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Long-Term Antiretroviral Treatment Outcomes in Seven Countries in the Caribbean

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Abstract

Objectives—To report long-term HIV treatment outcomes in 7 Caribbean countries.

Design—Observational cohort study.

Methods—We report outcomes for all antiretroviral therapy (ART) naïve adult patients enrolled on ART from program inception until study closing for cohorts in Barbados, the Dominican

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Please note: We feel that an extended author list should be justified because this study reports on long-term HIV treatment outcomes from 7 countries.

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Republic, Haiti, Jamaica, Martinique, Trinidad, and Puerto Rico. Incidence and predictors of mortality were analyzed by time-to-event approaches.

Results—8,203 patients started ART from 1998 to 2008. Median follow-up time was 31 months (interquartile range: 14 to 50 months). Mortality was 13% overall: 6% in Martinique, 8% in Jamaica, 11% in Trinidad, 13% in Haiti, 15% in the Dominican Republic, 15% in Barbados, and 24% in Puerto Rico. Mortality was associated with male gender (HR 1.58; 95% CI: 1.33 – 1.87), body weight (HR 0.85 per 10 pounds; 95% CI: 0.82 – 0.89), hemoglobin (HR 0.84 per g/dl; 95% CI: 0.80 – 0.88), CD4 cell count (0.90 per 50 CD4 cells; 95% CI: 0.86 – 0.93), **concurrent** TB (HR 1.58; 95% CI: 1.25 – 2.01) and age (HR 1.19 per 10 years; 95% CI: 1.11 – 1.28). After controlling for these variables, mortality in Martinique, Jamaica, Trinidad and Haiti was not significantly different. A total of 75% of patients remained alive and in-care at the end of the study period.

Conclusions—Long-term mortality rates vary widely across the Caribbean. Much of the difference can be explained by disease severity at ART initiation, nutritional status, and concurrent TB. Earlier ART initiation will be critical to improve outcomes.

Keywords

HIV/AIDS; HIV; antiretroviral therapy; tuberculosis; low and middle-income countries; Caribbean

INTRODUCTION

The Caribbean is the region most heavily affected by HIV outside of sub-Saharan Africa, with an overall adult HIV prevalence of 1.0%, and an estimated 240,000 patients living with HIV [1]. An estimated 12,000 persons die annually of AIDS-related illnesses [1], and AIDS is the leading cause of death in the Caribbean among men and women from 20 to 59 years of age [2]. As in the United States, the predominant HIV-1 subtype in the Caribbean is subtype B [3]. Due to its close proximity, the HIV epidemic in the Caribbean is also a major public health issue for the United States. Twenty-seven percent of new HIV diagnoses in New York City are among foreign-born persons [4]. The Caribbean accounts for more HIV diagnoses in New York City than any other region (38%), and if Puerto Rico is added, the region accounts for 56% of all new HIV diagnoses [4]. With frequent travel and migration between the Caribbean and the United States and Europe, the importance of HIV/AIDS in the Caribbean transcends regional boundaries.

With the global expansion of antiretroviral treatment (ART), an increasing number of studies have documented positive short-term outcomes of ART for early cohorts of patients in low and middle-income countries, including high adherence rates and favorable virological, immunological, and clinical responses [5–10]. In recent years, data on long-term outcomes of ART programs have begun to emerge, demonstrating that earlier successes can be maintained even as programs undergo rapid scale-up [11–30]. However, mortality rates in the first 6 months of ART are disproportionately higher in low and middle-income countries, compared to higher-income countries [8, 9, 18, 26], and there have been reports of high rates of program attrition after two years on therapy [31–33].

Published data on long-term HIV treatment outcomes in the Caribbean are limited [18, 34, 35], though ART coverage in the region has increased dramatically in the last decade. By the end of 2009, 48% of patients with a CD4 cell count < 350 cells/mm^3 in the region were receiving ART, compared to 1% of those eligible in 2004 [36, 37]. Countries in the Caribbean region vary widely in economic status, health infrastructure, culture, and

language. Long-term data on HIV treatment outcomes across the region are critically needed.

