkina Faso. *J Acquir Immune Defic Syndr* 2008; **49:** 17–25.

24 Boileau C, Nguyen VK, Sylla M, et al. Low prevalence of detectable HIV plasma viremia in patients treated with antiretroviral therapy in Burkina Faso and Mali. *J Acquir Immune Defic Syndr* 2008; **48:** 476–84.

25 Sylla M, Chamberland A, Boileau C, et al. Characterization of drug resistance in antiretroviral-treated patients infected with HIV-1 CRF02_AG and AGK subtypes in Mali and Burkina Faso. *Antivir Ther* 2008; **13:** 141–48.

26 Bourgeois A, Laurent C, Mougnutou R, et al. Field assessment of generic antiretroviral drugs: a prospective cohort study in Cameroon. *Antivir Ther* 2005; **10:** 335–41.

27 Kouanfack C, Montavon C, Laurent C, et al. Low levels of antiretroviral-resistant HIV infection in a routine clinic in Cameroon that uses the World Health Organization (WHO) public health approach to monitor antiretroviral treatment and adequacy with the WHO recommendation for second-line treatment. *Clin Infect Dis* 2009; **48:** 1318–22.

28 Laurent C, Kouanfack C, Koulla-Shiro S, et al. Effectiveness and safety of a generic fixed-dose combination of nevirapine, stavudine, and lamivudine in HIV-1-infected adults in Cameroon: open-label multicentre trial. *Lancet* 2004; **364:** 29–34.

29 Laurent C, Kouanfack C, Koulla-Shiro S, et al. Long-term safety, effectiveness and quality of a generic fixed-dose combination of nevirapine, stavudine and lamivudine. *AIDS* 2007; **21:** 768–71.

30 Laurent C, Kouanfack C, Vergne L, et al. Antiretroviral drug resistance and routine therapy, Cameroon. *Emerg Infect Dis* 2006; **12:** 1001–04.

31 Chaix ML, Rouet F, Toni T, et al. Low rate of resistance to antiretroviral drugs 6 months after HAART initiation in HIV-1-infected sub-Saharan African: the ANRS 1269 TRIVICAN trial. 14th Conference on Retroviruses and Opportunistic Infections; Los Angeles, CA, USA; Feb 25–28, 2007. Abstract 646.

32 Djomand G, Roels T, Ellerbrock T, et al. Virologic and immunologic outcomes and programmatic challenges of an antiretroviral treatment pilot project in Abidjan, Côte d'Ivoire. *AIDS* 2003; **17** (suppl 3): S5–15.

33 Seyler C, Anglaret X, Dakoury-Dogbo N, et al. Medium-term survival, morbidity and immunovirological evolution in HIV-infected adults receiving antiretroviral therapy, Abidjan, Côte d'Ivoire. *Antivir Ther* 2003; **8:** 385–93.

34 Seyler C, Adje-Toure C, Messou E, et al. Impact of genotypic drug resistance mutations on clinical and immunological outcomes in HIV-infected adults on HAART in west Africa. *AIDS* 2007; **21:** 1157–64.

35 Sow PS, Otieno LF, Bissagnene E, et al. Implementation of an antiretroviral access program for HIV-1-infected individuals in resource-limited settings: clinical results from 4 African countries. *J Acquir Immune Defic Syndr* 2007; **44:** 262–67.

36 Sarna A, Luchters S, Geibel S, et al. Short- and long-term efficacy of modified directly observed antiretroviral treatment in Mombasa, Kenya: a randomized trial. *J Acquir Immune Defic Syndr* 2008; **48:** 611–19.

37 Lennemann T, Rabenau HR, Tsasanyana T, et al. Patients in Mafeteng on antiretroviral therapy (PIMA)—a cross-sectional study of patients receiving antiretroviral treatment (ART) within the national ART program of Lesotho. 17th International AIDS Conference 2008; Mexico City, Mexico; Aug 3–8, 2008. Abstract CDB0218.

38 van Oosterhout JJ, Bodasing N, Kumwenda JJ, et al. Evaluation of antiretroviral therapy results in a resource-poor setting in Blantyre, Malawi. *Trop Med Int Health* 2005; **10:** 464–70.

39 Marazzi MC, Liotta G, Germano P, et al. Excessive early mortality in the first year of treatment in HIV type 1-infected patients initiating antiretroviral therapy in resource-limited settings. *AIDS Res Hum Retroviruses* 2008; **24:** 555–60.

