Tropical Medicine and International Health doi:10.1111/j.1365-3156.2009.02259.x

VOLUME 14 NO 5 PP 556–563 MAY 2009

Reduced morbidity and mortality in the first year after initiating highly active anti-retroviral therapy (HAART) among Ugandan adults

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Summary

OBJECTIVE To evaluate the effect of highly active anti-retroviral therapy (HAART) and cotrimoxazole prophylaxis on morbidity after HAART eligibility.

METHODS Between 1999 and 2006, we collected morbidity data from a community-based cohort of HAART-eligible patients, comparing patients initiating HAART and those non-HAART. Patients aged 15 years or older visited the clinic every 6 months and when ill. Baseline data on patients' characteristics, WHO stage, haemoglobin and CD4+ T-cell counts, along with follow-up data on morbidity (new, recurrent and drug-related), were collected for the first year after initiating HAART or becoming HAART-eligible. We estimated the overall effect of HAART on morbidity; adjusted for the effect of cotrimoxazole prophylaxis by Mantel–Haenszel methods. A negative binomial regression model was used to assess rate ratios (RR) after adjustment for other confounders, including cotrimoxazole.

RESULTS A total of 219 HAART patients (median age 37 years; 73% women; 82% using cotrimoxazole prophylaxis, median haemoglobin 11.7 g/dl and median CD4+ 131 cells/μl) experienced 94 events in 127 person-years. 616 non-HAART patients (median age 33 years; 70% women; 26% using cotrimoxazole prophylaxis, median haemoglobin 11.2 g/dl and median CD4+ 130 cells/μl) experienced 862 events in 474 person-years. The overall morbidity during the first year of HAART was 80% lower than among non-HAART patients (adjusted RR = 0.20, 95% CI: 0.12–0.34). Cotrimoxazole prophylaxis also reduced morbidity (adjusted RR = 0.65, 95% CI: 0.45–0.94).

CONCLUSION These results confirm the reduction in morbidity due to HAART, and the additional protection of cotrimoxazole prophylaxis.

keywords highly active anti-retroviral therapy, cotrimoxazole prophylaxis, morbidity, adverse events

Introduction

Treatment with highly active antiretroviral therapy (HAART) has dramatically reduced morbidity and mortality associated with human immunodeficiency virus (HIV) (Egger *et al.* 1997, Patella *et al.* 1998). In Switzerland, the risk of an initial AIDS diagnosis after CD4+ T-cell counts fell below 200 cells/μl reduced by 42% with HAART compared with its absence (Egger *et al.* 1997). Most published data of the effect of HAART on morbidity originate from hospitalized patients, with limited information from outpatient clinics. Population or outpatient clinic based data are particularly scarce from resource-limited settings. Doubts have been raised about the adherence to, and effectiveness of HAART, under the circumstances typical of rural Africa (Hardon *et al.* 2007), and data are needed to study this question under 'real life' conditions.

The effects of HAART on morbidity depend on several factors: past medical history, stage of HIV disease, demographic characteristics, presence of co-morbidities, HAART drug regimes, duration of HAART, use of cotrimoxazole prophylaxis and adherence (Bonnet *et al.* 2005, Mermin *et al.* 2006, Manzardo *et al.* 2007, Fielden *et al.* 2008). Patients with a history of hospitalization prior to initiating HAART, and those initiating HAART with CD4+ T-cell counts <50 cells/μl, had a higher risk of hospitalization while on HAART than patients without such a history (Fielden *et al.* 2008). In poor settings, HIV patients are exposed to other infectious agents and already existing co-morbidities, which may limit the effectiveness of HAART and increase the risk of adverse effects among

patients taking HAART (Ssali *et al.* 2006, Subbaraman *et al.* 2007).

Cotrimoxazole prophylaxis has reduced morbidity and mortality among patients with HIV disease (Mermin *et al.* 2006; Watera *et al.* 2006, Fairall *et al.* 2008) and is now recommended by national policies in many African countries, including Uganda (Moh *et al.* 2005). Cotrimoxazole prophylaxis is usually continued indefinitely after patients commence antiretroviral drugs, as guidelines on discontinuing cotrimoxazole prophylaxis have not yet been developed. This study provides an opportunity to evaluate the additional benefit of cotrimoxazole to HIV-infected patients during the first year after initiating HAART.