In 2006, the Trans-Caribbean HIV/AIDS Research Initiative (TCHARI) was launched to develop a cohesive HIV/AIDS research agenda that would address the specific issues relating to HIV/AIDS in the Caribbean. This is the first study to be conducted in the TCHARI network and includes data from seven countries: Barbados, Dominican Republic, Haiti, Jamaica, Martinique (France), Puerto Rico (United States), and Trinidad. This is the first multi-cohort study to present regional outcomes for ART across countries in the Caribbean, as well as the first regional outcomes paper on health in the Caribbean.

METHODS

Participants and Settings

TCHARI is a collaboration among several of the largest HIV/AIDS clinical and research centers in the Caribbean and the National Institutes of Health Office of AIDS Research. The TCHARI sites include: 1) Ladymeade Reference Unit, St. Michael's, Barbados; 2) Comprehensive Care Units of Centro Sanitario de Santo Domingo and Hospital Luis E. Aybar, Santo Domingo, Dominican Republic; 3) Haitian Study Group for Kaposi's Sarcoma and Opportunistic Infections (GHESKIO), Port-au-Prince, Haiti; 4) The University Hospital Centre for HIV/AIDS Research, Education and Services and the Comprehensive Health Centre, Kingston, Jamaica; 5) Infectious Diseases Unit/Inserm CIE 802, Centre Hospitalier Universitaire, Fort-de-France, Martinique; 6) the Medical Research Centre, Port of Spain, Trinidad and Tobago; and 7) Retrovirus Research Center of the Universidad Central del Caribe, Ramon Ruiz Arnau University Hospital, Bayamon, Puerto Rico. Institutional Review Board approval was obtained by all local and partner academic sites.

This study includes all ART-naive HIV-infected patients of age 13 years or older who were consecutively enrolled on ART at these 7 sites during the study period, beginning at program inception at each site. The study dates vary among sites, but all patients initiated ART between January 1, 1998 and December 31, 2008. Table 1 describes the country and program characteristics of sites participating in TCHARI. Across the Caribbean region, HIV-infected patients consistently tend to be members of marginalized populations that experience economic disparity.

Data Collection and Measurement

At each site, de-identified data were entered into a Microsoft Access database (Microsoft, Redmond, Washington) and sent to GHESKIO, where they were checked for errors, inconsistencies, and missing data. These were compiled into queries which were addressed by each site. Baseline weight, hemoglobin, and CD4 cell count were defined as the measurement closest to the date of ART initiation, but not more than 2 weeks after ART initiation. ART was defined as a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI), or three NRTIs. Clinical stage of disease was defined according to World Health Organization guidelines [38]. Tuberculosis (TB) and ART co-treatment was defined as any overlap of treatment with these two therapies.

Outcomes

The primary outcomes were all-cause mortality and retention in care over the duration of the study. Time was measured from the date of ART initiation to the date of death, loss to follow-up (LTFU), or closing date of the study. Death was ascertained through several strategies. In Barbados, deaths were determined by chart review. In Haiti, deaths were

ascertained by chart review, phone calls to next of kin, and home visits. In Jamaica and Martinique, deaths were ascertained by chart review, ART treatment database, phone calls to next of kin, and a centralized death registry. In Trinidad, Dominican Republic and Puerto Rico, deaths were ascertained by reviewing clinical and hospital records, tracking patients that were LTFU, taking reports from family members, and reviewing death certificates, as necessary. The study closed on May 3, 2008 in Puerto Rico, February 28, 2009 in Barbados, May 15, 2009 in the Dominican Republic, June 18, 2009 in Trinidad, December 15, 2009 in Martinique, and December 31, 2009 in Haiti and Jamaica. Patients were considered alive and in-care if they were not known to be dead and had at least one visit within 6 months of the closing date of the database. The data were analyzed by an intention-to-treat approach.

Statistical Analysis

Data were entered into the Access database described above. All analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC). Kaplan-Meier survival analyses were used to estimate the time from initiation of ART to death, and results were plotted at the country cohort level. Patients who were transferred to other clinics were censored at their last visit. Cox proportional-hazards models were used to assess the relationship between demographic and clinical variables, treatment site, and time to death.