40 Marcelin AG, Jarrousse B, Derache A, et al. HIV drug resistance after the use of generic fixed-dose combination stavudine/lamivudine/nevirapine as standard first-line regimen. *AIDS* 2007; **21:** 2341–43.

41 Maldonado F, Biot M, Roman F, et al. Viraemia and HIV-1 drug resistance mutations among patients receiving antiretroviral treatment in Mozambique. *Trans R Soc Trop Med Hyg* 2009; **103:** 607–12.

42 San Lio MM, Carbini R, Germano P, et al. Evaluating adherence to highly active antiretroviral therapy with use of pill counts and viral load measurement in the drug resources enhancement against AIDS and malnutrition program in Mozambique. *Clin Infect Dis* 2008; **46:** 1609–16.

43 Idigbe EO, Adewole TA, Eisen G, et al. Management of HIV-1 infection with a combination of nevirapine, stavudine, and lamivudine: a preliminary report on the Nigerian antiretroviral program. *J Acquir Immune Defic Syndr* 2005; **40:** 65–69.

44 Idoko JA, Agbaji O, Agaba P, et al. Direct observation therapy-highly active antiretroviral therapy in a resource-limited setting: the use of community treatment support can be effective. *Int J STD AIDS* 2007; **18:** 760–63.

45 Meloni ST, Ekong E, Onwujekwe DI, et al. Evaluation of ART in the Harvard PEPFAR treatment program in Nigeria. 14th Conference on Retroviruses and Opportunistic Infections; Los Angeles, CA, USA; Feb 25–28, 2007. Abstract 544.

46 Fischer A, Karasi JC, Kibibi D, et al. Antiviral efficacy and resistance in patients on antiretroviral therapy in Kigali, Rwanda: the real-life situation in 2002. *HIV Med* 2006; **7:** 64–66.

47 Canestri A, Sow PS, Vray M, et al. Poor efficacy and tolerability of stavudine, didanosine, and efavirenz-based regimen in treatment-naive patients in Senegal. *MedGenMed* 2007; **9:** 7.

48 Etard JF, Ndiaye I, Thierry-Mieg M, et al. Mortality and causes of death in adults receiving highly active antiretroviral therapy in Senegal: a 7-year cohort study. *AIDS* 2006; **20:** 1181–89.

49 Landman R, Diallo MB, Poupard M, et al. Efficacy and safety at 96 weeks of the new WHO first line regimen: tenofovir-emtricitabine-efavirenz in HIV-1 infected adults in Senegal. 4th International AIDS Society Conference; Sydney, Australia; July 22–25, 2007. Abstract WEPEB061.

50 Laurent C, Diakhate N, Gueye NF, et al. The Senegalese government's highly active antiretroviral therapy initiative: an 18-month follow-up study. *AIDS* 2002; **16:** 1363–70.

51 Laurent C, Ngom Gueye NF, Ndour CT, et al. Long-term benefits of highly active antiretroviral therapy in Senegalese HIV-1-infected adults. *J Acquir Immune Defic Syndr* 2005; **38:** 14–17.

52 Vergne L, Kane CT, Laurent C, et al. Low rate of genotypic HIV-1 drug-resistant strains in the Senegalese government initiative of access to antiretroviral therapy. *AIDS* 2003; **17** (suppl 3): S31–38.

53 Charalambous S, Innes C, Muirhead D, et al. Evaluation of a workplace HIV treatment programme in South Africa. *AIDS* 2007; **21** (suppl 3): S73–78.

54 Barth RE, Wensing AM, Tempelman HA, Moraba R, Schuurman R, Hoepelman AI. Rapid accumulation of nonnucleoside reverse transcriptase inhibitor-associated resistance: evidence of transmitted resistance in rural South Africa. *AIDS* 2008; **22:** 2210–12.

55 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): S464–68.

56 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.

57 Black V, Hoffman RM, Sugar CA, et al. Safety and efficacy of initiating highly active antiretroviral therapy in an integrated antenatal and HIV clinic in Johannesburg, South Africa. *J Acquir Immune Defic Syndr* 2008; **49:** 276–81.

58 Boulle A, Van Cutsem G, Cohen K, et al. Outcomes of nevirapine- and efavirenz-based antiretroviral therapy when coadministered with rifampicin-based antitubercular therapy. *JAMA* 2008; **300:** 530–39.

