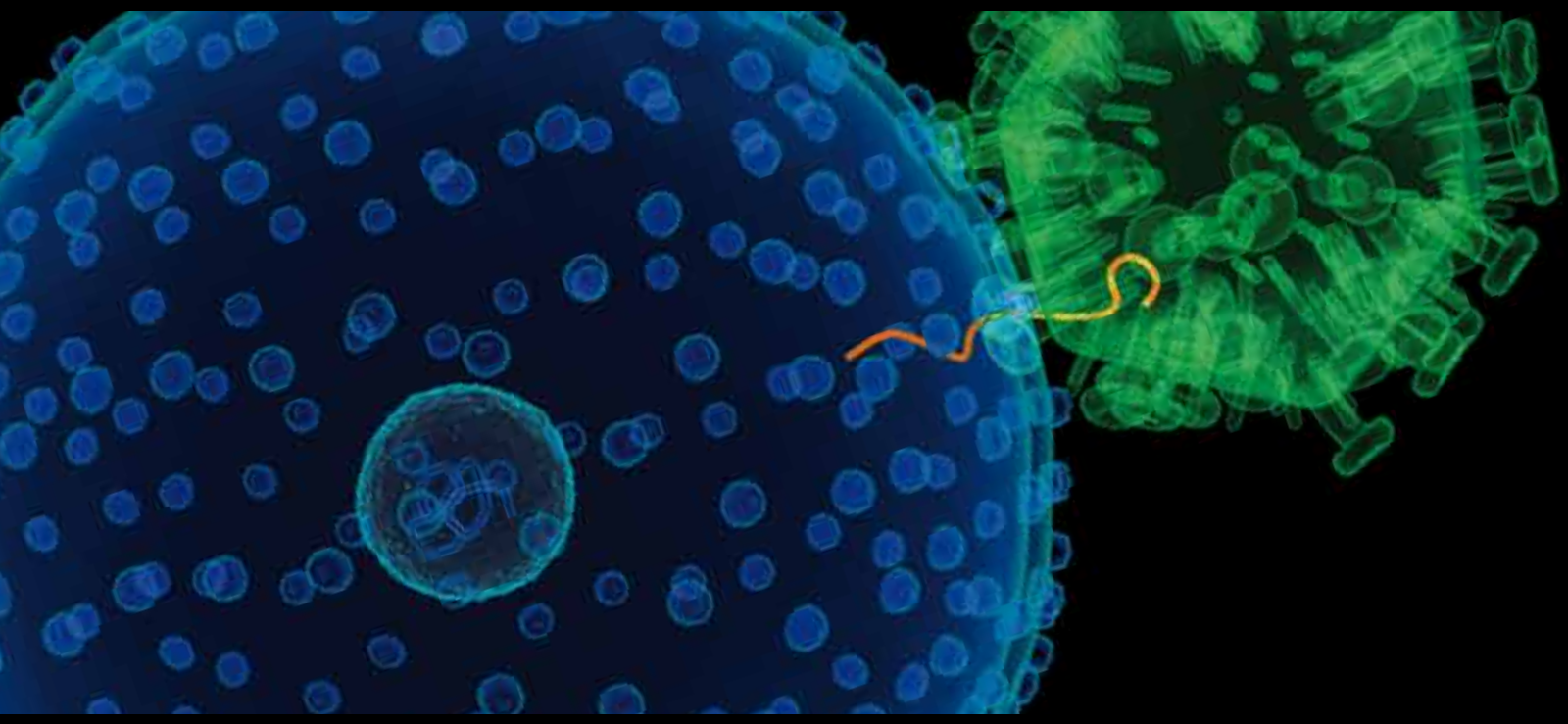
AIDS Research and Treatment

Antiretroviral Treatment in Resource-Limited Settings 2012

Guest Editors: Ann Duerr, Frederick L. Altice, Anthony D. Harries, and Annette H. Sohn



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Editorial Board

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Hindawi Publishing Corporation
AIDS Research and Treatment
Volume 2012, Article ID 346708, 3 pages
doi:10.1155/2012/346708

Editorial

Antiretroviral Treatment in Resource-Limited Settings 2012

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Received 21 May 2012; Accepted 21 May 2012

Just over 30 years after the beginning of the HIV epidemic, there is evidence that the global response is starting to catch up with the epidemic, at least in some places. This scaling up and treatment response has made enormous progress in providing access to care for HIV-infected persons, even in the least developed countries (LDCs). This special issue examines the current state of HIV care in resource-poor settings. The papers included in this issue examine questions central to expanded treatment in resource-poor settings such as access to antiretroviral therapy (ART), adherence and retention, management of HIV-associated cancers and opportunistic infections (OIs), and treatment complications. The issue also addresses arenas where progress has been slower than anticipated, such as the prevention of mother-to-child HIV transmission (PMTCT) and the need for more effective tuberculosis (TB) integration and TB treatment campaigns for people living with HIV/AIDS (PLWHA).

The global effort to make ART available to all HIV-infected persons has made great progress in the past decade. By the end of 2010, 6.65 million people were receiving ART globally [1]. Impressive as this number appears, it woefully represents less than half of those who need treatment. The scale of the epidemic and the response to it demand expanded and innovative responses from international organizations, national governments, care providers, and PLWHA themselves. Among the questions that must be answered as the HIV treatment world transitions from management of a crisis to management of a chronic disease are how will care be maintained and expanded in an era of decreasing donor funding? [2, 3] How can programs be most appropriately tailored for local epidemics, especially those that are expanding rapidly? How can the HIV care continuum (HIV testing, linkage to care, adherence, and retention) be strengthened and integrated into other local health services provision?

Four papers in this issue address these broad themes. One examines the potential role of PLWHA as "expert patients" who provide psychosocial and adherence support as well as provision of ART to stable patients (*"Are expert patients an untapped resource for ART provision in Sub-Saharan Africa*?" by T. Decroo et al.). Results from a study in Kenya and programmatic data from Mozambique suggest that this approach can support high retention in care while dramatically reducing clinic burden. Two other studies examine the HIV care continuum in 18 sites in the Asia-Pacific region ("*Loss to followup in HIV-infected patients from Asia-Pacific region: results from TAHOD*" by J. Zhou et al.) and 10 treatment programs in Central Africa *("Older adults accessing HIV care and treatment and adherence in the IeDEA Central Africa cohort"* by J. Newman et al.). Regional and local analyses of such data will be important to identify individuals, such as younger patients, at risk for poor adherence and loss to follow-up and ultimately provide effective solutions. A fourth study *("Short-term rationing*

of combination antiretroviral therapy: impact on morbidity, mortality, and loss to follow-up in a large HIV treatment program in western Kenya" by A. J. Bell et al.) retrospectively demonstrates increased mortality and loss to follow-up during a 6-month interruption in ART supply—a cautionary note to program officials and practitioners about the crucial need for drug forecasting, timely drug procurement, and efficient drug distribution as key priorities. Mitigation of the potential threat that reduced funding poses to the benefits gained to date will require multilateral efforts, integration of prevention and treatment efforts, reallocation of health-related human resources, and access to less costly medications and interventions.

Although HIV-related mortality was reduced for the first time globally in 2009 [4], a number of medical conditions continue to fuel HIV-related morbidity and mortality among PLWHA. For those not accessing ART, OIs and malignancies continue to dominate complications from HIV. For those who access ART, increased age-matched morbidity and mortality persist related to a number of conditions, including TB, end-stage liver disease, renal and neurological deterioration, non-AIDS-associated malignancies, and lipodystrophic syndromes. In this issue, H. Francis et al. describe how treatment of endemic Kaposi's sarcoma can be provided in LDCs in Sub-Saharan Africa, yet mortality remains high and underscores the need for palliative care (*"A prospective study assessing tumour response, survival, and palliative care outcomes in patients with HIV-related Kaposi's sarcoma at Queen Elizabeth Central Hospital, Blantyre, Malawi" by* H. Francis et al.). Achhra et al. demonstrate that ART regimens differ between LDCs and resource-rich regions. Such regimens utilized in LDCs may ultimately impact long-term complications of ART, including hyperlipidemia, which in turn may influence the development of cardiovascular-related morbidity and mortality *("Differences in lipid measurements by antiretroviral regimen exposure in cohorts from Asia and Australia*" by A. C. Achhra et al.).

At a global level, HIV-related mortality has been reduced by 19% overall [4], but these effects have not been experienced uniformly. For example, HIV-related mortality increased by 24% in Eastern Europe and Central Asia where the epidemic is largely concentrated among people who inject drugs, which are primarily opioids [5]. Unlike the laudatory successes of ART rollout in the most affected regions of Sub-Saharan Africa, ART coverage in these regions remains less than 5% [6]. In such settings, medically treatable comorbid conditions, including alcohol use disorders and opioid dependence [5], remain untreated and are critical to optimize early HIV diagnosis, entry into care, ART initiation, and ART adherence [5, 7]. In this issue, M. G. Neuman et al. systematically review the negative impact of alcohol use disorders on ART adherence and other adverse consequences *("Alcohol consumption, progression of disease and other comorbidities, and responses to antiretroviral medication in people living with HIV"* by M. G. Neuman et al.). Indeed, mathematical models suggest that the most effective and cost-effective method to reduce new HIV infections among injection drug users is to provide effective treatment for the underlying substance use disorder [8].

Not only do ART access disparities persist geographically but also remain problematic for pregnant women and children. Cumulative and incident cases of global pediatric HIV infections reflect ongoing difficulties in implementing a range of effective perinatal prevention interventions. The individual failures at each step of the "PMTCT cascade" of care from pregnancy to early infancy resulted in only 28% of HIV-exposed infants receiving an HIV test by the age of two months [9]. The three pediatric studies in this issue help to show the consequences of these gaps in care and the potential for closing them.

Even in major referral "centers of excellence" in Uganda, children continue to present at older ages with advanced clinical and immunologic disease *("Barriers to initiation of pediatric HIV treatment in Uganda: a mixed-method study*" by T. S. Boender et al.). In order to identify them before they develop complications of HIV such as malnutrition *("Challenges in the management of HIV-infected malnourished children in Sub-Saharan Africa*" by I. Trehan et al.), we need broader implementation of more strategic approaches, such as that reported in Kenya *("Towards elimination of mother-to-child transmission of HIV: the impact of a rapid results initiative in Nyanza Province, Kenya*" by L. L. Dillabaugh et al.). The Kenya example demonstrates how a local assessment and tailored intervention led to significant improvements in uptake of maternal and infant ART prophylaxis. Given that ART coverage among the estimated 2 million children who need it is only 23%—less than half that of adults—finding better solutions to both prevent new infections and refer infants immediately into testing and care is imperative.

Another arena that needs more focused attention is the interface between TB and HIV. In 2010, there were an estimated 1.1 million adults and children with HIV-associated TB of whom 350,000 died [10]. Just over 80% of this morbidity and mortality occurs in Sub-Saharan Africa, with 9 countries in the southern part of the continent accounting for over half of the burden of disease [10]. Recognized strategies to reduce the dual burden of disease include the following: (1) preventing TB in HIV-infected persons through the "Three I's" (intensified case finding, infection control, and isoniazid preventive therapy) and early ART initiation and (2) providing HIV care and treatment for coinfected TB patients through HIV testing, with cotrimoxazole preventive therapy and timely ART for those diagnosed with HIV.

This supplement features two additional papers from Kenya that partly address these issues. R. Granich et al. (*"Achieving universal access for human immunodeficiency virus and tuberculosis: potential prevention impact of an integrated multi-disease prevention campaign in Kenya*" by R. Granich et al.") report on a community-based multi-disease prevention campaign targeting 5000 people with an intervention incorporating HIV counseling and testing, condoms, insecticide-treated bed nets, and water filters. There was a high uptake of HIV testing, and of those testing HIV positive, the CD4-lymphocyte counts were significantly higher than in patients admitted and HIV-tested at a district hospital. The authors project the potential HIV and TB prevention impact of this campaign strategy for different

ART initiation scenarios, concluding that such campaigns could significantly contribute to TB prevention efforts in high-burden countries. D. N. Shaffer et al. *("Successes and challenges in an integrated tuberculosis/HIV clinic in a rural, resource-limited setting: experiences from Kericho, Kenya"* by D. N. Shaffer et al.") show that even in a rural, resource-limited district hospital it is possible to run an integrated HIV/TB clinic and implement recommended interventions, all of which led to improved treatment outcomes and reduced mortality during a five-year period.

In summary, enormous progress has been made in the last 8 years with the scale-up of ART in low- and middle-income countries. WHO data document that over 6.5 million people accessed this treatment by the end of 2010; without this intervention, often provided primarily to those with advanced immunodeficiency, the lives of millions of PLWHA would have been lost. There is much, however, left to do. ART expansion is urgently needed in several regions globally, and where there are current success stories, ART needs to be sustained. This is crucially dependent on secure, regular, and timely financial resources and greater national commitment to domestic health programs. The authors who contributed to this issue and their counterparts in the global HIV/AIDS treatment effort remind us that continued commitment to successful strategies and dedicated searches for solutions to the ongoing challenges and obstacles will be necessary if we are to achieve an "AIDS-free generation."

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Hindawi Publishing Corporation
AIDS Research and Treatment
Volume 2012, Article ID 814564, 9 pages
doi:10.1155/2012/814564

Clinical Study

Short-Term Rationing of Combination Antiretroviral Therapy: Impact on Morbidity, Mortality, and Loss to Follow-Up in a Large HIV Treatment Program in Western Kenya

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Received 15 September 2011; Accepted 14 March 2012

Academic Editor: Ann Duerr

Background. There was a 6-month shortage of antiretrovirals (cART) in Kenya. *Methods*. We assessed morbidity, mortality, and loss to follow-up (LTFU) in this retrospective analysis of adults who were enrolled during the six-month period with restricted cART (cap) or the six months prior (pre-cap) and eligible for cART at enrollment by the pre-cap standard. Cox models were used to adjust for potential confounders. *Results*. 9009 adults were eligible for analysis: 4,714 pre-cap and 4,295 during the cap. Median number of days from enrollment to cART initiation was 42 pre-cap and 56 for the cap ($P < 0.001$). After adjustment, individuals in the cap were at higher risk of mortality (HR = 1.21; 95% CI : 1.06–1.39) and LTFU (HR = 1.12; 95% CI : 1.04–1.22). There was no difference between the groups in their risk of developing a new AIDS-defining illness (HR = 0.92 95% CI 0.82–1.03). *Conclusions*. Rationing of cART, even for a relatively short period of six months, led to clinically adverse outcomes.

1. Introduction

Since the beginning of the HIV pandemic, almost 60 million people have been infected with HIV and 25 million have died from HIV-associated illnesses [1]. Sub-Saharan Africa is the region most affected by the pandemic and is home to 68% of all people living with HIV worldwide [1]. Since 2002, the international drive to scale up antiretroviral treatment has gained tremendous momentum [2], and by the close of 2009, an estimated 5.2 million persons were receiving combination antiretroviral treatment (cART). While this represents important progress, this still is only about 35% of the people who are estimated in need of treatment according to current standards of care [1].

HIV/AIDS has largely been transformed into a manageable, chronic disease for those with access to cART [3]. The clinical benefits of cART for individuals living in resource-poor settings, including slow disease progression and reduced mortality, have been documented in multiple studies [4–6]. More specifically, recent data from Uganda demonstrated that morbidity in HIV-infected individuals decreased after the introduction of antiretroviral therapy (ART); the decline became more apparent with increasing duration on ART [7]. Nonetheless, questions remain about the optimal time to begin treatment [8, 9].

Recent observational data from North America show that the risk of death increased by 69% when initiation of therapy is delayed until after the CD4 count drops below

350 cells/μL [8]. The nadir CD4 count is predictive of the benefit that will be gained from cART initiation [8, 10]. Prior to November 2009, guidelines for low-income settings recommended initiating treatment when a patient's CD4 count dropped below 200 cells/μL [11]. The guidelines were revised in November 2009 and now recommend initiation of treatment earlier in the course of the disease, when the CD4 cell count falls below 350 cells/μL [12]. Unfortunately, many clinics and treatment providers are already overwhelmed with the number patients presenting for treatment [13]. The capacity of the infrastructure to manage HIV as a chronic illness is stretched, and though the guidelines for cART initiation have been expanded, the capacity of clinics in resource-constrained settings to meet the increased demand is not clear [14]. Furthermore, international commitments to continued funding and expansion of HIV treatment programs are waning in the face of global financial constraints [15, 16]. Rationing and waitlisting for treatment initiation may continue to be a reality for many antiretroviral treatment programs given these circumstances. The impact of rationing treatment on patient clinical outcomes is not well described.

From March 12, 2007 through August 31, 2007, Kenya experienced a shortage of antiretroviral medications. The United States Agency for International Development (USAID) funded Academic Model Providing Access to Healthcare (AMPATH) was asked by the Government of Kenya to limit new cART initiations. The program agreed to limit new cART starts to patients with CD4 < 100 cells/μL, effectively "capping" new cART initiations for a period of 6 months. The primary objective of this analysis was to evaluate the impact of this restriction on morbidity, mortality, and loss to follow-up among HIV-infected patients who were eligible for cART. Our secondary objective was to determine factors associated with actually receiving cART among this population.

2. Methods

2.1. Study Design. This retrospective observational study was approved by the Indiana University School of Medicine Institutional Review Board and the Moi University Institutional Research and Ethics Committee. Informed consent was waived as a part of a general approval for conducting retrospective analyses with de-identified data collected as a part of routine care.

2.2. Study Setting. AMPATH, headquartered in Eldoret, Kenya, was established in 2001 as a partnership between Indiana University School of Medicine, Moi University School of Medicine, and the Moi Teaching and Referral Hospital. In 2004, AMPATH received funding from the United States Presidential Emergency Plan for AIDS Relief (PEPFAR) to create the USAID-AMPATH Partnership. The original goal of the program was to establish an HIV care network to serve the needs of patients in western Kenya. To date, the program has enrolled more than 135,000 patients in 25 Ministry of Health facilities and numerous satellite clinics around western Kenya. All HIV and tuberculosis-related care and treatment are provided without cost to patients through USAID-AMPATH and the Kenyan Department of Leprosy, TB, and Lung Disease.

2.3. Study Population. The study population was limited to patients who were not pregnant, aged 14 or older at enrollment, and who were eligible for cART at enrollment according to the pre-cap standard. Specifically, patients were eligible for cART if they had (1) CD4 < 200 cells/μL or (2) WHO stage IV illness or (3) WHO stage III AND CD4 < 350 cells/μL. These criteria are consistent with the 2006 HIV treatment guidelines from the World Health Organization [17]. Pregnant women were excluded from the analysis because they were exempted from the cap criteria (i.e., they continued to be initiated on cART as usual). There were two populations of eligible patients for this analysis: those who enrolled during the six months prior to the restricted cART period (September 1, 2006–March 11, 2007, called the "pre-cap" period) and those who enrolled during the restricted cART period (March 12–August 31, 2007, called the "cap" period).

2.4. Data Collection and Management. Clinicians completed standardized forms capturing demographic, clinical, and pharmacologic information at each patient visit. These data are then hand-entered into the AMPATH Medical Record System (AMRS), a secure computerized database designed for clinical management, with data entry validated by random review of 10% of the forms entered [18, 19]. At the time of registration, patients are provided with a unique identifying number. For this study, all data were de-identified before analysis.

2.5. Outcomes and Explanatory Variables. The primary outcomes for this analysis were morbidity, mortality (from all causes) and loss to follow-up (LTFU). Morbidity is defined as a new WHO Stage III or IV illness 60 days after enrollment to ensure that disease prevalent at enrolment was not accidentally counted as an incident infection due to delayed provider ascertainment. LTFU is defined as being absent from clinic for at least three months if on cART at the last visit and with no indication that the patient had died, or if not on cART at last visit, absent from clinic for at least six months, with no indication that the patient had died. AMPATH has a Standard Operating Procedure for reporting deaths, which includes a standardized death reporting form that is used for documentation of deaths by all clinic personnel. AMPATH also has an active peer-led outreach program which assists with death ascertainment. Outreach workers complete locator information for all new and returning patients in the clinical care program. The locator card includes contact information and a map to the patient's residence and is used to find the patient in the event of a missed appointment. The AMPATH Medical Record System (AMRS) produces a daily list of patients scheduled for appointments and patients that miss their appointment are listed for outreach based on a three-tier triage algorithm.

Adult patients on CART for less than three months are given priority. Outreach efforts for these patients are to commence within 24 hours of a missed appointment with a goal of locating the patient within seven days. For patients receiving CART for over three months, outreach is activated within seven days after a missed appointment. Individuals who do not receive CART are given 28 days from the missed appointment prior to initiation of outreach activities. However, there is undoubtedly underascertainment of deaths among patients LTFU—a recent evaluation of patients LTFU found that 20% of patients LTFU were in fact deceased.

Independent variables were both sociodemographic and clinical. We hypothesized that the following variables were actual or potential confounders of the relationship between the cap and death or LTFU and so were included in the analyses: age (continuous), sex (male/female), WHO stage (I, II, III, IV) and CD4 count (continuous) at enrollment, use of Cotrimoxazole or Dapsone at enrollment, whether the patient received TB treatment at enrolment, whether the patient was attending an urban or a rural clinic, and the time required for the patient to travel to clinic (<30 minutes, 30–60 minutes, 1-2 hours, >2 hours).

2.6. Statistical Methods. Enrollment cohort characteristics of the "pre-cap" group and "cap" group were compared using Fisher's Exact test for categorical variables and Kruskal-Wallis test for continuous variables. The Kaplan-Meier method was used to estimate the survival functions of time to morbidity, loss to follow-up and mortality. Time zero was the date of enrollment for the loss to follow-up and mortality analyses and 60 days after enrollment in the morbidity model. The event date of loss to follow-up was the date of the last clinic visit recorded in the database. Data on individuals known to have died within 3 months of their last clinic visit (if the patients were on cART, or 6 months if not on cART) were censored at the date of their last visit in the LTFU model. The patients on cART who are known to have died more than 3 months after their last clinic visit (or more than 6 months if not on cART) were treated as LTFU at the date of their last visit. Data for those who were still alive and not lost to follow-up by the administrative closure of the database were censored at the date of the last clinic visit. Survival distributions were compared using the Wilcoxon Log Rank test.

Cox Proportional Hazard models were used to calculate adjusted hazard ratios with 95% confidence intervals in individual predictive models for the primary outcomes (adjusting for the covariates described previously). In secondary analysis we explored the factors associated with cART initiation using Cox models. Statistical significance in the Cox model was assessed by the Wald test. Variables, if statistically significant at an alpha of 0.05 in the univariate model or, if believed to be potential confounders, were entered into the final model. All covariates in the tables were adjusted for in the multivariate models.

All statistical analyses were performed using R software (version 2.13.1; Vienna, Austria) and SAS (version 9.2; SAS Institute, Cary, NC).

3. Results

3.1. Participants. There were 9,009 adults eligible for analysis. Among whom, 60.2% were women, with a median age of 37.0 (interquartile range, IQR 30.9, 44.1). The median CD4 count at enrollment was 96 (IQR: 40, 162) cells/μL. Of the 9,009, 4,714 individuals were enrolled in the pre-cap period and 4,295 were enrolled during the cap period. Patients were followed for a median of 559 days (700 days in the pre-cap group and 512 for the cap group). This difference is to be expected since the pre-cap group were enrolled in the 6 months prior to the start of the cap period and thus had a longer potential follow-up period.

The clinical and sociodemographic characteristics of both groups are summarized in Table 1. Median CD4 count at enrolment was similar between the two groups (99 versus 94). The groups were well balanced on all enrollment characteristics except for use of Cotrimoxazole or Dapsone prophylaxis (81.7% in the pre-cap group versus 76.4% in the cap group, $P < 0.001$).

3.2. Time to cART Initiation. There were 3,684 (78.2%) individuals who initiated cART in the pre-cap group and 3,126 (72.8%) in the cap cohort ($P < 0.001$). The median number of days from enrollment to cART initiation was 50 days for the pre-cap cohort and 70 days for the cap cohort ($P < 0.001$). Factors associated with receiving cART are summarized in Table 2. Individuals were more likely to receive cART if they were receiving Cotrimoxazole or Dapsone ($P < 0.001$), if they were male ($P < 0.001$), if they were WHO Stage II, III, or IV (compared to stage I), or if they attended an urban clinic ($P = 0.030$). Patients were less likely to receive cART if they were enrolled during the cap period ($P < 0.001$), and if they were receiving TB treatment ($P < 0.001$). For each one cell increase in CD4 count there was a 0.5% reduction in the likelihood of getting cART (Hazard Ratio, HR: 0.995, 95% confidence interval, CI: 0.995-0.996).

3.3. Morbidity. There were 1,358 new AIDS defining events during the follow-up period including 573 among the cap group and 785 among the pre-cap group. After adjustment for potential confounders, there was no effect of the cap on the risk of developing a new WHO Stage III or IV illness (HR: 0.92; 95% CI: 0.82, 1.03) (Figure 1(a), Table 3).

3.4. Mortality. There were 1030 deaths during the follow-up period, including 538 among the cap group and 492 among the pre-cap group. Among patients who died, the median number of days to death in the cap group was 94 (IQR: 46, 201) compared to the pre-cap group which was 111 (44, 244). Among the 492 deaths in the pre-cap group, 191 (38.8%) died before starting cART, while for the cap group, 261 out of 538 deaths (48.5%) were before cART initiation ($P = 0.002$). The 1-year survival rate in the pre-cap group was 89.5% (95% CI: 88.5%, 90.4%), compared to 85.6% (84.4%, 86.8%) in the cap group (Figure 1(b)). After adjusting for covariates, the cap group had a significantly higher risk of mortality

Table 1: Enrollment sociodemographics and clinic characteristics of the comparison groups.

Variable	Pre-cap group ($n = 4714$), n (%)	Cap group ($n = 4295$), n (%)	P value
Sex			
Male	1849 (39.2)	1741 (40.5)	0.212
Female	2865 (60.8)	2554 (59.5)	
Missing	0 (0)	0 (0)	
Age[a]			
Median	37.0	36.9	0.255
IQR	31.0–44.1	30.6–44.0	
Missing	0 (0)	0 (0)	
Clinic location[a]			
Urban	2315 (49.1)	2176 (50.7)	0.146
Rural	2399 (50.9)	2119 (49.3)	
Missing	0 (0)	0 (0)	
Travel time to clinic[a]			
<30 minutes	1093 (23.4)	962 (23.1)	0.100
30–60 minutes	1467 (31.5)	1400 (33.6)	
1-2 hours	1266 (27.2)	1127 (27.0)	
>2 hours	836 (17.9)	683 (16.4)	
Missing	52 (1.1)	123 (2.9)	
WHO clinical stage[a]			
I	637 (15.1)	533 (14.5)	0.780
II	839 (19.8)	754 (20.6)	
III	2278 (53.9)	1977 (54.0)	
IV	476 (11.3)	400 (10.9)	
Missing	484 (10.3)	631 (14.7)	
CD4[a]			
Median	99.0	94.0	0.081
IQR	41.0–163	38.0–161	
Missing	59 (1.3)	49 (1.1)	
Use of Cotrimoxazole or Dapsone			
Yes	3851 (81.7)	3282 (76.4)	<0.001
No	863 (18.3)	1013 (23.6)	
Missing	0 (0)	0 (0)	
TB treatment[a]			
Yes	1180 (25.0)	1121 (26.1)	0.246
No	3534 (75.0)	3174 (73.9)	
Missing	0 (0)	0 (0)	

[a] At Enrollment.

(HR = 1.21; 95% CI: 1.06, 1.39) compared to the pre-cap group (Table 3).

3.5. Loss to Follow-Up. There were 3,537 patients lost to follow-up, including 1,665 in the cap group and 1,872 in the pre-cap group. The adjusted relative risk of becoming loss to follow-up was 1.12 (1.04, 1.22) times greater for those patients enrolled during the cap period versus the pre-cap period (Figure 1(c), Table 3).

3.6. Sub-Analysis for Pneumocystis Prophylaxis. The patients in the cap group were somewhat less likely to receive Cotrimoxazole or Dapsone compared to the pre-cap group. To explore whether residual confounding arising from this

Table 2: Cox proportional (unadjusted and adjusted) hazard ratios for predictors of cart initiation.

Covariate	Univariate analysis			Multivariate analysis[b]		
	Unadjusted hazard ratio	95% confidence interval (CI)	*P* value	Adjusted hazard ratio (AHR)	95% Confidence interval (CI)	*P* value
Enrolled in the cap period	0.86	0.82, 0.90	<0.001	0.87	0.83, 0.92	<0.001
Use of Cotrimoxazole or Dapsone[a]	3.22	2.98, 3.48	<0.001	2.08	1.89, 2.29	<0.001
On TB treatment[a]	0.77	0.73, 0.82	<0.001	0.60	0.56, 0.64	<0.001
Male gender	1.13	1.08, 1.19	<0.001	1.14	1.09, 1.21	<0.001
Age (per year increase)[a]	1.00	1.00, 1.00	0.100	1.00	1.00, 1.00	0.950
CD4 (per cell increase)[a]	0.995	0.994, 0.995	<0.001	0.995	0.995, 0.996	<0.001
WHO Stage I[a]	1.00			1.00		
WHO Stage II[a]	1.16	1.07, 1.26	<0.001	1.08	1.00, 1.17	0.053
WHO Stage III[a]	0.89	0.83, 0.95	0.001	1.20	1.11, 1.29	<0.001
WHO Stage IV[a]	1.33	1.20, 1.46	<0.001	1.86	1.67, 2.07	<0.001
Urban Clinic[a]	1.03	0.99, 1.09	0.162	1.06	1.01, 1.11	0.030
Travel time < 30 min	1.00			1.00		
Travel time 30–60 min	1.02	0.96, 1.09	0.494	0.99	0.93, 1.06	0.749
Travel time 1-2 hr	1.05	0.98, 1.12	0.151	0.99	0.92, 1.06	0.742
Travel time > 2 hr	1.11	1.03, 1.20	0.008	1.05	0.97, 1.14	0.246

[a]At Enrollment.
[b]Adjusted for all covariates.

explains the increases in mortality and loss to follow-up among the cap group, a sub-analysis was conducted in which we restricted the population to only those who received Cotrimoxazole or Dapsone. Our findings were marginally affected as a result (Mortality HR: 1.20, 95% CI: 1.04–1.40; LTFU HR: 1.18, 95% CI: 1.08–1.28).

4. Discussion

These data suggest that even a relatively brief restriction of cART initiation among otherwise eligible patients independently contributes to a higher risk of mortality and loss to follow-up. This is in spite of triaging the sicker patients (as measured by CD4 and WHO clinical stage) to receive cART before the healthier ones. These findings underscore the negative effects that can be expected from even a short-term delay in the initiation of cART among otherwise eligible patients. We believe that our study did not show an effect of increased morbidity while still showing increased mortality and LTFU because patients who developed new AIDS-defining illnesses died or became lost to follow-up before these illnesses could be diagnosed and/or documented in the clinical encounter.

In addition to the poor clinical outcomes arising directly from the delays, it can be expected that the long-term clinical effectiveness of cART once initiated may also be adversely affected by virtue of patients initiating treatment at more advanced levels of immune suppression [20]. Furthermore, there are important implications of delayed cART initiation on transmission of HIV and tuberculosis [3]. Prevention of mother-to-child transmission [21], post-texposure prophylaxis, and most recently HPTN 052 [22] have demonstrated the dramatic impact that combination antiretroviral treatment can have on HIV transmission. As such delayed cART initiation has multiple downstream consequences both for the patient themselves and for their partners, offspring and community. Given these recent data on treatment for prevention as well as data on the clinical consequence of ART delay, it is imperative that global community continues its commitment to providing cART in resource constrained settings. These data illustrate the stark consequences of failing to live up to these commitments and will put clinicians on the front-lines back in the unenviable position endured prior to the global scale-up of antiretroviral treatment delivery: having to choose who will live, and who will not.

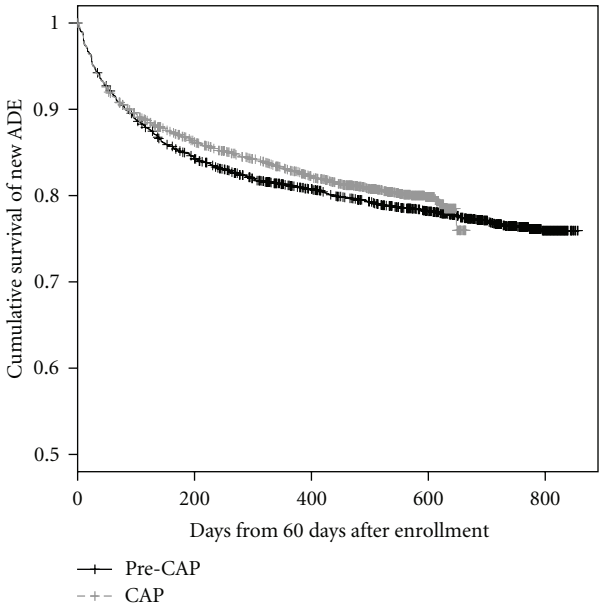
There are several strengths to this study. The first is that the USAID-AMPATH Partnership is a large clinical population, covering much of western Kenya, in both urban and rural settings. As a result, this sample provided ample statistical power to answer our primary question and is broadly generalizable to other sub-Saharan Africa settings. Second, AMPATH services are free to patients, eliminating confounding due to fee for service care structures. Last, because there were no pharmacy stock-outs during the study period (other than the one that caused the circumstances for the comparison), our findings are not confounded by other disruptions in the supply chain.

Limitations to this analysis include the potential random misclassification due to clinician error in recording. Similarly, incomplete ascertainment of outcomes may have particularly affected the morbidity analysis. Third, this is a retrospective study, with its inherent limitations including reliance on accuracy of written record and incomplete data.

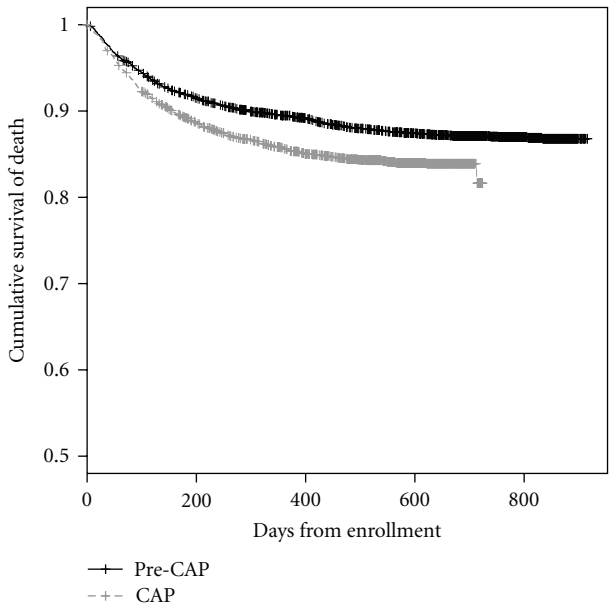
Table 3: Cox proportional (unadjusted and adjusted) hazard ratios and 95% confidence intervals for morbidity, loss to follow-up, and mortality.

	Morbidity				Loss to follow-up				Mortality			
	Unadjusted		Adjusted[b]		Unadjusted		Adjusted[b]		Unadjusted		Adjusted[b]	
Covariate	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Enrolled during cap period	0.93 (0.83, 1.03)	0.162	0.92 (0.82, 1.03)	0.152	1.19 (1.11, 1.27)	<0.001	1.12 (1.04, 1.22)	0.004	1.31 (1.16, 1.48)	<0.001	1.21 (1.06, 1.39)	0.006
Use of Cotrimoxazole or Dapsone[a]	0.66 (0.58, 0.76)	<0.001	0.67 (0.55, 0.80)	<0.001	0.39 (0.36, 0.42)	<0.001	0.58 (0.52, 0.65)	<0.001	0.49 (0.42, 0.56)	<0.001	0.46 (0.37, 0.57)	<0.001
TB treatment[a]	0.82 (0.72, 0.93)	0.003	0.68 (0.59, 0.78)	<0.001	1.04 (0.97, 1.12)	0.299	0.99 (0.90, 1.09)	0.850	1.11 (0.97, 1.27)	0.136	0.84 (0.72, 0.99)	0.033
Male gender	0.98 (0.88, 1.09)	0.718	0.95 (0.85, 1.07)	0.418	1.05 (0.98, 1.12)	0.187	1.01 (0.93, 1.10)	0.760	1.48 (1.31, 1.67)	<0.001	1.36 (1.19, 1.57)	<0.001
Age (per year increase)[a]	1.00 (0.99, 1.00)	0.333	1.00 (0.99, 1.01)	0.772	0.99 (0.98, 0.99)	<0.001	0.99 (0.98, 0.99)	<0.001	1.00 (1.00, 1.01)	0.388	1.00 (1.00, 1.01)	0.484
CD4 (per cell increase)[a]	0.999 (0.999, 1.000)	0.006	0.998 (0.998, 0.999)	<0.001	0.999 (0.999, 0.999)	<0.001	0.999 (0.999, 0.999)	<0.001	0.995 (0.994, 0.996)	<0.001	0.995 (0.994, 0.996)	<0.001
WHO Stage I[a]	1.00		1.00		1.00		1.00		1.00		1.00	
WHO Stage II[a]	1.24 (1.01, 1.51)	0.038	1.23 (1.01, 1.51)	0.044	0.95 (0.83, 1.09)	0.454	0.96 (0.83, 1.10)	0.543	1.19 (0.87, 1.63)	0.279	1.10 (0.80, 1.50)	0.572
WHO Stage III[a]	1.49 (1.26, 1.78)	<0.001	1.64 (1.36, 1.96)	<0.001	1.32 (1.18, 1.49)	<0.001	1.24 (1.10, 1.40)	<0.001	2.62 (2.02, 3.40)	<0.001	2.44 (1.87, 3.19)	<0.001
WHO Stage IV[a]	2.10 (1.68, 2.62)	<0.001	2.55 (2.01, 3.24)	<0.001	2.08 (1.80, 2.40)	<0.001	1.98 (1.70, 2.31)	<0.001	4.51 (3.37, 6.04)	<0.001	4.41 (3.24, 5.99)	<0.001
Urban Clinic[a]	0.99 (0.89, 1.10)	0.857	0.99 (0.88, 1.11)	0.856	1.05 (0.99, 1.12)	0.128	1.02 (0.94, 1.10)	0.651	0.76 (0.68, 0.87)	<0.001	0.80 (0.70, 0.92)	0.002
Travel time < 30 min	1.00		1.00		1.00		1.00		1.00		1.00	
Travel time 30–60 min	0.93 (0.80, 1.07)	0.305	0.95 (0.81, 1.10)	0.491	1.13 (1.03, 1.24)	0.009	1.14 (1.03, 1.27)	0.014	1.36 (1.14, 1.62)	<0.001	1.18 (0.97, 1.43)	0.098
Travel time 1-2 hr	1.04 (0.90, 1.21)	0.598	1.01 (0.86, 1.18)	0.908	1.07 (0.97, 1.17)	0.204	1.07 (0.96, 1.20)	0.231	1.30 (1.08, 1.56)	0.005	1.09 (0.89, 1.34)	0.390
Travel time > 2 hr	0.98 (0.83, 1.17)	0.846	0.93 (0.78, 1.12)	0.464	1.34 (1.20, 1.48)	<0.001	1.40 (1.24, 1.58)	<0.001	1.38 (1.12, 1.68)	0.002	1.16 (0.93, 1.45)	0.192

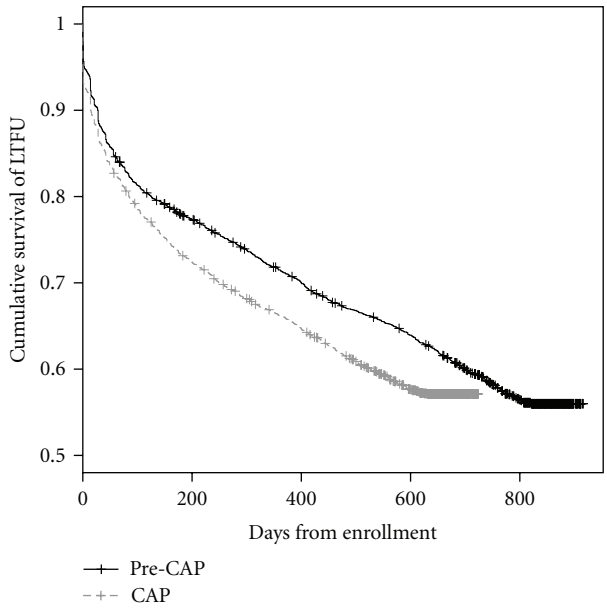
[a] At enrollment.
[b] Adjusted for all covariates.



(a) Kaplan-Meier estimates of cumulative survival function of time from 60 days after enrollment to new AIDS-defining events (ADE)s. Log-rank $P = 0.162$



(b) Kaplan-Meier estimates of cumulative survival function of time from enrollment to death. Log-rank $P < 0.001$



(c) Kaplan-Meier estimates of cumulative survival function of time from enrollment to loss to follow-up (LTFU). Log-rank $P < 0.001$

Figure 1: Kaplan-Meier estimates of cumulative survival function of time to (a) new AIDS defining event (ADE); (b) death; (c) loss to follow-up.

Fourth, there may be prescription bias, in which providers started cART on patients who did not meet the initiation guidelines but whom they felt would benefit from treatment nevertheless. If this occurred, it will have biased the results towards the null.

5. Conclusions

Given the certainty that more people will become eligible as early start strategies are implemented and that early start, itself, is a prevention strategy, this study highlights the need for international funding organizations and national governments to continue and expand their commitment to HIV care and treatment. Treatment programs can make the best use of resources through task-shifting [23–25] and other innovative models, such as community ART group models [26], to ensure the continuous provision of cART to those in need in resource-limited settings. The stakes for patients are high and these data demonstrate that even small delays in treatment initiation among patients who are immune

suppressed can be fatal. As the HIV pandemic begins to stabilize in sub-Saharan Africa, and as the population and economic benefits of treating HIV infection begin to accrue there as elsewhere [20, 27], these data remind us that turning back the clock and restricting even sick patients from accessing treatment is simply not a reasonable option.

Authors' Contribution

A. J. Bell, M.P.H., assisted with study design, analysis, and interpretation, wrote drafts, and made revisions of article and final approval for submission. K. Wools-Kaloustian, M.D., M.S., assisted with study design, acquisition of data, revision of article, and final approval for submission. S. Kimaiyo, M.B.Ch.B., M.med., assisted with acquisition of data, revision of article, and final approval for submission. H. Liu, Ph.D., assisted with study design and co-led the final analysis, revision of article, and final approval for submission. A. Katschke, M.S., assisted with study design, analysis and interpretation, drafts and revision of article, and final approval for submission. C. Shen, Ph.D., assisted with study design, analysis and interpretation, drafts and revision of article, and final approval for submission. G. Simiyu assisted with acquisition of data, reviewed drafts, and final approval for submission. B. S. Musick, M.S., prepared data for analysis, assisted with study design and analysis, reviewed drafts, and approved final draft for submission. J. E. Sidle, M.D., assisted with study design, acquisition of data, revision of article, and final approval for submission. A. Siika, M.B.Ch.B., M. med., assisted with study design, acquisition of data, revision of article, and final approval for submission. P. Braitstein, Ph.D., conceived the idea, led the study design, analysis, and interpretation, reviewed drafts and is responsible for final submission.

Conflicts of Interests

The authors declare that they have no conflict of interests.

Disclaimer

P. Braitstein and H. Liu had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Acknowledgments

The authors would like to thank all the nurses and clinicians in all the USAID-AMPATH Partnership clinics for their dedication in caring for patients and their attentiveness in accurately recording their patients' data. The authors would also like to thank all the data entry technicians, data managers, and administrative and clerical staff, for enabling the collection, management, interpretation, and publication of these data. The USAID-AMPATH Partnership is grateful to the Rockefeller Foundation for funding the development of the AMPATH Medical Records System and to the Kenyan Ministry of Health for their support. This paper was supported in part by a grant to the USAID-AMPATH Partnership (623-A-00-08-00003-00) from the United States Agency for International Development as part of the President's Emergency Plan for AIDS Relief (PEPFAR).

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Hindawi Publishing Corporation
AIDS Research and Treatment
Volume 2012, Article ID 246280, 9 pages
doi:10.1155/2012/246280

Clinical Study

Differences in Lipid Measurements by Antiretroviral Regimen Exposure in Cohorts from Asia and Australia

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Received 24 October 2011; Accepted 11 March 2012

Academic Editor: Ann Duerr

We explored the mean differences in routinely measured lipids (total cholesterol, triglycerides, and high-density lipoprotein cholesterol) according to exposure to different combination antiretroviral regimens in Asian ($n = 2051$) and Australian (predominantly Caucasian, $n = 794$) cohorts. The regimen was defined as at least 3 antiretroviral drugs with at least 2 nucleoside-reverse transcriptases (NRTIs) and either of at least one protease inhibitor (PI) or non-nucleoside-reverse transcriptases (NNRTIs). We categorised cART regimens as: NRTIs as tenofovir based or not; NNRTIs as nevirapine or efavirenz (but not both); and PI as atazanavir based or not. We found that the impact of various antiretroviral regimens on lipids in Asian and Australian cohorts was only different by cohort for total cholesterol (P for interaction between regimen and cohort: <0.001) but not in case of other lipids (P for interaction: >0.05). The differences in total cholesterol were however small and unlikely to be of clinical significance. Overall, tenofovir with nevirapine or atazanavir was associated with the most favorable lipids, while the PI regimens without tenofovir and atazanavir were associated with least favorable lipids. We conclude that the impact of various ART regimens on lipids is largely similar in Asian and Australian cohorts and that the newer drugs such as tenofovir and atazanavir are likely to provide similar benefit in terms of lipid profiles in both populations.