We conducted univariate and multivariate analyses using the following variables: year of ART initiation, ART regimen, and country as categorical variables; gender, history of intravenous drug use, and TB and ART co-treatment as binary variables; and age, baseline weight, hemoglobin, and CD4 cell count as continuous variables. WHO stage, income, and education were not included in the analyses, because they were not collected at all sites. We analyzed all variables with Cox proportional hazards models to determine predictors of time to death. In the multivariate model, we included all variables significant at the 0.05 level in univariate analyses. No sets of variables in the reported model showed signs of unacceptable colinearity.

We performed sensitivity analyses to assess the effect of LTFU on mortality rates. We reviewed the literature from tracking studies among ART patients presumed LTFU in low and middle-income countries. We considered a scenario with the lowest and highest mortality rates (27% and 87%, respectively) among patients presumed LTFU in the published literature [39, 40]. We also used the combined mortality from the meta-analysis of 17 studies reported by Brinkhof et al (combined mortality of 40% among patients presumed LTFU) [41]. Finally we considered the scenario where all patients that were LTFU with a CD4 cell count < 50 cells/mm^3 and < 100 cells/mm^3 had died.

RESULTS

A total of 8,203 ART-naive HIV-infected patients of age 13 years or older that were consecutively enrolled on ART were included in this study: 560 (7%) from Barbados, 1207 (15%) from the Dominican Republic, 4717 (58%) from Haiti, 476 (6%) from Jamaica, 325 (4%) from Martinique, 725 (9%) from Trinidad and 193 (2%) from Puerto Rico. Patient characteristics are summarized in Table 2 (note that percentages were computed using the number of patients with non-missing values). Across all countries, 51% were female and the median age at ART initiation was 38 years. Education was measured in all sites except Jamaica; overall 42% of patients attended no school or primary school only. Income was measured in Barbados, Haiti, Trinidad, and Puerto Rico, and 57% of patients in these cohorts lived on less than $US 1 per day.

Median baseline weight varied across countries, from a low of 111 pounds for women and 125 for men in Haiti, to highs of 139 pounds for women in Martinique and 152 for men in

Puerto Rico. Baseline hemoglobin values were lowest in Haiti and Trinidad (10.0 g/dl for women and 11.0 g/dl for men) and highest in Puerto Rico (11.8 g/dl for women and 13.2 g/dl for men). Intravenous drug use was common only in Puerto Rico (53%), and 534 of 565 cases of TB and ART co-treatment (95%) occurred in Haiti and the Dominican Republic. Among the 565 patients with concurrent TB and ART treatment, 266 (47%) were started on TB treatment prior to or at the same time as ART, 177 (31%) were started on TB treatment within the first 6 months after ART initiation, and 122 (22%) were started on TB treatment after at least 6 months of ART.

Seventy-six percent of patients initiated ART with a CD4 cell count < 200 cells/mm^3: 83% in Trinidad, 81% in the Dominican Republic, 78% in Haiti, 70% in Jamaica, 67% in Barbados, 51% in Martinique, and 46% in Puerto Rico. The median baseline CD4 cell count for the combined overall cohort was 118 cells/mm^3. Baseline CD4 cell count increased only slightly with expansion of access to ART, from 114 cells/mm^3 for those initiating ART in 2003–2004, to 137 cells/mm^3 for those initiating ART in 2007–2008 (see Web Appendix). Ninety percent of patients overall (n=7384) were treated with a first-line regimen containing a NNRTI; of these 4382 (59%) were treated with an efavirenz-based regimen and 3002 (41%) were treated with a nevirapine-based regimen. Martinique and Puerto Rico were the exceptions, treating over 80% of patients with a PI in the first-line regimen. Among the 271 patients in Martinique that received a PI-based regimen, 158 (58%) were treated with lopinavir/ritonavir, 79 (29%) with atazanavir, 23 (8%) with fosamprenavir, 8 (3%) with indinavir, and 3 (1%) with nelfinavir. In contrast, of 156 patients treated with a PI-based regimen in PR, 113 (72%) were treated with nelfinavir, 27 (17%) were treated with indinavir, 9 (6%) were treated with atazanavir, 6 (4%) were treated with other PI's, and only one patient was treated with lopinavir/ritonavir.