59 Cabrera Escobar M, Esterhuizen TM, Holmes M, et al. Virological and clinical outcomes of HIV-positive patients on antiretroviral therapy under different models of treatment and care in KwaZulu-Natal, South Africa. 17th International AIDS Conference 2008; Mexico City, Mexico; Aug 3–8, 2008. Abstract CDB0216.

60 Coetzee D, Hildebrand K, Boulle A, et al. Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa. *AIDS* 2004; **18:** 887–95.

61 Gandhi NR, Moll AP, Lalloo U, et al. Successful integration of tuberculosis and HIV treatment in rural South Africa: the Sizonq'oba study. *J Acquir Immune Defic Syndr* 2009; **50:** 37–43.

62 Innes C, Charalambous S, Maraisane M, et al. 24 and 36 month outcomes among HIV-infected individuals starting antiretroviral therapy in a workplace program in South Africa. 17th International AIDS Conference 2008; Mexico City, Mexico; Aug 3–8, 2008. Abstract MOPE0046.

63 Losina E, Chang Y, Kaplan R, et al. Immunologic benefits of complete vs partial virologic suppression in patients initiating ART in Gugulethu, South Africa. 15th Conference on Retroviruses and Opportunistic Infections; Boston, MA, USA; Feb 3–6, 2008. Abstract 823.

64 Marconi VC, Sunpath H, Lu Z, et al. Prevalence of HIV-1 drug resistance after failure of a first highly active antiretroviral therapy regimen in KwaZulu Natal, South Africa. *Clin Infect Dis* 2008; **46:** 1589–97.

65 Nachega JB, Stein DM, Lehman DA, et al. Adherence to antiretroviral therapy in HIV-infected adults in Soweto, South Africa. *AIDS Res Hum Retroviruses* 2004; **20:** 1053–56.

66 Nachega J, Goliath R, Efron A, et al. Randomized trial of trained patient-nominated treatment supporters providing partial directly observed ART in South African adults initiating HIV therapy. 16th Conference on Retroviruses and Opportunistic Infections; Montreal, Canada; Feb 8–11, 2009. Abstract 143.

67 Orrell C, Bangsberg DR, Badri M, Wood R. Adherence is not a barrier to successful antiretroviral therapy in South Africa. *AIDS* 2003; **17:** 1369–75.

68 Orrell C, Harling G, Lawn SD, et al. Conservation of first-line antiretroviral treatment regimen where therapeutic options are limited. *Antivir Ther* 2007; **12:** 83–88.

69 Ratsela A, Polis M. Phidisa II: a randomized 2×2 factorial trial comparing initial therapy of efavirenz with lopinavir/ritonavir and zidovudine + didanosine with stavudine + lamivudine in treatment-naive HIV-infected persons with <200 CD4+ cells/mm³ or a prior AIDS diagnosis. 16th Conference on Retroviruses and Opportunistic Infections; Montreal, Canada; Feb 8–11, 2009. Abstract no 594.

70 Wallis C, Bell C, Boulme R, et al. Emerging ART drug resistance in subtype C: experience from the 2 clinics in Johannesburg, South Africa. 14th Conference on Retroviruses and Opportunistic Infections; Los Angeles, CA, USA; Feb 25–28, 2007. Abstract 661.

71 Wouters E, Van Damme W, van Rensburg D, Meulemans H. Impact of baseline health and community support on antiretroviral treatment outcomes in HIV patients in South Africa. *AIDS* 2008; **22:** 2545–48.

72 Johannessen A, Naman E, Matee M, et al. Long-term virological results in HIV-infected patients on antiretroviral treatment in rural Tanzania. 17th International AIDS Conference 2008; Mexico City, Mexico; Aug 3–8, 2008. Abstract CDB0222.

73 Ramadhani HO, Thielman NM, Landman KZ, et al. Predictors of incomplete adherence, virologic failure, and antiviral drug resistance among HIV-infected adults receiving antiretroviral therapy in Tanzania. *Clin Infect Dis* 2007; **45:** 1492–98.

74 Ahoua L, Guenther G, Pinoges L, et al. Long term therapeutic outcomes in adults after 12 and 24 months of HAART in the HIV care program of North-Western Uganda. 4th International AIDS Society Conference; Sydney, Australia; July 22–25, 2007. Abstract WEPEB048.