1. Introduction

Combination antiretroviral therapy (cART) for HIV infection is associated with adverse changes in lipid profiles and can include elevation in total cholesterol and triglycerides, which may increase the risk of coronary heart disease (CHD) [1–4]. Moreover, different classes of cART and drugs within each class have differential impacts on lipids [2]. Protease-inhibitors (PIs) are associated with more significant changes in lipid profile than nucleoside and nonnucleoside reverse transcriptase inhibitors (NRTIs and NNRTIs, resp.) [2, 3, 5]. And within NNRTI class, efavirenz (EFV) is associated with greater changes in the lipid profile than nevirapine (NVP) [2, 5, 6]. Also tenofovir (TDF) and atazanavir (ATV) are known to have a favorable impact on lipids [5, 7, 8].

Drugs such as TDF, EFV, and ATV are becoming increasingly available in low-middle-income countries, including Asia [9, 10]. However, much of our knowledge about the relative impact of different cART regimens on lipids comes mainly from clinical trials and cohort studies from European or North-American settings [2, 4, 7, 8]. The impact of cART on lipids may vary in Asian settings due to differences in race/ethnicity, dietary, environmental, and lifestyle factors [11–13]. This has been demonstrated in other settings

where the magnitude of change in total cholesterol and triglycerides due to PIs differed between African Americans and Caucasians, highlighting the possible role of race [11, 12]. These findings illustrate the need for verifying our assumptions about the relative impact of different cART regimens on diverse populations, including Asian populations.

Observational cohort studies can complement information from clinical trials, and allow us to examine the effects of art medications in the context of combination regimens, as opposed to head-to-head comparisons of selected drugs in clinical trials. In the present study, we aim to compare the relative impact of various cart regimens on lipid profiles in Asian and Australian cohorts using data from the treat Asia and the Australian HIV observational databases (TAHOD and AHOD, resp.), which are formed on similar methodology and are known to be predominantly Asian and Caucasian, respectively [14].

2. Methods

2.1. The TAHOD and AHOD Cohorts. TAHOD and AHOD are clinical cohort studies of HIV-infected patients in Asia and Australia, respectively, and are part of the International Epidemiologic Databases to evaluate AIDS initiative. Both cohorts have similar methodologies, which have been previously published [15, 16]. Briefly, prospective data collection was commenced in 2003 for TAHOD and in 1999 for AHOD, with retrospective data being provided where available. In TAHOD, data are collected from 17 clinical sites in the Asian region, whereas for AHOD, data are collected from 27 clinical sites throughout Australia. Written informed consent was not a requirement of sites in TAHOD unless required by the site's local ethics committee because data are collected in an anonymous form, while in AHOD consent was obtained from all patients recruited at the time of enrolment. The TAHOD and AHOD cohorts are known to be predominantly of Asian and Caucasian ethnic composition, respectively [14].

Ethical approval for both the cohorts was obtained from the University of New South Wales, Sydney, Australia, and all other relevant institutional review boards. Data for both TAHOD and AHOD are transferred electronically to the Kirby Institute twice per year and include the same set of core variables. All data are subject to standardized quality control procedures.

2.2. Outcome. The outcomes of interest were mean (i) total cholesterol, (ii) triglycerides, (iii) high-density lipoprotein cholesterol (HDL-C) measured in mmol/L, and (iv) total cholesterol : HDL-C ratio. Lipid values are measured according to the local sites' standard of care in each cohort, and when measured, are captured during routine data transfer. TAHOD only records fasting lipids. In AHOD, both fasting and nonfasting lipids along with the fasting status are recorded. Further details of laboratory standards and methods at each site were not available.

Data collection on lipid profiles started later in AHOD (median date: January, 2007), compared to TAHOD (median date: March, 2006). The lipid values before starting cART (i.e., while patients were ART naive) were not available in most patients, and therefore changes from pre- to post-cART were not analysed. Mean lipid measurements were compared by different regimens and cohort.

2.3. Definition and Classification of Antiretroviral Regimens. The cART regimen variable was defined as a regimen containing at least 3 antiretroviral drugs, including at least two NRTIs and either of at least one PI or an NNRTI. In order to evaluate the net effect of a combination regimen, rather than that of a single drug or a class, we defined eight mutually exclusive regimens. We categorised cART regimens as: NRTIs as TDF based (NRTIs + TDF) or not (NRTIs); NNRTIs as NVP or EFV (but not both); and PI as ATV based (PI + ATV) or not (PI).

Based on these categories, the following mutually exclusive regimens were defined: (i) NRTIs (+TDF) + NVP; (ii) NRTIs (+TDF) + EFV; (iii) NRTIs + NVP; (iv) NRTIs + EFV; (v) NRTIs (+TDF) + PIs (+ATV); (vi) NRTIs (+TDF) + PI; (vii) NRTIs + PI (+ATV); (viii) NRTIs + PI. In all analyses, regimen (i) NRTIs (+TDF) + NVP was used as the reference group, as this regimen was thought to have the most favourable impact on lipids.

2.4. Inclusion Criteria and Time-Points Analysed. Patients from TAHOD and AHOD were eligible for inclusion in the analysis if they started cART and had at least one lipid measurement within the first 24 months of cART commencement. Time at risk was defined as time spent on any of the regimens described previously and risk time started from the commencement of that regimen. Follow-up was censored at first of 24-month exposure to regimen of interest, date of death, loss to follow-up, or 31 March, 2010. Lipids values measured at the 6-monthly intervals in the first 24 months of start of cART were used. Thus each patient on each regimen could have up to 4 measurements (1 in each interval). If more than one measurement was available in a given interval, one measured earliest in the given interval was used in the analysis. Intermittent changes in therapy including stopping part or all of a regimen for less than 14 days were not considered a stop in time at risk for that regimen. Each patient could contribute data to more than one regimen.

2.5. Variables and Statistical Analysis. The following *a priori* confounders were included in all models:

(1) fixed variables: cohort (TAHOD/AHOD), gender, HIV transmission group (homosexual contact ± intravenous drug user (IDU), IDU ± heterosexual, heterosexual, and other), and hepatitis B and C coinfection (defined as HBV surface antigen and HCV antibody positive, resp.);

(2) variables measured closest to the start of each cART regimen within past 6 months to 1 month after the

start of the regimen of interest: CD4+ T-cell count (categorised as <200, 200–350, and >350 cells/μL); HIV RNA viral load (categorised as <500, >500–<10,000, and >10,000 copies/mL); and body mass index (BMI) (categorised as <18.5, 18.5–25, 25–30, and >30 kg/m^2);

(3) variables recalculated at the start of each cART regimen: cumulative cART exposure and age.

We performed longitudinal data analysis using random effects models to take into account repeated lipid measures (defined previously). Since all lipid parameters were normally distributed with minimal skewness, data were not transformed. Separate models were fitted for each outcome. All models included time on regimen with lipid data, categorised as 6 monthly intervals. The interaction between the regimen and the cohort variables was assessed for each outcome. We also conducted the following sensitivity analyses: (i) restricting AHOD data to only lipid values which were documented to be taken as fasting in AHOD, (ii) excluding patients with missing BMI data, (iii) including only those with known Caucasian ethnicity in AHOD, and (iv) additional adjustment for stavudine (d4t) use in the multivariable model, as it was more common in TAHOD than AHOD.

Data were analysed using STATA version 10 (STATA Corporation, College Station, TX, USA).

3. Results

There were 2845 participants (2051 in TAHOD and 794 in AHOD) who met the inclusion criteria. In TAHOD, 736 (35.9%) were Chinese, 654 (31.9%) were Thai, 152 (7.4%) were Cambodian (Khmer), 100 (4.9%) were Japanese and 62 (3%) were Indian. Table 1 describes the patient characteristics at study entry for each cohort.

There were a total of 7897 total cholesterol values (5602 in TAHOD and 2295 in AHOD), 7293 triglyceride values (5002 in TAHOD and 2291 in AHOD), and 4669 HDL-C values (2949 in TAHOD and 1720 in AHOD). The frequency of total cholesterol measurements by regimen and cohort is shown in Table 2. The most common NRTI combinations for which total cholesterol measurements were available in TAHOD were zidovudine (AZT)/lamivudine (3TC) (39% of all measurements) and d4t/3TC (30% of all measurements) and in AHOD TDF/emtricitabine (FTC) (29% of all measurements) and abacavir (ABC)/3TC (18% of all measurements). The distribution was similar for triglycerides and HDL-C. In TAHOD and AHOD, 52% and 46% of measurements were taken while on NNRTI-based regimens, respectively. Of all the measurements on PI-based regimens, greater than 95% were on ritonavir-boosted regimens.

Patients contributed data to the median of 1 regimen (range: 1 to 4) with a median of 2 lipid measurements (IQR: 1–4) per patient. All measures of CD4 cell count, HIV viral load, and BMI were collected within 35 days of commencing the different ART regimens. Participants from TAHOD were more likely to be younger and female and have heterosexually acquired infection, hepatitis B coinfection, detectable HIV VL, lower median CD4+ count, shorter time spent on cART, lower BMI, lower mean total cholesterol, and higher HDL-C than those from AHOD (Table 1). Also a higher proportion of TAHOD participants had missing BMI and HIV viral load values compared with those in AHOD (Table 1).

3.1. Total Cholesterol. The relationship between mean total cholesterol and cART regimen differed by cohort (TAHOD/AHOD) ($P < 0.001$, test for interaction). Overall, the mean total cholesterol was slightly lower for TAHOD participants, compared to AHOD participants, after adjustment for demographic and HIV-related characteristics, in most of the regimens (Figure 1(a)). When compared to the NRTIs (+TDF) + NVP regimen (reference group), the NRTIs + PI regimen was associated with greater mean total cholesterol in both cohorts, with a slightly greater difference in AHOD participants (mean difference: +0.78 mmol/L, 95% CI: 0.57 to 1.00) compared to TAHOD participants (mean difference: +0.23 mmol/L, 95% CI: 0.02 to 0.44); NRTIs (+TDF) + PI (+ATV) regimen was associated with greater mean total cholesterol in AHOD (mean difference: −0.20 mmol/L, 95% CI: −0.43 to 0.02) as compared to TAHOD (mean difference: −0.62 mmol/L, 95% CI: −1.23 to −0.02).

3.2. Triglycerides, HDL-C, and Total Cholesterol: HDL-C Ratio. There was no significant interaction between cART regimen and the cohort type ($P > 0.05$, test for interaction) for triglycerides, HDL-C, and total cholesterol: HDL-C ratio. Table 3 provides adjusted analyses for each of these outcomes. As compared to the NRTIs (+TDF) + NVP regimen (reference group), the NRTIs + PI regimen was associated with the highest mean triglycerides (mean difference: 1.13 mmol/L, 95% CI: 0.83 to 1.43) and total cholesterol : HDL-C ratio (mean difference: 0.75, 95% CI: 0.47 to 1.03), followed by the NRTIs (+TDF) + PI regimen (mean difference in triglycerides: 1.06 mmol/L, 95% CI: 0.73 to 1.38, and mean difference in total cholesterol : HDl-C ratio: 0.66, 95% CI: 0.37 to 0.95), while NRTIs (+TDF) + PI (+ATV) regimen was not associated with a significant difference in triglycerides (mean difference: 0.15 mmol/L, 95% CI: −0.22 to 0.52) and total cholesterol : HDL-C ratio (mean difference: 0.29, 95% CI: −0.04 to 0.62). Also, the NRTIs + EFV regimen was associated with increase in triglycerides (mean difference: 0.64 mmol/L, 95% CI: 0.34 to 0.95) and total cholesterol : HDL-C ratio (mean difference: 0.29, 95% CI 0.01 to 0.56). The TAHOD cohort, as compared to AHOD, had higher mean triglycerides, but not total cholesterol : HDL-C ratio. Figures 1(b) and 1(c) provide the graphical representation of the adjusted mean triglycerides and total cholesterol : HDL-C ratio for each regimen and cohort, respectively.

When compared to the reference group, the NRTIs + NVP regimen and the NRTIs + EFV regimen were associated with higher mean HDL-C (mean difference of: 0.15 mmol/L, 95% CI: 0.08 to 0.21 and 0.09 mmol/L, 95% CI: 0.03 to 0.16,

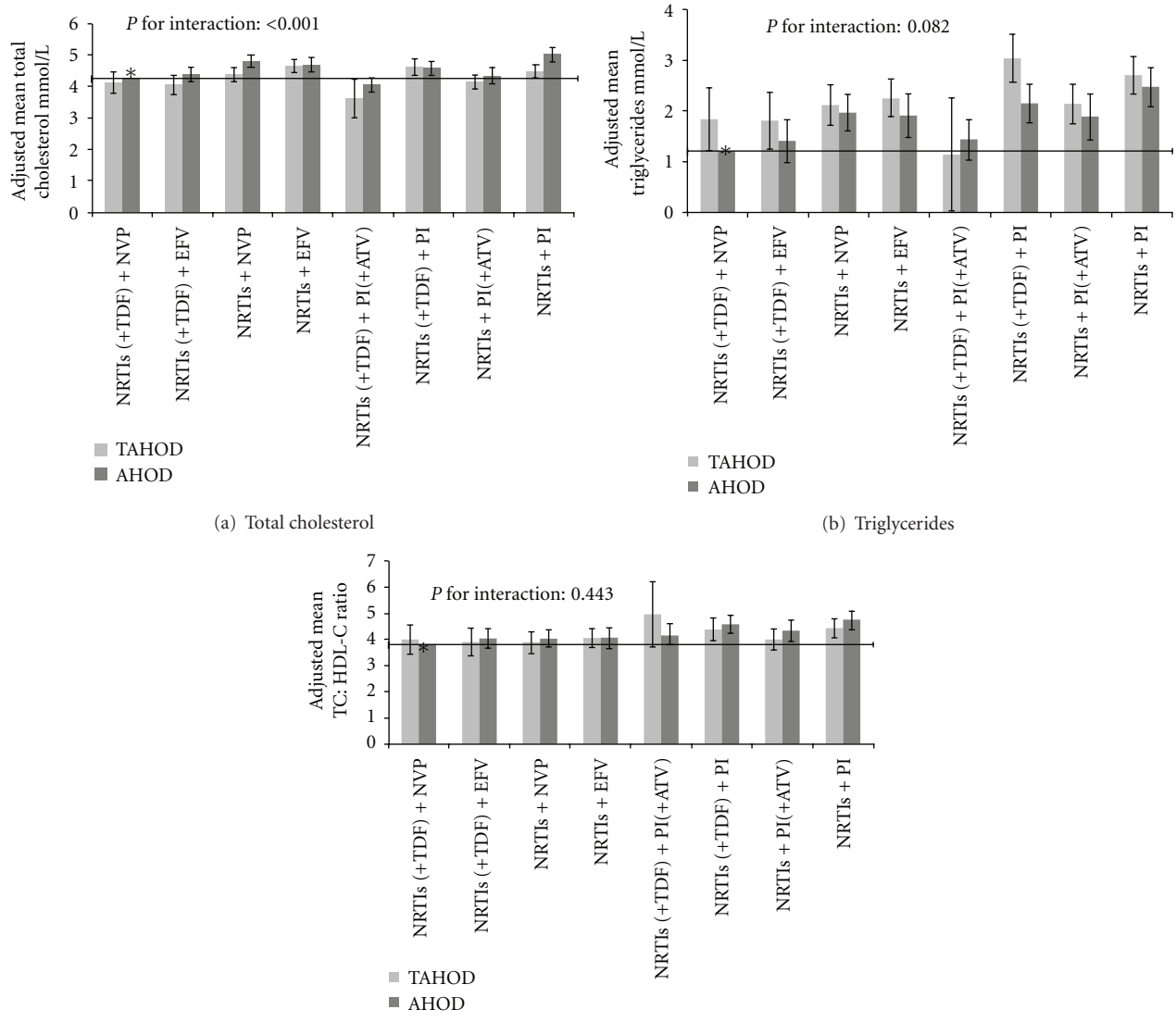

Figure 1: Adjusted Mean Lipids by regimen and cohort. Interaction between impact of regimen and cohort variables on lipids: (a) mean total cholesterol, (b) mean triglycerides, and (c) mean total cholesterol : HDL-C ratio. A statistically significant interaction suggests impact of regimen on lipids differed in magnitude by the cohort. Triglycerides were higher for TAHOD as compared to AHOD irrespective of the regimen, but the interaction between regimen and cohort was not significant. Means were *a priori* adjusted for time on given regimen, HBV and HCV confections, age, gender, HIV RNA viral load copies/mL, CD4+ T-cell count, BMI, cumulative exposure to cART at baseline, and HIV exposure category. *Reference category. Horizontal line shows the value of constant (mean lipid value in reference category). Error bars indicate 95% confidence interval. AHOD: Australian HIV Observational Database; ATV: Atazanavir; EFV: Efavirenz; NNRTIs: nonnucleoside reverse transcriptase inhibitors; NRTI: Nucleoside reverse transcriptase inhibitors; NVP: Nevirapine; PI: protease inhibitor; TAHOD: TREAT Asia HIV Observational Database; TDF: Tenofovir. *Key*. NRTIs are TDF based (NRTIs + TDF) or not (NRTIs) and PI as ATV based (PI + ATV) or not (PI).

resp.). Other regimens were not significantly different to the reference regimen.

3.3. Sensitivity Analyses. Forty-five percent of all of the AHOD measurements were taken fasting. Ethnicity was known in AHOD in 80% of participants, of whom greater than 80% were Caucasian. All of the sensitivity analyses, except for exclusion of missing BMI data, yielded very similar results, in terms of direction of effect, magnitude, and significance, as those from full analyses (data not presented). Since BMI was missing in a significant proportion of participants in both cohorts (Table 1), restriction of analysis to only patients with known BMI provided results that were of similar direction and magnitude of the effect, however in some cases less statistically significant, because of loss of power.

Table 1: Patient characteristics at study entry.

Characteristics	AHOD, $n = 794$ n (%)	TAHOD, $n = 2053$ n (%)	P^*
Age (years)			
Mean ± SD	45 (±9.8)	38.6 (±10)	<0.001
Gender			
Male	761 (96)	1,484 (72.2)	<0.001
Female	30 (3.8)	567 (27.6)	
Transgender***	03 (0.4)	02 (0.1)	
HIV exposure category			
Homosexual contact ± IDU	618 (78.4)	485 (23.7)	<0.001
IDU ± heterosexual	25 (3.2)	45 (2.2)	
Heterosexual	65 (8.2)	1,341 (65.6)	
Other	80 (10.2)	174 (8.5)	
Missing	06 (0.7)	08 (0.4)	
HBV coinfection			
Negative	649 (81.8)	1,376 (67)	<0.001
Positive	22 (2.8)	171 (8.3)	
Missing/never tested	123 (15.5)	506 (24.6)	
HCV coinfection			
Negative	631 (79.5)	1,365 (66.5)	<0.001
Positive	87 (11)	128 (6.2)	
Missing/never tested	76 (10)	560 (27.3)	
HIV RNA < 500 copies/mL	326 (41)	372 (18)	<0.001
Missing	58 (7.3)	880 (43)	
CD4+ count cells/μL	360 (219–569)	161 (50–280)	<0.001**
Median (IQR)			
Missing	58 (7.3)	264 (12.9)	
Cumulative exposure to cART in years			
Median (IQR)	2 (0–8.2)	0 (0–0.2)	<0.001**
Number ART naive	320 (40.3)	1460 (71)	
Body mass index (kg/m^2)			
Mean (±SD)	24 (±3.4)	21 (±3.4)	<0.001
Missing	528 (66.5)	1016 (49.5)	
Total cholesterol mmol/L			
Mean (±SD)	5.15 (±1.3)	4.88 (±1.4)	<0.001
Triglycerides mmol/L			
Mean (±SD)	2.44 (±2)	2.40 (±2.3)	0.678
HDL-C mmol/L			
Mean (±SD)	1.15 (±0.5)	1.25 (±0.4)	<0.001

*Comparison by t-test for continuous variables and the χ^2 test for noncontinuous variables. **Comparison by Wilcoxon rank-sum test. A: AHOD: Australian HIV Observational Database; T: TAHOD: TREAT Asia HIV Observational Database. cART: combinational antiretroviral therapy; HBV: hepatitis B coinfection; HCV: hepatitis C coinfection; IDU: Intravenous drug user; IQR: interquartile range; SD: standard deviation. ***Transgender participants were classified as males in the multivariable analyses.

4. Discussion

In this study, we examined the mean differences in lipids between various cART regimens in TAHOD and AHOD cohorts. We found that the relationship between regimen and lipids differed by cohort only in the analysis of total cholesterol level. For total cholesterol, the magnitude of effect of regimen differed between cohorts such that TAHOD participants tended to have slightly lower total cholesterol for most regimens (most notably for the NRTIs (+TDF) + PI (+ATV) and the NRTIs + PI regimens). Overall, we found that the NRTIs (+TDF) + NVP and the NRTIs (+TDF) + PI (+ATV) regimens were associated with the most favorable lipid profile, whereas the NRTIs + PI and the NRTIs + EFV regimens were associated with the least favorable lipid profiles.

These regimen/lipid association findings are consistent with the literature from Western countries [5–8, 17]. The few studies that have reported lipid results from Asian population also suggest an adverse impact of PI-based and EFV-based regimens on lipids as compared to non-PI-based and NVP-based regimens, respectively [18, 19]. However, these studies were performed in clinical-trial populations, and in one study [19], NVP was given at 400 mg once a day, instead of the recommended 200 mg twice a day dosing schedule. Also, they did not report usage of TDF- or ATV-based regimens.

The observed differences in mean total cholesterol between TAHOD and AHOD cohorts, though statistically significant, were of small magnitude. The differences could be due to variations in race/ethnicity or dietary, environmental, and lifestyle factors [20]. The clinical relevance of these differences, particularly the impact of these differences on overall risk of CHD, is uncertain. In our study, TAHOD participants had average total cholesterol up to 0.5 mmol/L lower than AHOD for the NRTIs + PI regimen (Figure 1(a)). Studies on treated HIV-infected populations have suggested that a difference of 1 mmol/L in total cholesterol may be associated with difference of about 25% in risk of CHD [21, 22]. Further, TAHOD participants, for any given regimen, had higher triglycerides which have been associated with greater risk of CHD [23]. The CHD events in cART-treated HIV patients are thought to be multifactorial in origin, with a possible role of dyslipidemia, cART, HIV-associated inflammatory process, and traditional risk factors [1, 21]. We did not have data on other CHD risk factors, with which we could calculate the overall Framingham risk score for each cohort. Future studies should therefore evaluate their impact on risk of CHD events in treated HIV populations in Asia.

There are further limitations to this study. We divided each class of ART according to those shown to have favorable impact on lipids, that is, TDF, ATV, and NVP [5, 7, 8]. However, such a classification did not allow us to examine the impact of other individual drugs in each class. Further, we did not have information on use of lipid-lowering medications, which are likely to differ between TAHOD and AHOD. It is likely that since TAHOD participants were younger and mostly from low-middle income countries, they may have a lower rate of use of lipid-lowering medications, as compared to those in AHOD.

Table 2: Number and frequency of total cholesterol measurements by type of regimen and cohort.

cART Regimen	AHOD No. of patients*	AHOD median (range) no. of measurements per patient	AHOD no. (%) of measurements	TAHOD no. of patients*	TAHOD median (range) no. of measurements per patient	TAHOD no. (%) of measurements
NRTIs (+TDF) + NVP	122	2 (1–6)	247 (10.8)	70	1 (1–4)	108 (1.9)
NRTIs (+TDF) + EFV	131	2 (1–4)	245 (10.7)	90	1 (1–4)	147 (2.6)
NRTIs + NVP	155	2 (1–6)	342 (14.9)	696	1 (1–8)	1157 (20.6)
NRTIs + EFV	97	2 (1–4)	211 (9.2)	684	2 (1–10)	1487 (26.5)
NRTIs (+TDF) + PI (+ATV)	140	1 (1–5)	266 (11.6)	20	1 (1–4)	28 (0.5)
NRTIs (+TDF) + PI	187	2 (1–7)	410 (17.9)	137	3 (1–6)	367 (6.5)
NRTIs + PI (+ATV)	78	2 (1–5)	178 (7.7)	232	3 (1–6)	610 (10.9)
NRTIs + PI	184	2 (1–6)	396 (17.2)	620	3 (1–12)	1698 (30.3)
Total	1094		2295 (100)	2548		5602 (100)

*Each patient could contribute to more than one regimen. AHOD: Australian HIV Observational Database; ATV: Atazanavir; EFV: Efavirenz; NNRTI: non-nucleoside reverse transcriptase inhibitors; NRTIs: nucleoside reverse transcriptase inhibitors; NVP: nevirapine; PI: protease inhibitor; TAHOD: TREAT Asia HIV Observational Database; TDF: tenofovir. *Key*. NRTIs are TDF based (NRTIs + TDF) or not (NRTIs) and PI as ATV based (PI + ATV) or not (PI).

Table 3: Adjusted analyses for triglycerides, HDL-C, and total cholesterol : HDL-C ratio.**

Covariate	Mean difference in triglycerides mmol/L (95% CI)	Mean difference in HDL-C mmol/L (95% CI)	Mean difference in total cholesterol : HDL-C ratio (95% CI)
Regimen			
NRTIs (+TDF) + NVP	Reference	Reference	Reference
NRTIs (+TDF) + EFV	0.17 (−0.19 to 0.53)	0.01 (−0.06 to 0.08)	0.16 (−0.16 to 0.47)
NRTIs + NVP	0.58 (0.29 to 0.87)	0.15 (0.08 to 0.21)	0.13 (−0.12 to 0.39)
NRTIs + EFV	0.64 (0.34 to 0.95)	0.09 (0.03 to 0.16)	0.29 (0.01 to 0.56)
NRTIs (+TDF) + PI(+ATV)	0.15 (−0.22 to 0.52)	−0.03 (−0.11 to 0.05)	0.29 (−0.04 to 0.62)
NRTIs (+TDF) + PI	1.06 (0.73 to 1.38)	−0.02 (−0.09 to 0.05)	0.66 (0.37 to 0.95)
NRTIs + PI(+ATV)	0.57 (0.24 to 0.90)	0.03 (−0.05 to 0.10)	0.34 (0.02 to 0.65)
NRTIs + PI	1.13 (0.83 to 1.43)	0.01 (−0.06 to 0.07)	0.75 (0.47 to 1.03)
P	<0.001	<0.001	<0.001
Cohort			
AHOD	Reference	Reference	Reference
TAHOD	0.33 (0.11 to 0.55)	0.04 (−0.01 to 0.09)	−0.16 (−0.40 to 0.08)
P	0.003	0.146	0.187

Table shows independent effects of regimen and cohort variables in adjusted analyses. Since the interaction term between these variables was not significant, it was not included in the models. Figure 1 shows the interaction between regimen and cohort variables.

**Multivariable models were *a priori* adjusted for time on given regimen, Hepatitis B and/or C coinfections, age, gender, HIV RNA viral load copies/mL, CD4+ T-cell count, BMI, cumulative exposure to cART at the start of regimen, and HIV exposure category. AHOD: Australian HIV Observational Database, ATV: Atazanavir; cART: combinational antiretroviral therapy; CI: confidence interval; EFV: Efavirenz; HBV: Hepatitis B co-infection; HCV: Hepatitis C co-infection; IDU: Intravenous drug user; NNRTI: nonnucleoside reverse transcriptase inhibitors; NRTI: nucleoside reverse transcriptase inhibitors, NVP: nevirapine, PI: protease inhibitor, TAHOD: TREAT Asia HIV Observational Database; TDF: Tenofovir. *Key*. NRTIs are TDF based (NRTIs + TDF) or not (NRTIs) and PI as ATV based (PI + ATV) or not (PI).

However, TAHOD participants had lower total cholesterol for most regimens than those in AHOD, suggesting residual confounding, racial differences, or possibly higher use of lipid lowering medications. Also, lipid values were measured in site-specific laboratories which may introduce variation in results. However, such a variation is unlikely to result in any systematic differences in total cholesterol that we observed. Furthermore, patients in AHOD tended to be more treatment-experienced than TAHOD; however, adjusting for cumulative cART exposure did not change our results. Nevertheless, any residual confounding from these and other unmeasured factors cannot be ruled out. Lastly, we did not have pre-cART lipid data to compare with post-cART data in each cohort, which would have provided clearer comparisons of change in lipids in response to cART between the cohorts. Keeping these limitations in mind, our results were however robust when restricted to those (i) documented to be taken after over-night fasting, (ii) with documented race/ethnicity,

and (iii) adjusting for differential use of d4t, suggesting that these factors were unlikely to impact our results.

Strengths of our study include TAHOD and AHOD being founded on similar methodology thereby reducing the likelihood of confounding due to methodological differences. Also, the large sample size available allowed us to analyse several regimens, including those with TDF and ATV, which are less frequently used in low-middle income countries [10]. Moreover, availability of lipid measurements on several timepoints on each regimen allowed us to adjust for time spent on each regimen of interest.

In summary, our findings suggest that the impact of various ART regimens on lipids is largely similar in TAHOD and AHOD cohorts and that the newer drugs such as TDF and ATV are likely to provide similar benefit in terms of lipid profiles in both populations. We also found that TAHOD participants may have slightly lower mean total cholesterol for most regimens, although the clinical significance of this difference is uncertain. These findings contribute to the gap in evidence from Asian settings. Future studies should report pre- to post-ART monitoring of lipids and information on Framingham risk score in diverse populations.

Funding

The TREAT Asia HIV Observational Database and the Australian HIV Observational Database are part of the Asia Pacific HIV Observational Database and are initiatives of TREAT Asia, a program of amfAR, The Foundation for AIDS Research, with support from the following institutes of the U.S. National Institutes of Health (NIH): National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Child Health and Human Development (NICHD), the Office of the Director (OD), and the National Cancer Institute (NCI), as part of the International Epidemiologic Databases to Evaluate AIDS (IeDEA) (Grant no. U01AI069907). Additional support is provided by the Dutch Ministry of Foreign Affairs through a partnership with Stichting Aids Fonds. The Kirby Institute for Infection and Immunity in society is funded by the Australian Government Department of Health and Ageing and is affiliated with the Faculty of Medicine, The University of New South Wales. The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of any of the institutions mentioned above.

Conflict of Interests

The authors declare that they have no conflict of interests.

Acknowledgments

The writing committee would like to acknowledge several thousands of patients, the *TAHOD Steering Committee* (C. V. Mean, V. Saphonn*, and K. Vohith, National Center for HIV/AIDS, Dermatology & STDs, Phnom Penh, Cambodia; F. J. Zhang*, H. X. Zhao, and N. Han, Beijing Ditan Hospital, Capital Medical University, Beijing, China; P. C. K. Li*, and M. P. Lee, Queen Elizabeth Hospital, Hong Kong, China; N. Kumarasamy*, S. Saghayam, and C. Ezhilarasi, YRG Centre for AIDS Research and Education, Chennai, India; S. Pujari*†, K. Joshi, and A. Makane, Institute of Infectious Diseases, Pune, India; T. P. Merati*, D. N. Wirawan and F. Yuliana, Faculty of Medicine Udayana University and Sanglah Hospital, Bali, Indonesia; E. Yunihastuti*, Working Group on AIDS Faculty of Medicine, University of Indonesia/Ciptomangunkusumo Hospital, Jakarta, Indonesia; S. Oka*, J. Tanuma, and M. Honda, National Center for Global Health and Medicine, Tokyo, Japan; J. Y. Choi*, S. H. Han, and J. M. Kim, Division of Infectious Diseases, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea; C. K. C. Lee*, B. L. H. Sim, and R. David, Hospital Sungai Buloh, Kuala Lumpur, Malaysia; A. Kamarulzaman*‡ and A. Kajindran, University of Malaya Medical Centre, Kuala Lumpur, Malaysia; R. Ditangco*, E. Uy, and R. Bantique, Research Institute for Tropical Medicine, Manila, Philippines; Y. M. A. Chen*, W. W. Wong, and L. H. Kuo, Taipei Veterans General Hospital and AIDS Prevention and Research Centre, National Yang-Ming University, Taipei, Taiwan; O. T. Ng*, P. L. Lim, A. Chua, and A. Loh, Tan Tock Seng Hospital, Singapore; P. Phanuphak*, K. Ruxrungtham and M. Khongphattanayothin, HIV-NAT/Thai Red Cross AIDS Research Centre, Bangkok, Thailand; S. Kiertiburanakul*, S. Sungkanuparph, and N. Sanmeema, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; T. Sirisanthana*, R. Chaiwarith and W. Kotarathititum, Research Institute for Health Sciences, Chiang Mai, Thailand; V. K. Nguyen*, V. H. Bui and T. T. Cao, National Hospital for Tropical Diseases, Hanoi, Vietnam; T. T. Pham*, D. D. Cuong, and H. L. Ha, Bach Mai Hospital, Hanoi, Vietnam; A. H. Sohn*, N. Durier* and B. Petersen, TREAT Asia, amfAR—The Foundation for AIDS Research, Bangkok, Thailand; D.A. Cooper, M. G. Law*, J. Zhou*, and A. Jiamsakul, The Kirby Institute, The University of New South Wales, Sydney, Australia. (*TAHOD Steering Committee member; †Steering Committee Chair; ‡Co-Chair.)) and the *AHOD Steering Committee* (The Australian HIV Observational Database: D. Ellis, General Medical Practice, Coffs Harbour, NSW; J. Chuah*, M. Ngieng, B. Dickson, Gold Coast Sexual Health Clinic, Miami, QLD; M Bloch, T. Franic, S. Agrawal, and N. Cunningham, Holdsworth House General Practice, Darlinghurst, NSW; R. Moore, S. Edwards, and P. Locke, Northside Clinic, North Fitzroy, VIC; D. Nolan, C. Forsdyke, and J. Skett, Department of Clinical Immunology, Royal Perth Hospital, Perth, WA; N. J. Roth*†, J. Nicolson, Prahran Market Clinic, South Yarra, VIC; D. Allen, P. Maudlin Holden Street Clinic, Gosford, NSW; D. Smith, C. Mincham, and C. Gray, Lismore Sexual Health and AIDS Services, Lismore, NSW; D. Baker* and R. Vale, East Sydney Doctors, Darlinghurst, NSW; D. Russell and S. Downing, Cairns Sexual Health Service, Cairns, QLD; D. Templeton, C O'Connor, Royal Prince Alfred Hospital Sexual Health, Camperdown, NSW; D. Sowden and K McGill, Clinic 87, Sunshine Coast and Cooloola HIV Sexual Health Service, Nambour, QLD; D. Orth and D. Youds, Gladstone Road Medical Centre, Highgate Hill,

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Hindawi Publishing Corporation
AIDS Research and Treatment
Volume 2012, Article ID 412643, 8 pages
doi:10.1155/2012/412643

Research Article

Achieving Universal Access for Human Immunodeficiency Virus and Tuberculosis: Potential Prevention Impact of an Integrated Multi-Disease Prevention Campaign in Kenya

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Received 30 November 2011; Revised 27 January 2012; Accepted 28 January 2012

Academic Editor: Anthony Harries

In 2009, Government of Kenya with key stakeholders implemented an integrated multi-disease prevention campaign for water-borne diseases, malaria and HIV in Kisii District, Nyanza Province. The three day campaign, targeting 5000 people, included testing and counseling (HTC), condoms, long-lasting insecticide-treated bednets, and water filters. People with HIV were offered on-site CD4 cell counts, condoms, co-trimoxazole, and HIV clinic referral. We analysed the CD4 distributions from a district hospital cohort, campaign participants and from the 2007 Kenya Aids Indicator Survey (KAIS). Of the 5198 individuals participating in the campaign, all received HTC, 329 (6.3%) tested positive, and 255 (5%) were newly diagnosed (median CD4 cell count 536 cells/μL). The hospital cohort and KAIS results included 1,284 initial CD4 counts (median 348/L) and 306 initial CD4 counts (median 550/μL), respectively (campaign and KAIS CD4 distributions $P = 0.346$; hospital cohort distribution was lower $P < 0.001$ and $P < 0.001$). A Nyanza Province campaign strategy including ART <350 CD4 cell count could avert approximately 35,000 HIV infections and 1,240 TB cases annually. Community-based integrated public health campaigns could be a potential solution to reach universal access and Millennium Development Goals.

1. Introduction

In 30 years since the start of the human immunodeficiency virus (HIV) pandemic over 25 million people have died [1, 2]. In 2010, an estimated 34 million people were living with HIV and 67% of them lived in sub-Saharan Africa [3]. Antiretroviral therapy (ART) has considerable potential to save lives while reducing the HIV transmission [4–7]. By the end of 2010, 6.6 million people were on antiretroviral treatment (ART) in the world [3]. Despite this remarkable achievement, an estimated 7.5 million people with CD4 cell counts <350/μL were still in need of treatment [3]. Without a dramatic reduction in HIV incidence it is unlikely that we will be able to meet the growing demand for ART [3, 8]. Addressing this prevention gap will require innovative approaches to improving access to HIV services including HIV testing and counselling (HTC) and ART.

Community-based efforts, including outreach beyond health facilities, may provide one approach to help bridge this gap. Of the 34 million people living with HIV, a majority are still unaware of their HIV status [3]. WHO, recognizing the need to markedly scale-up access to HTC, has recommended provider initiated HIV testing and counselling [9]. The Kenya National HIV and AIDS Strategic Plan III includes an HTC target of 18 million (80%) of people 15–49 years of age to be newly tested by 2013; however, despite increases

in facility-based HTC the 2007 Kenya Aids Indicator Survey (KAIS) found that only 36% of adults have ever had an HIV test, and less than 20% of HIV-infected adults know that they are infected [10, 11]. Obstacles to access to HTC include a shortage of trained counsellors, limited services, high transportation costs, limited test kit availability, and stigma [10–15]. Home-based HTC offers an important potential strategy to reach targets by expanding access beyond health care facilities. With a reported uptake of up to 90% in some settings, home-based HTC also provides an opportunity for couples counselling and mutual disclosure [15]. In Uganda's Bushenyi District, a 2.5 year multi-disease house-to-house HIV testing and counselling programme tested 264,996 (94% acceptance) people in 92,984 (63%) households [14].

Although home-based service delivery is feasible in many settings, it can be time and labour-intensive. Complementary community-based health campaigns are well suited to delivering services to the rural poor and have been used to deliver HIV counselling and testing and other simple interventions to large populations [16, 17]. By combining multiple interventions and placing a larger proportion of the transaction costs onto the provider, integrated multi-disease campaigns create efficiencies for both the consumer and provider [16–19]. There is considerable experience with the health campaign approach including the mass distribution of insecticide-treated bednets which have quickly reached high coverage levels at low cost and are associated with declines in child and adult mortality in east Africa [16–19]. More recent work in sub-Saharan Africa has focused on bundling multiple interventions into a multi-disease prevention package which includes long-lasting impregnated bednets, water purification systems, preventive health education, condoms, and cotrimoxazole prophylaxis for HIV-infected adults [16, 17, 20–22].

Building on the previous community-based campaign experience in Kenya's Kakamega District, in 2009 we implemented a similar multi-disease prevention (MDP) campaign in Kisii District, Nyanza Province [16]. We applied lessons learned to pilot streamlined HTC protocols, provide same-day, onsite access to CD4 cell counts, and strengthen linkage to care. Our study examines the HIV component of the Kisii District campaign and compares CD4 count distributions to explore whether a multi-disease campaign strategy can improve earlier access to HIV diagnosis and treatment. We also project the potential HIV and TB prevention impact achieved by reaching people earlier for different ART eligibility scenarios.

2. Methods

2.1. Multi-Disease Prevention Campaign. In 2008 the Ministry of Health Kenya, the United States Government Centers for Disease Control Kenya, Community Housing Foundation (a local NGO), and Vestergaard Frandsen (a private sector manufacturing company focused on products that address the MDGs) implemented a 7 day multi-disease prevention campaign that reached 47,311 (92%) of adults 15–49 years old in Kakamega District, Western Province of Kenya. The campaign was in line with the Kenyan National AIDS Strategic Plan III's target to reach 80% of 15–64 year olds and provided interventions to address HIV, malaria, and diarrhea [10, 16]. Point-of-care CD4 counts were also piloted in selected sites [16]. Nyanza Province in western Kenya, has a high incidence of malaria, diarrhoeal disease, and tuberculosis [3, 10, 11, 23–25]. In 2007, an estimated 15% of 15–64 year olds were living with HIV [11] which has contributed to the high annual TB incidence (353 per 100,000 population) [11, 24, 25]. Standard operating procedures from the Kakamega campaign [16] were modified for the Kisii District Campaign as described below.

In September 2009 we implemented a three-day multi-disease prevention campaign that targeted diarrhoeal diseases, malaria and HIV in Kisii District, Nyanza Province (population 4,392,000). Three peri-urban campaign sites were set up around health facilities in the periphery of Kisii (Figure 1 map). The campaign was designed to (1) apply lessons learned from previous campaigns to a peri-urban setting, (2) pilot improved HIV testing and counselling protocols, (3) strengthen the referral system for improved linkage to care, (4) determine the feasibility of providing same day CD4 cell count testing for all HIV-positive participants and, (5) explore the potential impact of campaigns for early identification for HIV prevention and care services, and (6) examine differences between campaign, hospital, and provincial populations.

The campaign was planned to provide services for 5000 adults within 3 days by using a specific protocol adapted to mass campaign settings. We conducted the campaign over a weekend (Saturday, Sunday, and Monday) to ensure maximum participation of both men and women and limit disruptions to routine services. A pre-campaign social mobilization exercise started one month before the start date and engaged the community using village "baraza" forums with local chiefs, radio and print messaging, and town cries with mobile trucks. Participants were informed about campaign services, campaign sites and provided health education messages around diarrhea, malaria, HIV, and STDs. They were offered services on a first-come first-serve basis and census lists from 2008, identification cards, and indelible finger print dye were used to ensure that participants could only participate once in the campaign (all participants received finger dye irrespective of the services accessed or serostatus). To ensure that people accessing services were from the immediate local area, we used village elders and government officers working at the village level to advertise the campaign and carefully recorded location information during the registration process.

A total of 90 counselors were hired and trained to use the mass testing protocol designed for community-based campaigns with a target of 25 clients per day. Pretest counselling was offered by trained Health Communication Officers to groups of 20 participants selected for age and gender as they waited to meet the HTC counsellors. Confidentiality, consent, and counselling were assured by issuance of cards with a unique identifier number during the registration process and it was emphasized to all participants that HTC was entirely voluntary and that everyone would receive the other interventions whether or not they opted for HIV

Figure 1: Map of Kenya showing Kisii, Nyanza Province, and inset showing the location of the three campaign sites and Kisii Level 5 Hospital (Kisii Town).

testing. HTC was provided on an "opt-in" basis and written consent was required for testing. Quality of HTC was insured by the use of certified counsellors, refresher training courses, a supervision system which employed one supervisor for every 10 counsellors, sending 1 out of 50 blood samples for reconfirmation with a different diagnostic method (PCR), and exit interviews by trained staff for all campaign participants. The exit interviews were used to assure quality and to improve services on a real-time basis.

Participants who tested HIV positive received a 3-month supply of cotrimoxazole, same-day on-site CD4 count measurement, psychosocial support, local referral for further care, and were offered enrolment in a support network by peer counsellors. Linkage to care was given a high priority and planned for through various interventions. Counselors emphasized the importance of care during post-test counselling. Members from local people living with HIV (PLWHA) support networks were enrolled and trained for the implementation of the PLWHA *navigator* approach. As part of the *navigator* strategy, people testing HIV positive were offered further counselling by assigned PLWHA counsellors and, with consent, were enrolled into local support groups. Most participants opted to allow follow-up visits and provided name, address, unique identifier number, and phone number. PLWHA counsellors, using a list of clients, checked in with health centers on a monthly basis and, if necessary, made follow-up household visits [26].

The Kisii campaign included provision of one long-lasting insecticide-treated net per participant, water filters (individual filter for men, household filter for women), 60 condoms per person, and health education encompassing HIV, sexually transmitted infections, malaria, and water-borne diseases. The unit cost per person by disease was $6.27 for malaria (nets and training), $15.80 for diarrhea (filters and training), and $9.91 for HIV (test kits, counselling, condoms, and CD4 testing) [16, 27]. Using logistic and expenditure data from the 2008 Lurambi District Campaign, [16] the cost of a scaled-up replication (SUR) was estimated assuming reliance on local managers, potential efficiencies of scale, and other adjustments (Jim Kahn, personal communication). The SUR cost of $31.98 per person included 67% for commodities (mainly water filters and bed nets) and 20% for personnel.

2.2. Measurement and Analysis of CD4 Cell Count Distributions. Absolute CD4 cell counts and total lymphocyte counts were performed by portable Guava AUTOCD4 flow cytometers manufactured by Millipore. All three sites were equipped with a unit with a single 150 amperes battery (7 hour off-grid capacity). Samples were processed in batches and had a 45-minute incubation time and 4-minute processing time. Each unit had a trained machine operator and a trained nurse or other health care provider responsible for drawing 10 μL of whole blood (EDTA) and preparing samples for analysis. As patients waited for their results, they were given additional psychosocial counselling by a counsellor living with HIV. For external quality control, 5 percent of all blood samples were sent for confirmation at Kisii Level 5 Hospital Laboratory using a Becton Dickinson Facs Calibur Flow Cytometer. The Kisii Hospital laboratory routinely sends 10% of blood samples to CDC Kisumu for external quality control.

To create a matching historical cohort and a baseline for comparison, we abstracted the medical records, including the first measured CD4 count, for all newly diagnosed patients aged 15 and above from March to August 2009 at the HIV/AIDS Patient Support Center in the Kisi District Level 5 Hospital (apex of district health care facilities). All CD4 measurements for this cohort were made using the same Kisii Level 5 Hospital laboratory Becton Dickinson Facs Calibur Flow Cytometer.

We analyzed the CD4 data from the Kisii campaign, the reference hospital and Nyanza province data from the recently performed KAIS survey [11]. The 2007 KAIS is the first national population-based survey of Kenya that obtained representative estimates on behavioral, clinical and biologic indicators for HIV/AIDS. The 2007 KAIS was conducted among a sample of households selected from all eight provinces in the country, covering both rural and urban areas (more detailed methods are described in detail elsewhere) [11].