We investigated the effects of HAART and of cotrimoxazole prophylaxis on morbidity (including HAART-associated toxicities) in the first 12 months after HAART eligibility in an outpatient setting working under resource-limited conditions in Uganda, where most HAART medications typically comprise protease inhibitor-sparing regimes.

Methods and study population

In 1995 an open cohort of HIV-1-infected patients, aged 15 years or older, living within 40 km of Entebbe and attending one of two outpatient clinics, was established to evaluate effects of new interventions to reduce disease progression and death (French *et al.* 2000; Watera *et al.* 2006). Patients were given 6-monthly clinic appointments for regular clinical, haematological and immunological evaluation. All patients had access to free outpatient and hospital care whenever ill, although participants had to meet transport costs for unscheduled interim clinic visits. Standard procedures were used to diagnose sick patients, including the collection of clinical and laboratory data for definitive diagnosis whenever possible.

At each scheduled clinic visit, patients were examined and classified according to the World Health Organization (WHO) clinical staging system (WHO 1993) and samples taken for haemoglobin, differential blood cell and CD4+ T-cell counts. From August 2000, cotrimoxazole prophylaxis was introduced to all eligible patients at their scheduled clinic visits (Watera *et al.* 2006). In 1999, HAART was available through private clinics (selectively accessible to patients who were able to pay), in 2004 was made available to some study patients, and from May 2005 became generally available to patients through public clinics.

Cohort members initiating HAART between July 1999 and April 2006 were identified. HAART-eligibility was defined as any WHO stage 4 event, recurrent WHO stage 3 events, pulmonary tuberculosis with CD4+ T-cells <350 cells/μl, or CD4+ T-cells <200 cells/μl. Some patients initiated HAART outside these criteria and they were excluded from the comparative analysis, although they were included in analysis of HAART-related toxicities. Patients were excluded from the analysis if, they had started HAART before joining the cohort, or were enrolled in a randomized controlled trial to study alternative HAART monitoring strategies (DART). Those who started HAART after enrolment into this cohort were not excluded from the analysis. A historical comparison group was identified from patients who were eligible for HAART but had not received it. The comparison group was chosen to have a similar distribution for sex and CD4+ T-cell counts as the HAART-exposed patients at the time of eligibility for HAART. For patients on HAART, the period of analysis started the date they started HAART. For patients who did not receive HAART, the analysis started from the date they were first seen to be eligible for HAART.

We extracted data on patient demographics, HAART status, cotrimoxazole usage, baseline WHO staging, haemoglobin and baseline CD4+ T-cell counts from the cohort database. From the start date (either start of HAART or HAART eligibility), a retrospective review of patient records collected data on new opportunistic events, toxicity events and other diseases experienced in the 12 months following this date. The study stopped at the end of July 2006 and all patients with less than 12 months follow up were censored at that date. Patients in the comparison group were censored at the date they initiated HAART if this was within 12 months of their eligibility. Cotrimoxazole prophylaxis binary status was defined as an affirmative response to cotrimoxazole ingested for the 14 days prior to the clinic visit. Clinical events included both definitive (laboratory confirmed) and clinical diagnosis (for diseases where laboratory confirmation was not feasible such as oral and esophageal candidiasis). Person-years of follow up were defined as 12 months following the start date or to the date of censoring.

Data were entered in MS Access (MS Corp, Redmond USA) and analysed using STATA 9.2 (Stata Corp, Texas, USA). Demographic and clinical characteristics were described using means, medians and proportions as appropriate and compared using chi-squared and Kruskal–Wallis tests. Incidence rates and 95% confidence intervals (CI) for each group were obtained by dividing the number of events by the person-years at risk in each group. Rate ratios (RR) and 95% CI were used to compare the groups. The morbidity events in each group were stratified by use of cotrimoxazole prophylaxis; Mantel–Haenszel weighted rate ratios were obtained from the two strata and tested for heterogeneity. A negative binomial regression model was used to assess the independent effects of HAART,

cotrimoxazole prophylaxis usage, age, sex, baseline WHO stage, haemoglobin and CD4+ T-cell counts on the incidence of morbidity, allowing for multiple events per patient and simultaneous adjustment for possible confounders.

Results

A total of 232 patients initiated HAART after enrolment into the Entebbe cohort and the HAART regimes commonly used are shown in Table 1. In the first 12 months, 16 (7%) drug substitutions were made (6 to efavirenz; 7 to stavudine; 1 to nevirapine; 1 to didanosine; 1 to tenofovir). 14 (6%) were due to toxicity and two because of anticipated incompatibility between nevirapine and rifampicin. 21 patients (9%) experienced peripheral neuropathy, of whom 20 were receiving stavudine; eight (3%) patients experienced anaemia, all of whom were taking zidovudine. Five (2%) patients experienced drug rashes on the skin, all of whom were taking nevirapine, and three (1%) patients experienced psychosis or depression, all of whom were receiving efavirenz.