75 Alibhai A, Kipp W, Okech-Ojony J, Konde-Lule J, Saunders LD, Kiweewa F. Outcomes of a community-based HAART program for rural patients in western Uganda. 17th International AIDS Conference 2008; Mexico City, Mexico; Aug 3–8, 2008. Abstract CDB0217.

76 Baker CA, Emenyonu N, Ssewanyana I, et al. Profile of immunologic recovery in HIV-infected Ugandan adults after antiretroviral therapy. *AIDS Res Hum Retroviruses* 2007; **23:** 900–05.

77 Chang LW, Alamo S, Guma S, et al. Two-year virologic outcomes of an alternative AIDS care model: evaluation of a peer health worker and nurse-staffed community-based program in Uganda. *J Acquir Immune Defic Syndr* 2009; **50:** 276–82.

78 Kamya MR, Mayanja-Kizza H, Kambugu A, et al. Predictors of long-term viral failure among ugandan children and adults treated with antiretroviral therapy. *J Acquir Immune Defic Syndr* 2007; **46:** 187–93.

79 Kebba A, Atwine D, Mwebaze R, Kityo C, Nakityo R, Peter M. Therapeutic responses to AZT + 3TC + EFV in advanced antiretroviral naive HIV type 1-infected Ugandan patients. *AIDS Res Hum Retroviruses* 2002; **18:** 1181–87.

80 Martin J, Emenyonu N, Bwana M, et al. Initial treatment outcomes from a rural-based ART scale-up program in East Africa: the UARTO cohort. 15th Conference on Retroviruses and Opportunistic Infections; Boston, MA, USA; Feb 3–6, 2008. Abstract 816.

81 Munderi P, Walker S, Kityo C, et al. Discordance between virological/immunological and clinical outcomes at 48 weeks, in a randomised comparison of ZDV/3TC/NVP and ZDV/3TC/ABC in 600 patients with low CD4 counts in Africa. 4th International AIDS Society Conference; Sydney, Australia; July 22–25, 2007. Abstract WEAB1LB.

82 Nakanjako D, Kiragga A, Ibrahim F, Castelnuovo B, Kamya MR, Easterbrook PJ. Sub-optimal CD4 reconstitution despite viral suppression in an urban cohort on antiretroviral therapy (ART) in sub-Saharan Africa: frequency and clinical significance. *AIDS Res Ther* 2008; **5:** 23.

83 Oyugi JH, Byakika-Tusiime J, Charlebois ED, et al. Multiple validated measures of adherence indicate high levels of adherence to generic HIV antiretroviral therapy in a resource-limited setting. *J Acquir Immune Defic Syndr* 2004; **36:** 1100–02.

84 Oyugi JH, Byakika-Tusiime J, Ragland K, et al. Treatment interruptions predict resistance in HIV-positive individuals purchasing fixed-dose combination antiretroviral therapy in Kampala, Uganda. *AIDS* 2007; **21:** 965–71.

85 Reynoids SJ, Nakigozi G, Newell K, et al. Failure of immunologic criteria to appropriately identify antiretroviral treatment failure in Uganda. *AIDS* 2009; **23:** 697–700.

86 Spacek LA, Shihab HM, Kamya MR, et al. Response to antiretroviral therapy in HIV-infected patients attending a public, urban clinic in Kampala, Uganda. *Clin Infect Dis* 2006; **42:** 252–59.

87 Weidle PJ, Wamai N, Solberg P, et al. Adherence to antiretroviral therapy in a home-based AIDS care programme in rural Uganda. *Lancet* 2006; **368:** 1587–94.

88 Pillay D, Kityo C, Robertson V, et al. Emergence and evolution of drug resistance in the absence of viral load monitoring during 48 weeks of combivir/tenofovir within the DART trial. 14th Conference on Retroviruses and Opportunistic Infections; Los Angeles, CA, USA; Feb 25–28, 2007. Abstract 642.

89 DART Virology Group and Trial Team. Virological response to a triple nucleoside/nucleotide analogue regimen over 48 weeks in HIV-1-infected adults in Africa. *AIDS* 2006; **20:** 1391–99.

90 Goldman JD, Cantrell RA, Mulenga LB, et al. Simple adherence assessments to predict virologic failure among HIV-infected adults with discordant immunologic and clinical responses to antiretroviral therapy. *AIDS Res Hum Retroviruses* 2008; **24:** 1031–35.