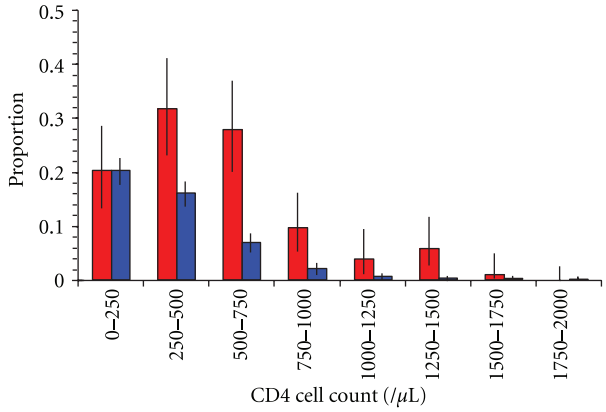

Figure 2: Comparison of the CD4 cell count distribution in Nyanza Province (red; KAIS survey) and the Kisii Hospital cohort (blue). The data for the hospital cohort are scaled to match the KAIS data for the lowest CD4 cell count range and the differences in the heights of the bars for the higher ranges show the proportion that are missed in the hospital cohort.

2.3. Projecting the Potential HIV and TB Prevention Impact of Early Detection. For our comparison and projections we used data from those who were reported as being newly diagnosed—all were assumed to be ART naive. Cumulative distribution functions were compared using the standard Kolmogorov-Smirnov test. We estimated the potential benefits of early identification and starting ART for three scenarios (1) <250 CD4 cells (status quo), (2) <350 CD4 cells, and (3) immediate ART irrespective of CD4 cell count.

To estimate the proportion of people with CD4 cell counts that are missed under passive clinic-based case-finding but would be found using a campaign approach, we assumed that everyone with a CD4 cell count below 250/μL will present to a health facility before they die. We scaled the proportions in the "hospital reference" data so as to match the proportion in the KAIS data set below 250/μL (Figure 2). Applying the scaling proportion allows us to see the differences in proportions of people that are missing in the hospital cohort at the higher CD4 levels. This in turn enables us to obtain an approximate estimate of the increase in the number of people who would be put onto ART and the number of TB cases that would be averted by adopting a campaign approach.

The population of Nyanza province is 4.4 million of whom 2.9 million are adults with around 435,000 (15%) who are estimated to be HIV positive [11]. We estimated the number of HIV-positive TB patients in Nyanza Province in two ways. First, the case-notification rate of HIV-positive TB patients in Nyanza is 189 per 100,000 population giving about 8,314 HIV/TB cases per year [25]. Second, the life-time risk of TB for those not receiving ART has been estimated to be 13% [28]. With a mean life expectancy of HIV-positive people of ten years, this means that the annual risk of TB-disease is 1.3% and we expect there to be about 435,000 $\times$ 0.013 = 5655 case of TB in HIV-positive people in the province each year. Taking the average of these two estimates, the expected number is 6,985 per year. ART reduces the incidence of TB by about 71% [28], so that if everyone started ART immediately they were found to be HIV-positive the number of TB cases averted would be 4,959. This enables us to estimate the reduction in the number of TB cases that we expect each year under the campaign and passive clinic-based case-finding approaches.

To estimate the number of new HIV transmissions averted, we assumed that the epidemic is in a steady state so that each person with HIV infects one other person before they die. Assuming that the CD4 cell count is 750/μL immediately after seroconversion [29] we multiply the number started on ART by the proportion of time for which they are on ART (the CD4 cell count at the time at diagnosis in the different scenarios is used to calculate the amount of time on and off ART). To derive the HIV infections averted we compared the projected outcome using these assumptions with "no ART." To simplify the analysis, we did not include the additional prevention benefits of the long-term reduction in TB transmission and treatment of identified TB cases. We also did not factor in WHO recommended IPT or infection control for TB which is not yet in widespread use in Kenya [30].

The study protocol was reviewed by the Kenya Ministry of Public Health and Sanitation and considered to be part of on-going program monitoring and evaluation. The study represented a private-public partnership and funding for the study was provided by the Kenya Ministry of Public Health as part of routine public health services. Ministry of Health Kenya and Vestergaard Frandsen funded the campaign; MOH provided campaign personnel, HIV test kits, and condoms. The decision to conduct, analyse, and submit the study was taken by the Ministry of Health and WHO.

3. Results

3.1. Multi-Disease Prevention Campaign. Over a three-day period, the campaign reached 5198 individuals aged over 15 years with a 100% uptake of the HIV counselling and testing and multi-disease preventive package. Counselors worked 8 hour days starting from 8:00 AM and tested around 25 clients per day (100% of target). Clients who were found to be HIV negative were provided HTC in about 20 minutes, while those who were diagnosed with HIV were given HTC counseling in about 38 minutes. The process from drawing blood to getting CD4 cell count results usually took around two hours (mean 119; range 47–191 minutes).

Of the 5198, 2090 (40%) were males. Of the 329 participants who tested HIV positive, 71 (22%) were males; HIV prevalence among males was 3.3% and 8.3% for females. This difference of HIV prevalence between genders reflects the 2010 antenatal care sentinel surveillance results of 8.7% among women in Kisii District sites [31]. A separate study that included a subsample of the people from the Kisii campaign and others evaluated factors affecting linkage to care and found that 81% of people who consented to follow-up visited the referral clinic by 10 months after the campaign [26].

Table 1: CD 4 values from the campaign, hospital reference, and KAIS data sets. The table gives *N*, the number of people for whom a CD4 cell count was done, the median CD4 cell count, and the proportion of those tested that are below 250, 350, and 500 cells/μL. Numbers in brackets are percentages. Using a Kolmogorov-Smirnov test, The CD4 cell count distribution for the Hospital Reference data set is significantly different from the other two ($P < 0.001$ in both cases) but the Campaign and KAIS data sets are not significantly different ($P = 0.346$).

	Campaign	Hospital reference	Nyanza KAIS
N	255	1284	306
Median/μL	536	348	550
$N < 250$	33 (13%)	436 (34%)	52 (17%)
$N < 350$	64 (25%)	642 (50%)	92 (30%)
$N < 500$	112 (44%)	899 (70%)	141 (46%)
$N < 750$	187 (74%)	1137 (89%)	220 (72%)
$N < 1000$	228 (90%)	1215 (95%)	258 (84%)

3.2. Analysis of CD4 Cell Count Distributions. Of the 258 (4.9%) who were newly diagnosed with HIV (71 knew their status before campaign), CD4 count determination was performed for 255 (98%). The median CD4 count was 536 cells/μL (IQR 348 to 760;) with 13% having a CD4 count <250 cell/μL and 25% a CD4 cell count <350 cells/μL (Table 1).

Of the 1284 patients in the Kisii Hospital reference cohort, 350 (27%) were male (age range 15–61; CD4 count range 1–1862) and 934 (73%) were female (age range 15–69; CD4 count range 1–2560). The first CD4 counts from the 1284 patients had a median of 348 (IQR 185 to 551) with 34% having a CD4 count <250 cell/μL and 50% a CD4 cell count <350 cells/μL (Table 1).

The results obtained from the 2007 KAIS data base for Nyanza Province included 1585 females, 1386 (87%) tested, 240 (17%) HIV positive, 218 (91%) not on ART, and 203 (85%) with CD4 counts. Of the 1229 males surveyed, 994 (81%) were tested, 123 (12%) HIV positive, 108 (88%) not on ART, and 103 (95%) with CD4 counts. The median CD4 count overall was 550 cells/μL (IQR 305 to 785). Table 1 shows that the CD4 cell count data from the campaign for Kisii are not significantly different from the KAIS data for Nyanza ($P = 0.346$).

3.3. Projecting HIV and TB Prevention Impact of Early Detection. Figure 2 shows that the Hospital reference cohort has significantly lower median CD4 cell counts when compared with the Campaign and KAIS data. Table 2 shows that using our scaled estimation approach with either campaign or hospital-based strategies, current ≤250 ART eligibility criteria results in around 38,000 people started on ART and about 645 cases of TB will be averted in Nyanza Province. Increasing the CD4 cell count eligibility to ≤350 combined with the passive case-finding approach increases the number starting ART to 56,000, averts 26,000 new HIV infections, and prevents 942 TB cases. However, the ≤350 ART eligibility criteria combined with the campaign approach would translate into an estimated 74,000 people starting ART, thereby averting 35,000 new HIV infections and preventing 1,240 TB cases per year. Starting at a CD4 cell count of 500/μL gives an even greater relative advantage to the campaign approach with 129,000, or 2.6 times as many people started on ART, and 2,182 total or 2.6 times as many TB cases averted using the campaign approach when compared with the passive case-finding approach.

4. Discussion

This three-day integrated multi-disease prevention campaign reached over five thousand people in Kisii district including over 200 people who were unaware that they were living with HIV. The uptake of HCT in the campaign is comparable to the high rates of over 90% observed in home-based, door-to-door testing interventions implemented in Uganda [15, 32, 33] and Kenya [34] and was achieved in considerably less time. Similar to previous campaigns, [16] successful implementation of this campaign may have been due to the engagement of the community leadership, delivery of services at convenient locations near participants' homes and the multi-disease prevention approach which included concomitant distribution of free nets, water filters, and condoms. Although access to laboratory tests including CD4 levels has been a major barrier to expanding access to ART [35, 36], the campaign successfully delivered same-day CD4 level testing results for all of the newly identified people with HIV.

Delayed diagnosis and access to ART have significant public health implications for both the individual and the community. Expanded access to HCT linked with point-of-care CD4 testing has considerable potential to support the implementation of WHO's recommendation to start ART for everyone with a CD4 ≤ 350/μL [37]. Comparison of CD4 counts from campaign participants with the hospital cohort CD4 data and the recent national survey suggests that the campaign identified people significantly earlier in the course of their HIV disease. This makes intuitive sense as it reaches people before they are symptomatic and is supported by other studies examining the use of community-based services outside health facilities [38]. Although we do not present the data, the 80% linkage to care for people diagnosed with HIV in this campaign at 10 months was better than in many other settings [39] but required setting up a robust follow-up system. The data also suggest that increasing the threshold to 350/μL combined with the standard passive facility-based case-finding approach could increase the number of people in Nyanza who need to start ART by a factor of 1.9 or 56,000 people. However, the campaign approach combined with optimal linkage to care could increase the number receiving ART by a factor of 3.7 or 74,000 additional people—an additional 18,000 people who were unaware of their HIV status and who were eligible but not on ART. Our simple projections using a stable generalized epidemic setting suggest that an active campaign approach to identify those with CD4 cell count <350 could prevent 10,000 HIV transmissions, 76,000 deaths and 3600 TB cases per year. Although more complex projections for the province and country are beyond the scope of this paper, improving access to early

Table 2: Projected prevention impact of campaign approach by CD4 eligibility criteria for Nyanza Province.

	Campaign approach				Passive case-finding			
CD4 cell count at start of treatment (/μL)	HIV-positive population started on ART (%)	Number started on ART (thousands)	HIV infections averted per year (thousands)	TB cases averted per year	HIV-positive population started on ART (%)	Number started on ART (thousands)	HIV infections averted per year (thousands)	TB cases averted per year
≤250	13	38	13	645	13	38	13	645
≤350	25	74	35	1240	19	56	26	942
≤500	44	129	86	2182	27	79	53	1339
Immediate	100	294	294	4959	38	112	112	1884

ART through a campaign approach could have significant public health and economic benefits including preventing morbidity, mortality, disease transmission, and reducing costs to the individual, health system, and society [4, 6, 40].

Short intense multi-disease campaigns face a number of challenges including maintaining efficiency and quality of service provision and linkage to care while dealing with large numbers of people. Previous work in Kenya and elsewhere suggests that careful consensus building and micro-planning with community leaders and key health care providers is required to mobilize resources and provide high-quality services for the temporary surge of participants in the campaign [16]. The various TB and HIV prevention scenarios modeled would only be achievable under conditions of a high linkage to care after the campaign which requires postcampaign systems monitoring health care facility attendance, active followup, and local support networks. Another significant challenge is the cost of the campaign. Preliminary analyses suggest that despite the relative high costs per person [27] the campaign is likely to be cost effective in part due to the multi-disease approach and the numbers of people reached in a short period of time. Arguably, delivering health care services from fixed facilities is also costly and often does not reach stated objectives.

There are important limitations to our study. The comparison of the hospital, province, and campaign CD4 data may have been influenced by a number of biases introduced from the selection of the three populations. Specifically, it is difficult to say with certainty that the three subpopulations that we compared are similar given the different ways that people accessed the hospital, campaign and KAIS survey (e.g., nonresponse, refusal, and missing CD4 counts). Additionally, there are potential confounders that may have affected the CD4 results including the difference in methods to determine CD4 counts, diurnal rhythms, physical and psychological stress, pregnancy, drug administration, tuberculosis, and viral infections. However, the similarity of the campaign data with the provincial data for Nyanza is reassuring and the lower CD4 counts of those who are ill and seeking care in a hospital setting make sense. Our assumption that people coming into the hospital for care were not referred from a peripheral site and the high linkage to care may have resulted in optimistic projections favoring the campaign strategy. However, despite our lack of certainty regarding the projected benefits which relied on crude estimates, we are likely to be directionally correct and a more sophisticated modeling approach may provide additional insights.

We are far from achieving universal access and there is increasing interest in new approaches to ensuring early and equitable access to ART and other HIV services. This multi-disease prevention campaign presents an operational proof of concept for the expanded access to HTC and same-day CD4 testing that is required for many countries to reach national HIV and TB prevention goals. Multi-disease integrated campaigns have considerable potential and may represent an important conceptual breakthrough in our efforts to achieve national health objectives reflected in the Millennium Development Goals [41].

Authors' Contribution

R. Granich is the Lead Author. R. Granich, N. Muraguri, A. Doyen, N. Garg, and B. Williams made the study design; N. Muraguri, A. Doyen, and N. Garg were responsible for the collection of data; B. Williams, A. Doyen, and R. Granich made the analysis; R. Granich, N. Muraguri, A. Doyen, N. Muraguri, and B. Williams were responsible for interpretation of data; R. Granich, N. Muraguri, A. Doyen, N. Garg, and B. Williams made the draft paper; R. Granich, N. Muraguri, A. Doyen, N. Muraguri, and B. Williams prepared the final paper.

Disclaimer

The opinions and statements in this paper are those of the authors and do not represent the official policy, endorsement, or views of the World Health Organization.

Conflict of Interests

None of the authors has conflict of interests to declare.

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Hindawi Publishing Corporation
AIDS Research and Treatment
Volume 2012, Article ID 749718, 8 pages
doi:10.1155/2012/749718

Review Article

Are Expert Patients an Untapped Resource for ART Provision in Sub-Saharan Africa?

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Received 29 November 2011; Revised 23 January 2012; Accepted 24 January 2012

Academic Editor: Ann Duerr

Since the introduction of antiretroviral treatment, HIV/AIDS can be framed as a chronic lifelong condition, requiring lifelong adherence to medication. Reinforcement of self-management through information, acquisition of problem solving skills, motivation, and peer support is expected to allow PLWHA to become involved as expert patients in the care management and to decrease the dependency on scarce skilled medical staff. We developed a conceptual framework to analyse how PLWHA can become expert patients and performed a literature review on involvement of PLWHA as expert patients in ART provision in Sub-Saharan Africa. This paper revealed two published examples: one on trained PLWHA in Kenya and another on self-formed peer groups in Mozambique. Both programs fit the concept of the expert patient and describe how community-embedded ART programs can be effective and improve the accessibility and affordability of ART. Using their day-to-day experience of living with HIV, expert patients are able to provide better fitting solutions to practical and psychosocial barriers to adherence. There is a need for careful design of models in which expert patients are involved in essential care functions, capacitated, and empowered to manage their condition and support fellow peers, as an untapped resource to control HIV/AIDS.

1. Introduction

By the end of 2010, approximately 5,1 million people were receiving antiretroviral therapy (ART) in sub-Saharan Africa (SSA) representing only 49% of people in need of treatment [1]. For those fortunate enough to access ART, HIV infection became a chronic disease requiring lifelong treatment. However, retention in ART is a huge challenge. In 2010, a systematic review reported 80.2% (CI 78.0–82.4%), 76.1% (CI 72.4–79.7%), and 72.3% (67.4–76.9%) retention in ART at 12, 24, and 36 months of treatment, respectively, [2].

Frequently mentioned barriers to adherence in SSA are stigma, forgetfulness, lack of awareness, and loss of employment due to frequent absences from work. Shortage of human resources results in inaccessible staff, long waiting times, and poor quality of health services. Moreover, long distances to health facilities, scarce availability and high cost of transport limit access [3, 4].

Although barriers to retention in ART are well studied, they remain in place as a large number of patients keep on defaulting. We postulate that the dominant provider-centred ART delivery model needs to be challenged, taking into account supporting factors for adherence such as adequate information, sense of self-worth, acquisition of problem solving skills, community support, and self-management [4–7].

When PLWHA use their insider's knowledge about their condition, develop self-management skills, have worked out what services exist and when and how to access them, and make day-to-day decisions to enhance their well-being, they can be considered expert patients, exerting a significant control over their own lives. This perception can be accelerated by involving actively PLWHA as expert patients in medical ART care [8].

ART care is a combination of several types of functions such as complicated clinical decision making, routine clinical checkups, ART provision, adherence counselling, social

support, and laboratory monitoring. Some of these functions can be standardized and simplified to involve less qualified health cadres and PLWHA in ART delivery [9]. Various care models showed the added value of involving PLWHA in psychosocial and adherence support [5, 10, 11]. However, we believe that more functions, including standardized medical functions such as ART provision could be shifted towards PLWHA to obtain a more demedicalized ART delivery model, primarily based on the communities and expert patients, with professional backup when needed [8, 9]. This participation of PLWHA as expert patients in standardized medical tasks is proposed to streamline the process to access ART, to improve adherent behaviour, psychosocial wellbeing and retention in care [6, 8, 9, 12]. The result is a modified patient-professional partnership, defined by the paradigm of collaborative care. Both patients and healthcare workers can use their expertise, patients as experts about their lives and needs and healthcare workers as experts about diseases [13].

For the scope of this paper, we analysed how PLWHA can become expert patients and get involved in ART provision. To do so, we developed a conceptual framework in which self-management can reinforce PLWHA to become expert patients. We reviewed the literature for examples of involvement of PLWHA in ART provision. We focused on the context of SSA, where staggering workforce shortages limit the response to the HIV epidemic, and where social support networks are an essential element of personhood [14].

2. Methods

Based on our own experience, working in an HIV program in Tete, Mozambique, where patients are involved in the ART provision through community ART groups, we wanted to analyse how PLWHA can become expert patients and get involved in ART provision. In order to structure our thinking about the involvement of PLWHA as expert patients, we developed a framework to illustrate the different elements required to reinforce HIV self-management and to empower PLWHA to become engaged in the care for their condition as expert patients (Figure 1).

To increase their level of self-management and to become expert patients, PLWHA need to be (1) adequately informed and capable of acquiring self-management skills, (2) motivated to take day to day responsibility for their own care, and (3) part of a peer support network [6].

In order to compare our own experience with other HIV care delivery models featuring involvement of PLWHA in ART provision in SSA, we searched the literature on PubMed, the Cochrane database, and Google Scholar from 2000 to 2011. In addition, we reviewed article reference lists and searched websites of WHO and international HIV agencies. A combination of key search terms "SSA", "HIV", "AIDS", "delivery of health care", "community networks", "community health services", "peer support", "self-help groups", "expert patient", "self-management", "treatment outcomes," and "retention in care" was used. The search was limited to English literature. All retrieved abstracts were reviewed by FR and TD. We only selected articles that explicitly described PLWHA involvement in ART provision in SSA.

Papers on psychosocial and adherence support and ART provision by lay providers, who were not explicitly PLWHA, were excluded, as the added value of these strategies is already extensively described in the literature. Also studies with PLWHA involvement during a short time period were not considered as we focused on long-term solutions to empower PLWHA.

We applied the conceptual framework on the selected studies.

3. Results

The literature search for involvement of PLWHA as expert patients in ART provision in SSA produced 50 articles. Twenty-four articles were excluded as they did not reveal information on PLWHA involvement in care or ART provision. Of the 26 remaining articles, 6 were excluded as they described a nurse-based care model without an explicit involvement of PLWHA. Another 9 articles were excluded as lay providers were involved in psychosocial support and adherence support, but not in ART provision, and PLWHA were not involved or PLWHA involvement was not explicitly described.

Three articles illustrated the positive impact of involvement of PLWHA in psychosocial and adherence support on adherence and treatment outcomes. But as these articles did not mention an involvement of PLWHA in ART provision, they were excluded for further analyses [5, 10, 11].

In addition, we excluded 4 articles from rural Uganda where community health care workers (CHWs) or volunteers provided ART at patients' homes without involving PLWHA. The CHWs were trained, salaried, and equipped with a motorbike and mobile phone, whereas social recognition was the main motivation for the volunteers. Outcomes obtained were comparable with conventional care. It is hypothesized that these ART delivery models, primarily based on CHW and volunteers, could serve as a role model for further involvement of PLWHA in ART provision and care [15–18].

We only found four articles, including our own experience in Tete, involving PLWHA in ART provision in SSA. One article described the increased medication adherence as a result of a peer-delivered direct observed treatment (DOT) strategy during the first 6 treatment weeks of antiretroviral treatment at a health facility in Mozambique [19]. This study was further discarded, as PLWHA were involved only in the initial 6 weeks of ART provision, and since to our understanding DOT is not compatible with the proposed process of reinforced self-management for PLWHA to become expert patients. Figure 2 describes the research strategy and results.

Table 1 summarizes the three articles retrieved describing PLWHA involvement in ART provision. We did not find published examples of PLWHA involved in decision making of ART initiation.

The first two articles discuss the same cluster randomized controlled trial in *Kenya*, comparing a community-based care model to a conventional-clinic-based care model.

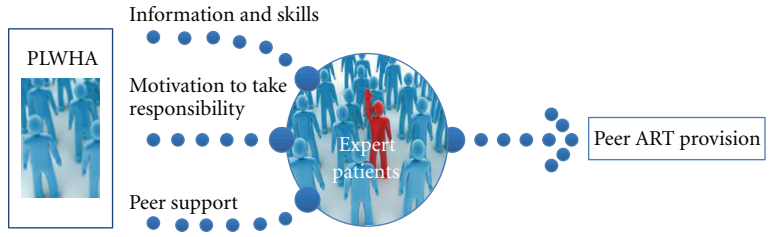

Figure 1: Conceptual framework: elements required to reinforce PLWHA to become expert patients.

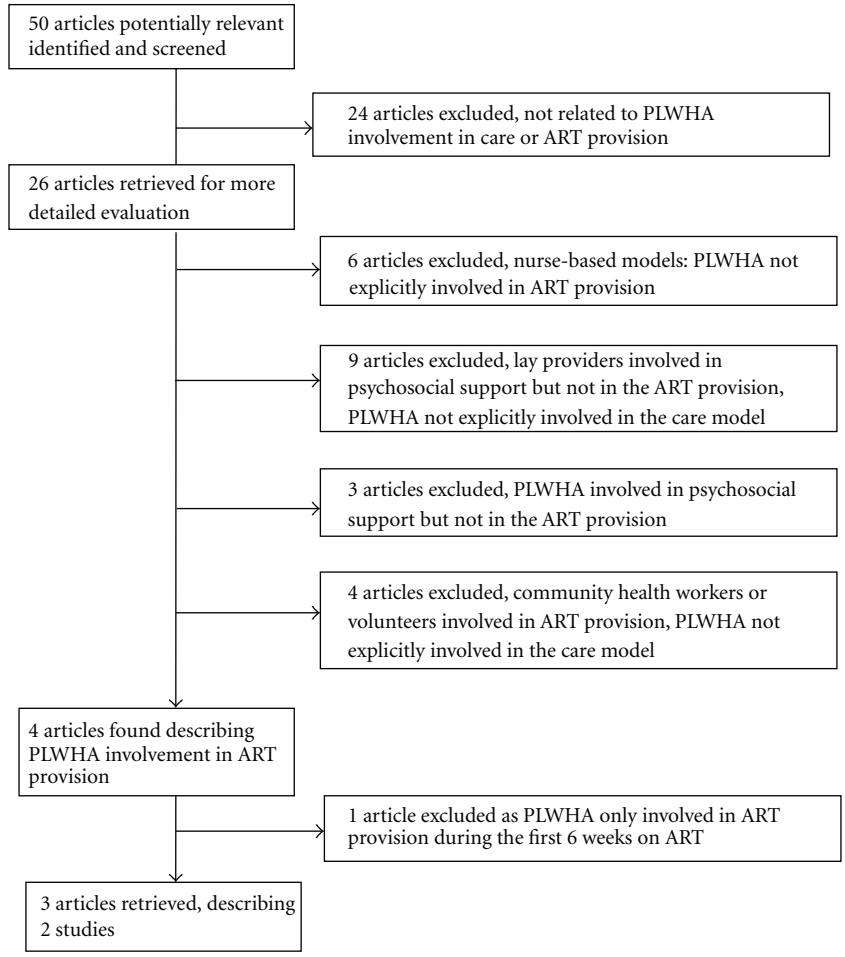

Figure 2: Results of literature search on PLWHA involvement in ART provision.

Trained PLWHA, known as Community Care Coordinators (CCC), delivered ART monthly at the patients' homes and referred patients if clinical problems occurred. Every three months patients were invited for a routine visit at the clinic. Each CCC took care of 8 to 20 clinically stable adult patients on ART. Patients perceived CCC as their confidents and advocates. By playing this role, CCC obtained insights into adherence and psychosocial issues. The clinic regarded the CCC as an extension of the clinic staff. The outcomes obtained were comparable to those with conventional care but clinic visits were reduced by 50%. The authors concluded that trained PLWHA have the additional advantage of their day to day experience of living with HIV [20, 21].

We documented our own experience in *Mozambique*, where PLWHA are involved in community ART provision with as main objective to improve the retention in care and relieve the health facilities. Adult patients stable on ART were invited to self-form peer groups of maximum six members, called community ART groups (CAG). Interested patients were capacitated during an information session on the CAG dynamic, including community ART delivery, adherence support, and social support. Monthly the CAG members meet in the community to check pill counts, to verify the health status of members, and to choose a representative to travel to the clinic. He/she reports the adherence and health outcomes and collects a drug refill for all CAG members

Table 1: Study characteristics of included articles.

Country	Inputs				Outcomes	Method
	Tasks of PLWHA	Training	Salary	Equipment		
Kenya [20, 21]	*Community care coordinators*, each responsible for 8–20 adults: (i) Monthly drug refills (ii) Pill count (iii) Monitoring (iv) Referral of problem cases	(i) 1-week theoretical, (ii) 2-months practice, on the job training	Yes	(i) Mobile device (ii) Mobile phone	208 patients stable and at least 3 months on ART were randomly assigned to: community-based care ($N = 96$) and clinic-based care ($N = 112$): (i) 50% reduction clinical visits when in community-based care (ii) 5% LFU rate in both arms at 12 months follow-up time	Cluster RCT
Mozambique [22]	*PLWHA organized in community ART groups* in which 6 members are responsible for (i) Monthly drug refills (ii) Pill count (iii) Self-reporting (iv) Self-referral	(i) Information session on day of inclusion in a CAG (ii) 6 monthly interactive group sessions (iii) No formal training	No	No	1,301 patients at least 6 months stable on ART were enrolled CAG. After median follow-up time of 12,9 months: (i) 0.2% LFU (ii) 2.3% died (iii) 97.5% retained	Cohort study

RCT: randomised controlled trial; PLWHA: people living with HIV/AIDS; LFU: lost to followup; CAG: community ART groups.

at the clinic. Every six months, all members are invited for a routine clinic visit, CD4 check and an interactive group session. This dynamic is driven by mutual support and the need to obtain an easier refill, integrated in the patients' daily life in the community. No financial or material incentives were given. Of the patients in CAG, 97.5% were retained after a median follow-up time of 12.9 months [22].

Both programs fit in the concept of the expert patient, as PLWHA were motivated to acquire skills to manage their condition and to support fellow peers, using their day-to-day experience of living with HIV (Table 2). In both programs PLWHA functioned as partner in care and a bidirectional referral system was installed, as sick patients were referred to the clinic and the community network was used for tracking of patients lost to followup.

In both Kenya and Mozambique PLWHA acquired skills to provide ART, to refer sick patients to the clinic, to report on treatment outcomes, and to give psychosocial support [20–22]. In Kenya, CCC were trained in medical and psychosocial tasks to become expert patients. Being PLWHA, they were able to understand and resolve psychosocial barriers to adherence of their peers in the community to an extent that was not obtained during consultations at the health facility [20, 21]. In Mozambique, all patients in CAG were engaged on a voluntary basis and capacitated to participate in the daily care of themselves and their peers. PLWHA self-formed support groups and met monthly in the community to share information and problem-solving skills regarding physical and psychosocial issues. Major problems were reported to the health staff and feedback was debated at the next meeting in the community, resulting in an information loop between health facilities and the community [22].

In Kenya the CCC benefitted from a formal training and were remunerated as CHW. There was a solid monitoring system in place to facilitate regular control and supervision by the healthcare workers, and CCC were held accountable for their daily performances [20, 21]. In Mozambique the peers were involved from the start in the process of planning and implementation of the CAG dynamic, which resulted in a feeling of ownership and motivated the PLWHA to stay involved in the CAG dynamic. Affordability and accessibility of ART refill was improved for CAG members. These direct benefits were a straightforward incentive to motivate PLWHA to become engaged in their own care [22].

In both countries the motivation for expert patients to take responsibility was strengthened through the proximity with their fellow peers in the community, as they added their day-to-day expertise of living with HIV to their acquired knowledge. This resulted in unique relationships among peers, built on common needs, confidence, and reciprocity [20–22]. CCC in Kenya were perceived by the patients as their advocates, a relationship which enabled them to bring practical solutions for psychosocial problems related to adherence where the traditional care providers had failed, and to ensure the communication between the PLWHA in the community and the healthcare workers [20, 21].

4. Discussion

4.1. Expert Patient in Chronic Lifelong Conditions. The increase in chronic lifelong conditions (CLLCs), such as

Table 2: Application of conceptual framework to the programs in Kenya and Mozambique.

	Essential elements to become expert patients		
Country	Information and skills	Motivation to take responsibility	Peer support
Kenya [20, 21]	CCC (i) Trained in medical and psychosocial tasks (ii) Offer psychosocial support (iii) Deliver ART in the community (iv) Refer problem cases when needed	(i) Formal training (ii) Remuneration (iii) Strict control and supervision (iv) Proximity with fellow peers (v) Recognition by PLWHA and HCW	CCC (i) Better understanding of psychosocial barriers (ii) Rely on day-to-day experience living with HIV/AIDS (iii) Considered as advocates (iv) ↑ Communication between HCW and community
Mozambique [22]	Information loop between HCW and CAG members and sharing information and skills in the community: (i) ↑ Information circulating in the community (ii)↑ Skills of CAG members to (a) Provide ART in the community (b) Overcome daily obstacles to adherence (c) Offer psychosocial support (d) Refer problem cases when needed	(i) Direct social, health and economic benefits (ii) Proximity with fellow peers, reinforced during continuous contacts in the community and periodic group sessions (iii) Recognition by PLWHA and HCW	CAG members (i) Social relationship networks contributes to: (a) Continuous information sharing (b) Problem solving skills (ii) Proximity—mutual psychosocial or financial support to address common challenges

ART: antiretroviral treatment, CAG: community ART groups, CCC: community care coordinators, HCW: health care worker, PLWHA: people living with HIV/AIDS.

diabetes and hypertension, is severely burdening health systems in many countries. The commonly used provider-centred models are resource intensive, as they require high inputs in skilled health workers. Consequently, it is becoming increasingly difficult to keep up with growing needs and demands of people living with CLLC, even in high-income countries.

Therefore, there is a growing interest in strengthening self-management, putting patients with CLLC at the centre of a web of support, surrounded by expert patients, peer groups, and health professionals. In this way, patients could be empowered to manage their own CLLC and take full responsibility for their conditions and their lives [23]. This is thought to have the potential not only to contain the escalation of health care costs, but also to improve outcomes. People for whom a CLLC is diagnosed reach a turning point in their life. They need to "rebalance" their daily habits to the requirements of their condition and play as such a crucial role in the management of their condition.

Indeed, people living with CLLC take daily decisions linked to pill intake and interpretation of signs and symptoms, requiring often subtle adaptations in diet or behaviour. Such daily adaptations and long-term management often turn them into real experts in living with a chronic condition. Their engagement can be expanded and patients can become more autonomous, as already commonly practiced in diabetes care in high-income countries.

We believe that there is a need to frame HIV/AIDS as a CLLC, requiring lifelong adherence to medication. When PLWHA acquire self-management skills and are empowered to become expert patients, their physical and psychosocial well-being is expected to improve as PLWHA will function more autonomously, which is essential to sustain lifelong adherence to treatment. In addition, their dependency on scarce skilled medical staff is expected to decrease. The latter is particularly relevant for SSA, where the burden for HIV is the highest and health systems the weakest, and where big proportions of populations remain unattended to today [8, 9, 12]. Involvement of PLWHA as expert patients in simplified care tasks, which represent the bulk of HIV services, can relieve the weak health systems in most SSA countries with high HIV prevalence, in order to cope with the increasing patient load. Hence, involvement of PLWHA as expert patients can bring advantages for both the provider and the patient.

A Cochrane review showed that adequate information and practice of medication management skills among PLWHA resulted in better adherence, which is known to result in better treatment outcomes [7]. The process of information exchange can be boosted through social interactions among peers, who add to their acquired knowledge their expertise of day-to-day living with the disease [8, 9]. To reinforce their level of self-management and to become expert patients, PLWHA need to acquire self-management skills for three sets of tasks faced by people with chronic conditions: (1) medical management of their condition such as taking medication and self-monitoring, (2) developing and maintaining supportive social relationships with healthcare workers and community members, and (3) coping with psychological distress such as fear for stigma and anger, frustration, and the sadness of having a lifelong condition ("living positively") [13, 24].

Adequate information and practice of self-management skills are not enough to achieve and sustain behavioural change. They need to be combined with motivation, defined as the driving force by which humans achieve their goals [6]. The motivation to take responsibility in self-care to achieve adherent behaviour depends on the importance given to

treatment and adherence, the confidence in the care provider and the net effectiveness of the treatment, and the self-confidence to be able to manage challenges inherent to lifelong treatment. Group education, shared decision making and social support motivate and empower PLWHA who wish to become better self-managers [6]. Community participation, as described in Mozambique, responding to real needs and involving the communities straight from the start in the planning and the implementation will motivate and empower those engaged and is a precondition for sustainability of activities embedded in the community [25].

To be successful, service delivery in SSA should be adapted to African personhood, grounded in social integrity and the need to maintain social support networks [14]. In our experience with the CAG in Mozambique, social relationship networks among CAG members in a context of economic hardship are used to overcome social, financial, and practical difficulties. They are based on trust, cooperation, reciprocity, and sociability. They contain a silent agreement about being supported and supporting, knowing that these roles can change over time and what is invested will give a return [26]. CAG members in Mozambique have a mutual agreement to support each other on a daily basis. As a result, such social networks can be an important resource to reinforce self-management and adherence [22].

4.2. Examples of Expert Patient Involvement in ART Provision in SSA. We looked at the literature for examples of involvement of PLWHA as expert patient in the ART provision in SSA and found only two published examples: one example of trained PLWHA in Kenya and another of self-formed peer groups in Mozambique. In both models, ART refill is dissociated from clinic visits. Routine clinic visits are scheduled three- or six-monthly, respectively, in Kenya and Mozambique. In between, patients can go to the clinic whenever they are sick. Community ART provision improved the accessibility and affordability of ART, as it decreased direct costs for transport and indirect costs due to time spent travelling and queuing in a health facility. Both programs had similar or improved treatment outcomes compared to conventional care and a reduced workload in the health facilities. Both programs fit in the concept of the expert patient, as PLWHA were motivated to acquire self-management skills to manage their condition and to support fellow peers, using their day-to-day experience of living with HIV. The major difference between both programs is that the trained PLWHA in Kenya are remunerated, equipped, and considered as an extension of the health care system, whereas in Mozambique the CAG are more community owned [20–22].

A possible limitation of the literature review is publication bias, selecting only field experiences resulting in positive outcomes. In addition, many interesting experiences are local problem-solving strategies, which are never reported in the scientific literature. However, these pilot models confirm results of recent reviews indicating that task-shifting to PLWHA as expert patients can be effective under certain conditions and can increase significantly the number of services provided and population reached at a given level of quality and cost [27, 28]. There is a need to assess further the potential of care models based on voluntarism in Mozambique versus remunerated expert patients in Kenya in terms of effectiveness, efficiency, and sustainability. For example the cost-effectiveness of both strategies needs to be measured and compared. Additional staff such as peer CHW in Kenya require additional means to pay them salaries and to train and equip them, whereas full responsibility of PLWHA for medical care functions as in Mozambique implies an inevitable loss of control for the provider. It is important to balance both the costs and the yield of each approach, in terms of impact on treatment outcomes and quantity of services provided for a given cost.

4.3. Possible Concerns. Often mentioned concerns related to community-embedded ART programs are stigma and fear for reduced quality of care. Stigma is a known barrier to adherence as it threatens social integrity and patients run the risk of becoming isolated. The impact of the visibility of HIV-related activities on stigma in the community needs further investigation. In Kenya peer CHW were named health counsellors to avoid the AIDS label [20]. On the other hand, when PLWHA support each other and form a social network, the negative impact of stigma can be overcome, as documented in Mozambique [29]. In South Africa it was found that buddies, support groups, and CHW predict and sustain treatment success [5].

Quality of care related to task shifting and other innovative models of service delivery is another concern raised. However, when considering survival as the most important indicator of quality of care, peer provision of ART will always compare favourably with no treatment as ART is the only effective clinical intervention to reduce HIV-related mortality [30]. Community-based ART by lay workers in Uganda led to a 90% reduction of mortality among adults and a large reduction of mortality among their children in a population that otherwise would have had difficulties to access care [17].

However, involving PLWHA as expert patients in their own lifelong care is not a panacea. Models engaging communities should not be shaped just to fill the gaps in the health system or to strengthen it. Instead, they should be based on the needs of the PLWHA, thus requiring their involvement in the design and planning of the program [25]. There is a need to develop both the community and the clinical platform as complementary pillars of health systems [31].

4.4. Future Prospects for HIV Self-Management. Once the concept of the expert patient is accepted and established, we think there are several further prospects that could be explored. First, once oral HIV tests will be available on African markets, there is a potential to expand testing in communities [32]. Second, the use of point-of-care testing could be further explored. For example, point-of-care CD4 techniques can be integrated in community delivered services, so that trained expert patients could assume medical tasks such as HIV testing, CD4 counts, and possibly deciding on ART initiation for uncomplicated patients [8]. Third,

community support and self-management for groups such as adolescents, pregnant women, pre-ART patients and TB patients need to be studied. Fourth, to facilitate access to ART, drug refill points could be integrated in and managed by communities, schools, market places, and the workplace [33]. Fifth, the use of new communication technologies like cell phones and smart phones can contribute to PLWHA empowerment and improved self-management, strengthening communication within the community and with the health sector [34]. And, last but not least, the potential future implementation of a treatment-as-prevention strategy will have to rely heavily on PLWHA' involvement in chronic care and lifelong adherence to make this strategy feasible [35].

5. Conclusion

In SSA, a huge proportion of the population needs to adhere daily to life-preserving medication, a process which requires an uninterrupted supply integrated in daily life in the community. We found two innovative pilot models in SSA showing the feasibility of involving PLWHA in tasks such as ART provision. Both models reduced barriers to ART refill, decreased dependency on health services and resulted in health outcomes comparable to facility-based care. Using their day-to-day experience of living with HIV, expert patients were able to provide better fitting solutions to practical and psychosocial barriers to adherence. These results seem consistent with theoretical insights and practical experiences from diabetes and other chronic diseases in the West. An extension of these pilots is needed to evaluate the scalability in different contexts. There will be a need for careful design of such models according to the local contexts and realities to explore if PLWHA can become expert patients, capacitated and empowered to manage their HIV and support fellow peers, as an untapped resource to control HIV/AIDS.

Conflicts of Interests

There was no conflicts of interests.

Acknowledgments

The authors thank Marthe Frieden for the many debates and ideas shared and Kristof Decoster for careful editing of the paper.

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Hindawi Publishing Corporation
AIDS Research and Treatment
Volume 2012, Article ID 602120, 6 pages
doi:10.1155/2012/602120

Research Article

Towards Elimination of Mother-to-Child Transmission of HIV: The Impact of a Rapid Results Initiative in Nyanza Province, Kenya

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Received 30 November 2011; Accepted 16 January 2012

Academic Editor: Annette H. Sohn

Many HIV-positive pregnant women and infants are still not receiving optimal services, preventing the goal of eliminating mother-to-child transmission (MTCT) and improving maternal child health overall. A Rapid Results Initiative (RRI) approach was utilized to address key challenges in delivery of prevention of MTCT (PMTCT) services including highly active antiretroviral therapy (HAART) uptake for women and infants. The RRI was conducted between April and June 2011 at 119 health facilities in five districts in Nyanza Province, Kenya. Aggregated site-level data were compared at baseline before the RRI (Oct 2010–Jan 2011), during the RRI, and post-RRI (Jul–Sep 2011) using pre-post cohort analysis. HAART uptake amongst all HIV-positive pregnant women increased by 40% (RR 1.4, 95% CI 1.2–1.7) and continued to improve post-RRI (RR 1.6, 95% CI 1.4–1.8). HAART uptake in HIV-positive infants remained stable (RR 1.1, 95% CI 0.9–1.4) during the RRI and improved by 30% (RR 1.3, 95% CI 1.0–1.6) post-RRI. Significant improvement in PMTCT services can be achieved through introduction of an RRI, which appears to lead to sustained benefits for pregnant HIV-infected women and their infants.

1. Introduction

Despite extensive scaleup of prevention of mother-to-child transmission (PMTCT) services in Sub-Saharan Africa, many HIV-infected pregnant women and their HIV-exposed infants are not receiving the complete package of preventive and treatment services they need to reduce the risk MTCT of HIV to <2% [1, 2]. Without effective PMTCT intervention, the risk of MTCT during pregnancy and birth is 15–50% and another 5–20% will become infected through breastfeeding. Estimates in 2009 revealed that among 1.4 million HIV-positive pregnant women, (over 90% of which were in Sub-Saharan Africa) only 53% had received antiretrovirals (ARVs) to reduce MTCT risk [3]. A substantial portion of HIV-positive pregnant women qualify for more than preventive ARVs and need highly active antiretroviral therapy (HAART) for their own health and to significantly reduce the risk of MTCT [3–5]. However, according to the World Health Organization (WHO), in 2009 only 51% of HIV-positive pregnant women had been clinically or immunologically assessed and among those eligible, only 15% were provided HAART [3, 4]. HIV-exposed children face a similar situation. Early infant diagnosis (EID) using DNA polymerase chain reaction (PCR) testing to determine infant HIV status is a matter of urgency in infancy, yet only 15% of exposed infants were tested within the first two months of life [3].

Successful delivery of PMTCT relies on a cascade of successful steps including HIV counseling and testing, assessment of HAART eligibility through CD4+ testing and clinical staging, and ARV prophylaxis (including HAART) provision, infant testing, and HAART provision for HIV-positive infants [5–9]. Considerable challenges interfere with PMTCT delivery, particularly with respect to HAART uptake for qualifying women and infants. These include health systems infrastructure limitations such as inefficient laboratory flow, inconsistent commodity supply for essential lab services or drugs, and poor provider knowledge [9–13]. Low stakeholder involvement, poor integration of services, and ineffective referrals are other important factors. Low patient, partner, and community PMTCT knowledge, as well as social stigma, fear, and denial, can also prevent women from accessing or following through with the HIV care and treatment they need [14, 15]. Collectively these challenges make provision of PMTCT services at each step difficult, contributing to compromised PMTCT quality of care.

Many strategies for improving health system delivery have been utilized in developing country settings such as continuous quality improvement (CQI) and Plan, Do, See, Act (PDSA). The Rapid Response Initiative (RRI) is an approach that has been refined over the past 40 years to affect organization change and improve performance. It is widely used by the World Bank to facilitate projects and optimize limited resources [16, 17]. The RRI approach borrows key components from the CQI and PDSA processes but focuses on achieving ambitious change rapidly with dramatic and sustainable results. An RRI includes a results-oriented approach, that is fast, multidisciplinary, empowering and fosters innovation and learning. RRI often include 2 key phases: (1) needs assessment and (2) implementation and monitoring. By structuring goals into short cycles (such as 60 days), programs can quickly introduce health system strengthening and improvement along with self-monitoring and real-time response to challenge areas. The limited time cycle allows programs to quickly review effective strategies and avoids workforce fatigue that may be associated with CQI or PDSA approaches. Many African communities have adopted the RRI approach with impressive results such as country-wide HIV program implementation in Eritrea and HIV testing and voluntary medical male circumcision in Kenya [18–20].

In order to address PMTCT service challenges, Family AIDS Care and Education Services (FACES) in collaboration with the Kenyan Ministry of Health (MOH) and other stakeholders developed and implemented an RRI to increase service provision and uptake, including HAART initiation for eligible HIV-positive mothers and infants. Key indicators were compared at baseline, during the RRI, and post-RRI to determine if this targeted approach resulted in improved PMTCT services.

2. Methods

2.1. Rapid Results Initiative Process. The RRI was structured in 3 stages: (1) needs assessment, (2) implementation and monitoring, and (3) followup for sustainability (Figure 1). First, a joint-needs assessment at a provincial level using a Strengths, Weaknesses, Opportunities, and Threats (SWOT) analysis was conducted by FACES and the Kenyan MOH in January 2011. Specific objectives were agreed on and targets set for each measurable outcome over a 60-day implementation timeframe scheduled to begin in April 2011. Specific objectives included (1) increase assessment of HAART eligibility and uptake amongst HIV-positive pregnant women, (2) improve uptake of testing for HIV-exposed infants, and (3) increase HAART uptake amongst HIV-positive infants.