Using the same HAART-eligibility criteria, clinical records of 219 HAART patients were compared with those of 616 patients who did not receive HAART when eligible. At baseline, patients on HAART were older, had higher haemoglobin levels and a higher percentage of them used cotrimoxazole prophylaxis than the non-HAART comparison group. A lower percentage of patients in the HAART group were diagnosed with WHO stages 3 and 4 (47% *vs.* 57%; $P = 0.002$) although the CD4+ T-cell distribution was similar in both groups (Table 2). For those on HAART, record review started on the day they initiated HAART and the median time between HAART initiation and record review was 245 days (range: 10–2892), with 28 (12.8%) patients initiating HAART before 1st January 2004. Among non-HAART patients, record review started the day they became eligible for HAART and median time between HAART eligibility and record review was 405 days (range: 1–2629) with 432 (70.1%) starting record review before 1st January 2004. Of the 835 patients, 367 (44%) patients had a full year of follow up: 49 (22%) in the HAART group and 318 (52%) in the comparison group, including 27 who subsequently received HAART (more than a year after first becoming eligible) and thereby contributed to the HAART group (Table 2). Within 12 months of the start of the review 255 patients died (13 in the HAART group and 242 in the comparison group; $P < 0.001$). 213 patients were censored, 157 (72%) of those on HAART and 29 (5%) of those non-HAART at the last clinic visit by July 2006 and 27 (4%) patients of the non-HAART group because they started HAART during the year after becoming eligible.

There was a 60% reduction in all-cause morbidity associated with HAART initiation during the first year of follow up (Table 3). No cases of muco-cutaneous candidiasis or non-typhi *Salmonella* bacteraemia occurred

Table 1 HAART regimes used among 232 study patients analysed for the prevalence of related toxicity during the study period

HAART regime	Started *n* (%)	Changed to
Stavudine/d4T, lamivudine/3TC, nevirapine/NVP	88 (37.9)	2* efavirenz/EFV (1 month)
Zidovudine/AZT, lamivudine/3TC, nevirapine/NVP	58 (25.0)	2* stavudine/d4T (1 month) stavudine/d4T (3 month) 2* efavirenz/EFV (1 month) efavirenz/EFV (4 months) stavudine/d4T & efavirenz/EFV (1 month)
Zidovudine/AZT, lamivudine/3TC, efavirenz/EFV	48 (20.7)	2* stavudine/3TC (2 months) nevirapine/NVP (2 months)
Stavudine/d4T, lamivudine/3TC, efavirenz/EFV	29 (12.5)	1* tenofovir/TDF (7 months)
Other†	9 (3.9)	7* drug substitutions
Total	232	

†Other regimes included:
Stavudine/d4T, didanosine/ddI, indinavir/IDV.
Stavudine/d4T, didanosine/ddI, efavirenz/EFV.
Lamuvidine/3TC, didanosine/ddI, indinavir/IDV.
Zidovudine/AZT, lamuvidine/3TC, indinavir/IDV.
Zidovudine/AZT, lamuvidine/3TC, tenofovir/TDF.
Zidovudine/AZT, lamuvidine/3TC, kaletra/(LPV/RTV).
HAART, highly active anti-retroviral therapy.

Table 2 Demographic and clinical characteristics of patients at the beginning of follow up in this cohort

Variable	HAART-exposed patients *n* = 219	Non HAART patients *n* = 616	*P*-value
Median age (range) in years	37 (23–67)	33 (18–75)	$P < 0.001$
Women *n* (%)	160 (73)	434 (70)	$P = 0.5$
WHO stage *n* (%)			
1	12 (6)	42 (7)	$P = 0.002$
2	103 (47)	218 (35)	
3	75 (34)	293 (48)	
4	29 (13)	58 (9)	
Missing	0 (0)	5 (1)	
Median haemoglobin (IQR) in g/dl	11.7 (10.7–12.8)	11.2 (9.9–12.6)	$P < 0.001$
Median CD4+ T cells per μl (Range)	131 (1–645)	130 (1–437)	$P = 0.3$
CD4+ T-cell categories *n* (%)			
<50	34 (16)	100 (16)	$P = 0.26$
50–99	26 (12)	112 (18)	
100–149	53 (24)	133 (22)	
150–199	81 (37)	202 (33)	
200+	25 (11)	69 (11)	
Cotrimoxazole prophylaxis use during follow up *n* (%)			
Used	179 (82)	159 (26)	$P < 0.001$
Not used	32 (14)	323 (52)	
Not known	8 (4)	134 (22)	
Outcome at completion of follow up *n* (%)			
Death	13 (6)	242 (39)	$P < 0.001$
Alive at 1 year	49 (22)	318 (52)	
Censored	157 (72)	56 (9)	