The median follow-up time across sites was 31 months (interquartile range [IQR]: 14 to 50 months), ranging from 20 months (IQR: 9 to 33 months) in the Dominican Republic to 52 months (IQR: 33 to 70 months) in Barbados (Table 3). A total of 1048 patients (13%) were known to have died during the study period. Mortality rates varied widely by country, as follows: 6% in Martinique, 8% in Jamaica, 11% in Trinidad, 13% in Haiti, 15% in the Dominican Republic, 15% in Barbados, and 24% in Puerto Rico.

The overall mortality rate was highest in the first 3 months (20.9 deaths/100 person-years [PY]), and it progressively declined to 4.7 deaths/100 PY at 5 years. Figure 1A shows the Kaplan-Meier plots of mortality over the study duration. The high early mortality was most pronounced in the Dominican Republic (34.2 deaths/100 PY) and Haiti (21.8 deaths/100 PY), the countries with the lowest baseline body weight and nearly all of the cases of TB and ART co-treatment, and Trinidad (17.2 deaths/100 PY), which had the lowest median CD4 cell count at ART initiation.

Table 4 shows the univariate and adjusted hazard ratios (HRs) for mortality for the combined cohort. In the univariate analyses, older age, male gender, TB and ART co-treatment, intravenous drug use, and lower baseline weight, hemoglobin, and CD4 cell count were associated with mortality. ART regimen was not associated with mortality (p-value=0.3164). In the multivariate analyses, higher body weight (HR 0.85 per 10 pounds; 95% CI: 0.82 – 0.89; p<0.0001), higher hemoglobin (HR 0.84 per g/dl; 95% CI: 0.80 – 0.88; p<0.0001), and higher CD4 cell count (0.90 per 50 CD4 cells; 95% CI: 0.86 – 0.93; p<0.0001) at ART initiation were associated with a lower hazard of death. Male gender (HR 1.58; 95% CI: 1.33 – 1.87; p<0.0001), TB and ART co-treatment (HR 1.58; 95% CI: 1.25 – 2.01; p=0.0002) and increased age (HR 1.19 per 10 years; 95% CI: 1.11 – 1.28; p<0.0001) were associated with an increased hazard of death. In the multivariate analysis, year of ART initiation and intravenous drug use were not associated with mortality.

In the univariate analysis, mortality varied by country, with HR 0.43 (95% CI: 0.28 – 0.67; p=0.0002) for Martinique, 0.58 (95% CI: 0.42 – 0.80; p=0.0010) for Jamaica, 0.68 (95% CI: 0.53 – 0.86; p=0.0013) for Trinidad, 0.91 (95% CI: 0.72 – 1.14; p=0.4209) for Barbardos, 1.40 (95% CI: 1.18 – 1.66; p<0.0001) for the Dominican Republic, and 1.59 (95% CI: 1.17 – 2.18; p=0.0033) for Puerto Rico, compared to Haiti (reference group). These country-level differences decreased after adjusting for other variables. In the multivariate analysis (with Haiti as reference), there was no association between site and mortality for Jamaica, Martinique, and Trinidad. Higher hazard ratios persisted in the multivariate analysis for the Dominican Republic (HR 1.72: 95% CI: 1.34 – 2.21; p<0.0001), Barbados (HR 1.95: 95% CI: 1.37 – 2.76; p=0.0002), and Puerto Rico (HR 2.25; 95% CI: 1.04 – 4.87; p=0.0389).

Seventy-five percent of patients in the overall cohort were alive and in-care at the end of the study. Figure 1B shows the Kaplan-Meier plots of retention in care over the study period. The relative positions of the countries on the retention plots are similar to those for survival, with the exception of Jamaica, which had the second-lowest mortality rate (8%) but the second-highest LTFU rate (16%) out of the 7 countries in the study. Long-term retention in care was 89% in Martinique, 82% in Trinidad, 78% in Barbados, 76% in Jamaica, 75% in Haiti, 72% in the Dominican Republic, and 29% in Puerto Rico. A total of 13% of patients were LTFU during the study period (see Table 3). The rate of LTFU was highest in the first 6 months (14 patients LTFU/100 PY), and it progressively declined to 4.7 patients LTFU/100 PY at 5 years.