The implementation phase was organized by provincial and district-level multidisciplinary taskforces including laboratory, monitoring and evaluation, community liaison and clinical staff. Strategies for achieving targets were formulated at both provincial and district levels and are described below. Followup and sustainability efforts are ongoing and include routine support supervision and monitoring of PMTCT activities conducted jointly by FACES and the MOH as well as continuous quality improvement exercises conducted quarterly.

2.2. Strategies. In addition to strategic approaches for each objective, three overarching strategies were identified as cross-cutting to accomplish all three objectives: (1) MOH leadership and involvement through joint planning, implementation, and support supervision, (2) increased male partner involvement through invitational letters requesting male partners to accompany their pregnant partner to the clinic for HIV couples counseling and testing, and (3) focused community mobilization which involved engaging local opinion leaders, community health workers, and mass media on high impact days such as market days.

2.3. Objective 1 Strategies. To increase HAART eligibility assessment among HIV-positive pregnant women, laboratory network for CD4 sample and result transport was harmonized between facilities and hubs; sample transport was increased to daily or twice weekly; access to cell stabilizer tubes was increased to allow for daily blood drawing at peripheral sites; and CD4 samples from ANC were flagged at the lab for prioritization. To increase HAART uptake for eligible women, health care providers were notified of eligible CD4 counts; ART was integrated into ANC clinics to increase access at some sites previously without ART; and cell phones were used to contact eligible women.

2.4. Objective 2 Strategies. To improve exposed infant testing uptake, the focus was on (1) improved identification of HIV-exposed infants by prioritizing infant exposure status assessment in the mother's ANC record (national mother-child booklet), offering to test women of unknown HIV status, and conducting same-day dried blood spot sampling for PCR testing for exposed infants, (2) decreased turnaround time for PCR results through laboratory strengthening mentioned above, facility-level problem-solving to reduce delays, and use of mobile phones to rapidly communicate positive results, and (3) staff training and mentorship was conducted.

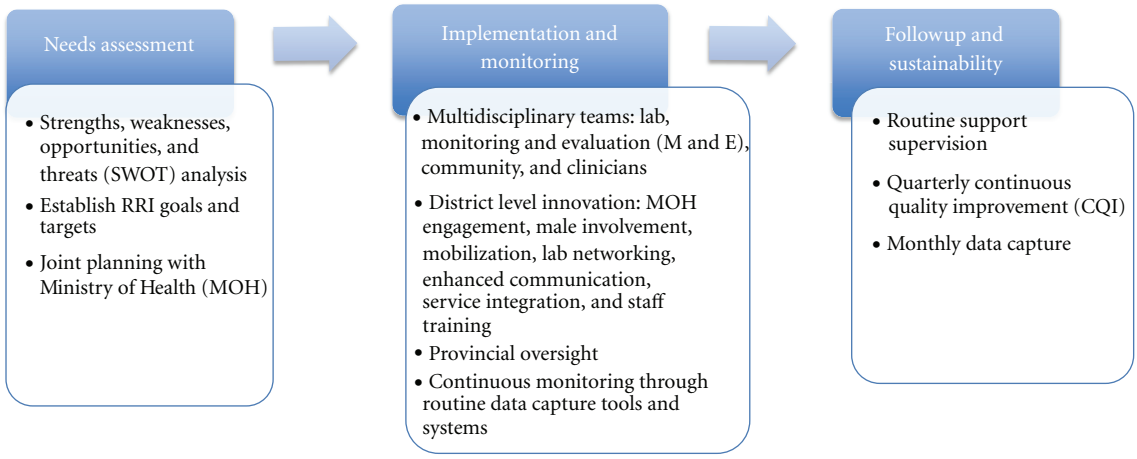

Figure 1: Rapid Results Initiative Approach.

2.5. Objective 3 Strategies. To increase HAART uptake amongst HIV-positive infants. HIV-positive PCR results were flagged at district hospital labs and immediately communicated by phone to facilities. Facility staff then contacted parents by phone or sent a community health worker to notify parents of the HIV-positive results and ensure return to the facility. Staff were trained and empowered to rapidly initiate HAART on HIV-infected infants. In facilities where HAART was not available, ART was integrated into ANC/MCH clinics, or referrals to HAART sites were facilitated.

2.6. Setting. FACES delivers a comprehensive HIV prevention, care and treatment program in Nyanza Province, where HIV prevalence and infant mortality are highest in the country at 14.9% and 95 per 1000, respectively [21, 22]. FACES, a collaboration between the University of California San Francisco (UCSF), the Kenya Medical Research Institute (KEMRI), and the Kenyan MOH, works to build the capacity of the Kenyan government to implement quality HIV services through targeted technical support, training, and health care workforce support.

This intervention was implemented within 119 clinics in 5 districts in Nyanza Province. Clinics were included if they were supported by FACES and currently implementing PMTCT services. Eighty-two (69%) of the 119 clinics were also providing HAART at the time of RRI implementation. All levels of facilities were included including 6 district hospitals, 5 subdistrict hospitals, 26 health centers, and 82 dispensaries.

2.7. Measurement. Site-level data were captured at baseline, covering 12 weeks (October 2010–January 2011) and compared to the RRI 12-week period (April 2011–June 2011), and to a 12-week post-RRI period (July 2011–September 2011) to examine changes in testing and uptake of services across the sites. December 2010 data were omitted from baseline due to the shortened work month. Data were collected using routine program PMTCT monthly data collection tools. As part of standard care, maternal-child health (MCH) staff documented daily patient care in ANC, maternal (MAT), postnatal (POST), and HIV-exposed infant (HEI) MOH registers. PMTCT variables were extracted from the registers and entered in aggregated form into PMTCT monthly data collection tools. Key outcomes were assessed at baseline and were compared to RRI and post-RRI periods including (1) number of pregnant women counseled and HIV tested in ANC, (2) proportion of women tested for HIV in ANC who had a male partner HIV tested in ANC, (3) proportion of women tested in ANC with confirmed HIV-positive results, (4) proportion of HIV-positive women in ANC who had blood taken for CD4 testing in ANC, (5) proportion of HIV-positive women who initiated on HAART in ANC, (6) the number of exposed infants that had a HIV PCR test as a proportion of the number of HIV-positive women in ANC, (7) proportion of exposed infants that were HIV-positive, and (8) proportion of HIV-positive infants initiated on HAART.

2.8. Statistical Methods. Data obtained during the baseline, RRI and post-RRI periods were compared to assess whether there were significant changes during the three periods using pre-post cohort analysis using Stata 10 (StataCorp, College Station, TX, USA). Temporal changes in indicators were considered significant at a P value of < 0.05. The risks, risk difference, and risk ratios (95% confidence Intervals) were reported for each indicator with the RRI baseline period as the reference point.

2.9. Ethical Review. The FACES' program evaluation protocol was reviewed and approved by the KEMRI Ethical Review Committee, UCSF Committee on Human Research, and Centers for Disease Control and Prevention NCHHSTP ADS/ADLS Review Committee.

3. Results

3.1. HIV Counseling and Testing. During the baseline period, 8591 women were newly HIV-tested in the ANC. During the sixty-day RRI, 9123 women were counseled and tested, with

a significant increase of 9.1% (95% CI 8.8%–9.8%). In the post-RRI period, women counseled and tested dropped to 8068, below baseline levels, with a 6.1% decrease (95% CI 5.6%-6.6%). The proportion of women testing HIV-positive varied slightly from baseline (19.3%) during the RRI (20.7%) and post-RRI (18.9%) periods (RR 1.07, 95% CI 1.01–1.14; RR 0.98, 95% CI 0.92–1.04, resp.).

3.2. HAART Eligibility Assessment and HAART Uptake. HAART eligibility assessment was measured as the number of HIV-positive women receiving CD4 test results. CD4 testing increased from a baseline of 980 (59.0%) CD4 tests out of 1662 HIV-positive pregnant women to 1258 (66.6%) tests out of 1890 women during the RRI phase (RR 1.13, 95% CI 1.1-1.2) and remained higher in the post-RRI period; 966 (63.3%) CD4 tests were performed out of 1526 HIV-infected women (RR 1.1, 95% CI 1.0-1.1) (Table 1). The relative proportion of HAART uptake compared to all HIV-positive women improved significantly by 40% from 13.7% at baseline to 19.7% (RR 1.4, 95% CI 1.2–1.7) during the RRI period and by 60% to 21.7% (RR 1.6, 95% CI 1.4–1.8) in the post-RRI period (Table 1).

3.3. Early Infant Diagnosis and HAART Uptake in HIV-Positive Infants. During the baseline period, 768 (46%) HIV-PCR tests from HIV-exposed infants were performed amongst 1662 HIV-positive pregnant women, which significantly increased to 1149 (61%) PCR tests out of 1890-HIV positive pregnant women (RR 1.3, 95% CI 1.2–1.4) during the RRI and to 1327 (87%) out of 1526 positive women (RR 1.9, 95% CI 1.8–2.0) in the post-RRI period. This demonstrates a significant increase in EID uptake; with HIV exposed infants 30% more likely to be tested during RRI and 90% more likely to be tested post-RRI. HIV-positive results by PCR varied slightly between 12.1%, 13.8%, and 11.5% during baseline, RRI, and post-RRI periods, respectively. The proportion of eligible infants initiated on HAART went from 54.8% to 60.1% (RR 1.1, 95% CI 0.9–1.4) during the RRI and to 69.0% post-RRI (RR 1.3, 95% CI 1.0–1.6) reflecting that infected infants were 30% more likely to initiate HAART post-RRI (Table 1).

3.4. Male Partner Involvement. Male partners HIV testing in the ANC improved more than two-fold from 7.7% of all women counseled and tested at baseline to 16.4% during the RRI (RR 2.1, 95% CI 2.0–2.3). In the post-RRI period, the proportion of men tested for HIV decreased to 11.5% but remained 1.5 times above baseline figures (RR 1.5, 95% CI 1.4–1.7) (Table 1).

4. Discussion

This RRI was implemented to address key PMTCT service challenges and to specifically increase uptake of HAART in HIV-positive pregnant women and infants. The RRI was associated with a 13% increase in assessment for HAART eligibility via improved CD4 testing, which translated to 66.6% of HIV positive pregnant women getting CD4 testing. CD4 testing uptake was sustained in the post-RRI period. More encouraging was uptake of HAART for pregnant women, which increased during the RRI by 44% from baseline and by 58% post-RRI, showing an increased capacity for HAART uptake. By improving HAART uptake, facilities are closer to reaching the 30% of expected eligible HIV-positive women. Improved clinical staging likely also contributed to increased HAART uptake however, government data collection tools used during the intervention did not document clinical staging making it difficult to determine its contribution. Due to the cohort nature of this evaluation, it is not possible to determine the eligibility of each individual woman; however it is clear that despite substantial progress in HAART initiation, many are still not accessing this critical service since uptake still lags below 30%. Reasons likely include incomplete assessment for eligibility, failure to return to the ANC clinic for CD4 results and HAART initiation (despite tracing efforts and counseling), and lack of availability of HAART services at smaller health facilities resulting in unsuccessful linkage to a health facility providing full HIV services including HAART.

Early infant diagnosis via PCR testing is a key step in increasing uptake of HAART for HIV-infected infants. The RRI was associated with a 30% increase in PCR testing from baseline, which further improved by 90% from baseline compared in the post-RRI period. Additionally, review of many facility records showed a faster turnaround time for PCR testing (data not shown). Along with improved identification of HAART-eligible infants, actual HAART uptake increased modestly 1.1-fold during the RRI but 1.3-fold in the post-RRI period. Similar to HAART uptake amongst HIV-positive pregnant women, uptake of HAART in HIV-positive infants remained a challenge despite RRI efforts. Further evaluation of barriers to HAART uptake should be reviewed and best practices implemented.

Male involvement as measured by partner HIV testing also significantly increased during the intervention. Male partner HIV testing increased 2.1-fold during the RRI and was sustained at 50% increased level of testing in the post-RRI period. However, the absolute percentage of women attending ANC whose partner came for HIV testing remained low (<20%). We believe this is an essential component to PMTCT service uptake and retention. Women who fail to disclose to their partners due to fear, stigma, or denial are much more likely to default care, and less likely to deliver in a health facility [14, 15]. HIV couples counseling and testing provide a facilitated environment for HIV testing where issues of blame, discordance, and future care options are explained [14, 15].

We believe community mobilization as well as leadership and involvement of the MOH, though difficult to measure, contributed significantly to success of the RRI. Ultimately, health-seeking behavior is determined at an individual level but heavily influenced by family and community attitudes and behaviors. The use of opinion leaders such as chiefs, district administration, peer educators, and community health workers likely sensitized the community to the importance of PMTCT services. Which particular activities within community mobilization are most effective in changing attitudes, and behavior is a key research topic for future

Table 1: Comparison of key PMTCT outcomes at baseline, and during the Rapid Results Initiative (RRI) and the post-RRI periods.

	Baseline period Oct 2010–Jan 2011*	RRI period Apr–Jun 2011		Post-RRI period Jul–Sep 2011	
	N (%)	*N* (%)	Risk ratio (95% CI)+	*N* (%)	Risk ratio (95% CI)+
Maternal outcomes					
HIV testing	8591	9123		8068	
HIVpositive	1662	1890		1526	
CD4 testing	980/1662 (59.0%)	1258/1890 (66.6%)	1.1 (1.1-1.2)^	966/1526 (63.3%)	1.1 (1.0–1.1)
HAART initiation	228/1662 (13.7%)	373/1890 (19.7%)	1.4 (1.2–1.7)^	331/1526 (21.7%)	1.58 (1.4–1.8)^
HIV-exposed infant outcomes					
PCR testing	768/1662 (46.2%)	1149/1890 (60.8%)	1.3 (1.2–1.4)^	1327/1526 (87.0%)	1.9 (1.8–2.0)^
PCR positive	93/768 (12.1%)	158/1149 (13.8%)	1.1 (0.9–1.4)	152/1327 (11.5%)	0.9 (0.7–1.2)
HAART initiation	51/93 (54.8%)	95/158 (60.1%)	1.1 (0.9–1.4)	105/152 (69.0%)	1.3 (1.0–1.6)
Male partner engagement outcome					
HIV testing	660/8591 (7.7%)	1496/9123 (16.3%)	2.1 (2.0–2.3)^	939/8068 (11.6%)	1.5 (1.4–1.7)^

* December 2010 data excluded.
+Results compared to baseline survey period.
^Statistically significant.

evaluations. Given the setting of the RRI primarily within government health facilities in rural communities and the need to build sustainable and lasting interventions, it was essential to have MOH ownership and leadership for this intervention.

Strengths of this study include its applicability and reproducibility in other PMTCT programs. Governments, nongovernmental organizations (NGOs), and other partners implementing PMTCT services can adapt the RRI concept to their particular settings and assess its impact. Weaknesses include difficulty in assessing the impact of particular strategies including community mobilization and male partner involvement. Additionally, this was a nonrandomized intervention. Community and facility level confounders cannot be ruled out. Furthermore, data were collected by facilities and technical staff supporting those facilities that had an interest in seeing improvements based on their work. Routine data quality audits were conducted at a portion of sites by an independent team, the monitoring and evaluation officers.

The ultimate goal of PMTCT programs is to provide high quality, cost-effective services that translate into saved lives and reduced morbidity among women and children. While the RRI concept focuses on intensive intervention over a short period, the program was designed to use strategies that build healthcare worker capacity and strengthen overall systems such as laboratory networking that lead to sustained improvements in outcomes. While we found that the RRI was associated with a relatively short-term sustained improvement in most indicators, further research is required to determine its longer term impact, the need for repeat RRIs, and newer evidence-based practices such as ANC and HIV care and treatment service integration. The followup phase of the RRI is ongoing and includes routine support of implementation of PMTCT services, which includes support supervision, mentorship, technical support, and CQI activities. A truly integrated multidisciplinary approach which engages key stakeholders including the local community, such that promoted during the RRI, will play an important role towards reaching the goal of eliminating mother-to-child transmission of HIV and improving health outcomes for HIV-positive women.

Acknowledgments

Support for Family AIDS Care and Education Services is provided by the Centers for Disease Control/President's Emergency Plan for AIDS Relief (PEPFAR) PS001913-01. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the U.S. Centers for Disease Control and Prevention. The authors would like to acknowledge the significant contributions of the following people to the planning and implementation of the RRI: Dr. Patrick Oyaro, Eliud Akama, George Agengo, Samuel Apuot, Dr. Maricianah Onono, Noel Odhiambo, John Paul Otieno as well as FACES and Kenya Ministry of Health staff.

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Hindawi Publishing Corporation
AIDS Research and Treatment
Volume 2012, Article ID 312564, 6 pages
doi:10.1155/2012/312564

Clinical Study

A Prospective Study Assessing Tumour Response, Survival, and Palliative Care Outcomes in Patients with HIV-Related Kaposi's Sarcoma at Queen Elizabeth Central Hospital, Blantyre, Malawi

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Received 14 September 2011; Revised 30 November 2011; Accepted 28 December 2011

Academic Editor: Ann Duerr

Background. Human-Immunodeficiency-Virus- (HIV-) related Kaposi's sarcoma (KS) has a high prevalence in Africa; however, there is minimal published data on treatment and outcomes in this population. *Objective and Design*. This was a prospective study of 50 patients, aiming to assess the impact of vincristine therapy on tumour response and survival and to assess palliative care outcomes in patients with HIV-related KS. *Methods*. 50 consecutive patients were recruited during 2008. Vincristine therapy and highly active antiretroviral therapy (HAART) were given. Tumour response, survival, and chemotherapy-related toxicities were documented. Palliative care outcomes were assessed using the African Palliative Care Association (APCA) Palliative Outcome Scale (POS). *Results*. The majority of patients were male, and the median age was 33 years. At baseline assessment, the median CD4 T-cell count was 263, and 50% patients had evidence of peripheral neuropathy. The overall response rate was 64% at 6 weeks, and median progression-free survival was 30 weeks. Treatment was generally well tolerated, with peripheral neuropathy the main dose-limiting toxicity. *Conclusion*. The combination of vincristine and HAART is feasible and effective in a low resource setting, although peripheral neuropathy is a dose-limiting factor. This patient group carries a high mortality and as such adequate access to palliative care is crucial.

1. Introduction

Kaposi's sarcoma (KS) is the most common human-immunodeficiency virus- (HIV-) related malignancy, and the most common malignancy in Malawi, explaining at 54% of cancer diagnoses in males, and 27% in females from 1994–1998 [1]. Although widespread access to highly active antiretroviral therapy (HAART) has resulted in the reduction in prevalence of KS in the developed world [2, 3], there is minimal data regarding the impact of increased access to HAART in Sub-Saharan Africa. KS accounted for 5–10% of new registrations for HAART in Malawi in 2005 and was associated with a poorer outcome than for other patients on HAART [4]. Since antiretroviral therapy became available to patients in Malawi from 2004, a fixed dose combination of nevirapine, stavudine, and lamivudine has been utilized as first line therapy for HIV.

Malawi is one of the poorest countries in Sub-Saharan Africa and has an estimated HIV seroprevalence of approximately 12% [5]. Delivery of appropriate health care in these circumstances presents a significant challenge, with a lack of human resource, unpredictable drug stocks, and poor laboratory facilities. Infrastructure and expertise required to administer and support combination chemotherapy are lacking in most facilities. Until recently, HAART was available only to patients in industrialized countries; however, by December 2005, over 800,000 patients had been commenced on HAART in Africa [6]. Guidelines published by the Government of Malawi Ministry of Health advocate the use of single agent vincristine chemotherapy in association with

HAART for the management of moderate-advanced KS [7]. This approach is utilized in other similar settings, although there is a paucity of data relating to the objective response rate of this treatment regimen.

Tiyanjane Clinic, at Queen Elizabeth Central Hospital in Blantyre, Malawi, provides an outpatient palliative care service and is a referral point for patients with moderate-advanced cases of KS. Pharmacological therapy is given alongside holistic care and support, where psychological, social, and spiritual issues are discussed and explored. The overall aim of the service is to improve the quality of life of those with advanced disease.

Although palliative care services in Sub-Saharan Africa are growing and improving, assessment of such services (as with palliative care services world-wide) remains challenging and outcomes largely unknown [8, 9]. The African Palliative Care Association (APCA) Palliative Outcome Scale (POS), in the appendix [10], is a simple and brief multidimensional outcome measure intended to assist in measuring palliative outcomes in routine clinical practice.

2. Objectives

This was a prospective study to assess the impact of vincristine therapy on tumour response and survival and to assess the feasibility of utilizing the APCA POS in patients with HIV-related KS. Chemotherapy related toxicities were documented.

3. Methods

Fifty patients being treated at the Tiyanjane Clinic were recruited from April 2008 to December 2008. All patients referred to the clinic that satisfied inclusion criteria were offered enrollment in the study and none declined. Informed consent was obtained from all patients at the time of enrollment, with thumbprints taken from those unable to write. Ethics approval was obtained from the College of Medicine Research Ethics Committee, College of Medicine, University of Malawi.

Patients were eligible if they were aged 18–70, HIV seropositive, had a clinical diagnosis of Kaposi's sarcoma, and fulfilled criteria for vincristine according to the Malawi National Guidelines [7], those being as follows:

(i) presumed/confirmed visceral disease,

(ii) cutaneous disease causing symptoms significant enough to impair function,

(iii) progressive disease despite use of ART.

Patients were excluded if they had significant preexisting myelosuppression (baseline hemoglobin levels <8 g/dL and a platelet count of $<50/mm^3$), preexisting grade 3 or 4 peripheral neuropathy, clinical jaundice or known chronic liver disease, pregnancy, or had received chemotherapy or radiotherapy within last 6 weeks. Those considered to have a life expectancy of less than 2 weeks and those with active opportunistic infection (other than patients stable on tuberculosis treatment) were also excluded.

Baseline assessment included detailed history, physical examination, full bloods count, and CD4 count. Further CD4 counts were not routinely performed given logistical and funding constraints. Vincristine was given intravenously at a dose of 2 mg weekly for 6 doses, followed by 2 mg fortnightly for 6 doses, followed by 2 mg monthly until progression or unacceptable toxicity. At each consultation, holistic palliative care was administered focusing on physical, psychosocial, and spiritual issues. The treating team included a UK-trained palliative care physician, an Australian medical oncologist, and local nursing staff trained in palliative care. All patients had WHO stage IV HIV by definition [11].

3.1. Outcome Measures. The primary outcome measure was tumour response. Patients were defined as having complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) as defined by the AIDS Clinical Trials Group (ACTG) response criteria [12], utilizing serial measurements and photographs of indicator lesions. Secondary endpoints were progression-free survival (PFS), defined as the time from study enrolment to either progression or death from any cause, chemotherapy-related toxicity, and palliative care outcomes as measured using the APCA POS tool. The APCA POS consists of a 10-point questionnaire covering physical, psychological, and spiritual domains. Although this tool is able to be self-administered, those patients unable to read or write had the questions read to them by a study nurse. Patients were given a choice of responding to either the Chichewa or English version of the tool.

Chemotherapy-related toxicities were classified according to the Common Terminology Criteria for Adverse Events (Version 3.0, 2006).

3.2. Followup. Patients were reviewed every 3 doses of vincristine, which equated to a review at 3 weeks, 6 weeks, 12 weeks, 18 weeks, and 30 weeks. Tumour response and chemotherapy toxicities were recorded at each review. An APCA POS questionnaire was completed at each review.

3.3. Translational. The APCA POS tool, patient information leaflet, and informed consent form were translated from English to Chichewa by clinical staff fluent in both Chichewa and English. The standard methodology of translation, back-translation, and resolution of the differences between back translation and the original was used.

3.4. Data Management and Analysis. Microsoft access was used to record and analyze data. Each study proforma was entered as a separate table linked in the database by the unique identifier assigned to each study subject. Personal identifiers were maintained separately in one main file in a password-protected computer file and used only as necessary to match this information with the other databases. Only the investigators of the study had access to this information, which is securely stored and will be destroyed after seven years. Descriptive statistics are used to describe most results. Survival curves are presented and both intention-to-treat (ITT) and per-protocol analyses of median PFS are

Table 1: Baseline patient characteristics.

Characteristic	Baseline
Age, (median (IQR)), years	33.5 (28–41)
Male (%)	40 (80.0)
KPS, median (IQR)	70 (50–80)
CD4 count, median (IQR)	263 (119–408)
Peripheral neuropathy (%)	25 (50)
Grade 1 (%)	18 (72%)
Sensory (%)	21 (84%)
HAART at baseline (%)	37 (74%)
Median time on HAART prior to recruitment (range)	6.8 months (1–60)

presented. The Mann-Whitney U test was used to explore associations between baseline CD4 counts and outcomes.

4. Results

Baseline demographic data are recorded in Table 1. Most patients were male and aged between 28 and 41. Baseline median Karnofsky performance status (KPS) [13] was 70 (range 50–80), indicating that most patients were self-caring however somewhat limited in their ability to perform active work. 50% patients had a preexisting peripheral neuropathy, which was predominantly sensory and grade 1. Three patients had grade 2 neuropathy at baseline.

All patients had clinical evidence of cutaneous KS. 40 patients (80%) had oral cavity involvement, and 31 (62%) had clinical evidence of nodal involvement. 9 patients (18%) had suspected visceral involvement, with 3 of these confirmed with either bronchoscopy or gastroscopy. The majority (37, 74%) of patients had been commenced on HAART prior to commencement of the study, for a median of 6.8 months. A further 8 patients commenced HAART after study enrollment. All patients receiving HAART received the standard regimen available in Malawi consisting of nevirapine, stavudine, and lamivudine.

45 patients were evaluable at 3 weeks, 40 at 6 weeks, 36 at 12 weeks, 33 at 18 weeks, and 25 at 6 months. 16 (32%) patients died during the study period and 9 (18%) defaulted despite intensive efforts at followup (including home visits and telephone calls). At 6 weeks, PR was seen in 32 (64%) patients, and stable disease in 14%, for a clinical benefit rate of 78%. At 12 weeks, ongoing PR was seen in 26 (52%) patients and a further 4 had stable disease. The vast majority of patients were taking oral HAART in addition to receiving vincristine, and so the above response rates reflect combination treatment with HAART and vincristine rather than vincristine alone.

16 patients died during the study period. PFS data are presented in Figure 1. Median PFS in the ITT population was 30 weeks (i.e., just reached at the end of the study followup period). Overall survival (OS) data are presented in Figure 2. Median OS had not yet been reached at the end of the followup period.

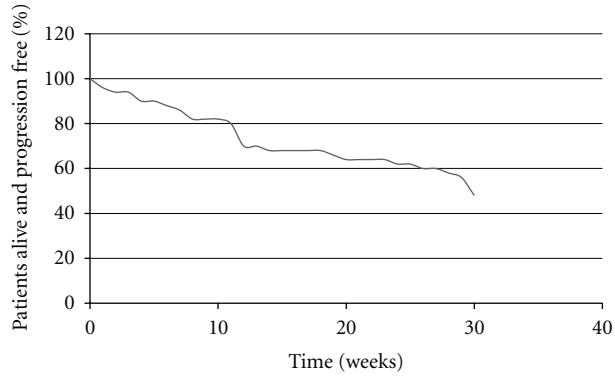

Figure 1: Progression-free survival (intention-to-treat analysis).

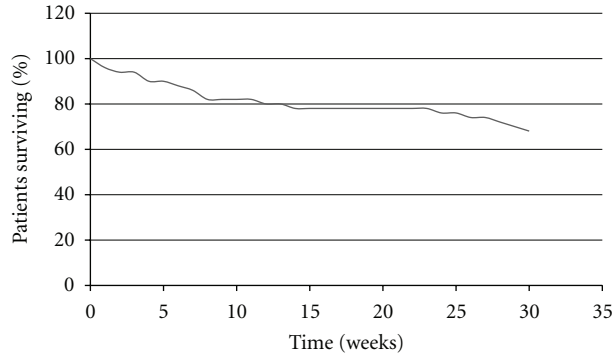

Figure 2: Overall survival.

There was no association between baseline CD4 count and disease progression (median CD4 333 versus 256 in progressors and nonprogressors, respectively, $P = 0.13$). However, there was a trend towards a lower CD4 count in those who died during study followup (149 versus 290 in those dead and alive, respectively, $P = 0.09$).

Peripheral neuropathy was documented in 25 of 50 patients at baseline, and 20 of 33 evaluable patients at 18 weeks. Vincristine was ceased in 8 patients due to worsening neuropathy (after a median of 6.5 doses). No significant myelosuppression occurred.

The baseline APCA POS assessment revealed moderate levels of need in most domains (pain, other symptoms, level of worry). Median pain scores and other symptom scores showed a trend towards improvement over time (Figure 3). Most responded positively to a question of life being worthwhile, and this did not alter during the course of the study (Figure 4). Median scores for a question of feeling at peace were low, as were scores regarding patients feeling they had been given sufficient advice for the future. These domains did not improve significantly during the study.

5. Discussion

This study is one of the few looking at patient outcomes in HIV-associated KS, in the era of widespread antiretroviral

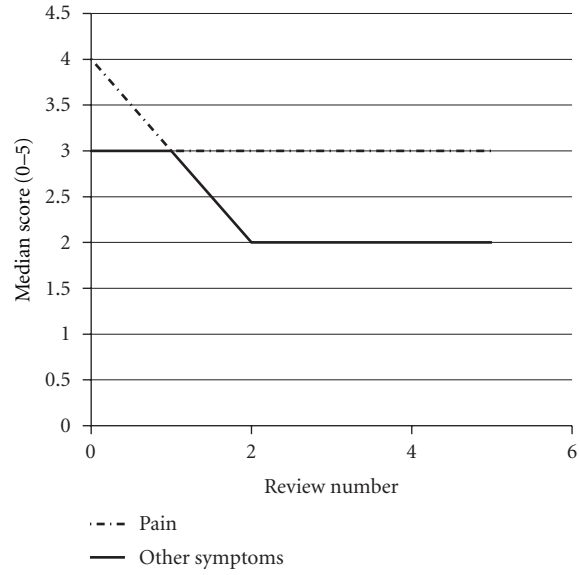

Figure 3: Changes in median APCA POS scores for pain and symptom control over time using the APCA POS. This graph depicts the changes in median scores for questions 1 and 2 from baseline to review number 5.

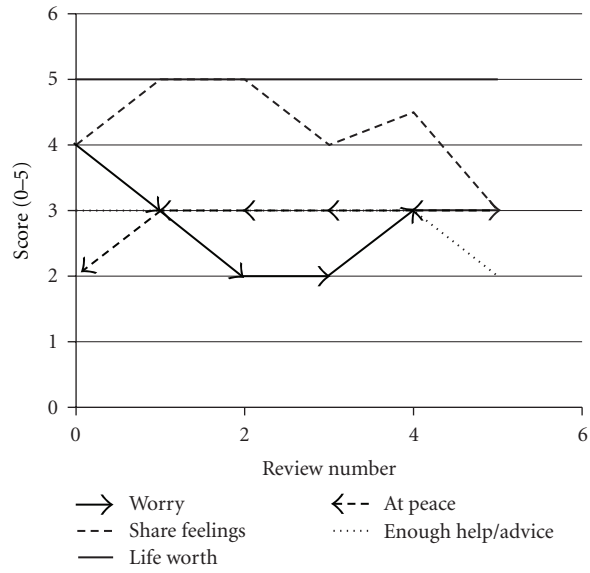

Figure 4: Changes in median APCA POS score for psychosocial domains. This graph depicts the changes in median scores for questions 3–7, from baseline to review number 5.

therapy in the developing world. We found that the combination of HAART and vincristine therapy is associated with an impressive response rate, although there were no reports of complete response in our study. Liposomal doxorubicin is considered the standard of care in the developed world on the basis of two large randomized clinical trials [14, 15]; however, it is not only expensive, but can be associated with myelosuppression and gastrointestinal side effects which would be difficult to manage currently in our setting. Northfelt et al. reported 1 complete response and 60 partial responses out of 133 patients who received liposomal doxorubicin, for an overall response rate of 45.9% in their study [14]. Median time to response was 39 days. The highly favourable response rate in our series is likely explained by a combination effect of vincristine, along with immune reconstitution associated with HAART.

The difficulties in distinguishing the antitumour effects of HAART from the effects of chemotherapy have been previously described [16]. The FDA has previously suggested that patients should receive an extended period of HAART prior to being considered for chemotherapy. The Malawian guidelines, for the use of vincristine described above, are consistent with this suggestion. In our study, 74% patients were receiving HAART for a median of 6.8 months prior to commencing vincristine, which was consistent with these guidelines.

There are few studies looking at the use of chemotherapy for HIV-associated KS in Sub-Saharan Africa. Olweny et al. [17] report on a randomized study of 495 patients in Zimbabwe comparing two chemotherapy regimens, radiotherapy and best supportive care. No complete responses were seen, however single agent etoposide was associated with improved quality of life, and a partial response rate of 31%. Combination chemotherapy (actinomycin-D, bleomycin, vincristine) was associated with a response rate of 49%, however with considerable toxicity (alopecia, mucositis, nausea/vomiting). No patient on this study received HAART. Bihl et al. report on a small South African study of 33 patients, randomized to HAART alone or HAART in combination with combination chemotherapy (doxorubicin, bleomycin, vincristine) [18]. Both arms produced a profound decline in KSHV viraemia and improved CD4 counts. 16 patients received HAART and chemotherapy, with 7 (44%) achieving a complete response and 7 (44%) achieving partial response when measured at 11 months, however the authors acknowledge considerable toxicity of this regimen.

In our study, the combination of vincristine and HAART was generally well tolerated, although peripheral neuropathy was a dose-limiting factor in some patients. We found a baseline peripheral neuropathy rate of 50%. The prevalence of HIV-related peripheral neuropathy varies in different published series from 9–63%. References [19–24], with higher rates seen in those with more advanced immunosuppression and those on HAART. A similarly high incidence of neuropathy was reported in a large cross-sectional Ethiopian study, with the majority of cases found in those receiving HAART [24]. Likely contributing factors in our series were stavudine-containing HAART, prior tuberculosis treatment, and HIV neuropathy. Peripheral neuropathy is a particular concern in this patient population, causing significant morbidity with a limited choice of agents available for symptom management.

16 patients died during the six-month study period, including 6 early deaths that occurred within 6 weeks of recruitment. The median PFS in the ITT analysis was 30 weeks in our study, which is comparable with survival data reported by Olweny et al. [17]. Additional analysis presuming all defaulted patients who had died revealed a median

progression-free survival of 24.5 weeks. This emphasizes the need for taking a holistic approach to patient management, aiming to improve quality of life for those in whom life expectancy is limited. Cause of death was difficult to ascertain in most cases given the majority of patients died at home. There was a trend towards a lower baseline CD4 count in those who died during the study. Given no clear association between lower baseline CD4 counts and KS progression, it is possible that opportunistic infections may have contributed to deaths more than progressive KS during the study period. Immune reconstitution inflammatory syndrome (IRIS) is well described in KS [25] and is another potential cause for deterioration in patients with KS receiving HAART. It is of interest that the baseline CD4 count of 263 in our study is somewhat higher than previously published. In similar cohorts [17, 26], further study regarding the causes of death in this group would be of interest.

In this study we rigorously attempted to contact patients who failed to attend appointments firstly by telephone and then by home visits. It is common cultural practice in Malawi to travel home to the family village as people near the end of their life. This may have contributed to at least 3 patients being lost to follow up. 3 others were known to have potentially life threatening conditions at the point of last contact—one with a large cerebrovascular accident, one with Stevens-Johnsons-syndrome thought secondary to HAART, and one with proven gastrointestinal KS. A prior study of patients on an antiretroviral programme in Lilongwe, Malawi, found that of those lost to follow-up, 41% were later found to have died [27]. It is likely that death was the cause of several defaults in this study.

Due to lack of access to prompt histopathological services, the diagnosis of KS in this study was made clinically by two experienced physicians. Histological confirmation would have been ideal if feasible.

The APCA POS tool has been validated for use in an African setting. We utilized it in this survey in an attempt to measure palliative care outcomes. Whilst some trends could be elucidated, we observed that the patients and families in our study found the questionnaire difficult to complete. They struggled to use numerical rating scales to express the magnitude of a subjective experience, even with the assistance of a research nurse. More refinement in such assessment tools is needed before they can be used reliably in our population group.

6. Conclusion

HIV-related KS is a common problem in Malawi. The combination of vincristine and ART is a feasible option for the treatment of patients with moderate-advanced disease in a low resource setting and is associated with good response rates; however, peripheral neuropathy is a dose-limiting factor. Given the poor prognosis in this patient group, adequate palliative care remains of upmost importance. Optimal utilization of a palliative care assessment tool remains a challenge in our setting.

Appendix

A. African Palliative Outcome Scale(APOS).

Study number _____ Staff name_____
Date _____ POS no 1st☐ 2nd☐ 3rd☐ 4th☐ 5th☐ 6th☐

Ask the patient

Q1. Please rate your pain (from 0 = no pain to 5 worst/overwhelming pain) during the last 3 days

Q2. Have any other symptoms (e.g., nausea, coughing or constipation) been affecting how you feel in the last 3 days?

Q3. Have you been feeling worried about your illness the past 3 days?

Q4. Over the past 3 days, have you been able to share how you are feeling with your family or friends?

Q5. Over the past 3 days have you felt that life was worthwhile?

Q6. Over the past 3 days, have you felt at peace?

Q7. Have you had enough help and advice for your family to plan for the future?

Ask the family carer

Q8. How much information have you and your family been given?

Q9. How confident does the family feel caring for ____?

Q10. Has the family been feeling worried about the patient over the last 3 days?

Possible responses

A1. 0 (no pain)–5 (worst/overwhelming pain)
0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

A2. 0 (not at all)–5 (overwhelmingly)
0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

A3. 0 (not at all)–5 (overwhelming worry)
0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

A4. 0 (not at all)–5 (yes, I've talked freely)
0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

A5. 0 (no, not at all)–5 (yes, all the time)
0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

A6. 0 (no, not at all)–5 (Yes, all the time)
0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

A7. 0 (not at all)–5 (as much as wanted)
0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

A8. 0 (none)–5 (as much as wanted)
N/A ☐
0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

A9. 0 (not at all)–5 (very confident)
N/A ☐
0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

A10. 0 (not at all)–5 (severe worry)
N/A ☐
0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

Acknowledgments

The authors thank Tiyanjane Clinic staff, patients, and their carers/families.

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Hindawi Publishing Corporation
AIDS Research and Treatment
Volume 2012, Article ID 751827, 14 pages
doi:10.1155/2012/751827

Review Article

Alcohol Consumption, Progression of Disease and Other Comorbidities, and Responses to Antiretroviral Medication in People Living with HIV

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Received 6 September 2011; Revised 13 December 2011; Accepted 2 January 2012

Academic Editor: Frederick L. Altice

The present paper describes the possible connection between alcohol consumption and adherence to medicine used to treat human deficiency viral (HIV) infection. Highly active antiretroviral therapy (HAART) has a positive influence on longevity in patients with HIV, substantially reducing morbidity and mortality, including resource-poor settings such as South Africa. However, in a systematic comparison of HAART outcomes between low-income and high-income countries in the treatment of HIV-patients, mortality was higher in resource-poor settings. Specifically, in South Africa, patients often suffer from concomitant tuberculosis and other infections that may contribute to these results. Alcohol influences the use of medicine for opportunistic infections (e.g., pneumonia, tuberculosis), or coinfections HIV-hepatitis viruses-B (HBV) and C (HCV), cytomegalovirus, or herpes simplex virus. Furthermore, alcohol use may negatively impact on medication adherence contributing to HIV progression. The materials used provide a data-supported approach. They are based on analysis of published (2006–2011) world literature and the experience of the authors in the specified topic. Intended for use by health care professionals, these recommendations suggest approaches to the therapeutic and preventive aspects of care. Our intention was to fully characterize the quality of evidence supporting recommendations, which are reflecting benefit versus risk, and assessing strength or certainty.

1. Introduction

Failure to recognize alcohol behaviour remains a significant problem that impairs efforts directed towards the prevention and management of patients with alcoholic liver damage. Although there are limitations in the available data, the World Health Organization's Global Alcohol database, which has been in existence since 1996, has been used to estimate worldwide patterns of alcohol consumption, and it allows comparisons of alcohol-related morbidity and mortality. The burden of alcohol-related disease is highest in the developing world, including South Africa. Pithey and Parry [1] describe the association between alcohol use and human immunodeficiency virus (HIV) infection in a systematic review of sub-Saharan African studies. The authors present studies that have quantified the association between alcohol consumption and HIV infection in this region. They analyzed work performed between 2000 and 2008 that reported relative measures of the association between alcohol use and HIV prevalence and/or seroconversion rates. However, the authors sustain that in order to confirm causality, the use of clearly defined standardised measures of alcohol use is needed [1]. Patterns of alcohol consumption are expressed and regulated differently in diverse geographical regions. There are contradictory

drinking guidelines defining low-risk and high-risk drinking in different countries. In the United States of America, the National Institute of Alcohol and Alcohol Abuse (NIAAA) and the United States Department of Agriculture define low risk drinking as ≤14 drinks/week and ≤4 drinks on any day for men. For women, the definition of low risk drinking is ≤7 drinks/week or ≤3 drinks on any day (http://www.rethinkingdrinking.niaaa.nih.gov/; http://www.cnpp.usda.gov/dgas2010-dgacreport.htm). Proposed guidelines specific for each nation make it difficult to conduct an international generalization of "moderate, low-risk drinking" versus "high-risk drinking."

2. Material and Methods

We performed a systematic review of published PubMed literature, searching for articles that contained information about "alcohol", "HIV" and "antiretroviral therapy" published between January 2006 and June 2011. We did not limit our search to literature published in English. We found over 365 results using the key words "alcohol," "adherence," "ART" and "HIV," from which we selected 230 articles that we analyzed.

From these initial results, we selected 25 articles to be included in the "disease progression" sections and 38 articles to be included in the "adherence" section. Particular attention was placed on those papers that provided an indication of the type and the amount of alcohol consumed. In order to obtain more focused results so that we could, where necessary, refer to South Africa, we also included the words "South Africa" in the search. However, we did not have "South Africa" as an exclusion criterion. Main reasons for excluding articles include poor characterization of alcohol consumption patterns, incomplete or poor characterization of adherence to medication or/and disease progression, *in vitro* or *in vivo* animal studies, and studies where the focus was on comorbid diseases and addictions, as well as treatments for these conditions, whose effects could have undermined that of alcohol (e.g., environmental habits (drugs of abuse, smoking), viral infections (cytomegalovirus, herpes simplex virus, hepatitis C, hepatitis B), malaria, tuberculosis).

Although not specific for the main topics discussed, some relevant papers published prior to 2006 contained important information that was used to reinforce our arguments and were therefore discussed as well.

Figure 1 illustrates the methods used for the literature search and the number of articles chosen for different subjects. Data accessible in this paper are descriptive in nature. All prevalence estimates of alcohol use are the data presented by their respective authors.

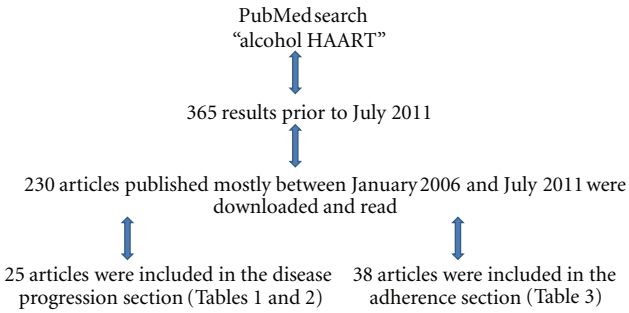

Figure 1: Methods used for literature search.

3. Results and Discussion

3.1. HIV and Alcohol Misuse. Rehm and Parry [2] described the link between alcohol consumption and infectious diseases in South Africa. Alcohol abuse is often associated with numerous facets of HIV disease progression, ranging from hepatotoxicity to immune system impairment. Table 1 presents the role played by alcohol on the progression of HIV-associated disease symptoms.

Neuman et al. [3], Núñez [4], and Barve et al. [5] extensively reviewed hepatotoxicity associated with alcohol use and highly active antiretroviral therapy (HAART) administration. The development of lung infection was reviewed by Rehm et al. [6] and Quintero and Guidot [7], while the progress of cardiovascular diseases was reviewed by Freiberg and Kraemer [8]. Rosenbloom et al. [9] reviewed detrimental effects on the structure, chemistry, and function of the central nervous system.

Neuman et al. [3] discuss the interactions between therapeutic drugs used to minimize and control drug and alcohol dependence. Furthermore, drug-drug interactions occur between HAART and alcohol, different HAART components and methadone, or each one of the therapies with the other, thus contributing to a higher toxicity level. With the evolution of effective antiretroviral therapy (ART), survival of persons living with HIV and acquired immunodeficiency syndrome (AIDS) has increased dramatically, leading to more interactions with other liver related comorbidities such as alcohol and viral hepatitis and the drugs used to treat these diseases.

The following section will review several studies that analyzed the relationship between alcohol misuse and HIV disease progression. Two important laboratory determinants of the rate of disease progression are the $CD4^+$ cell counts and the plasma viral load.

3.1.1. Role of Hepatitis Viruses on HIV. Hazardous drinking is often associated with liver disease [10, 11], particularly among hepatitis C virus (HCV) monoinfected patients and HIV/HCV coinfected patients [12]. Several interesting trends were observed in the MORTAVIC study, a multicentre prospective cross-sectional survey of French hospital departments of internal medicine and infectious diseases participating in the treatment of HIV-infected individuals [13, 14]. From 215 deaths that occurred in 2003 among 20940 HIV positive, 27 (12.6%) can be attributed to end-stage liver disease. Of these, HCV coinfection was present in 25 (92.6%) patients, alcohol consumption of any kind in 25 (92.6%) patients, moderate alcohol consumption (30–60 g/day) in 12 (44.4%) patients, and heavy alcohol consumption (>60 g/day) in 7 (26.0%) patients [13]. Over the previous decade, the proportion of patients dying from

Table 1: Interactions between Alcohol and HIV Disease Progression.