HAART, highly active anti-retroviral therapy.

Table 3 Rate of disease and effect of HAART on disease incidence in HIV positive patients eligible for HAART

Person years of follow up Morbidity event	HAART 127.4 *n* (*r*/100pyrs)	Non-HAART 473.6 *n* (*r*/100pyrs)	Crude rate ratios (95% CI)	*P*-value
All events	94 (73.8)	862 (182.0)	0.40 (0.32–0.50)	<0.001
Undiagnosed febrile events	28 (22.0)	204 (43.1)	0.51 (0.33–0.76)	<0.001
Tuberculosis	7 (5.5)	69 (14.6)	0.38 (0.15–0.82)	0.006
Ulcerative sexually transmitted infections	7 (5.5)	59 (12.4)	0.44 (0.17–0.98)	0.03
Pneumonia	4 (3.1)	42 (8.9)	0.35 (0.09–0.98)	0.03
Malaria falciparum	4 (3.1)	33 (7.0)	0.45 (0.12–1.27)	0.11
Herpes zoster	3 (2.4)	26 (5.5)	0.43 (0.08–1.40)	0.15
Chronic diarrhoea	2 (1.6)	31 (6.5)	0.24 (0.03–0.94)	0.022
Invasive cryptococcal disease	2 (1.6)	16 (3.4)	0.46 (0.05–1.98)	0.31
Pneumococcal bacteraemia	2 (1.6)	1 (0.2)	7.44 (0.39–439)	0.13
Kaposi's sarcoma	1 (0.8)	12 (2.5)	0.31 (0.01–2.09)	0.25
Oral candidiasis	0	42 (8.9)	0 (0–0.34)	<0.001
Vulvo-vaginal candidiasis	0	30 (6.3)	0 (0–0.49)	<0.001
Esophageal candidiasis	0	19 (4.0)	0 (0–0.80)	0.011
Non-typhi salmonella bacteraemia	0	5 (1.1)	0 (0–4.06)	0.30

pyrs, person-years; *n*, number of new events, *r*, incidence rate; HAART, highly active anti-retroviral therapy.

Table 4 The effect of HAART on disease incidence stratified by the use of cotrimoxazole prophylaxis, in HIV positive patients eligible for HAART

Group	No cotrimoxazole stratum†	Cotrimoxazole stratum‡	Mantel–Haenszel combined	Test for homogeneity
Effect of HAART	RR (95% CI)	RR (95% CI)	RR (95% CI)	
All events	0.39 (0.23–0.61)	0.52 (0.39–0.68)	0.47 (0.37–0.60)	0.29
Undiagnosed febrile events	0.45 (0.14–1.08)	0.53 (0.30–0.91)	0.51 (0.32–0.79)	0.75
Tuberculosis	0.28 (0.01–1.65)	0.75 (0.23–2.23)	0.56 (0.23–1.36)	0.4
Ulcerative sexually transmitted infections	0.29 (0.01–1.70)	0.59 (0.19–1.64)	0.49 (0.20–1.16)	0.5
Pneumonia	0.42 (0.01–2.56)	0.38 (0.07–1.44)	0.39 (0.13–1.15)	0.97
Malaria falciparum	1.36 (0.26–4.49)	1.38 (0.02–108.6)	1.37 (0.45–4.12)	0.99
Herpes zoster	0 (0–3.15)	0.70 (0.11–3.27)	0.47 (0.12–1.90)	0.5
Chronic diarrhoea	0.57 (0.01–3.61)	0.28 (0.01–2.47)	0.41 (0.09–1.72)	0.6
Invasive cryptococcal disease	0 (0–6.40)	2.77 (0.14–163)	1.06 (0.14–8.03)	0.4
Pneumococcal bacteraemia	0 (0–473)	N/A	13.8 (0.12–1546)	N/A
Kaposi's sarcoma	0 (0–5.53)	1.38 (0.02–108)	0.49 (0.04–6.50)	0.46
Oral candidiasis	0 (0–1.90)	0 (0–0.62)	0	1.0
Vulvo-vaginal candidiasis	0 (0–3.58)	0 (0–0.45)	0	1.0
Esophageal candidiasis	0 (0–3.58)	0 (0–3.34)	0	1.0
Non-typhi salmonella bacteraemia	0 (0–26.4)	0 (0–7.37)	N/A	1.0