In sensitivity analyses (see Table 5), overall mortality increased from 13% to 16% with the assumption that 27% of patients presumed LTFU had died. Overall mortality increased to 18% and 24% with the assumption that 40% and 87% of patients presumed LTFU had died, respectively. With the assumption that all patients presumed LTFU with a CD4 cell count < 50 cells/mm^3 were dead, overall mortality increased from 13% to 16%; mortality increased to 18% with the assumption that those LTFU with CD4 cell count < 100 cells/mm^3 were dead.

DISCUSSION

This is the first multi-cohort study to describe long-term HIV treatment outcomes in the Caribbean, and the only study to directly compare long-term HIV outcomes across a region. We observed excellent outcomes, with mortality rates comparable to other long-term cohorts in low and middle-income countries [11, 13–24, 30, 42, 43]. Overall mortality was 6% in Martinique, 8% in Jamaica, 11% in Trinidad, 13% in Haiti, 15% in the Dominican Republic, 15% in Barbados, and 24% in Puerto Rico. Much of the mortality difference between cohorts can be explained by severity of disease at presentation, concurrent active TB, gender, and nutritional status, with no difference in mortality between Haiti and Martinique, Jamaica, and Trinidad after controlling for these variables. There is increasing pressure to measure program effectiveness by comparing mortality across sites. Our findings demonstrate that great caution is indicated in making such comparisons.

Patient characteristics in our Caribbean cohort are more similar to those of other low and middle-income countries than those of the United States and Europe. Fifty-one percent of patients were female, and median weight and hemoglobin values were similar to those reported in African cohorts [10–16, 20, 42]. The median CD4 cell count at ART initiation was also similar to that reported in the Antiretroviral Therapy in Lower Income Countries Cohort (ART-LINC), with median CD4 cell count of 118 cells/mm^3 vs. 108 cells/mm^3 in ART-LINC, much lower than the 234 cells/mm^3 reported in the ART Collaboration (ART-CC) groups from Europe and North America [9, 44]. Martinique and Puerto Rico are the exceptions. These two islands have among the highest incomes in the region, and the

patients in these cohorts had higher CD4 cell counts at ART initiation and were more likely to receive protease inhibitors in the first-line regimen, compared with the other countries in this study [45].

Most countries in the Caribbean also had high early mortality rates, as has been reported in other low and middle-income countries [9, 12–23, 28], with overall mortality dropping from 20.9 deaths/100 PY in the first 3 months to 4.7 deaths/100 PY at 5 years. This early mortality was most pronounced in the Dominican Republic and Haiti, the two countries with the lowest baseline body weight and nearly all of the cases of TB and ART co-treatment, and Trinidad, which had the lowest median CD4 cell count at ART initiation. In comparison, Martinique and Puerto Rico had early mortality rates that were similar to industrialized countries.

Predictors of mortality in the Caribbean are similar to those reported in other studies from low and middle-income countries, and include older age, male gender, concurrent TB, and lower baseline body weight, hemoglobin, and CD4 cell count [10–12, 20–22, 30, 42, 43, 46]. Seventy-six percent of patients in these Caribbean centers initiate ART with a CD4 cell count < 200 cells/mm^3. It is worrisome that CD4 cell counts at ART initiation are not improving substantially over time, even though the number of counseling and testing centers has increased throughout the region [47]. This also remains a problem in most regions of the world, including both low and middle-income countries [30, 35, 46]. Improved linkage between testing and treatment centers, streamlined strategies to increase ART enrollment, and widespread implementation of the 2010 guidelines of the WHO, which recommend earlier ART initiation are necessary [48].

Low weight and hemoglobin are due to poor nutritional status as well as advanced AIDS. Improved nutritional supplementation will be critical to lowering mortality rates in undernourished patients. Active TB infection also remains an obstacle to HIV treatment in Haiti and the Dominican Republic. Further research is needed to evaluate the impact on mortality of newly implemented guidelines for earlier ART initiation in co-infected patients [48]. More aggressive TB screening is also indicated, particularly in Haiti, as early reports suggest that TB incidence in Port-au-Prince is increasing in the aftermath of the January 12, 2010 earthquake (unpublished GHESKIO data).