Ref.	Study settings	Population characteristics	Alcohol use patterns	Main findings
			Found an Association	
[11]	USA	696 HIV positive patients	10.4% reported hazardous drinking (>14 drinks/week or >4 drinks/occasion for men and >7 drinks/week or >3 drinks/occasion for women)	Hazardous drinking associated with liver disease, defined as aspartate aminotransferase to platelet ratio index >1.5 (RR 3.72, 95% CI 1.40–9.87)
[12]	Italy	190 patients (71 HIV monoinfected, 53 HCV monoinfected and 66 HIV/HCV coinfected)		The extent of advanced liver fibrosis, defined as liver stiffness ≥9.5 kPa, correlate with alcohol intake (nonsignificant in HIV monoinfected patients, $P < 0.001$ in HCV monoinfected patients and $P < 0.04$ in HIV/HCV coinfected patients), but not with HAART exposure or duration of HAART
[13]	France	20940 HIV positive patients	Alcohol consumption of any kind in 25 (92.6%) of 27 patients who died from end-stage liver disease	Proportion of excessive alcohol consumption higher in 2003 compared to 1995 ($P < 0.05$)
[14]	France	24000 HIV positive patients	Excessive alcohol consumption (>30 g/day) reported in 23 (47.9%) of 48 patients who died from end-stage lived disease	The combination of alcohol and HCV coinfection led 12 (25.0%) deaths Consuming alcohol in excess of 30 g/day associated with death due to end-stage liver disease ($P = 0.005$)
[15]	France	210 HIV positive patients with a history of injectable drug use or HCV (60 HIV positive and 150 HIV-negative). There were 41 (19.5%) cases of liver cirrhosis	76 patients suffered from excessive drinking, with similar rate between HIV positive individuals and HIV-negative individuals	HIV positivity (OR 2.2, CI 1.1–4.5) and excessive drinking (OR 1.9, CI 1.0–3.9) independently associated with cirrhosis
[16]	Spain	2168 HIV positive patients, including 181 (8.3%) cases of cirrhosis	95 (52.5%) cirrhotic patients admitted current or past alcohol abuse	Alcohol consumption associated with cirrhosis (OR 3.5, 95% CI 2.5–4.8, $P < 0.01$)
[17]	Spain	91 HIV positive patients 30 (33.0%) patients suffered from liver toxicity 10 (11.0%) patients suffered from severe liver toxicity 43 (47.2%) patients coinfected with HCV and/or HBV		High alcohol consumption risk factor for liver toxicity (OR 3.35, 95% CI 2.43–4.62, $P = 0.01$)
[20]	USA	164 HIV positive patients	Patients consumed alcohol 88 (53.6%) were hazardous drinkers	Hazardous drinking associated with worsening of dyslipidemia (OR 3.18, 95% CI 0.99–12.05, $P = 0.04$)
[21]	USA	300 HIV positive patients, 82 (27.3%) patients experienced pneumonia	60% of sample reported prior or current alcohol abuse	Alcohol use independent predictor for pneumonia in HIV positive smokers ($P = 0.004$)
[22]	Spain	122 HIV-infected adults		Alcohol abuse independent predictor for bacteremic pneumococcal disease (OR 5.28)
[23]	Spain	25 HIV-1-postive patients with cerebrovascular ischemia		Cerebrovascular ischemia associated with history of high alcohol intake (OR 7.13, 95% CI 1.69–30.11, $P = 0.007$)
[25]	USA	72 HIV-negative light/nondrinkers, 70 HIV positive light/nondrinkers, 70 HIV positive heavy drinkers and 56 HIV-negative heavy drinkers	142 (53.0%) light/nondrinkers 126 (47.0%) heavy drinkers	Synergistic interaction between alcohol abuse and HIV infection with respect to motor and visuomotor speed

Table 1: Continued.

Ref.	Study settings	Population characteristics	Alcohol use patterns	Main findings
[26]	USA	31 male HIV positive patients, 27 patients with alcoholism, 43 patients with HIV infection and alcoholism comorbidity, and 22 normal healthy controls	70 (56.9%) patients with alcoholism	HIV and alcoholism comorbidity impair upper motor limb to a greater degree that HIV alone ($P = 0.068$) or alcoholism alone ($P = 0.062$)
[27]	USA	40 HIV positive patients, 38 alcoholic patients, 47 alcoholic HIV positive patients, and 39 controls	85 (51.8%) patients with alcoholism	Immediate episodic memory impaired in HIV positive patients with alcoholism comorbidity
			Did Not Find an Association	
[24]	USA	1539 HIV positive patients 881 (57.2%) reported HIV-associated sensory neuropathy, of which 335 (38.0%) reported neuropathic pain	845 (54.9%) had a history of alcohol abuse or dependence	History of alcohol abuse or dependence not associated with neuropathic pain caused by HIV-associated sensory neuropathy
[28]	Italy	76 HIV positive patients with bacterial community-acquired pneumonia 32 (42.1%) were receiving ART	25 (32.9%) alcohol abusers	Alcohol abuse not associated with a longer time before clinical stability was achieved
[29]	USA	299 HIV positive patients. Abnormal liver test results observed in 80 (26.8%) patients		Amount of alcohol consumed per week or alcohol overuse not predictors of liver test abnormalities
[30]	France	1175 HIV-infected patients 1048 (89.2%) were HCV coinfected		Alcohol consumption not associated with HCV-related serious adverse reactions

AIDS decreased and the number of patients dying from end-stage liver disease remained relatively constant. In recent times, the proportion of patients dying from end-stage liver disease is significantly higher (21 out of 1426 deaths (1.5%) in 1995 versus 27 out of 215 (12.6%) deaths in 2003, $P < 0.01$). Among patients dying from end-stage liver disease, the proportion of patients with HCV coinfection alone and the proportion of excessive alcohol consumption were significantly higher in 2003 compared to 1995 [13].

From 287 deaths that occurred in 2005 among 24000 HIV positive patients followed at multiple centers in France, 48 (16.7%) can be attributed to end-stage liver disease [14]. Of these, hepatitis virus coinfection was present in 45 (93.8%) patients, with 38 (79.2%) patients suffering from HCV coinfection. Excessive alcohol consumption (>30 g/day) was reported by 23 (47.9%) patients in this subsequent study [14]. Alcohol consumption was related to death in 4 HCV/HIV coinfected patients (10.5%), while HCV coinfection led to an additional 8 deaths (21.0%) in HIV positive patients who abused alcohol, as assessed by the patients' physicians. An additional case of lethal cirrhosis was identified independent of alcohol consumption or viral hepatitis coinfection [14]. Overall, 36 (75.0%) patients died from cirrhosis, 7 (14.6%) patients died from HCV coinfection and 5 (10.4%) patients died from hepatitis B virus (HBV) coinfection. Hepatitis virus coinfection ($P < 0.001$) and consuming alcohol in excess of 30 g/day ($P = 0.005$) were significantly associated with death due to end-stage liver disease [14].

3.1.2. Role of Cirrhosis in Disease Progression. While both HIV positivity and excessive drinking were independently associated with cirrhosis, the proportion of patients with cirrhosis was higher in HIV positive individuals (18/60, 30.0%), compared to HIV-negative individuals (23/150, 15.3%) ($P < 0.0001$) in another French study [15]. There were no differences in the incidence of cirrhosis between HIV positive excessive drinkers and HIV-negative excessive drinkers. This should be interpreted with care, as the low number of patients included in this study, particularly HIV positive patients, could prevent the identification of an interaction between HIV positivity and excessive drinking with respect to the development of cirrhosis [15].

Among 181 cases of liver cirrhosis in a large sample of 2168 HIV positive patients, 149 (82.3%) were caused by HCV, 3 (1.6%) were caused by HBV, 5 (2.8%) were caused by dual HBV/HCV coinfection, and 12 (6.6%) were caused by triple HBV/HCV/hepatitis D virus coinfection [16]. Alcohol consumption, significantly associated with a diagnosis of cirrhosis, was found to be more frequent among patients with chronic viral hepatitis compared to patients without these coinfections ($P < 0.001$). Interestingly, alcohol was not found to be the only cause of cirrhosis in any one patient [16]. Aside from high alcohol consumption, coinfection with HCV and/or HBV are risk factors for developing liver toxicity (OR 10.36, 95% CI 1.38–77.56, $P = 0.03$) [17].

3.1.3. Alcohol-Induced Inflammation Leads to Progression of HIV and Other Comorbid Reactions. Many processes related to the consumption or breakdown of alcohol that

contribute to alcohol-induced liver disease are mediated by small proteins known as cytokines, which are produced and secreted by liver cells and many other cells throughout the body [18]. Through a variety of actions, cytokines regulate certain biochemical processes in the cells that produce them, as well as in neighbouring cells. For example, in the case of HIV infection, they attract white blood cells to the tissue, triggering an inflammatory response. In the liver, persistent cytokine secretion resulting in chronic inflammation leads to conditions such as hepatitis, fibrosis and cirrhosis. Cytokines also regulate a process known as programmed cell death, or apoptosis, which is in part responsible for alcohol-induced loss of liver tissue [19].

Dyslipidemia, consisting of hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, and elevated low-density lipoprotein (LDL) cholesterol, is being observed with increasing frequency among persons living with HIV. Hazardous alcohol consumption, particularly among Hispanic individuals and in individuals consuming the highest amounts of alcohol, worsens dyslipidemia [20].

Alcohol use and not being on HAART ($P < 0.001$) are independent predictors of pneumonia in HIV positive smokers [21]. The incidence of pneumonia was significantly lower in the HAART era compared to the pre-HAART era ($P < 0.01$), although alcohol abuse remains an independent risk factor for developing bacteremic pneumococcal disease [22].

Cerebrovascular ischemia was associated with a history of high alcohol intake, and fewer months on HAART (OR 0.97, 95% CI 0.96–0.99; $P < 0.001$). This suggests that long-term HAART has a protective effect against cerebrovascular ischemia, yet this effect is countered by a history of alcohol abuse [23].

A history of alcohol abuse or dependence was not associated with neuropathic pain caused by HIV-associated sensory neuropathy [24].

Significant differences were found between HIV positive heavy drinkers and HIV-negative light drinkers with respect to motor and visuomotor speed, pointing to a synergistic interaction between alcohol abuse and HIV infection [25].

Impaired upper limb function was observed between clinical groups (HIV positive patients, patients with alcoholism, and patients with HIV infection and alcoholism comorbidity) and controls in terms of upper motor composite score ($P = 0.008$ for HIV group, $P = 0.031$ for alcoholism groups and $P = 0.003$ for HIV and alcoholism comorbidity group) and slower fine finger movement ($P = 0.004$ for HIV group, $P = 0.033$ for alcoholism groups and $P = 0.0003$ for HIV and alcoholism comorbidity group) [26]. Although not significant, HIV and alcoholism comorbidity impair upper motor limb function to a greater degree that HIV alone or alcoholism alone. There were significant differences between groups with respect to closed eye composite scores (stand heel-to-toe, walk heel-to-toe, and stand on one leg with eyes closed tasks) ($P = 0.013$) [26]. These differences could not be explained by the presence of peripheral neuropathy, HAART, or AIDS-defining events [26].

Immediate episodic memory was found to be impaired in HIV positive patients suffering from alcoholism, compared to either HIV positive patients without a drinking problem, HIV-negative patients suffering from alcoholism or normal controls [27]. Interestingly, these results could not be explained by the amount of alcohol consumed over a lifetime, $CD4^+$ cell counts, AIDS diagnosis, or HAART medication. HIV infection or alcoholism alone did not affect immediate episodic memory. Also, working memory and the ability to retain information over time were not impaired by HIV infection or alcoholism [27].

Alcohol abuse was not associated with a longer time before clinical stability was achieved among patients who developed bacterial community-acquired pneumonia [28].

3.1.4. Nonalcoholic Steatohepatitis and HIV Disease Progression. While alcohol abuse is generally associated with HIV disease progression, several studies did not find such an association. For example, Crum-Cianflone et al. [29] found that the most common diagnosis among HIV positive patients with liver test abnormalities was that of non-alcoholic fatty liver disease. The amount of alcohol consumed per week and alcohol abuse were not predictors of liver test abnormalities. The low number of patients suffering from viral hepatitis coinfection was not high enough to uncover any effect of these comorbidities. While ART use overall did not predict liver test abnormalities, the use of protease inhibitors did ($P = 0.04$) [29]. A separate study found that alcohol consumption was not associated with HCV-related serious adverse reactions in a cohort of 1175 HIV-infected patients (1048 (89.2%) were HCV coinfected) [30].

3.1.5. Injecting Drug Users and HIV. Compared to healthy noninjecting drug users (IDU), HIV patients who were not alcohol abusers (control population), HIV IDU only, HIV alcohol abusers, and IDU alone were each significantly associated with a lower level of $CD4^+$ lymphocyte recovery ($P < 0.04$) [31]. However, no such association was found with respect to alcohol abuse alone. Compared to patients who did not abuse either alcohol or injectable drugs, no significant differences in terms of virological response (i.e., undetectable viral load) were found for either of the three study groups [31]. Unfortunately, the effects of alcohol consumption on HAART adherence are not analyzed in this study [31].

3.2. The Role of Alcohol Consumption on the Immune System and the HIV Viral Load. Table 2 presents some recent data on the role played by alcohol on $CD4^+$ cell counts and the plasma viral load.

Alcohol abuse after contacting HIV seems to accelerate disease progression through a direct effect on $CD4^+$ cells. Of note is the detrimental role played by alcohol consumption on $CD4^+$ cell counts, particularly among individuals not on ART [32–36]. Heavy alcohol consumption is associated with a four times lower chance of achieving undetectable viral load and a two times higher chance of having low $CD4^+$ cell counts, compared to moderate alcohol consumption or abstinence [33]. Alcohol is an immunosuppressant acting directly through T-cell apoptosis, mitochondrial damage, and inhibition of T-cell responses, natural killer cell activity

Table 2: The Role of Alcohol on the Immune System and the HIV Viral Load.

Ref.	Study settings	Population characteristics	Alcohol use patterns	Main findings
[33]	USA	220 HIV-1-infected IDUs receiving HAART	Heavy alcohol consumption (daily or 3-4 times per/week) reported in 139 (63.2%) patients. Men (OR 2.6, 95% CI 1.13–5.99, $P = 0.013$) and participants between 35 and 45 years of age more likely to be heavy alcohol users ($P = 0.006$)	Heavy alcohol consumption associated with 4 times lower chance of achieving undetectable viral load and 2 times higher chance of having a $CD4^+$ cell count of <500 cells/μL, compared to moderate alcohol consumption or abstinence
[34]	USA	595 HIV positive patients	245 (41.2%) subjects consumed alcohol	Heavy alcohol consumption associated with lower $CD4^+$ cell counts only among subjects not on ART ($P = 0.03$)
[35]	USA	231 HIV positive drug users	126 (54.5%) participants consumed alcohol There were 53 (22.9%) frequent alcohol users (≥2 alcoholic drinks daily). No differences in alcohol consumption between patients on ART and patients not on ART	Frequent alcohol use (≥2 drinks/day) associated with $CD4^+$ cell counts ≤200 cells/μL (OR 2.907, 95% CI 1.233–6.855, $P = 0.015$). Frequent alcohol intake associated with higher viral load over time ($P = 0.038$)
[36]	USA	391 HIV positive patients	154 (39.4%) report past week alcohol consumption with mean number of 4 drinks 62 (15.8%) consumed >5 drinks/week	Consuming >5 drinks/week predictor for unsuppressed viral load (≥400 copies/mL) (OR 4.2, 95% CI 1.1–18.5, $P = 0.046$)
[38]	USA	2056 HIV-infected women and 569 HIV-uninfected women	33.6% of HIV positive women consumed ≥8 drinks/week 51.8% of HIV positive women consumed 1–7 drinks/week	Consuming ≥8 drinks/week related to higher risk of death (OR 3.39, 95% CI 1.54–7.44, $P < 0.002$)
[39]	USA	2702 HIV positive patients	Individuals were categorized as nondrinkers (no alcohol consumption), hazardous drinkers (consume ≥5 standard drinks on drinking days), and nonhazardous drinkers (consume <5 standard drinks on drinking days)	Nonhazardous alcohol consumption decreased survival by >1 year if frequency of consumption was ≥1/week, and by 3.3 years with daily consumption (from 21.7 years to 18.4 years). Hazardous alcohol consumption decreased overall survival by >3 years if frequency of consumption was ≥1/week, and by 6.4 years with daily consumption (from 16.1 years to 9.7 years)

and macrophage phagocytic activity. Alcohol consumption may increase susceptibility to opportunistic infections and accelerate disease progression among HIV positive individuals. Additionally, alcohol leads to impaired viral load response and reduced $CD4^+$ cell reconstitution [35]. Frequent alcohol use is significantly associated with low $CD4^+$ cell counts and higher viral loads over time [35].

In patients not on ART, heavy alcohol consumption was associated with lower $CD4^+$ cell counts compared to patients with a history of abstinence. At-risk drinkers (4 drinks/week for women and 5 drinks/week for men) were less likely to have a current HAART prescription ($P < 0.05$) and were less likely to have suppressed viremia if they had a current HAART prescription ($P < 0.05$), compared to nondrinkers [36]. Consuming more than 5 drinks/week is a predictor for not being on HAART and for having an unsuppressed viral load [36]. Moreover, the risk of opportunistic infections increases as $CD4^+$ cell counts decline.

The type of alcohol being consumed is important with regards to outcome in HIV positive patients currently taking HAART [37]. In subjects consuming only beer or wine, increases in thymus size and in $CD4^+$ cell counts were observed following HAART initiation. In contrast, consumption of only liquor was associated with decreases in both thymus size and in $CD4^+$ cell counts, particularly evident in women. Míguez-Burbano et al. [37] conclude that liquor consumption is associated with thymus deterioration and poor virologic and immunologic control in HIV positive patients taking ART.

Moderate alcohol use (<1 drink per day for the past 6 months) did not significantly increase the rate in $CD4^+$ cell count decline to ≤200 cells/μL, compared to abstainers. Frequent alcohol use (>2 drinks/day) resulted in a risk of $CD4^+$ cell counts decline that was almost three times higher than that for moderate alcohol use. $CD4^+$ cell counts decline was faster in frequent alcohol users who were not on ART than in those who were on ART [34, 35]. $CD4^+$ cell counts decline was faster in frequent alcohol users who combined alcohol with crack cocaine. Viral load was found to be 0.259 log10 units higher in frequent alcohol users than in moderate alcohol users and abstainers. This relationship was found to be significant in patients who were receiving ART.

Alcohol use had no impact on HIV viral loads in patients not receiving ART. One possible explanation for these findings in that heavy alcohol use is deleterious in patients on ART because it might decrease patient adherence to ART, rather than alcohol having a direct effect on viral load [34, 35]. A drop in $CD4^+$ cell counts is mediated by the direct toxic effect of alcohol on these lymphocytes, which appears to be independent of the viral load. At the same time, Samet et al. [34] argue that the beneficial effect of ART on $CD4^+$ cell counts may account for a lower toxicity seen when alcohol is abused in the presence of ART.

Consuming ≥8 alcoholic drinks/week was related to a higher risk of death [38]. In fact, Braithwaite et al. [39] found that alcohol consumption of any kind decreases survival in HIV positive patients.

3.3. The Role of Alcohol Consumption on Medication Adherence. Drug and/or alcohol abuse and suboptimal ART adherence are predictors of virological failure [40]. Table 3 presents studies in which alcohol consumption modulates medication adherence.

Following the introduction of HAART in 1996, individuals living with HIV taking this form of medication have benefited from improvements in immunological and virological parameters, as well as an improved quality of live and longevity [41]. However, adherence to HAART in excess of 95% is often regarded as optimal in order to benefit from this treatment [41].

3.3.1. Alcohol Consumption and Nonadherence to ART. Numerous studies from around the world document the detrimental effect of alcohol on HAART adherence, from the United States [36, 42–55], to Europe [56–61], Australia [62], Africa [63–69], South America [70, 71], and Asia [72, 73]. Alcohol consumption is associated with the first nonstructured treatment interruption, early (within the first year) versus late treatment interruption, and interruption of longer duration (≥6 months) [53, 66].

In addition to nonadherence, at-risk drinkers were less likely to have a current HAART prescription. As a result, at-risk drinking was a predictor of not being on HAART [36, 51]. In fact, all levels of drinking were associated with higher odds of not using HAART compared to alcohol abstinence [54], such that dose-dependent worsening of adherence was found with increasing alcohol consumption [49, 54, 60]. The highest degree of nonadherence was found in cases where alcohol use was classified as problem drinking (defined as meeting NIAAA criteria for at-risk drinking or diagnostic criteria for an alcohol use disorder) (OR 0.474, 95% CI 0.408–0.550), while it was lower in studies examining any or global alcohol use (OR 0.604, 95% CI 0.531–0.687) [41]. In the combined analysis of 40 studies reviewed in a meta-analysis, alcohol drinkers were approximately 50–60% as likely to be classified as adherent (OR 0.548, 95% CI 0.490–0.612) compared with abstainers (or those who drank relatively less) [41].

Concurrent crack cocaine use is associated with even lower adherence (OR 3.61, 95% CI 1.56–8.35, $P < 0.01$) [51], as is a lifetime history of being an IDU (OR 2.17, 95% CI 1.16–4.05, $P = 0.015$) [70].

Nonadherence is often associated with unsuppressed viremia. For example, Shacham et al. [36] found that consuming more than 5 drinks/week is a predictor for having an unsuppressed viral load.

The reasons behind the association between alcohol consumption and nonadherence are varied. For example, due to the belief that alcohol should not be mixed with their medication, people living with HIV/AIDS may interrupt their medication when they are drinking [52] or delay HIV treatment while trying to cope with alcohol dependence [64]. Forgetfulness does seem to play an important role, as substance use by the caregiver was associated with higher odds of ART nonadherence among children in their care [42, 65]. Alcohol also appears to affect adherence to ART through conscious decisions to skip medication while drinking and not through drunken forgetfulness [45]. Based on their research, Sankar et al. [45] found that light drinkers are the most likely subgroup to miss medication.

3.3.2. Other Factors Linked to Nonadherence. Drinking patterns were found to differ across gender and ethnic groups. For example, hazardous drinking was more predominant among African-American ($P < 0.01$) and mixed race ($P < 0.04$) patients, compared to white patients, and African American patients were less likely to report 100% adherence (OR 0.35, 95% CI 0.17–0.71, $P < 0.01$) [55]. Afrodescent was marginally associated with poor adherence in a Brazilian study as well (OR 1.55, 95% CI 0.97–2.47, $P = 0.068$) [70]. The detrimental effects of alcohol on medication adherence seem to affect women to a greater degree than men [44, 50].

Several other factors are also related to nonadherence. Each additional year of life was associated with further decrease in adherence (OR 0.96, 95% CI 0.92–1.00, $P < 0.04$), while a higher level of medication-specific social support (e.g., companionship or assistance) diminished the negative effects of alcohol consumption on ART adherence (OR 1.06, 95% CI 1.01–1.12, $P = 0.01$) [55].

Significance of alcohol consumption diminishes once stress is factored in, suggesting that life stress may be one of the main causes for alcohol and drug consumption in HIV positive individuals, and alcohol consumption may in turn lead to nonadherence [47].

An interesting observation reported in a South African study is that many participants refused to disclose their HIV status to their family out of fear that their family would consume alcohol as result of such news, highlighting the wide-spread alcohol consumption in some communities [63].

Based on findings from these studies, it is recommended that HIV treatment programs address at-risk drinking as well [51]. The clinical evaluation of a person living with HIV should also determine the prevalence of alcohol use and/or the presence of alcohol use disorders. Moreover, an assessment of concomitant drug and alcohol use, as well as comorbidities, is needed in both men and women.

There have also been reports of no association between alcohol consumption and delayed HAART initiation [74],

Table 3: Alcohol Consumption and Nonadherence to ART.

Ref.	Study settings	Population characteristics	Alcohol use patterns	Main findings
			Found Nonadherence	
[36]	USA	391 HIV positive patients	154 (39.4%) report past week alcohol consumption, for a mean number of 4 drinks	At-risk drinkers (4 drinks/week for women and 5 drinks/week for men) are less likely to have current HAART prescription ($P < 0.05$). At-risk drinking a predictor for not being on HAART ($P = 0.025$)
[40]	USA	1074 HIV positive patients	315 (29.4%) patients presented with current or past history of drugs and/or alcohol abuse	Current or past history of drugs and/or alcohol abuse (OR 2.10, 95% CI 1.32–3.35, $P = 0.002$) and suboptimal adherence (OR 2.84, 95% CI 1.77–4.55, $P < 0.001$) predictors for virological failure
[42]	USA	43 HIV positive children	Alcohol abused by caregiver	Substance use by the caregiver associated with having higher viral loads in children patients ($P = 0.007$)
[43]	USA	197 HIV-infected individuals with history of alcohol problems who were receiving HAART	79 (40.1%) use alcohol	HIV positive drinkers less adherent to HAART than HIV positive alcohol abstainers ($P < 0.05$)
[44]	USA	1944 HIV positive patients	55% of 640 men and 28% of 1304 women consumed low levels of alcohol 15% of men and 8% of women consumed high levels of alcohol 7% of men and 4% of women engaged in binge drinking	Binge drinking (OR 1.75, 95% CI 1.17–2.64, $P \leq 0.05$), moderate-to-heavy alcohol consumption (OR 1.47, 95% CI 1.08–1.99, $P \leq 0.05$) and low alcohol consumption (OR 1.28, 95% CI 1.05–1.54, $P \leq 0.05$) associated with nonadherence for women only
[45]	USA	82 HIV positive African-American patients		Alcohol can affect ART adherence through conscious decisions to skip medication while drinking and not through drunken forgetfulness
[46]	USA	5887 HIV positive patients	3573 (60.7%) respondents report alcohol use in past 12 months 630 (17.6%) alcohol users were nonadherent	Alcohol use in past 12 months associated with nonadherence (OR 1.3, 95% CI 1.1–1.5, $P < 0.05$)
[47]	USA	105 HIV positive patients without alcohol dependence	Mean monthly alcohol consumption was 4.64 ± 8.00 drinks/person	Monthly alcohol consumption associated with missed medication in the past 2 weeks (OR 1.08, CI 1.02–1.15, $P < 0.01$) and over the past weekend (OR 1.09, CI 1.03–1.15, $P < 0.01$) 47 (44.8%) patients missed a medication dose in the past 2 weeks, and 23 (21.9%) missed medication during the previous weekend
[48]	USA	275 HIV positive patients with alcohol use disorders 154 (56.0%) patients were nonadherent	An average of 84.9 standard drinks over the thirty days prior to the baseline interview	Alcohol consumption ($P = 0.001$) and number of drinks ($P = 0.002$) related to nonadherence
[49]	USA	1671 HIV positive women	60% of sample were abstainers and 26% were light drinkers (<3 drinks/week)	Light drinking (<3 drinks/week) (OR 1.51, CI 1.30–1.76, $P < 0.01$), moderate drinking (3–13 drinks/week) (OR 2.46, CI 1.96–3.09, $P < 0.01$), and heavy drinking (OR 4.37, CI 2.99–6.40, $P < 0.01$) associated with self-reported ART nonadherence
[50]	USA	67 HIV positive patients		Alcohol dependence is a specific and significant predictor of ART nonadherence in women only ($P < 0.05$)

Table 3: Continued.

Ref.	Study settings	Population characteristics	Alcohol use patterns	Main findings
[51]	USA	643 HIV positive IDUs		Fewer at-risk drinkers that nondrinkers reported receiving ART (OR 1.19, 95% CI 0.59–2.42)
[52]	USA	145 HIV positive patients	60 (41.4%) participants were current drinkers 11 participants (18% of drinkers) were problem drinkers (AUDIT score ≥8)	1 in 4 drinkers report stopping medication while consuming alcohol Alcohol use predicted treatment nonadherence ($P < 0.05$)
[53]	USA	335 HIV positive IDUs		Heavy alcohol use associated with first nonstructured treatment interruption (OR 1.58, 95% CI 0.92–2.70), early (within the first year) versus late treatment interruption (OR 1.55, 95% CI 0.51–4.73), and interruption of longer duration (≥6 months) (OR 3.21, 95% CI 0.83–12.5)
[54]	USA	1354 HIV positive women for whom HAART was indicated		Light drinking (OR 1.39, 95% CI 1.03–1.89, $P \leq 0.05$), moderate drinking (OR 1.72, 95% CI 1.10–2.70, $P \leq 0.05$) and heavy drinking (OR 2.29, 95% CI 0.96–5.47) associated with nonadherence, compared to nondrinking
[55]	USA	224 HIV positive patients	Baseline prevalence of past year hazardous drinking was 27% (AUDIT score ≥8)	Hazardous drinking associated with nonadherence
[56]	France	445 HIV positive patients	329 (73.9%) patients consumed ≤1 unit of alcohol/day at baseline 116 (26.1%) patients consumed >1 unit of alcohol/day at baseline	Baseline alcohol consumption associated with nonsignificant nonadherence after 4 months ($P = 0.09$)
[57]	France	276 HIV positive IDUs receiving HAART	Approximately 84% of patients report alcohol consumption during the past 6 months	Monthly alcohol consumption during past 6 months associated with ART nonadherence (OR 1.15, CI 1.08–1.23, $P < 0.001$)
[58]	France	1010 HIV positive patients	59 (5.8%) patients report daily alcohol consumption	Nonadherence more common among subjects who consume alcohol daily (OR 0.39, CI 0.20–0.58, $P < 0.001$)
[59]	France	2340 HIV positive patients receiving HAART. Harmful alcohol consumption was frequent	12% of patients had symptoms of potential alcohol abuse/dependence during the previous 12 months (CAGE questionnaire score of ≥2) 27% of patients suffered from hazardous drinking or alcohol use disorders (AUDIT-C questionnaire score of >4 for women and >5 for men) 9% of patients reported regular binge drinking (≥6 alcohol units drunk consecutively at least twice a month)	Harmful alcohol consumption associated with nonadherence to HAART ($P < 0.001$) for regular binge drinking and symptoms of alcohol abuse or dependence
[60]	Switzerland	6709 HIV positive patients		Increasing alcohol intake associated with deteriorating adherence to ART (OR 1.25, 95% CI 1.10–1.43)
[61]	Sweden	946 HIV positive patients	15.5% of patients report alcohol and drug problems	Adherent patients more likely not to have problems with alcohol (OR 1.8, 95% CI 9 1.18–3.01, $P = 0.008$)
[62]	Australia	1106 HIV-infected patients 867 (78.4%) report taking cART, 339 (39.1%) of which report difficulty adhering to medication		Alcohol use associated with self-reported nonadherence (OR 1.47, 95% CI 1.03–2.09, $P < 0.05$)

Table 3: Continued.

Ref.	Study settings	Population characteristics	Alcohol use patterns	Main findings
[63]	South Africa	12 HIV positive patients receiving HAART		Alcohol abuse identified as barrier to adherence
[64]	South Africa	8 male HIV positive patients		Patients delay HIV treatment while coping with alcohol dependence
[65]	South Africa	56 HIV positive children		Alcohol use by caregiver associated with poorer ART adherence in children patients ($P < 0.01$)
[66]	Cameroon	533 HIV positive patients	60 (11.3%) patients reported binge drinking	Binge drinking associated with interruption of ART
[67]	Ethiopia	422 HIV positive patients	31 (7.3%) subjects report alcohol consumption, 6 of which did so on a regular basis	Alcohol drinking associated with nonadherence (OR 0.210, CI 0.071–0.617, $P = 0.003$)
[68]	Botswana	300 adult HIV positive patients		Alcohol use predicted poor ART adherence ($P < 0.02$)
[69]	Benin, Côte d'Ivoire, and Mali	2920 HIV positive patients		Current drinking (OR 1.4, 95% CI 1.1–2.0), especially hazardous drinking (OR 4.7, 95% CI 2.6–8.6), associated with nonadherence
[70]	Brazil	306 HIV positive patients	37.6% of sample consumed alcohol in month prior to baseline interview	ART nonadherence associated with alcohol use in month before baseline interview (OR 1.61, 95% CI 1.08–2.39, $P = 0.018$)
[71]	Brazil	295 HIV positive patients	109 (37.3%) subjects consumed alcohol in month prior to baseline interview	Nonadherence to ART associated with alcohol use ($P < 0.001$)
[72]	Thailand	205 HIV positive patients	13 (6.3%) subjects report current alcohol use	Current alcohol use sole predictor of nonadherence to HAART (OR 1.67, CI 1.05–2.48, $P < 0.001$)
[73]	India	198 HIV-infected patients receiving HAART		Alcohol use associated with nonadherence (OR 5.68, 95% CI 2.10–15.32, $P = 0.001$)
		Did Not Find Nonadherence		
[74]	USA	1030 HIV-infected women		No delay in ART initiation between heavy drinkers and nondrinkers
[75]	USA	300 HIV positive men who have sex with men	43% of sample report alcohol consumption in first 2 weeks post-baseline	No association found between alcohol use and nonadherence
[76]	UK	394 HIV positive patients		Excessive alcohol consumption borderline significantly lower in patients receiving HAART ($P < 0.08$)
[77]	Uganda	2311 HIV positive patients 928 (40.2%) presented late for treatment	123 (5.3%) used moderate levels of alcohol and 360 (15.5%) used high levels of alcohol	Alcohol consumption in past year (assessed using AUDIT-C) negatively associated with late presentation for treatment (OR 0.65, 95% CI 0.44–0.96, $P = 0.03$ for moderate use and OR 0.79, 95% CI 0.61–1.00, $P = 0.05$ for heavy use)

HAART administration [29], and nonadherence [75], and even lower alcohol consumption among individuals receiving HAART [76] and earlier presentation for HAART initiation among patients consuming alcohol [77]. However, while important, such reports are relatively rare, and there is an overall considerable and consistent association between alcohol consumption and medication nonadherence [41].

3.3.3. ART Adherence and the Development of Class-Specific Medication Resistance. The association between ART adherence and the development of class-specific ART resistance represents a clinical problem. During multidrug therapy, differential drug exposure increases the likelihood of developing resistance. In addition, ART with higher potency and higher genetic barriers to resistance decrease the incidence

of resistance for companion ART at all adherence levels. Drug resistance mutations proliferate under conditions of nonsuppressive ART, which is usually the result of inadequate drug exposure [78]. As poor adherence is the major determinant of inadequate drug exposure, ART adherence is critically linked to the development of medication resistance. In low-income countries such as South Africa where alcohol consumption is very high, nonadherence is more often producing resistance mutations, therefore leading to inadequate suppression of the HIV virus. The present review concords with the systematic review of Shuper et al. [79], bringing evidence that alcohol affects the immune system, consequently contributing to a deteriorating course of HIV disease. In addition, alcohol misuse impacts on medication adherence.

4. Conclusions

The primary goal of ART is to increase disease-free survival through suppression of viral replication and improvement in immunological function. The optimal time to initiate treatment is influenced by these known benefits and the risk of drug toxicity, potential emergence of viral drug resistance, and the need for lifetime therapy. The complexities of adherence-resistance relationships are related to characteristics of the virus, the medication, misuse of alcohol, and their interactions. Nevertheless, the effectiveness of ART can be limited by lack of access to therapy. Additionally, a set of acquired behaviour, such as alcohol misuse and poor adherence and/or intolerance, can lead to ART resistance. Therefore, especially in low-income populations, the education of individuals who live with HIV and alcohol abuse is relevant.

Knowledge of class-specific adherence-resistance relationships may help clinicians and patients tailor therapy to match individual patterns of adherence in order to minimize the development of resistance and treatment failure. In addition, in low-income settings, this information may guide the selection of optimal drug combinations and regimen sequences to improve the durability of ART. Moreover, alcohol use and alcohol dependence are widespread in the general population. Many people suffering from alcohol use disorders also suffer from other psychiatric disorders including drug abuse disorders. Importantly, persons living with HIV should be assessed not only for their immunologic and virologic statuses, but also for comorbidities.

This is particularly important but rarely assessed or/and reported in the literature. Modeling or condition simulation may introduce these interactions in the context of the corresponding topic leading to possible interventions.

An important objective of our study is to bring awareness of these complex interactions in the medical and education fields. Awareness should lead to cooperation between patients living with HIV, their caregivers, and researchers looking into the mechanism of relationship between the virus, disease progression, alcohol, and its comorbidities. Multiple substances of misuse, such as combined alcohol and cocaine, might be associated with behaviour and metabolic consequences not measured or not considered in these analyses. These drug-induced biological phenomena may promote disease progression and $CD4^+$ cell loss, as well as poor adherence with prescribed medication and/or inadequate micronutrient and macronutrient intake. Because the patterns of substance abuse observed in these HIV positive cohorts might not be common or typical of other HIV populations, these findings can be generalized only to other infected populations with similar patterns of substance abuse. Further studies targeting HIV heavy alcohol users, that control for other confounding behavioural and metabolic variables, need to be conducted to confirm and extend the knowledge in this area. Moreover, a network of direct discussion is needed between people living with HIV/AIDS, medical personnel treating HIV and/or addictions, epidemiology researchers, as well as policy makers and treatment planners.

Acknowledgments

The authors acknowledge the US President's Emergency Fund for AIDS Relief (PEPFAR) through the US Centers of Disease Control and Prevention (CDC) (PO S-SF750-06-M-0781), and the South African Medical Research Council for funding some of the activities that informed this paper. Its contents, however, are solely the responsibility of the authors and do not necessarily represent the official views of the CDC, PEPFAR, or other organizations referred to above.

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Hindawi Publishing Corporation
AIDS Research and Treatment
Volume 2012, Article ID 790786, 8 pages
doi:10.1155/2012/790786

Review Article

Challenges in the Management of HIV-Infected Malnourished Children in Sub-Saharan Africa

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Received 15 September 2011; Revised 16 November 2011; Accepted 17 November 2011

Academic Editor: Anthony Harries

Infection with HIV, and oftentimes coinfection with TB, complicates the care of severely malnourished children in sub-Saharan Africa. These superimposed infections challenge clinicians faced with a population of malnourished children for whose care evidence-based guidelines have not kept up. Even as the care of HIV-uninfected malnourished children has improved dramatically with the advent of community-based care and even as there are hopeful signs that the HIV epidemic may be stabilizing or ameliorating, significant gaps remain in the care of malnourished children with HIV. Here we summarize what is currently known, what remains unknown, and what remains challenging about how to treat severely malnourished children with HIV and TB.

1. Background

An estimated 19 million children are severely wasted in developing countries—malnutrition is responsible for 11% of the total global disease burden and 35% of child deaths worldwide [1]. In some regions, notably sub-Saharan Africa, human immunodeficiency virus (HIV) infection poses an added challenge to the care of malnourished children. While the clinical context and interventions for many common causes of childhood mortality worldwide have been addressed over the last decade [2], the management of severe wasting disease and malnutrition in children—particularly in those infected with HIV and/or tuberculosis (TB)—remains poorly addressed [3]. This population of HIV- and TB-infected malnourished children is in many ways very different from the uninfected population for which international malnutrition guidelines [4–6] were originally developed.

In sub-Saharan Africa, the epidemiology of severe malnutrition has shifted to one where an increasing percentage of children requiring hospitalization is composed of those who are HIV infected or HIV exposed—often coinfected with TB—with case-fatality rates still as high as 20–50% [7]. Meanwhile, ready-to-use therapeutic foods (RUTFs) that facilitate effective home-based therapy have resulted in recovery rates for uncomplicated severe malnutrition approaching 90% [8–10], although the recovery rates remain much lower for those children with HIV [11].

In this paper, we present some of the challenges and unanswered questions in the management of malnourished children with HIV (and often TB) and summarize our approach to managing these problems in the absence of clear data to guide us.

2. The Magnitude of the Problem

The average estimated HIV prevalence in 2009 for African adults between the ages of 15 and 49 is about 4.7% [12], with a range from 0.1% to 26% depending on the individual country (Table 1). Meanwhile, there are 137 million children under the age of 5 in sub-Saharan Africa, of whom 12.3 million are wasted. Meanwhile, some 2.3 million children aged 0–14 in the region have HIV [13], and undoubtedly there is significant overlap in these two populations. An estimated 5% of the region's under-five mortality is due to HIV [14], but this is as high as 35% in South Africa [12].

Assessing the magnitude of TB incidence in children is less straightforward. The incidence of TB in the under-five age group can be estimated to be half of the adult male

Table 1: HIV prevalence in adults 15–49 years old in Africa [12].

Prevalence of HIV	Number of countries	Country
0–0.9%	7	Algeria, Comoros, Eritrea, Madagascar, Mauritania, Niger, Senegal
1–4.9%	19	Angola, Benin, Burkina Faso, Burundi, Central African Republic, Chad, Congo, Côte d'Ivoire, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Mauritius, Nigeria, Rwanda, Sierra Leone, Togo
5–9.9%	6	Cameroon, Equatorial Guinea, Gabon, Tanzania, Kenya, Uganda
10–19.9%	6	Malawi*, Mozambique*, Namibia*, South Africa*, Zambia*, Zimbabwe*
20–30%	3	Botswana*, Lesotho*, Swaziland*
Missing	5	Cape Verde, Democratic Republic of Congo, Ethiopia, Sao Tome and Principe, Seychelles

*These 9 countries account for 50% of the global burden of HIV-associated TB [15].

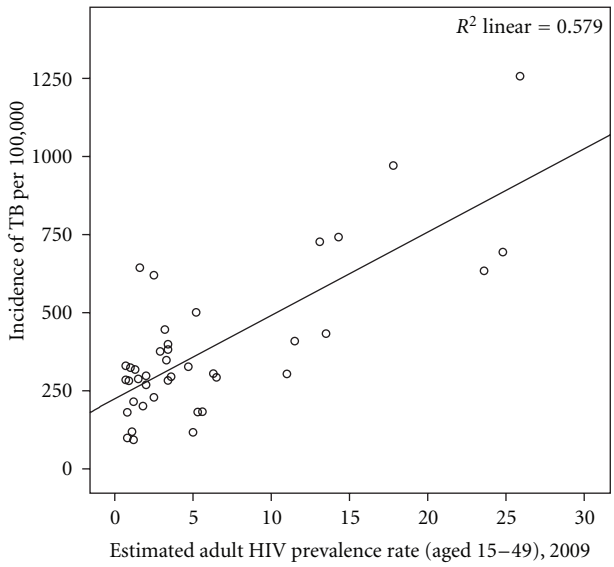

Figure 1: The association between HIV prevalence and TB in sub-Saharan Africa.

incidence and similar to the adult female incidence; following this, then there are at least 330,000 cases of TB each year in children under 5 in sub-Saharan Africa [16]. However, the incidence of TB among HIV-positive children is almost 1600 per 100,000, with a 24-fold higher risk of developing culture-confirmed TB in HIV-positive infants compared to HIV-negative infants [17]. Taking this into account would bring the total number of cases closer to 350,000 annually. Some 30% of all culture-confirmed TB cases who have had an HIV test are found to be HIV positive [17]. Given this and the fact that adults with HIV have an approximately 10% risk per year of developing TB, it is not surprising that countries with high HIV prevalence also have higher prevalence of TB [18] (Figure 1).

Children in sub-Saharan Africa who are HIV infected or HIV exposed are significantly more likely to be stunted, wasted, and underweight [19]. The high prevalence of HIV and TB in sub-Saharan Africa has created a large population of children who are malnourished and infected with both HIV and TB. In the long run, the most effective and efficient method of decreasing the population of HIV-infected children with malnutrition is an aggressive approach to the prevention of mother-to-child transmission (PMTCT) [20], and it is encouraging that a new emphasis has been placed on eliminating new cases of HIV in children [21]. A variety of implementation strategies to achieve this goal are available, and there is opportunity for innovative approaches to be developed locally. For example, Malawi has recently embarked on an aggressive plan to treat all HIV-positive pregnant and breastfeeding women with ART for life (referred to as Option "B+") [22]. The wide-scale rollout of ART in Malawi in general has also been linked to decreasing rates of TB [23], and we can anticipate that this benefit will continue as more active approaches to HIV control continue to expand, including more regular systematic tracking of patients not yet on ART. Despite these gains, we will continue to be faced with large numbers of malnourished children with HIV—and often TB also—unless and until that laudable goal is reached.

3. The Altered Clinical Presentation of Malnutrition in Children Infected with HIV

There are a number of clinical features that may be helpful in identifying those malnourished children who are also infected with HIV [24]. While HIV-infected children can present with either kwashiorkor (edematous malnutrition) or marasmus (severe wasting), just as those without HIV, a disproportionately larger number of children with HIV present with marasmus. Relative to HIV-uninfected children, malnourished children with HIV tend to be even more stunted and underweight. They more often present with severe oral and esophageal candidiasis, complicating attempts at therapeutic feeding. Greater susceptibility to a variety of infections, for example, cutaneous infections from the skin breakdown often seen with kwashiorkor, means they will often have protracted clinical courses and require more aggressive antimicrobial therapy, wound care, and have a higher caloric requirements. One of the most challenging and frustrating complications faced is persistent HIV-associated diarrhea, for which no specific therapy has been developed and for which no clinical trial evidence yet exists to guide optimal management. A diagnosis of HIV should be strongly suspected in unusually young

malnourished children (e.g., those under 6 months of age), in unusually old children (e.g., those over 5 years of age), and in those who do not respond appropriately to nutritional interventions, in addition to the usual suspicion that arises if a child presents with an opportunistic infection such as TB or *Pneumocystis jirovecii* pneumonia (PCP).

Response to therapy is also less predictable and less well-understood in HIV-infected children. Decreased food intake leads to wasting, with an associated reduction in organ system function and an increase in susceptibility to environmental perturbations and stress [25]. Since most of the metabolic responses described in severe malnutrition are based on children without HIV, the responses in HIV-*infected* malnourished children remain largely unknown [26]. When TB or other infections are further superimposed, even less is predictable [27].