91 Duse AG, Morar A, Landman I, et al. Short-term effectiveness and safety of HAART in the form of a generic fixed-dose combination of stavudine, lamivudine and nevirapine (Triviro) in HIV-1-infected adults in Zimbabwe. *South Afr J HIV Med* 2008; **9:** 51–56.

92 Kantor R, Zijenah LS, Shafer RW, et al. HIV-1 subtype C reverse transcriptase and protease genotypes in Zimbabwean patients failing antiretroviral therapy. *AIDS Res Hum Retroviruses* 2002; **18:** 1407–13.

93 Ledweba J, Pillay V, Dalai S, et al. Detection of drug resistance by population sequencing and allele specific PCR for K103N after nevirapine-based HAART in subtype C HIV-1 in Zimbabwe. 14th Conference on Retroviruses and Opportunistic Infections; Los Angeles, CA, USA; Feb 25–28, 2007. Abstract 643.

94 Zijenah LS, Kadzirange G, Rusakaniko S, et al. A pilot study to assess the immunologic and virologic efficacy of generic nevirapine, zidovudine and lamivudine in the treatment of HIV-1 infected women with pre-exposure to single dose nevirapine or short course zidovudine and their spouses in Chitungwiza, Zimbabwe. *Cent Afr J Med* 2006; **52:** 1–8.

95 Bisson GP, Gross R, Bellamy S, et al. Pharmacy refill adherence compared with CD4 count changes for monitoring HIV-infected adults on antiretroviral therapy. *PLoS Med* 2008; **5:** e109.

96 Nachega JB, Hislop M, Nguyen H, et al. Antiretroviral therapy adherence, virologic and immunologic outcomes in adolescents compared with adults in southern Africa. *J Acquir Immune Defic Syndr* 2009; **51:** 65–71.

97 Tuboi SH, Brinkhof MW, Egger M, et al. Discordant responses to potent antiretroviral treatment in previously naive HIV-1-infected adults initiating treatment in resource-constrained countries: the antiretroviral therapy in low-income countries (ART-LINC) collaboration. *J Acquir Immune Defic Syndr* 2007; **45:** 52–59.

98 Bennett DE, Bertagnolio S, Sutherland D, Gilks CF. The World Health Organization's global strategy for prevention and assessment of HIV drug resistance. *Antivir Ther* 2008; **13** (suppl 2)**:** 1–13.

99 Bartlett JA, DeMasi R, Quinn J, Moxham C, Rousseau F. Overview of the effectiveness of triple combination therapy in antiretroviral-naive HIV-1 infected adults. *AIDS* 2001; **15:** 1369–77.

100 Paredes R, Mocroft A, Kirk O, et al. Predictors of virological success and ensuing failure in HIV-positive patients starting highly active antiretroviral therapy in Europe: results from the EuroSIDA study. *Arch Intern Med* 2000; **160:** 1123–32.

101 Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. *N Engl J Med* 1999; **341:** 1865–73.

102 Bartlett JA, Fath MJ, Demasi R, et al. An updated systematic overview of triple combination therapy in antiretroviral-naive HIV-infected adults. *AIDS* 2006; **20:** 2051–64.

103 Riddler SA, Haubrich R, DiRienzo AG, et al. Class-sparing regimens for initial treatment of HIV-1 infection. *N Engl J Med* 2008; **358:** 2095–106.

104 Boyer PL, Sarafianos SG, Arnold E, Hughes SH. The M184V mutation reduces the selective excision of zidovudine 5Ľ-monophosphate (AZTMP) by the reverse transcriptase of human immunodeficiency virus type 1. *J Virol* 2002; **76:** 3248–56.

105 Ait-Khaled M, Stone C, Amphlett G, et al. M184V is associated with a low incidence of thymidine analogue mutations and low phenotypic resistance to zidovudine and stavudine. *AIDS* 2002; **16:** 1686–89.

106 Brenner BG, Oliveira M, Doualla-Bell F, et al. HIV-1 subtype C viruses rapidly develop K65R resistance to tenofovir in cell culture. *AIDS* 2006; **20:** F9–13.

107 Moore AL, Kirk O, Johnson AM, et al. Virologic, immunologic, and clinical response to highly active antiretroviral therapy: the gender issue revisited. *J Acquir Immune Defic Syndr* 2003; **32:** 452–61.