†A total of 355 patients were not taking cotrimoxazole prophylaxis, 32 on HAART, and 323 non-HAART (Table 2).
‡A total of 338 patients were taking cotrimoxazole prophylaxis, 179 on HAART and 159 non-HAART (Table 2).
RR, Rate Ratios; HAART, highly active anti-retroviral therapy.

among HAART patients. The overall reduction in morbidity after HAART initiation was greater than 60% for the incidence of tuberculosis, chronic diarrhoea, Kaposi's sarcoma and pneumonia.

After stratifying for cotrimoxazole prophylaxis usage, we observed a 53% reduction in all-cause morbidity after HAART initiation, compared to those who did not receive HAART within the first year of follow up (Table 4). There was no significant heterogeneity between the estimated effects of HAART in the 2 strata (those who received and those who did not receive cotrimoxazole prophylaxis). A negative binomial model, assuming multiple morbidity events per patient, estimated 79% reduction in all-cause morbidity due to HAART (Crude RR = 0.21: 95% CI 0.15–0.30, $P < 0.001$). This effect was unchanged after adjusting for age, sex, baseline WHO stage, haemoglobin, baseline CD4+ T-cell count and cotrimoxazole prophylaxis (Adjusted RR = 0.20: 95% CI 0.12–0.34, $P < 0.001$). Cotrimoxazole prophylaxis in the regression model, also showed a 35% reduction in all-cause morbidity within the first year of follow up (RR = 0.66: 95% CI 0.41–1.06, $P = 0.089$), after adjusting for HAART, age, sex, baseline WHO stage, haemoglobin and baseline CD4+ T-cell count.

Discussion

The focus of our study was to investigate the effect of HAART on morbidity among adult African patients from two busy outpatient clinics during the first year on HAART. We also observed a significant reduction in mortality in the HAART group compared to the non-HAART group. It was remarkable given that a high percentage of our patients had a baseline CD4+ T-cell count <50 cells/μl. This was consistent with other publications from East Africa (Mermin *et al.* 2008).

We saw a significant 80% reduction in all-cause morbidity during the first year on HAART compared to patients who were eligible for HAART but did not receive it. This was similar to other studies where opportunistic infections were significantly reduced following introduction of HAART (Patella *et al.* 1998; Mocroft *et al.* 2000). Among HIV-infected patients who did not receive HAART, the all-cause morbidity was high, with about two clinical events per patient per year, during the year after HAART-eligibility. The most common events reported among non-HAART patients in this study were undiagnosed fever, tuberculosis, genital ulcers and muco-cutaneous candidiasis, with an incidence similar to other studies in sub-Saharan Africa (Morgan *et al.* 2001; Brown *et al.* 2006, Watera *et al.* 2006).

In the year after HAART initiation, muco-cutaneous candidiasis and non-typhi salmonella bacteraemia were eliminated and only one case of Kaposi sarcoma was seen. These observed effects were larger than those in other studies, possibly because of the shorter follow-up period (Tumbarello *et al.* 2000, Hung *et al.* 2001, Gona *et al.*

2006). The reduced incidence of Kaposi's sarcoma is probably due to improved immune competence and reduced viraemia of both HIV and human herpesvirus 8 (HHV-8) (Bourboulia *et al.* 2004).

Other studies have shown a 40–80% reduction in TB incidence after HAART initiation, which was compatible with our observation (Badri *et al.* 2002, Brinkhof *et al.* 2007). There were similar reductions in the incidence of chronic diarrhoea (76%), pneumonia (65%), genital ulcers (56%) and undiagnosed febrile events (49%) attributed to HAART use in the first year after initiation, which were consistent with other studies (Pozio 2004; Gona *et al.* 2006). These improvements were due to restoration of the immune system among patients starting HAART (Meiderma *et al.* 1997, Autran *et al.* 1999).