4. Challenges in Community-Based Care for Severely Malnourished Children with HIV

The vast majority of children with severe malnutrition can and should be treated as outpatients [8, 9]. The advent and widespread acceptance of RUTF has revolutionized the care of severely malnourished children over the last decade, making it possible to treat children in the community setting. This has relieved much of the burden on inpatient nutritional rehabilitation units (NRUs), whose care can then be reserved for children with complications such as superimposed infections or protracted diarrhea requiring intensive rehydration. Community-based management is now considered the standard of care for children with uncomplicated malnutrition—which accounts for more than 90% of cases of severe malnutrition—who demonstrate an appropriate appetite and have reliable caregivers [10].

In our practice, we have observed that a large percentage of HIV-positive children have an episode of severe malnutrition as their first AIDS-defining illness. Given that children with HIV and severe malnutrition invariably have lower nutritional recovery and higher mortality rates than their HIV-negative counterparts [28] and that those who do recover take longer to achieve nutritional recovery [10], it is imperative that voluntary HIV testing and counseling be offered to all children with severe malnutrition in order to identify those with HIV. Children diagnosed with HIV should then be referred for PCP prophylaxis and ART as soon as possible—there is no evidence to indicate that delaying ART is of benefit to this population of children, with regards to either decreasing rates of the immune reconstitution inflammatory syndrome (IRIS) or to the adverse metabolic effects of ART. In fact, decreasing the metabolic and energy demands placed on the child's physiology due to uncontrolled HIV will in general speed up nutritional recovery as well [29].

In practice, there is often a delay in initiating ART in the community setting, due to delays in testing, counseling, drug procurement, and other steps in the process. Ideally, malnutrition and HIV services should always be available, complementary, and well coordinated in any normal daily clinic—rather than caretakers being required to return on multiple separate occasions to have each illness addressed individually. While this may initially be challenging in large health centers, the strong link between malnutrition and HIV makes this a worthy goal to work towards in our opinion. Linking these services together, providing efficient clinics, and decreasing the number of follow-up visits necessary for routine care are all efforts that may help increase retention and decrease the number of children lost to followup.

5. Challenges in the Hospital Care of Severely Malnourished Children with HIV

In the past, NRUs typically admitted sick severely malnourished children mostly during periods of food insecurity or in the postweaning period [30]. In sub-Saharan Africa, we now admit many HIV-infected malnourished children outside of these traditionally high-risk periods. These children frequently present with many superimposed infections, including (persistent) diarrhea, pneumonia, PCP, TB [31], extensive cutaneous infections, and oral and gastrointestinal candidiasis [32]. Case fatality rates are high in these children, especially those with profuse diarrhea, and their response to standard management protocols is poor [33]. Extremely wasted and stunted adolescents, previously seen only rarely outside the setting of famine, are now admitted frequently for nutritional recovery and often present with chronic HIV-related pathology such as chronic lung disease [34]. The percentage of children who are readmitted has also increased from 1-2% to more than 10% [35].

In Zambia and Malawi, for example, more than half of patients admitted to many NRUs these days are HIV positive, with case fatality rates of 40% or higher [31, 36]. Mortality in severe malnutrition is already known to be elevated whenever a child presents with superimposed infections [37, 38] and metabolic maladaptation.

Since early in-hospital mortality is high [35], improvements in initial treatment strategies depend on improved knowledge of the most common causes of infection and antibiotic sensitivities [39], pharmacokinetics of anti-infective medications in malnourished children, and potentially complex drug interactions and toxicities (e.g., ART and anti-TB therapy [40]). Bacterial susceptibility to first-line antibiotic treatment varies between centers, and the choice of empiric antimicrobials needs to be modified to suit local resistance patterns [39]. The effect of widespread usage of co-trimoxazole for PCP prophylaxis is already leading to resistance among the most common pathogens [41, 42]. In our setting, we see nearly 100% resistance to co-trimoxazole by *Streptococcus pneumoniae* [43], leading to increased use of second-line agents.

The metabolic and nutritional needs of HIV-infected children are not well known [44, 45]. In HIV-uninfected malnourished children, appetite is useful to guide nutritional rehabilitation, but this seems not to be the case in HIV-infected children since persistent anorexia is common. World Health Organization (WHO) guidelines for the management of children hospitalized with severe malnutrition

[4, 5] provide little specific guidance for the treatment of malnourished children with HIV [46]. Evidence from clinical trials on how the management of severe malnutrition should be modified for children with HIV is lacking, and treatment protocols remain based almost entirely on expert opinion and extrapolation from other populations. Given this absence of evidence, it is our practice to initially stabilize children with milk-based formulas such as F-75 [4]. These children are generally ill enough to require urgent stabilization of other physiological parameters as well, including correction of hypoglycemia, hypothermia, dehydration, and electrolyte imbalances. The use of empiric antibiotics and antihelminthic medication for presumed active infections and a presumed immune compromised state is often advocated as well [5]. After this initial stabilization phase, feedings can be advanced to a regimen of F-100 or RUTF, the latter being preferred so that children can be discharged to complete their care at home (thereby reducing crowding in the ward and the risk of nosocomial infections) that much sooner [9]. Unlike those without HIV, children with HIV frequently have difficulty tolerating an advancement of their feedings, and case fatality rates remain high during this period [47]. Evidence on the optimal feeding regimen to be used for HIV-infected children is lacking, and the choice is thus generally based on local preference and resources, with consideration given to the rate of weight gain and to adverse events such as persistent hypoglycemia and an increase in osmotic diarrhea or clinical signs of heart failure.

Suitable feeding and rehydration regimens are still needed for the severe diarrhea commonly observed prior to and during rehabilitation of HIV-infected severely malnourished children, which is often associated with hypoglycemia [48, 49] and high case fatality rates [33, 50]. In the past, adequate treatment regimens were developed for HIV-uninfected children to reduce diarrheal morbidity and mortality, induce catch-up growth, and improve nutritional outcomes [51]. Modified or improved rehydration regimens for HIV-infected children in this context may be helpful, although no specific regimens are available at this time.

The spectrum of organisms associated with bacteremia in this population [39, 52, 53] supports the importance of mucosal translocation [54] as the inciting event. Marasmic children in one Zambian study showed lower CD4 counts compared to children with edematous malnutrition (kwashiorkor), correlating with the protracted nature of diarrhea observed in these children from opportunistic enteropathogens such as *Cryptosporidium* [27]. Severe wasting makes the clinical assessment of dehydration difficult, so the presence of metabolic acidosis and lethargy are often the clinical indications available to prompt resuscitation. Unfortunately, there are also currently inadequate data on the optimum regimen of supportive care (e.g., for shock) in the malnourished child who has adapted to a reduced body mass and organ system function [38, 55].

There remains variation in how severely malnourished infants under 6 months of age are treated—explicit recognition of this population is only slowly emerging, and their mortality remains significantly higher than children older than 6 months [1]. Appropriate dietary therapies are needed for this increasing population, as the standard F-75 and F-100 formulas are likely unsuitable [6]. The poor socioeconomic background of these children often makes the use of commercial formulas for continued care as outpatients impractical [56].

6. Challenges with Initiating ART in Children with Severe Malnutrition

The optimal timing, regimen, and dosing of ART in the inpatient population of children with complicated malnutrition remain guided primarily by expert opinion due to a lack of prospective trial evidence [6, 29]. A number of observational studies have shown that HIV-infected children started on ART with more severe wasting have higher rates of mortality than those with less wasting [57–59], but no trial evidence exists to suggest that waiting until a child's nutritional status improves correlates with improved outcomes. In fact, an important recent retrospective study suggests that malnourished children who start ART promptly have higher rates of nutritional recovery and weight gain than those in whom ART is delayed [60].

A study in Zambia has shown that simply improving the nutritional status of severely malnourished HIV-infected children is insufficient to improve their immunological status without ART [27]. In fact, excellent responses in CD4 count and viral load have been demonstrated among those with severe malnutrition who do receive ART, just as in those with better baseline nutritional status [58]. In a cohort of Zambian children where 59% of the children were initially underweight and 72% stunted when starting ART, lasting improvements in both weight and height were observed, with weight-for-age Z-scores increasing during the first 6 months of treatment before stabilizing and with height-for-age Z-scores increasing consistently over time. In this cohort, children who were the most underweight experienced the greatest increases in weight [61], likely a regression to the mean phenomenon. This initial correction of wasting followed by a lasting correction of stunting has been documented in the rehabilitative process of HIV-uninfected malnourished children previously [51, 62]. In sum, it is clear that severely malnourished children are indeed able to respond appropriately to ART and nutritional supplementation in terms of both nutritional and immunological recovery. Therefore, these lifesaving medications should not be delayed, and child health systems should embrace this in a programmatic manner.

Admittedly, optimal timing for starting ART remains controversial due to concerns over IRIS [36, 63]. One case-control study comparing baseline factors related to the development of IRIS did show that children with at least one form of malnutrition (among stunting, wasting, and underweight) were more likely to develop IRIS [64]. Nevertheless, there were no fatalities among those that developed IRIS, and none required treatment interruptions from their ART. At the same time, delays in initiating ART while children are treated for TB has been shown to be detrimental to overall clinical response and mortality, particularly in

children with severe immune suppression [65]. Although the clinical presentation is not typical of any known ART toxicity, it is possible that ART initiated in children with severe malnutrition and immunosuppression may lead to a clinical deterioration and a syndrome mimicking kwashiorkor [63]. The low levels of circulating antioxidants and high levels of lipid peroxidation products seen in untreated TB patients [66] may be components of the perturbed physiologic state malnourished children find themselves in. These may further be part of their reductive adapted state, leading to a kwashiorkor-like presentation of IRIS. In the end, the data on this are relatively minimal and inconclusive, and ultimately clinical judgment will have to be applied on a case-by-case basis [67].

The alterations in body composition (decreased fat and lean body mass) and metabolic functions (changes in renal, hepatic, mitochondrial toxicity, and antioxidant capacity among others) in children with severe malnutrition has led to the concern that standard dosing of ART in these children may be inappropriate. On the one hand, these metabolic alterations perhaps lead to subtherapeutic drug levels that may contribute to viral resistance, while on the other hand these medications may be given at levels too toxic for these fragile children to tolerate safely. Unfortunately, only limited data exists to guide dosing recommendations for ART in malnourished children. One observational study on the pharmacokinetics of nevirapine in 37 Malawian children showed that suboptimal dosing was not more prevalent among moderately malnourished children [68]. As far as we are aware, there are no studies that present data on toxicity or other adverse effects from ART in severely malnourished children nor is there any literature to guide which initial ART regimen is best to start.

Further research evaluating the effects of ART in children with severe malnutrition is clearly necessary, and initial studies are underway in Malawi. High-priority areas for study include the optimal choice and timing of the initial ART regimen, an assessment of toxicity and pharmacokinetics, and an evaluation of the incidence and risk factors for IRIS.

Implementation challenges in starting and maintaining children on ART also persist and are found throughout the chain of care in sub-Saharan Africa, especially in rural areas. We have firsthand observed inconsistent supplies of testing kits, reagents, and trained staff to provide voluntary testing and counseling. Once testing is done and HIV-infected children identified, there are often further delays in referrals for group counseling, individual counseling, and ultimately initiation of therapy—all of which require trained staff and clinic facilities—and which often occur in different locations and at different times, placing a further burden on caretakers. Finally, supplies of ART and follow-up clinical and laboratory monitoring remain inconsistent, leaving patients vulnerable to treatment interruptions, which could compound HIV control efforts by increasing rates of viral drug resistance and spread. Aggressive investments in expanding national HIV prevention and treatment programs [69] must also address these and other challenges, which are often faced most severely by rural health centers.

7. Challenges in Detecting Tuberculosis in Malnourished Children with HIV

TB is notoriously difficult to diagnose in children. When a child has both severe malnutrition and HIV, diagnostic testing becomes even more difficult and, ultimately, also that much more important [70]. The tuberculin skin test (TST), long the first-line screening test, suffers from poor sensitivity and specificity. Sensitivity suffers further when the child is immunocompromised from HIV and severe malnutrition, which blunt the type IV hypersensitivity reaction needed to demonstrate a reactive TST. Given the high background rate of TB in sub-Saharan Africa (with childhood HIV-TB coinfection rates as high as 50% [71]), diagnosis is often left to clinical judgment in those children with an exposure history or with signs or symptoms or perhaps a chest radiograph suggestive of TB [72]. Undoubtedly, this leaves many children with TB undiagnosed and untreated, as well as many children without TB treated unnecessarily. Local health systems are unfortunately often too overburdened to pursue contact tracing when a case of TB is identified, but this remains an important component of the public health approach to minimizing the spread of TB by providing isoniazid preventive therapy (IPT) to children exposed to adults and older siblings with active TB. IPT can also be considered for all HIV-infected children and adults not yet on ART, as has recently been recommended in Malawi [69].

Aside from traditional means of improving the microbiological sensitivity of TB diagnosis in children such as the string test or induced sputum [71], newer nucleic acid amplification methods such as the Xpert MTB/RIF test show great promise as screening tools for TB, even in malnourished children from a population with a high rate of HIV [73]. The relative affordability of these tests, along with the speed with which results are available, has the potential to revolutionize TB care and has recently led to their endorsement by the WHO [74]. Nevertheless, implementation of such testing is likely to remain years away in most of sub-Saharan Africa, and thus clinicians will need to continue to have a low threshold for diagnosis of TB based on clinical and epidemiological suspicion. As with the challenges involving ART described earlier, no evidence exists on whether the dosing, timing, or medication choice of anti-TB regimens need modification in this population of children.

8. Looking Ahead: An Agenda for Research

Undernutrition, HIV, and TB all contribute to a large proportion of child deaths worldwide, and this high mortality rate is as avoidable as it is complex. As progress in the rollout of ART and PMTCT accelerates in sub-Saharan Africa, there are hopeful early signs that the number of children with severe malnutrition and HIV will decrease in the future. Nevertheless, for the foreseeable time, this population of patients will continue to challenge practitioners on the frontline, and the evidence base for practice is limited.

Table 2: Selected examples of open research questions in the care of HIV-infected children with severe malnutrition.

ART in malnourished children
Appropriate medication regimen?
Changes based on maternal nevirapine exposure?
Appropriate dosing?
Optimal timing of initiating ART?
Adverse effects of ART in malnourished children?
Clinical or laboratory markers of adverse effects?
Risk factors or preventive measures for IRIS?
Interactions with TB medications?
Diarrhea in HIV-infected malnourished children
Optimal rehydration regimen?
Modified rehydration solutions (both oral and parenteral)?
Role for antibiotics or antiparasitics?
Role for zinc, glutamine, or probiotics?
Nutritional therapy in HIV-infected malnourished children
Need to modify screening criteria for enrollment into nutritional care?
Need to modify criteria for younger (<6 mos) and older (>5 yrs) children?
Optimal initial choice of therapeutic food?
Optimal choice of therapeutic food during transition phase?
Need to modify criteria for graduation from nutritional care?
Adjuncts to nutritional therapy in HIV-infected malnourished children
Vitamin A?
Empiric choice of antibiotics and antiparasitics?
TB diagnosis in HIV-infected malnourished children
Accuracy of traditional methods for diagnosis (e.g., chest X-ray, TST)?
Accuracy of newer methods for diagnosis (e.g., Xpert MTB/RIF)?
Operational challenges
How to implement the above findings and guidelines at each level of care?
Prenatal and perinatal care?
Rural health center?
District hospital?
Central referral hospital?

A number of lingering questions remain that deserve the attention of researchers in this setting (Table 2). Aside from pursuing these specific questions in the context of patient-oriented clinical trials, implementation of any findings remains a further challenge for overburdened local health systems. Operational research on the best means of implementing these findings and how efficacious these findings would be in practice would thus also be useful in order to inform the most cost-effective therapy for HIV-infected children with malnutrition.

Acknowledgments

The authors thank Hoosen Coovadia, Mark Manary, Nigel Rollins, and Haroon Salojee, for innumerable thoughtful discussions and insights over many years related to this topic. They also thank the peer reviewers and editors for their excellent suggestions on how to improve this paper. Dr. I. Trehan is supported by NIH training grant T32-HD049338.

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Hindawi Publishing Corporation
AIDS Research and Treatment
Volume 2012, Article ID 375217, 10 pages
doi:10.1155/2012/375217

Clinical Study

Loss to Followup in HIV-Infected Patients from Asia-Pacific Region: Results from TAHOD

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Received 26 October 2011; Accepted 14 December 2011

Academic Editor: Anthony Harries

This study examined characteristics of HIV-infected patients in the TREAT Asia HIV Observational Database who were lost to follow-up (LTFU) from treatment and care. Time from last clinic visit to 31 March 2009 was analysed to determine the interval that best classified LTFU. Patients defined as LTFU were then categorised into permanently LTFU (never returned) and temporary LTFU (re-entered later), and these groups compared. A total of 3626 patients were included (71% male). No clinic visits for 180 days was the best-performing LTFU definition (sensitivity 90.6%, specificity 92.3%). During 7697 person-years of follow-up, 1648 episodes of LFTU were recorded (21.4 per 100-person-years). Patients LFTU were younger ($P = 0.002$), had HIV viral load ≥500 copies/mL or missing ($P = 0.021$), had shorter history of HIV infection ($P = 0.048$), and received no, single- or double-antiretroviral therapy, or a triple-drug regimen containing a protease inhibitor ($P < 0.001$). 48% of patients LTFU never returned. These patients were more likely to have low or missing haemoglobin ($P < 0.001$), missing recent HIV viral load ($P < 0.001$), negative hepatitis C test ($P = 0.025$), and previous temporary LTFU episodes ($P < 0.001$). Our analyses suggest that patients not seen at a clinic for 180 days are at high risk of permanent LTFU, and should be aggressively traced.

1. Introduction

Loss to followup (LTFU) in patients receiving antiretroviral therapy can cause serious consequences such as discontinuation of treatment and increased risk of death [1–3]. At a program level, LTFU can make it difficult to evaluate outcomes of treatment and care [4, 5]. In resource-limited settings, where treatment has become rapidly available following the rollout of antiretroviral therapy, LTFU presents even more challenging obstacles that require special consideration and approaches [6, 7].

One of the key questions in patient followup is how to define a patient as LTFU. This has varied in studies conducted in different settings [8–10]. Defining LTFU using a very early threshold, for example, a patient with no clinic visit in the last three months, may result in many patients being considered as LTFU who would return to clinic naturally at a later date. Defining LTFU with a long threshold, for example, one year, may mean delaying too long before any effort is made to track patients potentially at risk of LTFU.

The majority of research into LTFU in HIV-infected patients receiving antiretroviral treatment in resource-limited settings has been conducted in the sub-Saharan Africa region [3, 10–13]. A few studies have been conducted among Asian, mostly female, patients [14–16]. Using data from the TREAT Asia HIV Observational Database (TAHOD), this study was carried out to find the best-performing definition of LTFU and examine the characteristics of HIV-infected patients from the Asia-Pacific who were LTFU from treatment and care.

2. Methods

Established in 2003, TAHOD is a collaborative observational cohort study involving 18 sites in the Asia-Pacific region (see Acknowledgement). Detailed methods have been published previously [17]. Briefly, each site recruited approximately 200–300 HIV-infected patients, with recruitment based on a consecutive series of patients regularly attending a given site from a particular start-up time. Ethical approval for the study was obtained from the University of New South Wales Ethics Committee, Western Institutional Review Board, and respective local ethics committee from each TAHOD participating site.

The following data were collected: patient demographics and baseline data, CD4 and CD8 count, HIV viral load, prior and new AIDS defining illness (ADI), date and cause of death, prior and current prescribed antiretroviral treatment (ART), and reason for treatment change. Data were collected according to a common protocol. Upon recruitment, all available data prior to entry to TAHOD (considered as retrospective data) were extracted from patient case notes. Prospective data were updated six-monthly at each clinic and transferred to the data management centre for aggregation and analyses in March and September each year. TAHOD sites were encouraged to contact patients who have not been seen in the clinics in the previous 12 months.

TAHOD data submitted at March 2009 and March 2010 were used to find the best-performing definition of LTFU. TAHOD patients who had no followup after recruitment were not included in this analysis. Patients who were not seen in clinic for more than 12 months prior to the March 2010 data submission (i.e., last clinic visit prior to March 2009) were considered to be truly LTFU. The days between the last clinical visit and 31 March 2009 in the March 2009 data transfer were then used to find the interval that best classified a true LTFU in the following way. A series of cutoffs were considered, from ten to 365 days, to define patients as potentially LTFU. Each of these definitions of potential LTFU was compared with the gold standard of true LTFU, defined as no patient followup in the 12 months prior to 31 March 2010. The sensitivity and specificity of each cutoff in identifying true LTFU were calculated, and the best performing cutoff identified using the area under the receiver operator characteristic (ROC) curve. The optimal definition of LTFU identified in terms of maximising the sensitivity and specificity of true LTFU was found to be 180 days (see Results). This definition was then used in the risk factor analyses that follow.

Followup started from the last clinic visit at the March 2007 data submission. Patients who were considered LTFU before March 2007 (i.e., had no clinic visits 180 days before 31 March 2007) were excluded from the analysis. For patients enrolled after March 2007, the followup started at the time of enrolment. In terms of calculating person-years of followup, the end of followup for patients who had no clinic visit for 180 days and so were considered as LTFU was defined as 90 days after their last clinic visit. For patients not considered LTFU, the end of followup was also defined as 90 days after their last clinic visit. If a patient died, the followup was censored on the date of death if the date was within 180 days of their last clinic visit. Patients who died after March 2007 were considered to have complete followup. It should be noted that patients who were considered LTFU could return to clinic and reenter followup. The start of this reentry to followup was defined as 3 months prior to the first clinic visit that reinitiated followup. The patients that reentered followup could also be re-LTFU if the patient subsequently did not attend clinic for more than 180 days. The definitions we adopted were consistent with those in a previous study [18].

The rates of LTFU were calculated by the number of total LTFU periods divided by the total duration of followup contributed by the patients included in the analysis [18]. Because of the reentering and re-LTFU, patients could contribute more than one episode of LTFU in this analysis. The rates were further calculated in different strata, including age, sex, exposure category, hepatitis B and C infection, year since HIV infection, calendar year, the latest CD4 count and viral load, antiretroviral treatment status, CDC disease stages, prophylaxis (coded as receiving or not), and haemoglobin level, all taken at the start of each episode.

Factors associated with LTFU were assessed by multivariate Poisson regression models, using generalised estimating equations, to allow for multiple events of LTFU in the same patients. CD4 count, HIV viral load, antiretroviral treatment, AIDS diagnosis, and haemoglobin tests were included as

Table 1: Receiver operating characteristic (ROC) analysis for the best-performing definition for loss to followup.

Cutoff (days)	Sensitivity (%)	Specificity (%)	Area under ROC	Cutoff (days)	Sensitivity (%)	Specificity (%)	Area under ROC
10	99.67	16.97	58.32	160	90.96	90.77	90.87
20	99.02	24.32	61.67	170	90.64	91.44	91.04
30	98.05	31.31	64.68	175	90.64	92.05	91.34
40	96.82	39.90	68.36	**180**	**90.55**	**92.26**	**91.41**
50	96.34	49.52	72.93	185	90.23	92.53	91.38
60	95.77	57.20	76.48	190	89.33	93.01	91.17
70	95.28	65.52	80.40	200	88.52	93.44	90.98
80	95.11	71.26	83.19	210	87.79	94.13	90.96
90	94.71	77.62	86.16	240	85.26	95.25	90.26
100	94.22	80.91	87.57	270	83.55	96.43	89.99
120	93.24	86.18	89.71	300	82.00	97.04	89.52
150	91.53	90.17	90.85	365	78.99	97.73	88.36

True LTFU defined as no patient followup in the 12 month prior to 31 March 2010. Each cutoff used as a potential definition of LTFU was the days between last clinical visit and 31 March 2009 in the March 2009 data transfer. The sensitivity and specificity of each cutoff in identifying true LTFU were calculated, and the optimal cutoff identified based on ROC analysis.

time-dependent variables and updated at the time the new measurement or diagnosis was available.

Patients who had at least one episode of LTFU were then categorised into two groups: those who had no more clinical visits in the database (permanently LTFU) and those who later reentered followup (temporary LTFU). Multivariate logistic regression models were used to compare the characteristics in patients who were considered permanently LTFU with those who were temporary LTFU. All covariates were taken at the end of the episode in patients with truly LTFU or at the end of the first episode in patients considered temporary LTFU.

Multivariate models were built using a forward-stepwise approach. The final model included covariates that remained significant at the $P < 0.05$ level. Nonsignificant variables were also presented and adjusted for the final multivariate models. Data management and statistical analyses were performed using SAS for Windows (SAS Institute Inc., Cary, NC, USA) and Stata (StataCorp, STATA 10.1 for Windows, College Station, TX, USA).

3. Results

In March 2007, there were 2565 patients in the database. 1061 patients were subsequently enrolled in TAHOD up to March 2010. A total of 3626 patients from TAHOD who had follow-up visits in the clinic were included in this analysis. During the study period (from March 2007 to March 2010), there were 54 patients who died and considered to have complete followup.

Using days between last clinic visit and 31 March 2009 in the March 2009 data transfer, we identified the interval that best classifies a true LTFU (i.e., no clinic visit after 31 March 2009). An interval of 180 days was determined as the best-performing definition (Table 1, sensitivity 90.6%, specificity 92.3%). Using 180 days as the LTFU cutoff, during 7697 person-years of followup, a total of 1648 episodes of LTFU from 1298 patients were identified, giving a crude LTFU rate of 21.4 per 100 person-years (95% confidence interval, CI, 20.4 to 22.5). Of those 1648 episodes of LTFU identified using 180 days as the cutoff, 48% were considered permanently LTFU (i.e., the patient did not return to clinic before 31 March 2010), corresponding to 45% of the 1298 patients.

The patient characteristics are summarised in Table 2. The majority of patients were male (71%), aged between 36 and 45 years (40%), and reported heterosexual transmission (64%). Chinese (27%), Thai (26%), and Indian (11%) were the main ethnic groups. At recruitment, approximately 12% did not have a CD4 count test, and of those tested, the majority had a CD4 count more than 200 cells/μL. Nearly half (45%) did not have an HIV viral load test, and of those tested, the majority were below 500 copies/mL. Close to half of the patients (46%) were diagnosed with an AIDS defining illness at recruitment, with tuberculosis being the main illness. Most patients (63%) had been reported to be diagnosed with HIV for less than 6 years when recruited to TAHOD (measured as the time from first reported positive HIV test). Less than 10% of the patients were coinfected with either hepatitis B or hepatitis C. At recruitment, the majority of patients had normal haemoglobin level. At the start of study followup, most of the patients were on antiretroviral therapy including three or more drugs in combination including at least one nucleoside reverse transcriptase inhibitor (NRTI) and one nonnucleoside reverse transcriptase inhibitor. Over 20% of patients were in a combination with at least one NRTI and a protease inhibitor (PI). All patients were receiving, or started, antiretroviral therapy during followup.

Table 3 summarises univariate and multivariate analyses of factors associated with LTFU using 180 days as cut-off. In univariate analyses, the rate of LTFU was significantly lower in patients with a current CD4 counts above 200 cells/μL compared to patients with a CD4 count less than 100 cells/μL, but this was not significant in the final multivariate model. In the final multivariate model (Table 3), factors associated

Table 2: Patient characteristics.

Total	3626	
Characteristics	Number	%
Sex		
Male	2567	71
Female	1059	29
Current age (years)		
≤35	1383	38
36–45	1449	40
46+	794	22
Reported exposure		
Heterosexual contact	2337	64
Homosexual contact	749	21
Injecting drug use	263	7
Other/unknown	277	8
Ethnicity		
Chinese	989	27
Indian	390	11
Thai	933	26
Other/unknown	1314	36
Baseline CD4 count (cells/μl.)		
≤100	239	7
101–200	406	11
201+	2531	70
Missing	450	12
Baseline HIV RNA (copies/ml)		
≤500	1482	41
501+	379	10
Missing	1765	49
CDC disease stage at baseline		
Stage A	1621	45
Stage B	321	9
Stage C	1684	46
Tuberculosis diagnosis at baseline		
No	2758	76
Yes	868	24
Time since HIV infection (years)		
≤5	2295	63
6+	1246	34
Missing	85	2
Hepatitis B infection		
No	2297	63
Yes	257	7
Not tested	1072	30
Hepatitis C infection		
No	2007	55
Yes	324	9
Not tested	1295	36
Anemia at baseline		
No	2480	68
Yes	597	16
Haemoglobin not tested	567	16
Antiretroviral treatment at baseline		
3 + (NRTI + NNRTI)	2224	61
3 + (NRTI + PI)	744	21
No/mono/double drug	583	16
3 + (other combination)	75	2

Anemia: haemoglobin <13 g/dl (male), <11 g/dl (female); NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; PI: protease inhibitor.

with LTFU included age (younger patients had higher rate of LTFU), current HIV viral load (either patients with HIV viral load ≥500 copies/mL or no tests in recent 180 days had higher rate of LTFU), history of HIV infection (patients with shorter history of HIV infection had higher rate of LTFU), hepatitis C infection (patients with positive hepatitis C antibody had higher rate of LTFU), and, finally, current combination of antiretroviral treatment (compared to patients on triple-drug regimen with at least one NRTI and one NNRTI, patients receiving no-, single-, or double-drug antiretroviral therapy, or a triple-drug regimen containing at least one NRTI and one PI, had higher rate of LTFU).

Table 4 shows factors that predict permanent LTFU among patients who had no clinic visit for 180 days and so met our optimal definition of LTFU. In the final multivariate model, patients permanently LTFU were more likely to be older, have not been anemic, have no recent HIV viral load test, have tested negative for hepatitis C infection or have never tested for hepatitis C, and have had more than one episode of previous temporary LTFU.

4. Discussion

We found that an interval of 180 days between clinic visits was the best-performing definition of LTFU based on sensitivity and specificity in identifying true LTFU. By this definition, we observed that approximately one in five patients in our cohort would miss clinic visits for more than 180 days and so become defined as LTFU. Among these patients in our cohort close to half eventually returned to followup, with half becoming truly lost to HIV-related treatment and care.

The 180-day cutoff has been used by other studies as a working definition of LTFU [10, 19–21]. Other intervals have also been proposed as measurements of classifications of LTFU, such as 90 days [8] and 365 days [9]. Regional- and cohort-dependent characteristics, such as scheduled clinic visits, patient burden, and drug availability could result in specific intervals that best categorise patients at risk of LTFU. Nevertheless, a 180-day (or 6-month) cutoff is an appealing and easy-to-apply definition that could be used in different clinical settings in the Asia-Pacific region to flag patients at risk of being permanently lost to treatment and care. Our analyses suggest patients with no clinic visits for six months

Table 3: Factors associated with permanent or temporary LTFU, defined as no clinic visit for 180 days, among all patients under followup.

	Person-years	Number LTFU	Crude Rate[1]			Adjusted				
				95% CI	IRR[2]	95% CI	*P* value	IRR[2]	95% CI	*P* value
Sex										
Male	5468.1	1206	22.06	(20.85, 23.34)	1.00			1.00		
Female	2229.2	442	19.83	(18.06, 21.77)	1.10	(0.98, 1.24)	0.090	1.04	(0.93, 1.17)	0.446
Current age (years)										
≤35	2210.4	575	26.01	(23.97, 28.23)	1.00			1.00		0.002[3]
36~45	3320.2	718	21.62	(20.10, 23.27)	0.82	(0.74, 0.92)	0.001	0.89	(0.79, 1.00)	0.050
46+	2166.6	355	16.39	(14.77, 18.18)	0.69	(0.60, 0.79)	<0.001	0.76	(0.66, 0.88)	<0.001
Reported exposure										
Heterosexual contact	5144.5	985	19.15	(17.99, 20.38)	1.00			1.00		
Homosexual contact	1707.2	344	20.15	(18.13, 22.40)	1.10	(0.93, 1.29)	0.275	1.05	(0.89, 1.25)	0.540
Injecting drug use	344.3	125	36.31	(30.47, 43.27)	1.21	(0.97, 1.51)	0.098	1.10	(0.86, 1.40)	0.437
Other/unknown	501.3	194	38.70	(33.62, 44.55)	1.64	(1.37, 1.98)	<0.001	1.56	(1.29, 1.88)	<0.001
Current CD4 count (cells/μl.)										
≤100	233.7	69	29.52	(23.32, 37.38)	1.00			1.00		
101–200	635.7	136	21.40	(18.09, 25.31)	0.92	(0.68, 1.22)	0.551	0.96	(0.72, 1.29)	0.800
201+	6327.6	1181	18.66	(17.63, 19.76)	0.75	(0.58, 0.96)	0.023	0.79	(0.61, 1.02)	0.071
Missing	500.3	262	52.37	(46.40, 59.11)	1.18	(0.90, 1.55)	0.235	0.99	(0.74, 1.31)	0.922
Current HIV RNA (copies/ml)										
≤500	4213.7	679	16.11	(14.95, 17.37)	1.00			1.00		0.021[3]
501+	537.1	158	29.42	(25.17, 34.38)	1.71	(1.43, 2.04)	<0.001	1.24	(1.03, 1.51)	0.026
Missing	2946.4	811	27.52	(25.69, 29.49)	1.75	(1.55, 1.98)	<0.001	1.64	(1.45, 1.86)	<0.001
CDC disease stage										
Stage A	3205.1	828	25.83	(24.13, 27.65)	1.00			1.00		
Stage B	801.6	118	14.72	(12.29, 17.63)	0.93	(0.76, 1.14)	0.507	0.95	(0.77, 1.17)	0.623
Stage C	3690.5	702	19.02	(17.67, 20.48)	0.84	(0.75, 0.93)	0.001	0.92	(0.82, 1.02)	0.125
Tuberculosis diagnosis										
Yes	1806.7	372	20.59	(18.60, 22.79)	1.00			1.00		
No	5890.6	1276	21.66	(20.51, 22.88)	1.04	(0.92, 1.18)	0.537	0.98	(0.87, 1.12)	0.801
Time since HIV infection (years)										
≤5	3477.2	785	22.58	(21.05, 24.21)	1.00			1.00		0.005[3]
6+	4115.7	844	20.51	(19.17, 21.94)	0.84	(0.75, 0.94)	0.002	0.89	(0.79, 1.00)	0.048
Missing	104.3	19	18.21	(11.61, 28.55)	0.58	(0.36, 0.94)	0.027	0.49	(0.30, 0.79)	0.004
Hepatitis B infection										
Yes	584.5	112	19.16	(15.92, 23.06)	1.00			1.00		
No	5101.9	883	17.31	(16.20, 18.49)	0.93	(0.76, 1.13)	0.474	0.90	(0.74, 1.10)	0.319
N/A	2010.8	653	32.48	(30.08, 35.06)	0.98	(0.80, 1.21)	0.859	1.07	(0.85, 1.35)	0.548
Hepatitis C infection										
Yes	541.4	149	27.52	(23.44, 32.31)	1.00			1.00		0.030[3]
No	4692.8	796	16.96	(15.82, 18.18)	0.81	(0.67, 0.98)	0.029	0.81	(0.67, 0.98)	0.034
N/A	2463.0	703	28.54	(26.51, 30.73)	0.75	(0.62, 0.91)	0.004	0.77	(0.63, 0.93)	0.008
Current anemia (male < 13 g/dl, female < 11 g/dl)										
Yes	1021.1	155	15.18	(12.97, 17.77)	1.00			1.00		
No	5771.6	1157	20.05	(18.92, 21.24)	1.09	(0.92, 1.30)	0.302	1.11	(0.94, 1.32)	0.227
N/A	904.5	336	37.15	(33.38, 41.34)	1.31	(1.07, 1.59)	0.008	1.09	(0.89, 1.34)	0.382

Table 3: Continued.

	Person-years	Number LTFU	Crude Rate[1]	95% CI	IRR[2]	95% CI	P value	IRR[2]	95% CI	P value
						Adjusted				
Current ART[4]										
3 + (NRTNRTI)	4830.8	942	19.50	(18.29, 20.79)	1.00			1.00		0.001[3]
3 + (NRTI + PI)	1898.3	377	19.86	(17.95, 21.97)	1.21	(1.06, 1.38)	0.005	1.22	(1.07, 1.39)	0.003
No/mono/double ARV	762.7	300	39.33	(35.12, 44.05)	2.18	(1.90,2.50)	<0.001	1.92	(1.66, 2.22)	<0.001
3 + (other combination)	205.4	29	14.12	(9.81, 20.32)	0.95	(0.65, 1.38)	0.786	1.01	(0.69, 1.47)	0.975

(1) Crude rate, per 100 person-years.
(2) Stratified by TAHOD sites.
(3) Overall for test for trend (ordinal categorical covariates) or for homogeneity (nominal categorical covariates).
(4) ART: NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; PI: protease inhibitor.

are at high risk of being permanently lost and should be aggressively traced.

Chi et al. also found that a cutoff of 180 days was optimal to define LTFU after analysing data from the Africa, Asia, and Latin America regions of the IeDEA collaboration (including data from our cohort) [22]. There are some methodological differences between our analyses, principally regarding minimum numbers of patients for site inclusion. Chi et al. found quite extensive heterogeneity between sites, something we also found to a lesser extent. However, it is nevertheless reassuring that we found a similar optimal cutoff of 180 days without clinic visits to define LTFU. With rapid scaling up of antiretroviral treatment taking place globally, there is a need to adopt a universal consistent definition of LTFU, or a general algorithm to define cutoffs, to evaluate HIV treatment programs in different regions [6, 7, 19].

Over one in five patients in our cohort failed to come to clinic for more than 180 days in a given year. Similar rates have also been found in patients from Africa [3, 11]. However, the LTFU rate was lower in EuroSIDA [23], a large prospective cohort study with HIV-infected patients mainly from Europe (using one year as a cutoff). Approximately half of the patients who experienced LTFU in our study later came back to clinic, and patients who had a previous episode of LTFU were more likely to prove to be true LTFU, similar to previous findings [18].

We found that younger patients, patients infected with hepatitis C, and patients with detectable or unmeasured viral load were more likely to experience LTFU. These findings are all consistent with previous study findings [10, 11, 24–26]. Patients with undetectable viral load are likely to be motivated and adherent to antiretroviral treatment and thus remain in care. Among those patients who experienced LTFU, we found that those who tested negative for hepatitis C infection or were never tested for hepatitis C were more likely to be permanently LTFU. This finding seems counterintuitive, but it might be that patients who have tested positive for hepatitis C receive more medical attention from their clinicians and thus prove less likely to be permanently LTFU. Among patients identified as LTFU, anemic patients were also more likely to be permanently lost to treatment and care. Anemia has been shown to be a strong prognostic marker for HIV disease progression and survival [27], which could, at least in part, explain these patients failing to return to followup.

Compared to patients on NNRTI-based regimen, patients receiving no-, single-, or double-drug antiretroviral therapy or a triple-drug regimen containing PI were more likely to experience LTFU. The reasons for this are not clear. The greater loss to followup may be associated with increased drug toxicity, either resulting in a patient receiving mono- or dual therapy or from receiving a PI. Patients receiving PI-based regimens are also those who are more likely to be on a second line regimen, a regimen that may be substantially more expensive than first line. In the Asia Pacific region, out-of-pocket expenses are needed to pay for treatment in some clinics. Hence, the lost to followup may be associated with drug availability or affordability. It is worth noting that patients receiving mono- or dual therapy, or a PI based regimen, were also associated with being less likely to be permanently lost to followup, that is to say more likely to return to clinic (albeit not quite statistically significantly so). This possibly supports the idea of these regimens being associated with short-term drug availability or affordability issues. Unfortunately, data are not available to address this issue in any greater detail.

It has been shown that, in resource-limited settings, predominantly in Africa, patients who are LTFU have a much poorer prognosis than patients who remain in followup [5]. In part, this is due to a proportion of patients who die not having vital status information updated at their treatment site. The extent to which this occurs in TAHOD is uncertain. While it seems likely that at least some patients who are LTFU have died without this information reaching the site, the lack of association between key measures of HIV disease progression, such as CD4 count and AIDS defining illnesses, and LFTU suggests it may be lower than in African settings. However, this association between LTFU and poorer prognosis underpins the need for consistent definitions of

Table 4: Factors that predict permanent LTFU in patients without a clinic visit for 180 days.

	Number	True loss	%	OR[1]	95% CI	*P* value	Adjusted OR[1]	95% CI	*P* value
Sex									
Male	1206	584	48.4	1.00			1.00		
Female	442	209	47.3	0.89	(0.69, 1.15)	0.359	0.80	(0.61, 1.05)	0.104
Current age (years)									
≤35	568	278	48.9	1.00			1.00		0.097[2]
36~45	717	340	47.4	1.33	(1.03, 1.71)	0.031	1.31	(1.00, 1.72)	0.050
46+	363	175	48.2	1.27	(0.94, 1.72)	0.118	1.28	(0.93, 1.77)	0.128
Reported exposure									
Heterosexual contact	985	443	45.0	1.00			1.00		
Homosexual contact	344	199	57.8	1.12	(0.78, 1.60)	0.532	1.24	(0.85,1.81)	0.262
Injecting drug use	125	55	44.0	1.01	(0.59, 1.73)	0.969	1.32	(0.72, 2.41)	0.364
Other/unknown	194	96	49.5	1.07	(0.69, 1.64)	0.773	1.22	(0.78, 1.93)	0.382
Current CD4 count (cells/μl.)									
≤100	58	36	62.1	1.00			1.00		
101–200	129	66	51.2	0.76	(0.36, 1.60)	0.471	0.99	(0.47, 2.13)	0.989
201+	1068	465	43.5	0.62	(0.33, 1.18)	0.144	0.82	(0.42, 1.59)	0.551
Missing	393	226	57.5	1.50	(0.77, 2.93)	0.238	1.18	(0.58, 2.42)	0.649
Current HIV RNA (copies/mL)									
≤500	598	230	38.5	1.00			1.00		0.011[2]
501+	153	78	51.0	1.02	(0.68, 1.52)	0.924	0.94	(0.62, 1.42)	0.767
Missing	897	485	54.1	2.13	(1.63, 2.80)	<0.001	1.54	(1.13, 2.09)	0.006
CDC disease stage									
Stage A	828	413	49.9	1.00			1.00		
Stage B	121	54	44.6	0.77	(0.48, 1.22)	0.258	0.70	(0.43, 1.14)	0.154
Stage C	699	326	46.6	1.00	(0.78, 1.27)	0.975	1.05	(0.81, 1.36)	0.702
Tuberculosis diagnosis									
Yes	361	186	51.5	1.00			1.00		
No	1287	607	47.2	0.87	(0.66, 1.16)	0.342	0.85	(0.63, 1.15)	0.297
Time since HIV infection (years)									
≤5	771	400	51.9	1.00			1.00		
6+	858	389	45.3	1.25	(0.98, 1.60)	0.076	1.03	(0.79, 1.34)	0.835
Missing	19	4	21.1	0.37	(0.12, 1.17)	0.091	0.43	(0.13, 1.43)	0.170
Hepatitis B infection									
Yes	112	47	42.0	1.00			1.00		
No	883	431	48.8	1.30	(0.84, 2.03)	0.243	1.35	(0.84, 2.16)	0.222
N/A	653	315	48.2	1.31	(0.82, 2.09)	0.253	1.03	(0.60,1.76)	0.908
Hepatitis C infection									
Yes	149	66	44.3	1.00			1.00		0.004[2]
No	796	376	47.2	1.57	(1.01, 2.45)	0.046	1.66	(1.04, 2.66)	0.034
N/A	703	351	49.9	1.96	(1.26, 3.05)	0.003	2.16	(1.35, 3.46)	0.001
Current anemia (male < 13 g/dL, female < 11 g/dL)									
Yes	141	87	61.7	1.00			1.00		<0.001[2]
No	1065	456	42.8	0.53	(0.35, 0.81)	0.003	0.50	(0.32, 0.76)	0.001
N/A	442	250	56.6	1.15	(0.73, 1.81)	0.549	0.78	(0.49, 1.26)	0.310
Current ART**									
3 + (NRTI + NNRTI)	911	404	44.3	1.00			1.00		
3 + (NRTI + PI)	356	167	46.9	0.76	(0.57, 1.02)	0.072	0.74	(0.54,1.01)	0.057
No/mono/double ARV	352	209	59.4	0.93	(0.69, 1.26)	0.644	0.78	(0.57, 1.08)	0.137
3 + (other combination)	29	13	44.8	0.89	(0.40, 1.98)	0.770	0.85	(0.38, 1.94)	0.707

Table 4: Continued.

	Number	True loss	%	OR[1]	95% CI	*P* value	Adjusted OR[1]	95% CI	*P* value
Previous episode of temporary LTFU									
None	1298	589	45.4	1.00			1.00		<0.001[2]
Once	296	158	53.4	2.79	(2.05, 3.80)	<0.001	2.71	(1.97, 3.72)	<0.001
Twice	54	46	85.2	31.76	(13.91, 72.52)	<0.001	27.75	(12.03, 64.01)	<0.001

(1) Stratified by TAHOD sites.
(2) Overall for test for trend (ordinal categorical covariates) or for homogeneity (nominal categorical covariates).
(3) ART: NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; PI: protease inhibitor.

LTFU in research cohort studies, and where there are possible active patient tracing strategies or at least sampling-based approaches [28] to ensure comparability of results across studies and settings.