The association between male gender and mortality observed in this cohort has also been reported in studies from China, Cambodia and some countries in Africa [11, 12, 21–23, 42], but not in Latin America [30, 35]. This gender difference has been attributed to lower adherence, older age, and more advanced disease in males at presentation, but two studies have found that mortality differences persist even after controlling for these variables [42, 49]. Further studies on biological, behavioral, and occupational factors that could explain the higher mortality in males are warranted to reduce this gender disparity in treatment outcomes.

Seventy-five percent of patients in the overall cohort were alive and in-care at the end of the study. Retention rates generally mirrored survival rates; Jamaica was an exception, with lower mortality but higher LTFU than the overall cohort. The proportion of patients that were alive and in-care was 89% in Martinique, 82% in Trinidad, 78% in Barbados, 76% in Jamaica, 75% in Haiti, 72% in the Dominican Republic, and 29% in Puerto Rico. The high mortality and high LTFU rate in Puerto Rico is likely due to high rates of intravenous drug use [50–52], high rates of hepatitis C even among patients that are not IVDU, and a population that is highly migratory. With the exception of Puerto Rico, the proportion of patients that were alive and in-care in the Caribbean were higher than those reported from several African countries [5, 16, 20, 21, 33, 53]. A systematic review of 32 publications

from sub-Saharan Africa reported that African ART programs retain about 60% of patients in the first 24 months [31]. A follow-up meta-analysis of 39 African cohorts found a median retention rate of 70% [32]. The Caribbean sites generally retain patients at similar rates to the middle income African countries [13, 14, 20, 21, 28, 54]. This is likely because the treatment programs at these Caribbean sites are well-established, all antiretroviral therapy and HIV clinic visits are provided free of charge, all sites track patients that miss visits, and most programs subsidize transportation fees.

Our study is limited by a lack of definitive outcomes for patients who are presumed LTFU. Multiple tracking studies from low and middle-income countries have found that a significant proportion of these patients have died [32, 40, 41, 55–59]. It is possible that we may have under-estimated mortality rates, but it is noteworthy that retention in care in the Caribbean is similar or superior to reported rates from other low and middle-income countries. We also lacked data on adherence to therapy as a predictor of mortality. This and other unmeasured variables, such as incarceration or migration status, could explain the higher hazard ratios for mortality that persisted in the multivariable analysis for the Dominican Republic, Barbados, and Puerto Rico. Median follow-up times also varied between countries, with Barbados having the longest duration of follow-up. In addition, it is important to note that though we have a large sample size of patients that included from 7% to 71% of patients on ART in each country, treatment outcomes from these sites may not always be representative of whole countries, particularly as some sites are non-governmental organizations and others are public.

In summary, this study provides the first multi-cohort data on long-term HIV treatment outcomes in the Caribbean. Outcomes across the region are excellent, and similar to reports from other low and middle-income countries. Mortality rates vary widely by country, but much of the difference in mortality can be explained by disease severity at ART initiation, concurrent TB, gender, and nutritional status. Earlier ART initiation and augmented nutritional supplementation for undernourished patients will be critical to improve outcomes. Further studies are necessary to identify the reasons for the gender disparities in treatment outcomes.

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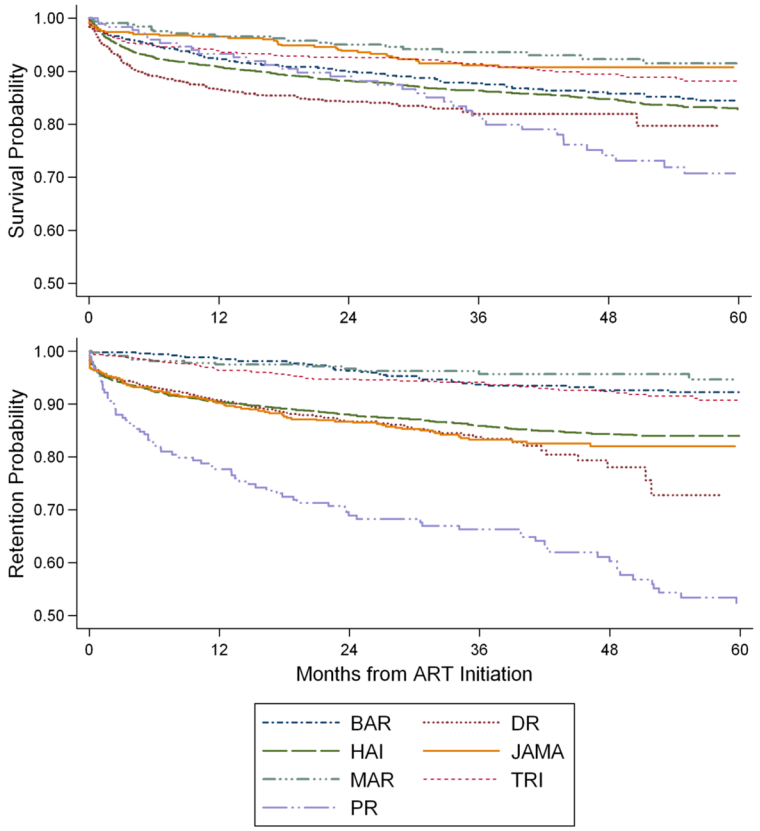