Cotrimoxazole prophylaxis showed an independent, additional 35% reduction in all-cause morbidity after HAART initiation, thus providing a strong case for continuing with cotrimoxazole prophylaxis. Cotrimoxazole reduces the incidence of chronic diarrhoea through its activity on enteric infections, such as *Isospora belli, Cyclospora cayetanensis*, non-typhi *Salmonella* and *Campylobacter* species (Pape 1988, Verdier *et al.* 2000, Brink *et al.* 2002). The reduced incidence of malaria in this study could be explained by the activity of cotrimoxazole on malaria parasites (Thera *et al.* 2005). This is consistent with two other studies among HIV-infected patients in Uganda where cotrimoxazole prophylaxis reduced malaria incidence by 76% and 69% (Mermin *et al.* 2006; Watera *et al.* 2006). Unlike Mermin, after stratifying for cotrimoxazole prophylaxis HAART we saw no significant protection against the incidence of malaria in our study.

Our study had some limitations. Firstly, the use of a historical comparison group brings some possible bias from unknown changes, such as improved patient management, which may have occurred over time. Socio-economic status was not included in the selection criteria yet access to HAART via private clinics in late 1990s was partly influenced by this variable. As this was a retrospectively nested cohort, there were no reliable socio-economic data to control for this confounding variable, but only 28 patients accessed HAART prior to 2004. Secondly, as 72% of patients on HAART were censored at the end of this study in July 2006, before completing 12 months of follow up, we may have over-estimated the incidence of disease in the first year after HAART initiation. Thirdly, cotrimoxazole prophylaxis (a binary variable) was taken by 82% of patients on HAART, but by only 26% of those non-HAART and this imbalance in numbers reduced the power of the stratified analysis. The median duration on cotrimoxazole could not be ascertained in each group to determine potential differential bias. The negative binomial regression model adjusted the effect of HAART on all cause morbidity, for the independent effect of cotrimoxazole prophylaxis, but this model incorrectly assumed proportional hazards between the morbidity among patients on HAART and those non-HAART over the period at risk. At the beginning of follow up the risk of morbidity may have been similar between the two groups, but the risk among patients on HAART patients reduced with time, and the risk among those non-HAART increased with time. This may partly explain why the effect estimated by Mantel–Haenszel methods differed from the effect estimated by the negative binomial regression model. Fourthly, patients who did not receive HAART started observation under follow up on the day they become HAART-eligible but patients receiving HAART started observation on the day they initiated HAART, which for some patients was up to 12 months after first becoming HAART-eligible. Fifthly, the 400 patients who left our cohort to join a different ART trial may have introduced some selection bias, as they could not be included in this analysis. Lastly, there were 27 patients who contributed time at risk to both study groups which may have limited the comparability of the two groups.

During the first year after HAART initiation there were few (7%) HAART drug substitutions. Other studies from resource-limited settings have reported 15–21% of patients needing HAART drug substitutions because of toxicity (Coetzee *et al.* 2004, Forna *et al.* 2007, Sow *et al.* 2007). The proportion of patients seen with peripheral neuropathy (9%), anaemia (3%), drug rash (2%) and psychosis (1%) in this study was lower than those reported in other studies (Ssali *et al.* 2006).

Our cohort has been maintained for over a decade using the same methods for clinical, laboratory and data management (French *et al.* 2000; Watera *et al.* 2006). Most diagnoses in this study were definite, supported by quality laboratory services. Our laboratory continuously participates in a UK-based external quality scheme (Watera *et al.* 2006). Eligibility for HAART was assessed using CD4+ T-cell counts and WHO criteria (WHO 1993).

Our results contribute to the accumulating body of evidence showing that dramatic improvements in the health status of HIV-infected patients are seen within a short time after initiating HAART. We confirm the complementary benefit of cotrimoxazole prophylaxis in the first year that patients receive HAART. More research is needed to assess the potential, long-term, harmful effects from the interaction between some HAART drugs and cotrimoxazole (Moh *et al.* 2005, Watera *et al.* 2007), and to provide guidelines as to when cotrimoxazole prophylaxis can be discontinued safely among

immuno-competent patients receiving HAART in resource-limited countries.

Acknowledgements

We thank the medical, nursing and support staff at the study clinics for their role in recruitment, follow up, medical and psychosocial support given to the patients and administration of the study as well as the MRC/UVRI Unit statistical and laboratory staff for all the services offered. We also specially recognize the patients for agreeing to take part in the study and The Aids Support Organization (TASO) for their permission to use their premises and to invite their clients for the research.

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