Several limitations should be considered in interpreting the results in this paper. First, TAHOD participating sites are generally urban referral centres, and the patients recruited in TAHOD were those regularly attending a given TAHOD site. Hence, TAHOD patients are not representative of all HIV-infected patients in the Asia and Pacific region. The overall rate of LTFU we saw in our study is therefore likely to be an underestimate of rates across the region. However, the effect of these sampling biases on the optimal definition of LTFU and on the covariate analyses is arguably less strong. It is reassuring that our estimate of the optimal definition of LTFU is consistent with that seen across Africa and Latin America [22]. Second, since antiretroviral treatment has become more decentralised and available in distant or rural communities with rapid scale-up programs, patients might choose to receive treatment and care locally rather than at tertiary and referral centres [29, 30]. Consequently, patients may have been retained in care but not necessarily in the clinics involved in this study. Information on referral to other health facility was only recently included in the data collection, so we could not further verify if patients were retained in care or truly loss to health services. Third, we do not collect data on the measures TAHOD sites undertake to routinely trace patients who are LTFU. These measures differ across sites according to local practices and conditions. Effective patient tracking and recording are essential to program evaluation and maintenance of treatment and care [1, 18]. What patient tracking measures are effective in retaining patients in treatment and care in the Asia-Pacific region is an area that deserves further research. We also do not have data on transportation [31], social and economic status [32], pregnancy for women [10], and community support [33], all of which have been found to be important determinants of LTFU. Lastly, the patients included in this study were all receiving, or started, antiretroviral treatment and had clinical assessments. Consequently, the results cannot be extrapolated to patients not yet initiated on antiretroviral therapy. Research into followup among HIV-infected patients not receiving antiretroviral treatment in the Asia-Pacific region needs to be considered [34–36], particularly in the context of the move to start treatment earlier.

5. Conclusion

With rapid scaleup of antiretroviral treatment, it is essential to study factors that predict loss to followup and identify patients at risk of loss to treatment and care, particularly in resource-limited settings. At the treatment and care level, this can maintain efficacy of antiretroviral therapy and avoid adverse events. At the program evaluation level, the impact of loss to followup on overall treatment outcome, disease progression, and survival can then be accounted for with appropriate statistical adjustments. Collaboration with HIV treatment programs in other regions in studies on LTFU and in particular standardisation of LTFU definitions are essential for reporting and program evaluation.

Acknowledgments

The TREAT Asia HIV Observational Database and the Australian HIV Observational Database are part of the Asia Pacific HIV Observational Database and are initiatives of TREAT Asia, a program of amfAR, The Foundation for AIDS Research, with support from the following institutes of the US National Institutes of Health (NIH): National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Child Health and Human Development (NICHD), the Office of the Director (OD), and the National Cancer Institute (NCI), as part of the International Epidemiologic Databases to Evaluate AIDS (IeDEA) (Grant no. U01AI069907). Additional support is provided by the Dutch Ministry of Foreign Affairs through a partnership with Stichting Aids Fonds and from the Austrian AIDS Life Association (AALA). The National Centre in HIV Epidemiology and Clinical Research is funded by the Australian Government Department of Health and Ageing and is affiliated with the Faculty of Medicine, The University of New South Wales. The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of any of the institutions mentioned above.

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Hindawi Publishing Corporation
AIDS Research and Treatment
Volume 2012, Article ID 725713, 8 pages
doi:10.1155/2012/725713

Clinical Study

Older Adults Accessing HIV Care and Treatment and Adherence in the IeDEA Central Africa Cohort

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Received 15 September 2011; Accepted 5 December 2011

Academic Editor: Annette H. Sohn

Background. Very little is known about older adults accessing HIV care in sub-Saharan Africa. *Materials and Methods*. Data were obtained from 18,839 HIV-positive adults at 10 treatment programs in Burundi, Cameroon, and the Democratic Republic of Congo. We compared characteristics of those aged 50+ with those aged 18–49 using chi-square tests. Logistic regression was used to determine if age was associated with medication adherence. *Results*. 15% of adults were 50+ years. Those aged 50+ were more evenly distributed between women and men (56% versus 44%) as compared to those aged 18–49 (71% versus 29%) and were more likely to be hypertensive (8% versus 3%) ($P < 0.05$). Those aged 50+ were more likely to be adherent to their medications than those aged 18–49 ($P < 0.001$). Adults who were not heavy drinkers reported better adherence as compared to those who reported drinking three or more alcoholic beverages per day ($P < 0.001$). *Conclusions*. Older adults differed from their younger counterparts in terms of medication adherence, sociodemographic, behavioral, and clinical characteristics.

1. Introduction

2.8 million people living with HIV worldwide are over the age of 50 [1]. In the USA, 24% of all people living with HIV are older than 50 [2]. In sub-Saharan Africa, more than 14% of adults with HIV are 50 years or older, and this population is growing [3]. Perceived risk of contracting HIV among older adults is low [4] despite physiological changes associated with aging which place older adults at increased risk of contracting HIV [5, 6]. HIV disease progresses more rapidly among older adults than among their younger counterparts, and mortality among older adults is higher after developing an AIDS-defining illness [7, 8].

Older adults are more likely to be diagnosed at late stage of HIV disease progression than their younger counterparts [8, 9]. This may be due, in part, to low perceived susceptibility of HIV among older adults [10] as well as their healthcare providers [11]. Orel et al. [12] evaluated state departments of public health in the USA and concluded that there is a dearth of HIV/AIDS risk-reduction materials targeting older adults. A study conducted in eight sub-Saharan African countries found that older adults had lower levels of knowledge about

HIV, and, among older adults, women had the lowest levels of HIV-related knowledge [10]. Few prevention programs in this setting are aimed at older adults [6].

Interest in HIV and aging is mounting as evidenced by the increasing body of literature focused on aging, the emergence of meetings such as the 1st International Workshop on HIV and Aging held in Baltimore, MD, in 2010, and a growing number of advocacy activities such as the National HIV/AIDS and Aging Awareness Day, held annually in the USA since 2009. In turn, focus on behavioral and psychosocial issues associated with HIV and aging is building. Emlet [13] found that older adults were less likely to disclose their HIV serostatus to relatives, partners, mental health workers, neighbors, and church members than those aged 20–39 years. Negin et al. [10] found similar results in sub-Saharan Africa. One US-based study found that older adults were more likely than their younger counterparts to be adherent to their antiretroviral therapy (ART) regimens [14]. In contrast, others [15] have found that adherence to ART and other medications decreases as the number of chronic conditions increases among HIV-positive older adults.

Though strides have been made in treatment scale-up in sub-Saharan Africa, very little is known about older adults accessing HIV care and treatment in resource-limited settings. This paper examines whether sociodemographic, behavioral, and clinical characteristics of those aged 50+ differ from those aged 18–49 years. Being over the age of 50 was a predictor of self-reported adherence according to a previous analysis of the women in this cohort [16]. The current paper seeks to extend these findings by evaluating whether or not there was an association between age and adherence to ART or other HIV-related medications in the overall International Epidemiologic Databases to Evaluate AIDS (IeDEA) Central Africa region cohort.

2. Materials and Methods

The HIV-infected adults included in this analysis were receiving care at 10 HIV care and treatment facilities contributing data to the IeDEA Central Africa region database. The National Institute of Allergy and Infectious Diseases funded the IeDEA initiative to establish regional centers for the collection and harmonization of HIV-related data. This international research consortium has enabled researchers in participating regions to better describe regional trends as well as address unique and evolving research questions in HIV/AIDS currently unanswerable by single cohorts. The Central Africa region database includes data from existing healthcare facilities in the Democratic Republic of the Congo (DRC), where data collection began in 2007, and Cameroon and Burundi, where data collection began in 2008. Approval for this research was granted by the Institutional Review Board (IRB) at the Kinshasa School of Public Health in DRC and RTI International, as well as the national ethics committees in Burundi and Cameroon.

Sites providing data to the IeDEA Central Africa database were a combination of public and private hospital and ambulatory care units of varying size ranging from three patient beds at one clinic in DRC to 300 beds at the largest hospital in Cameroon. Participating sites served predominantly urban populations and offered primary care in DRC and tertiary care in Burundi and Cameroon. All participating sites recommended and provided routine HIV testing for participants' relatives, sex partners, and household members and had some level of linkage to programs providing prevention of maternal to child transmission (PMTCT) services. Participating sites in Cameroon were the first within the IeDEA Central Africa region to offer free ART for adults in 2000, while participating sites in DRC started in 2005, followed by the Burundi site in 2006.

All of the clinic sites contributing data for this analysis provided individual adherence counseling for patients. Many sites also offered group counseling on medication adherence. Frequency of counseling ranged from site to site, with some programs only providing adherence counseling in the event of virologic failure, while others provided counseling at initiation of therapy, and at follow-up clinic visits every one to three months.

Some sites were also able to provide other types of ART adherence support. Many of the sites in the DRC used follow-up appointments to assess adherence, and some distributed tools such as written or illustrated instructions on when to take each medication and, to a lesser extent, calendars, alarm clocks, watches, or pagers to be used as reminders. Other sites used teaching techniques such as quizzes on how and when to take each medicine as a method of reinforcing the information learned in the counseling. At the Cameroon and Burundi sites, the medical teams also incorporated a pharmacist into multidisciplinary teams of providers and some sites had videos with instructions on adherence for patients to view.

All patient-level adherence data were self-reported and assessed at each individual's last visit prior to this analysis. All adults, regardless of whether they were on ARVs, were asked whether they had missed taking their medication more than two consecutive days in the last month. For those not on ARVs, missed medications included, most commonly, cotrimoxazole prophylaxis and, to a lesser extent, tuberculosis (TB) prophylaxis and TB treatment. Length of time on ARVs was calculated by determining the length of time between the ARV start date and the last follow-up visit prior to this analysis and was coded as not on ARVs, <6 months, 6–24 months, and >24 months. Those on ART were followed every one to three months and those not on ART were followed every six months, unless there was a clinical event for which they needed to return to the clinic for evaluation and/or care. All patient-level data used in this analysis were collected during a face-to-face interview with a clinic doctor or nurse.

3. Statistical Analysis

All analyses were performed using SAS 9.1 for Windows [17]. We examined baseline sociodemographic, behavioral, and clinical characteristics of those aged 50+ with those aged 18–49 years using chi-square tests to determine if distributions between the two groups differed. We evaluated differences between countries using chi-square tests to determine if distributions between DRC, Cameroon, and Burundi differed.

We also examined whether age was associated with self-reported medication adherence. We defined nonadherence as missed doses (of ART or other HIV-related medications) for two or more consecutive days in the past 30 days. Logistic regression was used to determine if age was associated with medication adherence while controlling for variables such as country, marital status, gender, employment status, heavy drinking, education, clinical stage at enrolment into the IeDEA database, and length of time on ARVs. Included in the model were sociodemographic and clinical characteristics that we hypothesized a priori might affect adherence based on reported associations in the literature in the context of sub-Saharan Africa [18–20] while also considering completeness of data in the IeDEA Central Africa database.

4. Results

As of June 2011, there were 18,839 adults enrolled in HIV care in the IeDEA Central Africa region database and 2,819 (15%) were 50 years old or older (Table 1). The majority of adults (N = 10,647) were from DRC, 5,835 were from Cameroon, and 2,357 were from Burundi. Of adults aged 50+, the mean age in both DRC and Cameroon was 55 years (median 54 years) and 56 years in Burundi (median 55 years). Those aged 50+ were more evenly distributed between women and men (56% versus 44%, resp.) as compared to those aged 18–49 (71% versus 29%, resp.) ($P < 0.05$). Approximately 20% of both groups reported heavy drinking, defined as three or more alcoholic drinks per day on average.

Adults were asked about their marital status, whether they had any casual sex partners in the last 6 months (defined as an occasional sex partner in addition to the respondent's regular partner), whether they had a sex partner (regular or casual) that recently died, and whether they used condoms with their regular partner. One-quarter of those aged 18–49 reported being single, compared to only 5% of older adults ($P < 0.05$). Seventeen percent of adults 18–49 indicated they had a casual sex partner within the last 6 months as compared to 8% of those 50+ ($P < 0.05$). About half (42%) of adults aged 50+ reported having a sex partner that recently died as compared to 27% of those aged 18–49 years ($P < 0.05$). A higher proportion of those aged 18–49 reported using condoms with their regular partner (19%) as compared to those aged 50+ (11%) ($P < 0.05$).

We compared HIV serostatus disclosure of those aged 18–49 and 50+ at enrollment into the IeDEA Central Africa database. A higher proportion of those aged 18–49 as compared to those 50+ had shared their HIV test results with their partner or spouse (33% versus 27%, resp.) ($P < 0.05$). The majority had shared their results with a family member (57% for both groups), while few had shared their results with a friend (6% versus 4%, resp.), health worker (6% for both groups), or someone living in the home (2% for both groups). Few were referred for disclosure counseling at the baseline visit (3% versus 2%, resp.).

To examine whether older adults were living with fewer amenities than their younger counterparts, we reviewed four variables addressing socioeconomic status: education level, paid profession, access to electricity in the home, and running water in the home. Older adults were more likely to report no formal education than their younger counterparts (14% and 7%, resp.) ($P < 0.05$); however, there were no differences between the two age groups for having a paid profession (42% of both groups), electricity (approximately 78% of both groups) and running water (approximately 61% of both groups) in the home.

We compared the health status of those aged 18–49 and 50+ at enrollment into the IeDEA Central Africa database. The majority of both groups entered HIV care through voluntary counseling and testing (56% and 55%, resp.). The majority of both groups (64% and 65%, resp.) had moderate-to-severe HIV disease progression classified as WHO clinical stage 3 or 4 at enrollment into the IeDEA database. Of the 7,858 adults with CD4 counts available at enrolment into the IeDEA database, a higher proportion of those aged 18–49 years had CD4 cells counts less than 200 cells/mm^3 (44%) as compared to 37% of adults 50+ ($P < 0.05$). A higher proportion of those aged 50+ (8%) had a history of hypertension as compared to those aged 18–49 years (3%) ($P < 0.05$) while few had a history of diabetes (3% versus 1%, resp.). About 20% of both groups had a history of tuberculosis.

Recognizing the diversity of the countries included in the IeDEA Central Africa region, we examined the sociodemographic, behavioral, and clinical characteristics of the 18,839 HIV+ adults in the database by country (Table 1). A higher percentage of adults in the Cameroon sites, (35%) were single as compared to adults in the DRC and Burundi sites (17% for both) ($P < 0.05$). Few adults in the DRC and Cameroon sites (4% for both) reported having no formal education as compared to 37% of adults in Burundi ($P < 0.05$). A higher percentage of adults in the Cameroon sites, reported having a paid profession (51%), electricity (93%) and running water (68%) in the home as compared to those in DRC and Burundi ($P < 0.05$).

Table 2 presents the results of the logistic regression model used to determine if age was associated with medication adherence while controlling for variables such as country, marital status, gender, employment status, heavy drinking, education, clinical stage at enrolment into the IeDEA database, and length of time on ARVs. Those aged 50+ were more likely to be adherent to their medications than those aged 18–49 ($P < 0.001$). Older adults had 1.59 times the odds of being adherent to their medications as compared to their younger counterparts. In terms of other predictors of adherence, adults who were not heavy drinkers had 1.40 times the odds of being adherent as compared to those who reported drinking three or more alcoholic beverages per day. Those who were not taking ARVs had 2.05 times the odds of being adherent to other medications (i.e., cotrimoxazole prophylaxis) as compared to those on ARVs for less than 6 months. Adults from the Burundi site had 2.23 times the odds of being adherent to their medications as compared to those from the DRC sites ($P < 0.001$). Adults from the Cameroon sites had 1.98 times the odds of being adherent to their medications as compared to those from the DRC sites ($P < 0.001$).

Table 1: Characteristics of 18,839[a] HIV+ adults in IeDEA Central Africa database presented by age (18–49 years, 50+ years) and by country (DRC, Cameroon, Burundi).

Characteristic	18–49 years *N* (%)	50+ years *N* (%)	DRC *N* (%)	Cameroon *N* (%)	Burundi *N* (%)
*Sex**	*15,979*	*2,812*	*10,605*	*5,834*	*2,352*
Male	4,573 (28.6)	1,243 (44.2)	3,348 (31.6)	1,749 (30.0)	719 (30.6)
Female	11,406 (71.4)	1,569 (55.8)	7,257 (68.4)	4,085 (70.0)	1,633 (69.4)
Marital status^*	*15,662*	*2,781*	*10,252*	*5,835*	*2,356*
Single	4,002 (25.6)	138 (5.0)	1,694 (16.5)	2,053 (35.2)	393 (16.7)
Divorced	1,345 (8.6)	311 (11.2)	1,110 (10.8)	316 (5.4)	230 (9.8)
Widowed	2,807 (17.9)	1,120 (40.3)	2,469 (24.1)	916 (15.7)	542 (23.0)
Living together-not married	1,622 (10.4)	74 (2.7)	732 (7.1)	624 (10.7)	340 (14.4)
Monogamous marriage	5,407 (34.5)	1,009 (36.3)	3,841 (37.5)	1,751 (30.0)	824 (35.0)
Polygamous marriage	479 (3.1)	129 (4.6)	406 (4.0)	175 (3.0)	27 (1.1)
Education^*	*15,999*	*2,808*	*10,616*	*5,835*	*2,356*
None	1,110 (6.9)	385 (13.7)	371 (3.5)	253 (4.3)	871 (37.0)
Primary school	6,915 (43.2)	959 (34.2)	4,450 (41.9)	3,006 (51.5)	418 (17.7)
Secondary school	6,260 (39.1)	1,134 (40.4)	4,447 (41.9)	1,935 (33.2)	1,012 (43.0)
University	1,714 (10.7)	330 (11.8)	1,348 (12.7)	641 (11.0)	55 (2.3)
Socioeconomic indicators					
Paid profession^	6,727 (42.1)	1,187 (42.2)	4,127 (38.9)	2,984 (51.1)	803 (34.1)
Electricity in the home^	12,623 (78.9)	2,204 (78.3)	8,419 (79.3)	5,417 (92.8)	991 (42.1)
Running water in the home^	9,686 (60.5)	1,733 (61.6)	6,568 (61.8)	3,967 (68.0)	884 (37.5)
Entry into HIV care^*	*15,918*	*2,796*	*10,522*	*5,835*	*2,357*
PMTCT	381 (2.4)	7 (0.3)	69 (0.7)	246 (4.2)	73 (3.1)
TB clinic	495 (3.1)	65 (2.3)	262 (2.5)	277 (4.7)	21 (0.9)
STI clinic	330 (2.1)	75 (2.7)	59 (0.6)	341 (5.8)	5 (0.2)
VCT	8,902 (55.9)	1,523 (54.5)	6,164 (58.6)	2,343 (40.2)	1,918 (81.4)
No previous care	4,032 (25.3)	778 (27.8)	3,292 (31.3)	1,447 (24.8)	71 (3.0)
Other	1,778 (11.2)	348 (12.4)	676 (6.4)	1,181 (20.2)	269 (11.4)
Clinical stage (WHO) at enrollment into IeDEA database^*	*15,900*	*2,800*	*10,530*	*5,819*	*2,351*
1	2,387 (15.0)	303 (10.8)	989 (9.4)	915 (15.7)	787 (33.5)
2	3,348 (21.1)	658 (23.5)	2,469 (23.4)	1,136 (19.5)	401 (17.1)
3	8,603 (54.1)	1,588 (56.7)	6,443 (61.2)	2,911 (50.0)	836 (35.6)
4	1,562 (9.8)	251 (9.0)	629 (6.0)	857 (14.7)	327 (13.9)
CD4 count at enrollment into IeDEA database^*	*6,737*	*1,121*	*1,723*	*4,862*	*1,273*
<200	2,982 (44.3)	413 (36.8)	706 (41.0)	2,310 (47.5)	379 (29.8)
200–350	1,921 (28.5)	353 (31.5)	502 (29.1)	1,405 (28.9)	367 (28.8)
>350	1,834 (27.2)	355 (31.7)	515 (29.9)	1,147 (23.6)	527 (41.4)
Length of time on ARVs^*	*8,912*	*1,644*	*5,525*	*3,737*	*1,304*
<6 months	1,467 (16.5)	239 (14.5)	1,324 (24.0)	297 (7.9)	85 (6.5)
6–24 months	2,404 (27.0)	388 (23.6)	1,436 (26.0)	1,007 (26.9)	346 (26.5)
>24 months	5,041 (56.6)	1,017 (61.9)	2,765 (50.0)	2,433 (65.1)	873 (66.9)
Comorbidity history					
History of TB^	3,237 (20.2)	538 (19.1)	2,553 (24.1)	669 (11.5)	553 (23.5)
History of diabetes*^	213 (1.3)	71 (2.5)	194 (1.8)	68 (1.2)	22 (0.9)
History of high blood pressure*^	501 (3.1)	234 (8.3)	492 (4.6)	163 (2.8)	80 (3.4)

Table 1: Continued.

Characteristic	18–49 years *N* (%)	50+ years *N* (%)	DRC *N* (%)	Cameroon *N* (%)	Burundi *N* (%)
*Has had a casual sex partner in last 6 months**^*	2,673 (16.7)	232 (8.2)	1,082 (10.2)	1,569 (26.9)	254 (10.8)
*Sex partner (regular or casual) who has recently died**^*	4,360 (27.2)	1,188 (42.1)	2,703 (25.4)	1,955 (33.5)	890 (37.8)
*Condom use with regular partner**^*	2,968 (18.5)	311 (11.0)	985 (9.3)	1,648 (28.2)	646 (27.4)
Heavy drinking (on average 3+ drinks/day)*^	3,369 (21.1)	636 (22.7)	2,207 (20.9)	1,389 (23.8)	409 (17.4)
HIV test result disclosure					
Partner/spouse*^	5,255 (32.8)	771 (27.4)	2,755 (25.9)	2,093 (35.9)	1,178 (50.0)
Friend*^	908 (5.7)	113 (4.0)	277 (2.6)	406 (7.0)	338 (14.3)
Family member^	9,116 (56.9)	1,618 (57.4)	5,693 (53.5)	3,959 (67.8)	1,082 (45.9)
Health worker^	881 (5.5)	169 (6.0)	254 (2.4)	776 (13.3)	20 (0.8)
Someone living in the home^	311 (1.9)	68 (2.4)	308 (2.9)	39 (0.7)	32 (1.4)
Referral made for disclosure counseling	528 (3.3)	61 (2.2)	115 (1.1)	471 (8.1)	3 (0.1)

[a]Variables do not add to total number of adults in the database (18,839) due to missing data.
*Significant differences found between adults 18–49 years and adults 50+ years distributions ($\alpha = 0.05$).
^Significant differences found between DRC, Cameroon, and Burundi distributions ($\alpha = 0.05$).

5. Discussion

Fifteen percent of this large cohort of HIV-infected adults were 50 years old or older. Though older adults were more likely to report no formal education than their younger counterparts, they did not seem to be living with fewer amenities as per the socioeconomic variables examined in this study: having a paid profession, access to electricity, and running water in the home. We found that older adults were more likely to be adherent to their medications than their younger counterparts. In terms of other predictors of adherence, we found that adults who were not heavy drinkers reported better adherence as compared to those who reported drinking three or more alcoholic beverages per day.

Older adults have been found to be more adherent to HIV medications, including ART, than their younger counterparts, which may improve their survival and response to treatment [14]. Though we found adults aged 50+ years to be more adherent to their medications than those aged 18–49, further inquiry is needed to determine if the older adults in this cohort, in turn, experience an improved response to ART and survival.

Alcohol abuse has been found to negatively affect adherence in sub-Saharan Africa (see Mills et al. [19] for a review) and our results provide further support. We found that adults who were not heavy drinkers reported better adherence as compared to those who reported drinking three or more alcoholic beverages per day. A similar proportion of older and younger adults reported heavy drinking (23% and 21%, resp.). However, it is important to note that those aged 50+ were more evenly distributed between women and men as compared to those aged 18–49, and, in this cohort, men tended to report alcohol use more frequently than women. Our results suggest that those reporting heavy alcohol use may benefit from additional adherence counseling. Those who were not taking ARVs reported better adherence to other medications (i.e., cotrimoxazole prophylaxis) as compared to those on ARVs for less than 6 months, supporting the notion that additional adherence counseling for new ART users may be beneficial.

Older adults in sub-Saharan Africa have been found to be less likely to discuss HIV prevention with their partner as compared to their younger counterparts [10]. The results of the current study echo these findings. Disclosure of HIV test results with partners/spouse as well as condom use with regular partner was higher among those aged 18–49 as compared to those aged 50+. Further, HIV programming in sub-Saharan Africa is generally targeted towards younger adults, not those over 50 [3, 21]. Older adults as compared to their younger counterparts have been found to be less likely to have been tested for HIV [10] and experience delays in diagnosis and treatment [8, 9], as clinicians may not routinely screen older adults for HIV or recognize their signs and symptoms as those of HIV [11]. In the current study, the majority of both age groups had moderate-to-severe HIV disease progression classified as WHO clinical stage 3 or 4 at enrollment into the IeDEA database, which corresponded to entry into HIV care for many adults.

Older adults are at increased risk for HIV infection due to biological and social factors [5, 6]. For women, in particular, age is associated with thinning of vaginal membranes and reduced vaginal lubrication, which can lead to tearing during sexual intercourse [5]. Social factors may place older adults at risk for HIV, such as divorce or death of a spouse, which may lead to new sexual partners and thus risk of exposure [5]. In sub-Saharan Africa, cultural practices, such as wife inheritance, may also place women at risk of contracting HIV in the event of the death of a spouse [6]. In the current study, a greater proportion of older adults as compared to those aged 18–49 were widowed (40% versus 18%, resp.) or divorced (11% versus 9%, resp.).

Table 2: Adjusted[1] odds ratios and 95% confidence intervals for the association of medication adherence[2] and age.

Variable	*Medication adherence* Odds ratio	95% confidence interval	*P* value
Main effect variable			
Age			
18–49 years	*Ref*		<0.001
50+ years	1.59*	(1.21, 2.09)	
Covariates			
Country			
DRC	*Ref*		<0.001
Burundi	2.23*	(1.57, 3.15)	
Cameroon	1.98*	(1.60, 2.46)	
Marital status			
Single	*Ref*		0.848
Divorced	1.05	(0.76, 1.46)	
Widowed	1.11	(0.85, 1.44)	
Married/living together (includes monogamous and polygamous marriage)	1.09	(0.88, 1.36)	
Sex			
Female	*Ref*		0.569
Male	0.95	(0.78, 1.15)	
Employment status			
No paid employment	*Ref*		0.813
Paid employment	1.02	(0.86, 1.22)	
Heavy drinking			
Yes	*Ref*		<0.001
No	1.40*	(1.15, 1.70)	
Education level			
Secondary/University	*Ref*		0.216
Primary	0.94	(0.79, 1.12)	
No formal education	0.72	(0.50, 1.05)	
Clinical stage (WHO) at enrollment into IeDEA database			
I/II	*Ref*		0.774
III/IV	0.97	(0.82, 1.17)	
Length of time on ARVs			
<6 months	*Ref*		<0.001
6–24 months	0.69*	(0.53, 0.89)	
>24 months	1.12	(0.87, 1.45)	
Not on ARVs	2.05*	(1.51, 2.78)	

* $P < 0.001$.

[1]Adjusted for country, marital status, gender, employment status, heavy drinking, education, clinical stage at enrollment into IeDEA database, and length of time on ARVs.

[2]Nonadherence was defined as missed doses of ART or other HIV-related medications (most commonly cotrimoxazole prophylaxis and, to a lesser extent, TB prophylaxis and TB treatment) for two or more consecutive days in the past 30 days.

6. Limitations

Our results should be considered in light of several study limitations. The adherence data for this study were self-reported and collected during face-to-face interviews with a clinic doctor or nurse, which can lead to social desirability bias and, in turn, inflated adherence estimations [22]. Our baseline data were derived at enrollment into the IeDEA Central Africa database. For many adults, this also corresponded to enrollment into HIV care. Though we were able to determine

when ART was started, we were not able to assess how long the patient had been in HIV care before enrolling into the IeDEA database.

The data presented in this paper provide a snapshot of patient characteristics from a broad range of private and public hospitals and ambulatory care units of varying size and capacity. However, the data are not nationally representative as they were not derived from randomly selected HIV care facilities. Though describing regional trends was an objective of the larger study, exploring differences between age groups was not an original goal. Collecting additional data on psychosocial variables, such as social support, depression, stigma, and quality of life, would have been insightful for examining potential differences between older adults and their younger counterparts.

7. Conclusions

This is the first study to examine whether there are differences between older adults and their younger counterparts accessing HIV care and treatment in the central Africa region. These results are noteworthy as they provide insight into the sociodemographic, behavioral, and clinical characteristics of HIV-infected older adults in this region. Though we found older adults were more likely to be adherent to their medications than their younger counterparts, further inquiry is needed to better understand factors affecting ART adherence, response to treatment, and survival of older adults receiving HIV care in sub-Saharan Africa. We found that heaving drinking negatively affected medication adherence, which suggests that those reporting heavy alcohol use may benefit from additional adherence counseling.

Acknowledgments

The IeDEA-CA network is funded by the National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH/NIAID 1 U01 AI069927). The IeDEA-CA collaboration acknowledges the contribution of local staff and patients in this project as well as staff at the IeDEA regional office (Kinshasa, DRC): Mr. Christian Kondé, and Mr. Kashamuka Mwandagalirwa.

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Hindawi Publishing Corporation
AIDS Research and Treatment
Volume 2012, Article ID 238012, 8 pages
doi:10.1155/2012/238012

Clinical Study

Successes and Challenges in an Integrated Tuberculosis/HIV Clinic in a Rural, Resource-Limited Setting: Experiences from Kericho, Kenya

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Received 14 September 2011; Revised 11 November 2011; Accepted 28 November 2011

Academic Editor: Anthony Harries

Objective. To describe TB/HIV clinic outcomes in a rural, Ministry of Health hospital. *Design*. Retrospective, secondary analyses. Descriptive statistics and logistic regression analyses evaluated baseline characteristics and outcomes. *Results*. Of 1,911 patients, 89.8% were adults aged 32.0 (±12.6) years with baseline CD4 = 243.3 (±271.0), 18.2% < 50 cells/mm^3. Pulmonary (84.8%, (32.2% smear positive)) exceeded extrapulmonary TB (15.2%). Over 5 years, treatment success rose from 40.0% to 74.6%, lost to follow-up dropped from 36.0% to 12.5%, and deaths fell from 20.0% to 5.4%. For patients starting ART after TB treatment, those with CD4 ≥ 50 cells/mm^3 were twice as likely to achieve treatment success (OR = 2.0, 95% CI = 1.3–3.1) compared to those with CD4 < 50 cells/mm^3. Patients initiating ART at/after 2 months were twice as likely to achieve treatment success (OR = 2.0, 95% CI = 1.3–3.3). Yearly, odds of treatment success improved by 20% (OR = 1.2, 95% CI = 1.0–1.5). *Conclusions*. An integrated TB/HIV clinic with acceptable outcomes is a feasible goal in resource-limited settings.

1. Introduction

Tuberculosis (TB) remains the leading cause of death among persons living with HIV/AIDS with nearly 25% of HIV mortality attributable to TB and 380,000 deaths in 2009 related to HIV-associated TB [1]. In 2009, there were an estimated 1.1 million HIV-positive TB patients globally with nearly 80% living in sub-Saharan Africa [1]. While guidelines [2–5] and peer-reviewed journals [6–12] call for integrated TB/HIV services and clinical trials demonstrate early antiretroviral therapy (ART) in patients with TB/HIV coinfection result in better outcomes [13–16], experience from field implementation of TB/HIV integration is now critical.

The Kericho District Hospital (KDH), a Ministry of Health public hospital in rural Kenya, fully integrated HIV services into their TB clinic in 2005 quickly following the development of their HIV clinic services. Integration was deemed necessary for a variety of reasons: (1) treatment of one patient with two diseases (TB/HIV) seemed more practical in a single location; (2) both patients and clinicians preferred a combined TB/HIV care delivery system [10]; (3) the belief that treatment outcomes could be maximized by developing a cadre of health care providers capable of providing both TB and HIV treatments; (4) planned increases in HIV testing within the TB clinic would result in identifying large numbers of HIV-infected persons that could overwhelm a burdened HIV clinic (who would already received treatment in the TB clinic); (5) rudimentary infection control in the HIV clinic could be strengthened by caring for all TB/HIV suspects in the TB clinic rather than comingling in the HIV clinic.

The objectives of this study were to describe characteristics of patients enrolled in the TB/HIV clinic, consider

changes in treatment success over time, evaluate TB treatment outcomes given baseline CD4+ T-cell counts and timing of ART, and explore the relationship between baseline characteristics and treatment success.

2. Materials and Methods

2.1. Study Design. We conducted a retrospective, secondary analysis of KDH clinic electronic medical records.

2.2. Study Setting. KDH is located in Kericho among the tea fields and plantations of Kenya's southern Rift Valley Province 260 kilometers northwest of Nairobi. As a Ministry of Health (MoH) facility under the Ministry of Medical Services, KDH provides services to a rural, largely uninsured population, representative of the national statistic indicating that 46% of the population lives below the poverty line [17]. In 2010, approximately 12,000 patients received inpatient and approximately 160,000 patients received outpatient services [18]. Both HIV and TB services are provided by funding from the Government of Kenya/MoH [19, 20] and through donor programs, principally the President's Emergency Plan for AIDS Relief (PEPFAR) [21]. TB and HIV care services including HIV Counseling and Testing and Prevention of Mother- to- Child Transmission (PMTCT) operate in partnership with the Kenya Medical Research Institute/Walter Reed Project (KEMRI/WRP) HIV Program. The KEMRI/WRP partnership is part of the US Military HIV Research Program (MHRP), an international HIV vaccine research program under the Walter Reed Army Institute of Research (WRAIR) [22, 23].

The MoH in collaboration with KEMRI/WRP under the PEPFAR program supports HIV care, prevention, and treatment services in the southern Rift Valley Province of Kenya (population of approximately 2.5 million). Beginning with 4 initial treatment sites (including KDH) in 2004, program coverage now includes 11 district level, primary treatment facilities, 10 subdistrict hospitals, 75 dispensaries/rural health centers, and 403 PMTCT sites. Expansion has been based upon a network model focusing upon decentralization in an effort to bring services closer to communities and decongest primary treatment centers. After the initial KDH TB/HIV clinic opened in 2005, expansion of integrated TB/HIV services began in 2007 and currently includes 8 TB/HIV integrated clinics (Figure 1).

In late 2005, KDH opened the integrated TB/HIV clinic using current MoH TB and HIV guidelines as well as expert consultation (EJC). Operational components of the integrated TB/HIV clinic included (1) HIV Diagnostic Testing and Counseling (DTC) for patients and family members presenting to the TB clinic where >90% annual patient acceptance rate was achieved [18]; (2) use of "cough monitors" (trained lay individuals) to maximize sputum collection in an effort to improve case finding and categorization of TB disease, (3) referral to the TB clinic of all patients diagnosed with TB in the HIV clinic at KDH as well as local subdistrict hospitals and dispensaries/rural health centers; and, (4) treatment for HIV including ART in the TB clinic with patient referral for continued care to the HIV clinic on completion of TB therapy.

Trimethoprim/sulfamethoxazole prophylaxis is routinely provided to all HIV-infected patients. Patients receive multivitamins for nutritional supplementation as well as pyridoxine while on isoniazid for prevention of peripheral neuropathy. TB, HIV, and TB/HIV coinfection prevention, diagnoses, and treatments evolve based upon current national guidelines and are conducted with support from and under the auspices of Division of Leprosy, Tuberculosis, and Lung Diseases (DLTLD) and National AIDS and STI Control Programme (NASCOP) [3, 24–29]. The TB/HIV clinic is staffed primarily by clinical officers and nurses and is supplemented by DTC staff, cough monitors, and a nutritionist. Medical officers and consultants (mostly Internists) see patients 1-2 days a week or as needed.

TB intensive phase treatment consists of isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months in a fixed dose combination with followup weekly. TB continuation phase treatment initially consisted of isoniazid and ethambutol for 6 months in a fixed dose combination until 2009 when country guidelines changed the regimen to isoniazid and rifampin for 4 months in a fixed dose combination. Continuation phase visits were scheduled monthly. First-line ART prescribed in the TB clinic was in accordance with national guidelines and consisted initially of stavudine or zidovudine, lamivudine, and efavirenz until 2010 when tenofovir became available and stavudine was removed from first-line recommendations. TB and ART medications were dispensed on the same schedule. No drug stockouts of TB medications or ART were experienced during the study period. However, postelection violence occurred in Kenya beginning December 29, 2007 and resulted in the displacement of up to 600,000 individuals and over 1,000 deaths. The region of violence included Kericho and resulted in displacement of both patients and staff during the study period.

2.3. Data Collection and Variables. Data were collected from the KDH TB/HIV and HIV clinic electronic medical records systems. These KDH MS Access databases include clinical information from both clinic encounter forms and laboratory results. Data were extracted from both the TB/HIV and HIV clinic databases and merged by patient clinic number to allow evaluation of KDH HIV clinic followup. A final password protected, anonymous database was created for all retrospective, secondary analyses and stored in the KEMRI/WRP Clinical Research Center secured, double-locked Information Department. Basic demographic and medical information extracted included age, gender, baseline CD4+ T-cell count, TB type, treatment and referral categories, and TB treatment outcomes.

2.4. Statistical Analysis. Descriptive analyses including paired t-tests and chi-square or Fisher's exact tests where appropriate were used for baseline characteristics and follow-up outcomes. Unadjusted and adjusted multivariable logistic regression analyses were used to examine the relationship between baseline characteristics, clinic year, and outcomes.

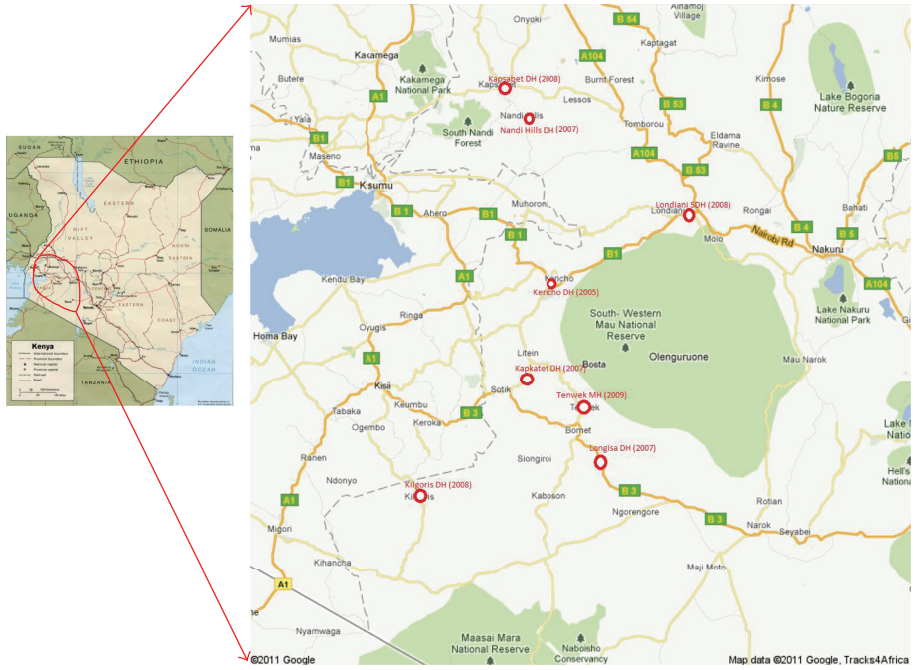

Figure 1: Kericho District Hospital Integrated TB/HIV Clinic (est. 2005) and subsequent roll-out of seven regional integrated TB/HIV clinics (est. 2007–2009). Notes: DH: District Hospital, MH: Mission/Faith Based Hospital, SDH: Sub-District Hospital.

Data compilation and statistical analyses were completed using Microsoft Excel and PC SAS (SAS Institute, Carey, NC). Further details are outlined in protocol RV215 [30].

2.5. Ethics Approval. This study was reviewed and approved by the Kenya Medical Research Institute, Lifespan, and Walter Reed Army Institute of Research respective Institutional Review Boards and/or Ethics Review Committees.

3. Results

3.1. Baseline Characteristics. Between 2005 and 2010, 1,911 TB/HIV coinfected patients were registered in the TB/HIV clinic: 1,716 adult (52.6% female) and 195 pediatric (58.5% female) (Table 1). Of the adults, 42.8% were in care in the HIV Clinic at the time of their TB diagnosis, resulting in enrollment at the combined clinic. Most adults (51.2%) had their TB diagnosis at the TB clinic and were diagnosed with HIV coinfection by HIV rapid testing in the TB clinic. The remaining adults were referred to the integrated clinic from outside facilities. For pediatric patients, this ratio was reversed with 59.0% cared for in the HIV clinic prior to TB diagnosis and 36.9% having TB diagnosed initially followed by HIV testing in the TB clinic.

Most adults (84.8%) presented with pulmonary TB (34.9% smear positive) and advanced HIV disease (mean CD4+ T-cell count = 216.4 ± 206.8 cells/mm^3, CD4+ T-cell count <50 cells/mm^3 = 18.4%). Although pediatric patients presented with similar frequencies of pulmonary TB, far fewer were smear positive (8.7%) but their HIV disease was advanced (CD4+ T-cell count <50 cells/mm^3 = 16.2%). Nearly all received chest X-rays (93.0% and 95.9%, resp.), contributing to diagnosis in smear negative cases.

Among the 1,911 enrolled in the TB/HIV clinic, 684 (35.8%) initiated ART through care in the integrated clinic while receiving TB therapy. Few patients (186 (9.7%)) were already treated with ART at the time of TB diagnosis and had care transferred to the integrated clinic. Most patients (1,041 (54.5%)) with higher CD4+ T-cell counts received ART in the HIV clinic after completion of TB therapy, reflecting treatment approaches prior to more recent guidelines.

3.2. TB Treatment Outcomes. Overall 5-year treatment success (cure or completion of therapy) frequencies were 74.7% in children but only 56.8% in adults (Table 2). Proportions lost to followup were high: 14.1% in children and 20.7% in adults. Frequencies of death (5.9% and 8.2%, resp.) were low, although these likely reflect an underestimate if the much larger proportions of lost to followup (14.1% in pediatrics and 20.7% in adults) included patients who died. For adult and pediatric patients over the 5-year period, treatment success rose from 40.0% in 2005 to 74.6% in 2010 (Figure 2). A notable, temporary decrease in treatment success occurred in 2007-2008. This reversal may reflect the societal unrest during the postelection violence that resulted in displacement of both patients and staff. Also during the 5-year period, proportions lost to followup (36.0% year-1 to 12.5% year-5) and having died (20.0% year-1 to 5.4% year-5) also improved.

In the 684 patients who started ART while on TB therapy, ART was initiated on average 74.0 (±93.1) days following TB treatment initiation. Review of TB treatment outcomes stratified by baseline CD4+ T-cell count distribution reveals that those patients with a CD4 count of <50 cells/mm^3 had the highest proportion of death (10.7%) and accounted for over half of the deaths in the entire cohort (Table 3(a)).

Table 1: Characteristics of TB/HIV coinfected patients upon enrollment in the Kericho District Hospital Integrated TB/HIV Clinic[1].

	Pediatric (≤15 years old) $n = 195$ (10.2%)	Adult (>15 years old) $n = 1,716$ (89.8%)	Overall $n = 1,911$
Age (yrs)[2]	6.6 (±4.0)	34.9 (±9.7)	32.0 (±12.6)
	6.0 [1–15]	34.0 [16–80]	32.0 [1–80]
Female (%)	58.5	52.6	53.2
CD4+ T-cell count (cells/mm^3)[2]	551.1 (±568.9)	216.4 (±206.8)	243.3 (±271.0)
	398.5 [2-3, 151]	153.0 [1-1, 609]	165.0 [1–3, 151]
CD4 distributions (%)[2]			
<50 (cells/mm^3)	16.2	18.4	18.2
50–99 (cells/mm^3)	5.4	16.3	15.4
100–199 (cells/mm^3)	7.7	24.3	22.9
200-349 (cells/mm^3)	16.2	21.3	20.8
≥350 (cells/mm^3)	54.6	19.8	22.6
TB type (%)			
(I) Pulmonary	84.1	84.8	84.8
(1.a) Smear positive[2]	8.7	34.9	32.2
(1.b) Chest X-ray done	95.9	93.0	93.3
(II) Extrapulmonary	15.9	15.2	15.2
Treatment category[3]			
New	93.3	89.0	89.5
Transfer in	1.0	3.7	3.4
Returned defaulter	0.5	2.9	2.7
Relapse	5.1	4.4	4.4
Referral origin[2]			
HIV clinic	59.0	42.8	44.5
TB clinic	36.9	51.2	49.8
Private	1.5	3.7	3.5
Other	2.5	2.2	2.2

[1] Data presented as proportion (%) or mean (±SD) and median [range]. Missing data: CD4 = 15.4%; TB type, treatment category, referral, and family testing <1.0%.
[2] $P < 0.05$.
[3] $P < 0.001$.

Table 2: TB treatment outcomes of TB/HIV coinfected patients enrolled in the Kericho District Hospital Integrated TB/HIV Clinic.

	Pediatric (<15 years old) $n = 195$	Adults (>15 years old) $n = 1716$
TB treatment outcome		
Cure	7 (4.1)	243 (16.0)
Treatment complete	120 (70.6)	621 (40.8)
Transferred out	9 (5.3)	217 (14.3)
Lost to Followup	24 (14.1)	315 (20.7)
Died	10 (5.9)	125 (8.2)
Treatment success	127 (74.7)	864 (56.8)

Notes:
(1) Data presented as number (percentage). Missing data for TB treatment outcome = 12.9% for pediatric and 11.3% for adult patients.
(2) Treatment success defined as cure or treatment complete.

Treatment success frequencies improved in relationship to increasing baseline CD4+ T-cell count. Lost-to-followup frequencies were high (10.9–12.8%) in all CD4+ T-cell strata less than 200 cells/mm^3. Lost-to-followup frequencies dropped by half in patients with CD4+ T-cell counts above 200 cells/mm^3. Similarly in review of outcome data by time of ART initiation, poor outcomes as defined by either death or lost to followup were highest in those who started ART earliest following TB treatment initiation, likely reflecting their advanced HIV disease (Table 3(b)). For patients who

Table 3: (a) TB treatment outcomes according to baseline CD4 category in patients initiating ART following TB treatment in the Kericho District Hospital Integrated TB/HIV clinic ($n = 684$). (b) TB treatment outcomes according to time of ART initiation in patients in the Kericho District Hospital Integrated TB/HIV Clinic ($n = 870$).

(a)

CD4 distributions (cells/mm^3)	TB treatment outcome				Row totals
	Treatment success	Transferred out	Lost to followup	Died	
<50	116 (66.3)	18 (10.3)	22 (12.8)	19 (10.7)	175 (28.6)
50–99	101 (68.7)	21 (14.3)	16 (10.9)	9 (6.1)	147 (24.0)
100–199	163 (77.3)	18 (8.5)	27 (12.8)	3 (1.4)	211 (34.5)
200–349	53 (86.9)	4 (6.6)	3 (4.9)	1 (3.1)	61 (10.0)
≥350	16 (88.9)	1 (5.6)	1 (5.6)	0 (0)	18 (2.9)

Notes:
(1) Data presented as number (percentage for row total). Data missing: 10.5% for combination of CD4 distributions and TB treatment outcome.
(2) Treatment Success defined as cure or treatment complete.

(b)

Time of ART	Tb Treatment Outcome				Row totals
	Treatment success	Transferred out	Lost to followup	Died	
ART Prior to TB Treatment	122 (75.3)	12 (7.4)	14 (8.6)	14 (8.6)	162 (20.5)
ART Following TB Treatment					
<2 weeks	39 (65.0)	5 (8.3)	10 (16.7)	6 (10.0)	60 (7.6)
2 weeks–<2 months	227 (66.8)	50 (14.7)	45 (13.2)	18 (5.3)	340 (43.0)
2–6 months	143 (81.7)	7 (4.0)	15 (8.6)	10 (5.7)	175 (22.2)
>6 months	49 (92.5)	1 (1.6)	2 (3.8)	1 (1.9)	53 (6.7)

Notes:
(1) Data presented as number (percentage of row total). Data missing: 10.1% for combination of time of ART and TB treatment outcome.
(2) Treatment success defined as cure or treatment complete.

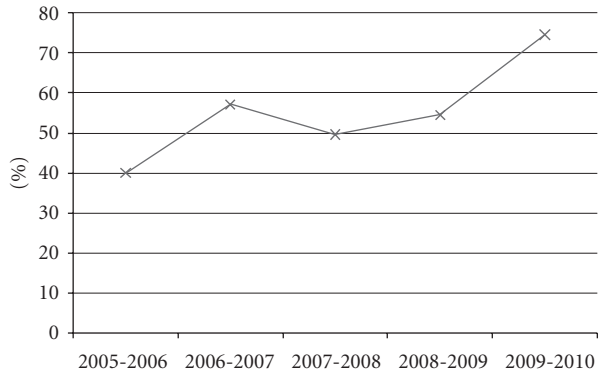

Figure 2: Overall treatment success by year in the Kericho District Hospital TB/HIV Clinic. Note: treatment success defined as proportion with cure or treatment complete.

survived the first two months of TB treatment to initiate ART, treatment success rose to 81.7–92.5%, clearly above the WHO target guidelines.

3.3. Baseline Characteristics, Clinic Year, and Treatment Success. Exploratory analyses were conducted in an effort to understand the relationship between baseline characteristics (age, gender, CD4+ T-cell count, and time until ART initiation), clinic year, and treatment success (cure or treatment complete versus death or loss to followup) (Table 4). Individually, CD4+ T-cell count, time until ART initiation, and clinic year were predictive of treatment success. TB/HIV coinfected patients with CD4+ T-cell counts greater than or equal to 50 or 200 cells/mm^3 were 2.0 to 3.5 times more likely to achieve treatment success (OR = 2.0 95% CI = 1.3–3.1 and OR = 3.5, 95% CI 1.4–8.9, resp.) compared to patients whose CD4+ T-cell counts were less than 50 or 200 cells/mm^3. Similarly, patients initiating ART after 2 weeks or 2 months were twice as likely to achieve treatment success (OR = 1.9, 95% CI = 1.0–3.5 and OR = 2.0, 95% CI = 1.3–3.3, resp.). Yearly, the odds of participants having treatment success improved by approximately 20% (OR = 1.2, 95% CI = 1.0–1.5). In multivariate analysis, CD4 category, time until ART, and clinic year remained significant.

4. Discussion

Our experience demonstrates that integrated TB/HIV care is feasible at a rural, public MoH hospital in Kenya. Our integrated clinic, staffed primarily by clinical officers and nurses with backup assistance by medical officers and consultants, successfully administered TB and ART care with acceptable TB treatment success frequencies that improved over time. Overall mortality was low in the TB/HIV clinic for both adult and pediatric patients. However, lost-to-followup frequencies were high and occurred early in care, particularly in those presenting with advanced HIV. Many of these patients lost to followup likely account for additional deaths. Our data suggest that achieving Kenyan national TB targets

Table 4: Relationship of treatment success in patients starting antiretroviral therapy after TB treatment in the Kericho District Hospital TB/HIV Clinic ($n = 684$).

Characteristic	Odds of treatment success (cure or treatment complete) versus death or loss to followup					
	Univariate model			Multivariate model[1]		
	OR	95% CI	P	OR	95% CI	P
Age						
Adult	0.4	0.1–1.5	0.2	—	—	—
Pediatric	reference					
Gender						
Male	0.7	0.5–1.1	0.09	—	—	—
Female	reference					
CD4 Category						
≥50 cells/mm^3	2.0	1.3–3.1	<0.01	1.7	1.0–2.7	0.04
<50 cells/mm^3	reference			reference		
CD4 Category						
≥200 cells/mm^3	3.5	1.4–8.9	<0.01	2.4	0.9–6.3	0.09
<200 cells/mm^3	reference			reference		
Time Until ART						
≥2 weeks	1.9	1.0–3.5	0.05	1.3	0.6–2.7	0.5
<2 weeks	reference			reference		
Time Until ART						
≥2 months	2.0	1.3–3.3	<0.01	1.8	1.1–3.0	0.03
<2 months	reference			reference		
Clinic Year						
Year (2–5, 1 year increment)	1.2	1.0–1.5	0.02	1.3	1.1–1.6	<0.01
previous year	reference			reference		

Notes:
OR: odds ratio, CI: confidence interval.
[1]Adjusted for CD4 categories, time until ART categories, and clinic year.

of 85% cure and 90% treatment completion rates regardless of HIV status can only be achieved if loss to followup is aggressively and promptly addressed.

Proportions of patients lost to followup improved from 36% in year 1 to 12.5% in year 5. Interventions employed by the TB/HIV clinic felt to have been beneficial in improving loss to followup rates include (1) early and continuous patient education regarding both TB and HIV therapies by both clinic staff as well as persons living with HIV/AIDS; (2) effort to rapidly identify patients who miss appointments with the use of "tracers" who use village maps obtained with patient permission upon clinic enrollment; (3) use of treatment partners and directly observed therapy (DOT). However, additional qualitative research is required to understand why patients disengage with health care, and innovative solutions are urgently required.

In parallel with the declining loss to follow-up, treatment success rose and death rates fell over time. One may speculate that these improvements reflect an increased experience and competency in managing well-described complications of TB/HIV treatments including immune reconstitution syndrome, drug interactions, and comorbidities in addition to increased attention to adherence and earlier treatment for patients with lower CD4+ T-cell counts as newer guidelines appeared [4, 5]. Given the Kericho District Hospital served as a regional hospital and was the first to provide comprehensive HIV services in the region, outcomes observed may also reflect a referral bias, which became less pronounced over time as other facilities became available and decentralization of services occurred.

We found baseline CD4+ T-cell count highly associated with treatment success. Patients with lower CD4 counts most in need of ART were less likely to achieve treatment success compared to those with higher CD4 counts, although treatment success improved over time. These findings underscore challenges in implementing early ART in patients with advanced immunosuppression and achieving results seen in recent clinical trials [14–16]. Challenges of introducing ART early during TB intensive phase treatment in patients with advanced immunosuppression in resource-limited areas are profound, and differences in outcomes observed in clinical trial versus clinical care settings well described in the resource-rich settings are likely magnified in resource-constrained settings [31]. Barriers to early ART are both medical (e.g., pill burden, adherence, toxicities, immune reconstitution syndrome, and comorbidities) and logistical (e.g., frequent appointments requiring travel time and costs, time away from family and work). Clinical trials are better

resourced to address these medical and logistical issues, not the case in resource-constrained health care systems. Innovation will be critical in solving these challenges.

Hospitalization, while theoretically practical for profoundly immunosuppressed patients who are initiating both TB treatment and ART, may often not be possible or ideal. The lack of strong infection control programs within hospitals in sub-Saharan Africa resulting in nosocomial TB transmission raises a cautionary note [32]. The risk of hospitalization with poor infection control is particularly problematic in areas such as Kenya where TB drug susceptibility data is lacking. Congregation of the most vulnerable (i.e., those with CD4+ T-cell count <50 cells/mm^3) with those with unknown rates of multidrug or extensively drug resistant TB has led to devastating consequences in South African settings [32]. Hospitalization to overcome challenges and logistical issues of TB/HIV treatments must therefore be initiated with programmatic interventions that can reduce risk.

"Know your status" campaigns combined with aggressive community-based TB case finding campaigns will offer long-term solutions [4, 5]. The former will avoid discovery of the HIV patient presenting late into care with a low CD4+ T-cell count. The later will reduce transmission risk for all. Until those public health interventions can be broadly implemented, the integrated TB/HIV clinical service must look for solutions to translate clinical trials findings and recommendations into best practice scenarios.

Perhaps the most notable strength of the Kericho integrated TB/HIV clinic was the very early recognition of the need for integrating services (one patient, one clinic) and the institution of an integrated clinic into routine practice at a Ministry of Health facility. The most important limitation to recognize is the retrospective, uncontrolled nature of our analyses and those limitations (e.g., missing data) and biases (e.g., selection, referral, and report biases) inherent in all such secondary analyses. To that end, analyses were identified as exploratory and results are best considered hypotheses supporting or generating. While particular caution should be given to interpretations of pediatric data alone due to the low proportion of pediatric patients, we feel that a strength of the integrated TB/HIV clinic is the inclusion of pediatric patients.

5. Conclusions

TB/HIV patients with advanced HIV disease can be successfully managed in integrated TB/HIV MoH clinics in rural Kenya. Treatment outcomes improve with time, likely reflecting a variety of factors certainly including additional expertise that follows experience. Baseline CD4+ T-cell count is a driving force in predicting outcomes. Loss to followup remains a critical challenge in care delivery that demands attention and innovation. With high loss to followup occurring early in care and likely representing further deaths, the benefits and challenges of early ART initiation in TB treatment in nonclinical trial, resource-limited, rural settings are underscored. This "TB/HIV timeline" conundrum underscores the need for increased efforts for early detection of TB/HIV coinfected patients combined with innovative case holding interventions. An integrated TB/HIV clinic (one patient, one clinic) is a feasible goal in resource-constrained settings.

Disclaimer

The content of this publication is the sole responsibility of the authors and does not necessarily reflect the views or policies of the Kenya Medical Research Institute, the Kenya Ministry of Health, the US Military HIV Research Program or Department of Defense, or Brown University.

Acknowledgments

The authors wish to acknowledge the support of Dr. Betty Langat (Kericho District Hospital Medical Superintendent) for her vision and commitment to strive to provide the best care possible to all patients as well as the staff in the TB/HIV clinic and patients for whom they care. The authors also wish to recognize the roles of the Division of Leprosy, Tuberculosis, and Lung Diseases (DLTLD), formally the National Leprosy & Tuberculosis control Program (NLTP), and National AIDS and STI Control Programme (NASCOP) in their oversight and support of both TB and HIV as well as integrated TB/HIV programs.

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Hindawi Publishing Corporation
AIDS Research and Treatment
Volume 2012, Article ID 817506, 10 pages
doi:10.1155/2012/817506

Clinical Study

Barriers to Initiation of Pediatric HIV Treatment in Uganda: A Mixed-Method Study

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Received 12 October 2011; Revised 28 November 2011; Accepted 29 November 2011

Academic Editor: Anthony Harries

Although the advantages of early infant HIV diagnosis and treatment initiation are well established, children often present late to HIV programs in resource-limited settings. We aimed to assess factors related to the timing of treatment initiation among HIV-infected children attending three clinical sites in Uganda. Clinical and demographic determinants associated with early disease (WHO clinical stages 1-2) or late disease (stages 3-4) stage at presentation were assessed using multilevel logistic regression. Additionally, semistructured interviews with caregivers and health workers were conducted to qualitatively explore determinants of late disease stage at presentation. Of 306 children initiating first-line regimens, 72% presented late. Risk factors for late presentation were age below 2 years old (OR 2.83, $P = 0.014$), living without parents (OR 3.93, $P = 0.002$), unemployment of the caregiver (OR 4.26, $P = 0.001$), lack of perinatal HIV prophylaxis (OR 5.66, $P = 0.028$), and high transportation costs to the clinic (OR 2.51, $P = 0.072$). Forty-nine interviews were conducted, confirming the identified risk factors and additionally pointing to inconsistent referral from perinatal care, caregivers' unawareness of HIV symptoms, fear, and stigma as important barriers. The problem of late disease at presentation requires a multifactorial approach, addressing both health system and individual-level factors.

1. Introduction

Despite the effectiveness of antiretroviral prophylaxis for the prevention of mother-to-child transmission (PMTCT) of HIV, approximately 370,000 children were newly infected with HIV in 2009. An estimated 2.5 million children are currently infected with HIV worldwide, of whom 2.3 million reside in sub-Sahara Africa [1]. HIV infected infants have much higher rates of disease progression and mortality than adults or older children, even with a relatively high percentage of CD4 T lymphocytes [2, 3]. Without treatment, over 50% of HIV-infected children are estimated to die before the age of two [4].

Despite the increased mortality in young infants, children in resource-limited settings generally initiate ART at an older age and with advanced disease [4, 5]. In 2008, the CHER trial in South Africa demonstrated a 76% mortality reduction among infants in whom antiretroviral treatment (ART)

Table 1: Characteristics of the Joint Clinical Research Centre (JCRC) sites.

	Kampala	Fort Portal	Mbale
Location	National capital	District capital	District capital
Population[a]	1,659,600	47,100	91,800
Catchment area	Urban	Urban and rural	Urban and rural
HIV prevalence[b]	5–9.9%	5–9.9%	5–9.9%
Number of adults in care at JCRC (% of total)[c]	15306 (85.7)	5880 (87.3)	3027 (85.7)
Number of children in care at JCRC (% total)[c]	2553 (14.3)	858 (12.7)	506 (14.3)
Number of adults receiving ART at JCRC (% of adults in care)[c]	6096 (39.8)	2575 (43.8)	2505 (82.8)
Number of children receiving ART at JCRC (% of children in care)[c]	888 (34.8)	340 (39.6)	349 (69.0)

[a]Source: Uganda Bureau of Statistics (UBOS) 2011.
[b]Source: UNAIDS Epidemiological Factsheet Uganda 2009.
[c]Source: Monitoring and Evaluation records at JCRC, 2011.

was initiated before 12 weeks of age, regardless of HIV symptoms or immunodeficiency, compared with those deferring therapy [6]. Based on these important findings, the World Health Organization (WHO) guidelines currently recommend that all HIV-infected children under the age of two should initiate treatment [7]. The WHO estimates that only 32% of HIV-infected children in East Africa requiring ART are currently treated [8].

Although government policies and efforts by international donors seek to make antiretrovirals (ARVs) freely available to children through national ART programs, other factors are holding back further scale-up of pediatric ART in Africa. A wide array of such factors or barriers has been put forward in the literature including health system and personal level barriers [9, 10]. The development of new strategies to overcome these barriers is essential to reduce child morbidity and mortality, thereby contributing to the achievement of the Millennium Development Goal 4 [11]. However, limited structured research has been performed and there is little setting-specific insight into health care barriers.

The Joint Clinical Research Centre (JCRC) is a main provider of HIV care and treatment in Uganda. It was founded in 1990 as a strategic partnership with the Ministry of Health and Makerere University Medical School. The national JCRC network—consisting of more than 50 clinical sites—has over 20 years of experience with ART, from conducting clinical trials to nationwide roll-out programs since 2003. This study describes the characteristics of children initiating HIV care at three JCRC clinical sites based in Kampala, Fort Portal, and Mbale. Drawing on both quantitative and qualitative data sources, we aimed to identify the most important factors influencing the timing of pediatric ART initiation.

2. Methods

2.1. Population, Setting, and Study Design. We used an observational study design with a mixed methodology. This allowed us to triangulate findings from both participants and methods and generate a deeper understanding of the barriers to initiation of pediatric HIV care. The present study was performed as part of the Monitoring Antiretroviral Resistance in Children (MARCH) observational cohort, monitoring HIV-infected children (below 12 years old) initiating ART at three JCRC sites. The clinical sites in Kampala, Fort Portal, and Mbale are Regional Centers of Excellence and provide ART for both adult and pediatric patients. The Kampala site, based in the national capital, houses JCRC headquarters and mainly serves an urban population. The sites in Fort Portal and Mbale are located in district capitals, serving the Rwenzori region in Western Uganda and the entire Eastern region of Uganda, respectively [12]. People attending these two clinical sites come from both urban and rural areas (Table 1).

The sample size was calculated based on the MARCH study objective to monitor HIV drug resistance. This cross-sectional, observational substudy aims to identify the most important factors influencing the timing of pediatric ART initiation at the three sites. Potential participants were informed of the study and screened for eligibility by the study staff at each clinic. All children that initiated ART were included; previous use of ARVs for the purpose of therapy (i.e., ART or mono/duo therapy) was an exclusion criterion. Previous use of ARVs for PMTCT was allowed. The ethical committees of JCRC and the Academic Medical Center of the University of Amsterdam approved the study protocol. The parent(s)/guardian(s) of all eligible children provided written informed consent. Children above the age of eight who were aware of their HIV status provided written informed assent. Routine sociodemographic, clinical, and laboratory data were collected using electronic case report forms, which were aggregated in a web-based data system. Whenever possible, the health status and medication use of the mother were also captured.

2.2. Quantitative Methods. Group comparisons for categorical data were performed using the chi-square test and for continuous data using Student's t-test. Nutritional status was assessed by means of the WHO Child Growth Standards: WHO Anthro version 3.2.2 (age 0–5) and WHO Reference 2007 for height and weight (age 5–19) [13, 14]. Severe immunodeficiency was classified according to the WHO guidelines: CD4 cell percentage <25% or CD4 cell count <1500 cps/mm^3 below 12 months old; CD4 cell percentage <20% or CD4 cell count <750 cps/mm^3 between 12 and 35 months old; CD4 cell percentage <15% or CD4 cell count <350 cps/mm^3 above 35 months old [15]. WHO clinical staging was used to define

early disease stage or late disease stage at presentation: children in stage 1 (asymptomatic) or 2 (mild symptoms) were considered to have early disease stage, and children in stage 3 (advanced symptoms) or 4 (severe symptoms) were considered to have late disease stage [16].

Multivariate logistic regression analysis with random intercepts was used to examine risk factors for late disease stage at presentation, while accounting for clustering of observations within sites. Results are expressed as odds ratios (ORs) with 95% confidence intervals (CIs) and P values, with two-sided P values < 0.05 considered statistically significant. A sensitivity analysis was performed, excluding children with unknown source of HIV infection. All analyses were performed with Stata version 10 (StataCorp LP, TX, USA).

2.3. Qualitative Methods. Qualitative semistructured interviews with both JCRC health workers and caregivers of children attending JCRC clinical sites were conducted to explore participants' views of key findings from the quantitative results, such as the late (disease stage) presentation of children for ART. Interviews consisted of open-ended questions to explore perceived barriers to ART initiation. Topics covered in the interview were the referral system, quality of care, HIV testing and treatment protocols, characteristics of the caregiver, transport to the clinic, and pharmacy and laboratory facilities. Pilot interviews were held with three local physicians; questions were adapted if necessary to ensure that they were appropriate for all participants. A separate questionnaire aimed at health workers, testing ART guideline knowledge, was developed in collaboration with a pediatric infectious disease specialist.

Interviews were conducted by the first author (TSB) in July 2011 at the three clinical sites. All caregivers of children below 12 years of age were identified by the doctor or counselor during a regular follow-up visit. Data were collected until the saturation point [17] was reached; we are therefore confident that the findings presented are internally valid. All health workers—pediatricians, clinicians, nurses, counselors, and adherence officers—involved in pediatric HIV care at JCRC were interviewed at all 3 clinics, to maximize health worker representation and internal validity.

All interviews took place in private settings where other people could not hear the respondents' answers. For interviews with caregivers, a local trained counselor assisted with translation and/or interpretation of questions. Interviews were recorded and transcribed in English. Using the framework approach for qualitative analysis [17], key issues and themes emerging from the data were identified, and responses were compared and contrasted among the different groups of study participants. Findings from the qualitative study were interpreted using Andersen's Behavioral Model of Health Services Use [18–20].

3. Results

3.1. Quantitative Results

3.1.1. Participant Characteristics. Between January 2010 and May 2011, 310 children initiating first-line ART were enrolled in the MARCH study (92 from Kampala, 113 from Fort Portal, and 105 from Mbale). After excluding a protocol violation ($n = 1$) and children with missing data on eligibility criteria ($n = 3$), 306 participants were included in the analysis. The median age was 4.8 years and 50% ($n = 152$) were boys (Table 2). The reported source of HIV infection was mother-to-child transmission (MTCT) in 284 (93%) participants. In 22 (7%) children, the source of infection was unknown. HIV-status was known for 208 (68%) of their mothers, of whom 195 (94%) were HIV infected, 1 (0.5%) was uninfected, and 12 (6%) were unaware of their HIV status. Among the HIV infected mothers, 45% were on ART, 49% were not on ART, and for the remainder ART usage was unknown.

At first presentation, 72% of participants were in WHO clinical stage 3 or 4 (40% in Kampala, 82% in Fort Portal, and 90% in Mbale). Severe immunodeficiency according to a decreased CD4 cell count-for-age was present in 31% of children and in 51% when based on CD4 cell percentage-for-age. Severe immunodeficiency was more prevalent in Kampala compared to Fort Portal and Mbale (Table 2). There was a poor correlation between clinical staging and immunological status: of children in clinical stage 3 or 4, 47% also had severe immunodeficiency according to CD4 cell percentage-for-age.

In children below 5 years of age, the prevalence of weight-for-age z-score < -2 standard deviation (SD) was 43%; height-for-age z-score < -2 SD was found in 62% (Table 3). Of children in clinical stage 3 or 4, 70% had HIV-related malnutrition. The nutritional status of children did not differ significantly between the clinical sites.

3.1.2. Risk Factors for Late Disease Stage at Presentation: Quantitative Results. Compared to children with early disease stage at presentation, children with late disease stage at presentation were more likely to be younger, to have an unemployed caregiver, and to have higher transportation costs. They were less likely to be living with both parents or to have a history of uptake of PMTCT services (Table 4). Late disease stage at presentation was not associated with sex, the caregiver's health status or education, transportation time, time between HIV-positive diagnosis and ART initiation, or waiting time at the clinic. The sensitivity analysis, excluding 22 children in whom MTCT was not confirmed, yielded similar associations (data not shown).

3.2. Qualitative Results

3.2.1. Participant Characteristics. Interviews were conducted with 19 health workers and 30 caregivers. Twenty-one caregivers were HIV infected, six were uninfected, and three reported they were unaware of their status. Among the HIV-infected caregivers, sixteen caregivers were in care at JCRC and the remaining caregivers were in care at another clinic. Five health workers were specialized pediatricians; others were clinicians ($n = 2$), nurses ($n = 6$), counselors ($n = 4$), or adherence officers ($n = 2$) with pediatric training. The caregivers included those of children participating in the MARCH study and those of other clinic attendants aged

Table 2: Clinical and demographic characteristics of the "Monitoring of Antiretroviral Therapy in Children" cohort participants.

		Overall	Study site			P value
		n = 306 (100)	Kampala n = 91 (29.7)	Fort Portal n = 112 (36.6)	Mbale n = 103 (33.7)	
Sex	Male	152 (49.8)	43 (47.3)	55 (49.1)	54 (52.9)	0.719
Age, median years (IQR)		4.8 (2.2–8.6)	4.0 (1.5–8.5)	4.2 (1.9–8.5)	5.8 (3.0–8.7)	0.127
Age groups	<2 years old	76 (24.8)	32 (35.2)	29 (25.9)	15 (14.6)	0.005
	2–5 years old	84 (27.5)	18 (19.8)	37 (33.0)	29 (28.2)	
	5–12 years old	146 (47.7)	41 (45.1)	46 (41.1)	59 (57.3)	
Age at (first) confirmed HIV+ test	Median (IQR)	3.7 (1.6–6.8)	3.0 (1.3–7.2)	3.3 (1.1–6.8)	4.5 (2.7–6.8)	0.264
WHO clinical stage	Stages 3 and 4	221 (72.2)	36 (39.6)	92 (82.1)	93 (90.3)	<0.001
HIV-TB coinfection	Pulmonary tuberculosis	31 (10.1)	18 (19.8)	6 (5.4)	7 (6.8)	0.001
Severe immunodeficiency[a]	CD4 count-for-age	67 (31.0)	36 (40.0)	9 (21.4)	22 (26.2)	0.047
	CD4 %-for-age	102 (51.3)	57 (63.3)	18 (42.9)	27 (40.3)	0.008
Viral load, median $\log_{10}$ cps/mL (IQR)[c]		5.0 (4.4–5.5)	5.2 (4.7–5.6)	5.1 (4.2–5.5)	4.7 (4.1–5.3)	0.001
Main reason for ART initiation[d]	HIV diagnosis <24 months	30 (9.8)	20 (22.0)	9 (8.0)	1 (1.0)	<0.001
	Immunological status	102 (33.3)	55 (61.4)	25 (22.3)	22 (21.4)	
	WHO clinical stage	174 (56.9)	16 (17.6)	78 (69.6)	80 (77.7)	
Time between HIV test and ART initiation, median days (IQR)	<2 years old	43 (19–85)	40 (18–66)	48 (23–103)	43 (26–86)	0.299
	2–5 years old	97 (26–400)	117 (34–309)	197 (29–546)	64 (15–180)	0.302
	5–12 years old	258 (29–802)	242 (28–634)	296 (35–757)	216 (21–848)	0.474
PMTCT exposed	Yes	14 (4.6)	11 (12.1)	3 (2.7)	—	<0.001
Drugs for PMTCT	Single dose NVP	9 (2.9)	6 (6.6)	3 (2.7)	—	0.025
	NVP	4 (1.3)	4 (4.4)	—	—	0.008
	AZT	2 (0.7)	2 (2.2)	—	—	0.093
	Unknown	1 (0.3)	1 (1.1)	—	—	0.306
Breastfeeding	Yes	24 (7.9)	10 (11.1)	12 (10.7)	2 (1.9)	0.023
"Is there enough food in the household?"	Yes	300 (98.0)	87 (95.6)	110 (98.2)	103 (100.0)	0.087

Data are presented as n (%) unless otherwise indicated.
[a]Severe immunodeficiency, defined as CD4 percentage < 25% or CD4 count < 1500 cps/mm^3 below 12 months old, CD4 percentage < 20% or CD4 count < 750 cps/mm^3 between 12 and 35 months old, and CD4 percentage <15% or CD4 count < 350 cps/mm^3 above 35 months old.
[b]CD4 count based on n = 218; CD4 percentage based on n = 201.
[c]Viral load based on n = 184.
[d]Main reason for initiation as indicated by clinician.

0–12 years old. All but four adults accompanying a child to the clinic were the primary caregivers. The caregivers were mostly self-employed; six were unemployed.

3.2.2. Health System Factors: Resources and Organization. Kampala is the only site with a separate pediatric outpatient clinic. All sites have access to local laboratory facilities (including HIV-DNA PCR testing for infants <18 months of age), first- and second-line ARVs, and ready-to-use therapeutic food products (i.e., *Plumpy'nut*). According to the physician respondents, the clinic's capital and labor resources are sufficient to take care of all children attending the clinic. Occasional stock-outs of specific drugs or fixed-dose combinations were reported, in which case drugs are borrowed from other clinics or doctors prescribe different formulations to reconstruct the same regimen. When pharmacy stocks are low, ARV prescriptions are given for one month at a time rather than the regular three months.

All doctors were aware that ART should be initiated in infants below the age of two years, irrespective of CD4 count or clinical condition. The general consensus among health workers was that enough qualified personnel are available at the clinic, although the workload is high. There was often insufficient time for thorough counseling, which can result in longer waiting times for patients and caregivers attending the clinic. Health workers evaluated the pediatric HIV care delivered at JCRC as better in comparison to other clinics. However, health workers also noted that it is necessary to spread information about the clinic in the community.

> *When we sit here and wait for people to come, we can wait for a long time. We have to go out there and tell about the available services so they can choose to come.*
> Female counselor, Mbale.

Table 3: Nutritional status of the "Monitoring of Antiretroviral Therapy in Children" cohort participants at presentation.

		$n = 306$
Underweight (WAZ < −2 SD)	<5 years old	42.7 (34.6–50.7)
	5–12 years old	24.5 (15.2–33.7)
Severe underweight (WAZ < −3 SD)	<5 years old	26.1 (18.9–33.3)
	5–12 years old	12.8 (5.5–20.0)
Stunting (HAZ < −2 SD)	<5 years old	62.0 (53.9–70.1)
	5–12 years old	39.0 (30.4–47.5)
Severe stunting (HAZ < −3 SD)	<5 years old	40.0 (31.8–48.2)
	5–12 years old	18.4 (11.5–25.3)
Wasting (WHZ < −2 SD)	<5 years old	21.7 (14.9–28.4)
	5–12 years old	NA
Severe wasting (WHZ < −3 SD)	<5 years old	7.0 (2.7–11.3)
	5–12 years old	NA
BMI-for-age z-score (< −2 SD)	<5 years old	16.3 (10.2–22.3)
	5–12 years old	8.6 (3.6–13.7)
Midupper arm circumference n (%)[a]	≤13.5 cm	55 (37.9)

Data are presented as percentage with 95% confidence interval (CI) unless otherwise indicated. No significant differences were found between clinical sites. Reference data used are WHO Anthro version 3.2.2, January 2011 for age 0–5 and Reference 2007 for age 5–19 [13, 14, 21]. 33 z-scores were excluded from analysis because of biological implausibility (WAZ $n = 9$, HAZ $n = 19$, WHZ $n = 3$, and BMI-for-age $n = 2$).

[a]Midupper arm circumference only applicable for children 1–5 years old ($n = 148$). WAZ: weight-for-age z-score, HAZ: height-for-age z-score, WHZ: weight-for-height z-score, and BMI: body mass index (in kg/m^2).

Health workers reported that many children are referred to JCRC after visiting private clinics, local hospitals, and sometimes traditional healers or herbalists for recurrent infections. There are no antenatal care (ANC) services at JCRC, and therefore only HIV-infected pregnant women who are already attending the JCRC adult clinic are immediately linked with pediatric care. Referral from external ANC clinics is limited. In Fort Portal, the regional general hospital offering ANC is adjacent to the JCRC clinic, which facilitates referral of HIV-infected pregnant women.

Family-centered care is not routinely offered at JCRC, but health workers encourage parents to bring their other children and family members. Disclosure issues play a role as health workers construct a family tree of the HIV status of the family members and ask to bring in any children with unknown status. When children and caregivers come for HIV testing, they receive a ticket with a number to match their test results. By using this method, people are assured of anonymous testing, thereby reducing fear of disclosure. Health workers' recommendations for improving access to care are listed in the Box 1 .

3.2.3. Population Factors: Living Situation and Transport. Both health workers and caregivers reported that children without parents are living under poorer conditions and present later in care. When the mother is receiving HIV care, the child is more likely to present early. The effect of living in an institution (e.g., orphanage) can go both ways. Some institutions bring their children early because they recognize the importance of HIV testing and can provide transport; others have fewer resources and do not prioritize HIV testing. Health workers pointed out that caregivers' financial constraints and lack of employment are important barriers to access health care. More highly educated caregivers seem to visit earlier, but taking time off work can be an obstacle. Some caregivers fear to disclose to their employers, and thus have a hard time justifying their absence to attend clinic visits. The unemployed have more time, but lack the money to visit the clinical sites.

> *When the caregiver is employed, they have the advantage of money for transport, but they can be too busy at work to come. For the unemployed it is difficult to pay for transport.*
> Female counselor, Fort Portal.

Transportation costs are prohibitively high when considered in comparison to the need for food. Furthermore, having to travel long distances to reach the clinic makes it difficult for people to leave and return home within one day, especially when no or limited public transport is available. This problem was more frequently reported in Fort Portal and Mbale compared to Kampala.

> *To some people transportation costs matter. For the ones living in the villages; they do not have the income, but they do have time.*
> HIV-positive mother of a five-year-old boy, Fort Portal.
>
> *My daughter lived in the villages and it was too far for her. That is why I am taking care of her daughter now. The mother is dead now. Just being a housewife, raising money for transport is hard.*
> HIV-negative grandmother of a ten-year-old girl, Mbale.

3.2.4. Population Factors: Knowledge, Stigma, and Fear. According to health workers, many women are delivered by traditional birth attendants and are not tested for HIV during pregnancy. This increases the likelihood that a child's infection remains unnoticed; the child may only be tested after becoming clinically ill or after the loss of one or both parents. Caregivers have often visited other clinics for the child's frequent infections before enrolling at the JCRC clinic. Health workers described that health-seeking behavior among caregivers can be delayed due to lack of knowledge or denial of HIV symptoms. Caregivers also reported that HIV is something people do not think about or do not want to think about. They are often not ready to disclose their or their child's HIV status to others. Health workers recommended involving men more actively in ANC, in order to improve the uptake of PMTCT measures and enrolment of HIV-exposed children in pediatric HIV care.

> *Men need more involvement, include men to PMTCT, now only very few come. They are the biggest decision makers in the home. This would strengthen adherence too.*
> Female pediatric counselor, Fort Portal.

Table 4: Risk factors for late disease stage at presentation (WHO stage 3 or 4).

		Univariate analysis			Multivariate analysis		
		OR	95% CI	*P* value	OR	95% CI	*P* value
Sex	Female	1					
	Male	0.99	0.56–1.74	0.963			
Age group	5–12 years old	1			1		
	2–5 years old	1.20	0.60–2.41	0.612	1.90	0.85–4.22	0.117
	0–2 years old	1.45	0.72–2.92	0.303	2.83	1.23–6.50	0.014
Current living situation	With both parents	1			1		
	With one parent	1.39	0.71–2.73	0.340	2.05	0.96–4.35	0.062
	With siblings/relatives/other caregiver/in institution	2.46	1.14–5.31	0.021	3.93	1.65–9.38	0.002
Primary caregiver	Mother	1					
	Father	0.80	0.22–2.94	0.738			
	Grandparent	3.07	1.06–8.92	0.039			
	Other relative/friend	0.92	0.45–1.91	0.826			
	Institution	3.09	0.54–17.64	0.203			
Mother's health status	Healthy	1					
	Sick	1.66	0.49–5.60	0.416			
	Deceased	1.59	0.71–3.58	0.260			
	Unknown	1.10	0.28–4.24	0.894			
Father's health status	Healthy	1					
	Sick	1.27	0.43–3.74	0.660			
	Deceased	1.78	0.82–3.85	0.142			
	Unknown	2.17	0.81–5.81	0.122			
Highest level of education of the caregiver	Illiterate	1					
	Literate/primary school	0.77	0.32–1.83	0.550			
	Secondary school	0.55	0.21–1.44	0.223			
	Postsecondary school	0.49	0.17–1.45	0.197			
Occupation of the caregiver	Wage-employed	1			1		
	Self-employed	1.82	0.78–4.26	0.166	2.50	1.00–6.28	0.051
	None/at home/student	3.24	1.43–7.34	0.005	4.26	1.75–10.35	0.001
PMTCT experienced	Yes	1			1		
	No	5.07	1.24–20.79	0.024	5.66	1.21–26.51	0.028
Time between HIV+ diagnosis and ART initiation	0–31 days	1					
	>30 days	0.93	0.50–1.73	0.818			
Transportation time	<1 hour	1					
	1 hour or more	0.85	0.45–1.58	0.606			
Transportation costs	1st quartile (UGX[a] 500–1500)	1			1		
	2nd quartile (UGX 1500–3000)	1.07	0.51–2.23	0.857	0.96	0.43–2.14	0.915
	3rd quartile (UGX 3000–4000)	0.89	0.34–2.33	0.818	0.85	0.30–2.38	0.756
	4th quartile (UGX 4000–15000)	2.09	0.85–5.15	0.108	2.51	0.92–6.85	0.072
Waiting time at clinic	<2 hours	1					
	2 hours or more	0.83	0.35–1.98	0.676			

Multilevel univariate and multivariate logistic regression analysis with random intercepts to examine factors associated with late disease at presentation (WHO stage 3 or 4), accounting for clustering of observations within sites.

[a]UGX 500 ≈ $0.18; UGX: Uganda Shilling.

(i) Improve antenatal care attendance and linkage to ART clinics.
(ii) Involve men during antenatal care.
(iii) Increase awareness of care and treatment services.
(iv) Improve community outreach for HIV testing.
(v) Facilitate transport to clinics.

Box 1: Health workers' recommendations to improve timely access to ART for children.

Health workers explained that sensitization campaigns by means of radio and advertisements were helpful to spread information about HIV prevention and care and decrease stigma. At the same time, they acknowledge that stigma experienced by caregivers remains an important barrier to care.

> *HIV is not a taboo anymore. There used to be a lot of stigma, in the '90 and early '00. There's been a lot of sensitization for HIV. You see more and more people test and seek care.*
> Male doctor, Mbale.
>
> *HIV is not a taboo anymore, but there's stigma. People do not want to associate with HIV. They fear to come to the clinic because someone might see them, which affects adherence. Stigma also delays the start of ART.*
> Female counselor, Fort Portal.

Fear was a major factor reported by caregivers as a barrier to visiting ART clinics. People fear to be seen at the clinic and fear that other people get to learn about their HIV status. Fear of disclosure appeared to be more common in the smaller towns compared to the city, as evidenced by the responses from both health workers and caregivers.

> *I never got married and feared to tell my mother. She is harsh and will tell everybody to stigmatize me. Nobody knows about my and my daughter's HIV status. They discriminate you, even at work.*
> HIV-positive mother of a three-year-old girl, Mbale.

4. Discussion

This mixed-method study examined factors influencing the timing of ART initiation among children attending HIV clinics in Uganda. Even though ART is now free and widely available in Uganda, 72% of the children in this study presented with advanced HIV disease at their initial visit. The main risk factors for this late disease stage at presentation identified in our study—from both quantitative and qualitative data—included lack of HIV-specific perinatal care, living without parents, financial constraints of the caregiver, caregivers' unawareness of HIV symptoms, stigma, and fear. Our study adds insight into the challenges of identifying HIV-infected infants and children sooner and recruiting them into care. In the setting of the JCRC network of HIV treatment sites in Uganda, linkage to the ANC systems and psychosocial support are recognized as priorities to improve pediatric access. Even though JCRC sites are at the high-end with respect to resources, infrastructure, staff, and available diagnostics, late disease stage at presentation was a frequent and important problem among children initiating ART. The barriers identified in our study are therefore likely of national relevance and applicable to other HIV clinics in Uganda.

4.1. Health System Factors. The linkage between ANC and pediatric ART clinics was found to be inconsistent. This lack of coordination across services is similar to previous studies investigating barriers to timely pediatric ART initiation in resource-limited settings [22, 23]. Failure to diagnose HIV in pregnancy, to provide PMTCT services, and to followup the HIV-exposed infant represent missed chances for prevention of HIV transmission. As previous research has also shown, integrating antenatal services, PMTCT, early infant diagnosis, and pediatric HIV care greatly improves outcomes for HIV-infected infants in resource-limited settings [24–28].

As ANC is not performed at JCRC, this challenge could be addressed by closer collaboration between JCRC Centers of Excellence and outside ANC providers. HIV-infected women should be routinely referred to have their infants tested after delivery and actively followedup to ensure they receive the results. Health workers at JCRC have suggested collaborating with traditional birth attendants to reach women who do not visit regular ANC service centers. Additionally, improving male involvement in ANC was proposed as men could be decision-makers in seeking care for the child. Studies have shown that male attendance in ANC is a cost-effective strategy to increase PMTCT uptake and is associated with reduced MTCT and infant mortality [29–31].

We examined the time between HIV test and ART initiation and found that it was increased in older children. It is possible that the first HIV-positive test was performed outside of JCRC, with a subsequent referral delay for ART initiation. Secondly, children might have been tested at JCRC in early disease stage and started ART later when immunological or WHO stage criteria were met. This is in line with the high numbers of children in care at JCRC in whom ART is not yet initiated (Table 1). Regression analysis showed that lag time between the first HIV diagnosis and ART initiation was not a significant risk factor for late disease stage at presentation.

Although the clinics in Fort Portal and Mbale have similar resources as the Kampala clinic, the latter was found to have a higher percentage of early disease stage presenters. The clinic urban setting likely contributes to improved accessibility, and stigma was reported less frequently in

the qualitative study compared to the other sites. Health workers at all JCRC clinics were well trained and consistently adhered to current pediatric HIV guidelines. The clinics could give more attention to community outreach and active case finding in order to increase parents' awareness and to identify HIV-infected children before the onset of symptoms. Community outreach could be targeted specifically at the most vulnerable children, such as those in orphanages. Alternatively, outreach could be performed by screening infants at immunization clinics [32].

Rates of underweight and stunted children were alarmingly high, which concurs with previous reports among HIV-infected children in Uganda [33, 34]. Malnutrition was a common clinical stage 3 or 4 defining symptom, and therefore timely referral to HIV care is perhaps the most critical nutritional intervention. JCRC routinely provides therapeutic foods. Additionally, nutritional education for caregivers and sufficient supply of micronutrients are important to decrease rates of underweight and stunting [35].

4.2. Population Factors. When examining individual-level barriers to care, the child's living situation was found to be an important determinant. This corresponds with earlier studies in which orphans were more likely to initiate ART at an older age with lower baseline CD4 levels and more advanced WHO staging [36, 37]. In addition, unemployment of the caregiver and high travel costs were risk factors for late disease stage at presentation in quantitative analysis. The qualitative interviews in our study confirmed these socioeconomic factors as important barriers, especially in the smaller towns. Prior studies from Uganda and other resource-limited settings have reported similar findings, suggesting that interventions such as community outreach, transportation refunds, home-based ART distribution, or outreach clinics in orphanages might be useful in overcoming these issues [38–42].

Other personal factors observed in the interviews were caregivers' unawareness of HIV symptoms, stigma, and fear, confirming that these personal beliefs discourage people from seeking ART [10, 22]. In addition to lack of knowledge of HIV symptoms, unawareness of free HIV services also impedes timely presentation [43]. Media campaigns designed to inform people about ANC, HIV testing, and free ART for children could be improved at relatively low cost [44, 45].

One of this study's strengths was the mixedmethod approach by which quantitative data could be contextualized and confirmed by qualitative study. Methodological triangulation increased the credibility of the findings and enhanced comprehensiveness of the study, creating a deeper understanding of the barriers to initiation of pediatric HIV care [46–49]. A limitation of the study is the cross-sectional design, making it difficult to establish causal relations in the quantitative analysis. In the qualitative study, there is a risk of socially desirable answers during the interviews.

Finally, different types of selection bias may have affected our study. First, late disease stage at presentation could have been overestimated as many children were referred to JCRC after visiting other clinics; the disease stage at presentation in the referring clinics was not part of our study. Second, our study did not take into account the HIV-infected children that died before reaching the clinic. As the median age was over 4 years old in our cohort, this population consisted of mostly medium and slow progressors. Younger children appeared to be a risk factor for late disease stage at presentation but this finding is subject to survival bias and should be interpreted accordingly. Additionally, other risk factors identified might not apply to children with fast disease progression. The specific barriers experienced by these children and their caregivers should be evaluated in longitudinal studies of HIV-exposed children.

In conclusion, although first-line ART has become widely available for HIV-infected children in Uganda, this alone does not ensure timely access. The problem of late disease stage at presentation requires a multifactorial approach, prioritizing community and orphanage outreach programs, and linkage of ANC systems to ART providers. Knowledge of these factors and their potential solutions is important in order to help health workers and ART program planners to create interventions to reach HIV-infected infants as early as possible and avoid preventable child mortality.

Authors' Contributors

C. Kityo, P. Mugyenyi and V. Musiime established the MARCH cohort and supervised data collection. K. C. E. Sigaloff and J. Kayiwa contributed to implementation. T. F. R. Wit, C. Kityo, K. C. E. Sigaloff, S. P. Geelen, J. Calis and T. S. Boender conceived the substudy. T. S. Boender analyzed the data and wrote the first draft of the manuscript with assistance from R. L. Hamers and K. C. E. Sigaloff. C. Kityo, V. Musiime, J. Calis, T. F. R. Wit and S. P. Geelen critically reviewed the paper. All authors contributed to subsequent drafts and reviewed and approved the final manuscript.

Conflict of Interests

There is no conflict of interests to declare.

Acknowledgments

The authors are grateful to all study participants and their caregivers, doctors and nurses, and support staff at JCRC and PharmAccess Foundation. At JCRC, they specifically thank Annet Nandudu, James Nkalubo, Isaac Egau, and Lincoln Mugarura from Kampala; Mary Kiconco, Michael Owor, Christine Matama, and Florence Nambaziira from Fort Portal; Mary Abwola, Fred Senono, Ronald Namisi, and Sylivia Nakusi from Mbale. At PharmAccess, the authors thank Cees Hesp for database design. Additionally, they thank Dr. Maiza Campos Ponce for critical review and support, Dr. Colleen M. Doak for assistance in interpreting nutritional status of the participants, and Dr. Sally Theobald for the review of the qualitative methods. The MARCH study is an initiative of JCRC and PharmAccess Foundation and funded by the European & Developing Countries Clinical Trials Partnership (EDCTP). The first author would like to thank Kees and Anneke Storm for funding the qualitative

data collection. The funders had no role in the study design, data collection, data analysis, data interpretation, decision to publish, or writing of the paper. The content of this paper is solely the responsibility of the authors and does not necessarily represent the official views of any of the institutions mentioned above.

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