Figure 1.
Cumulative estimates of survival and retention in care by treatment site

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2013 April 1.

Table 1

Country and Program Characteristics of the TCHARI sites

Country	Barbados	DR	Haiti	Jamaica	Martinique	Trinidad	PR
GDP per Capita ($US)*	13,849	5078	785	4705	39,922	19,076	17,100
Funding sources for ART	Ministry of Health with World Bank loan	Ministry of Public Health and Welfare with World Bank loan	GFATM and PEPFAR**	GFATM**	Ministry of Health	Governme nt of Trinidad	Ryan White
HIV prevalence (%) ***	1.4	0.9	2.2	1.7	0.3	2.0	0.2
% HIV-infected patients HBsAg-positive**	**Not known in HIV +; felt to be low**	**Not known in HIV+; felt to be low**	**4% of HIV+**	**Not known in HIV+; felt to be low**	**2.5% of HIV+**	**4.5% of HIV+**	**6% of HIV+ without IVDU; 7% of HIV+ with IVDU**
% HIV-infected patients HCV Ab positive**	**Not known in HIV +; felt to be low**	**Not known in HIV+; felt to be low**	**<1% of HIV+**	**Not known in HIV+; felt to be low**	**5.5% of HIV+ without IVDU; 96% of HIV+ with IVDU**	**Not known in HIV +; felt to be low**	**54% of HIV+ without IVDU; 96% HIV+ with IVDU**
Year of expanded ART access	2002	2003	2003	2004	1996	2003	1998
Total number of patients in the study	560	1207	4717	476	325	725	193
Total number of adults on ART at the of end 2009	793	14,000	25,673	6549	750	2335	Not calculated
Percentage of patients receiving free ART	100%	100%	100%	100%	100%	100%	85%
ART initiation criteria during the	WHO criteria****	WHO criteria****	WHO criteria****	WHO criteria****	CD4<350 cells/mm^3 or symptomatic HIV disease	CD4<250 cells/mm^3 or AIDS-defining condition	WHO criteria or clinical judgment of physician

Country	Barbados	DR	Haiti	Jamaica	Martinique	Trinidad	PR
study period							
Virologic monitoring during study period	Conducted routinely	Suspected treatment failure	Suspected treatment failure	Suspected treatment failure	Conducted routinely	Conducted routinely	Conducted routinely
Method of tracking patients that miss visits (contact is done with phone calls and/or home visits)	**Community nurse contacts patient if they miss 2 visits or are 6 months late**	**Peer counselors contact patient after one missed visit**	**Field workers contact patients within one week of each missed visit**	**Adherence counselors contact patients after 2 missed visits (visits usually every 3 months)**	**Phone and mail after one late visit.**	**Adherence nurse calls or visits patient at home after one late visit.**	**Phone call after 2 missed visits (visits usually every 6 months)**

* GDP (Gross Domestic Product). International Monetary Fund. Economic Outlook Database available at: http://imf.org/external/pubs/ft/weo/2009/01/weodata/index.aspx [60]

** GFATM (Global Fund to Fight AIDS, Tuberculosis and Malaria); PEPFAR (U.S. President's Emergency Plan for AIDS Relief); HBsAg (hepatitis B surface antigen); HCV Ab (hepatitis C antibody)

*** UNAIDS database, 2010 [61]; for Haiti, Republique d'Haiti Programme National de Lutte contre le Sida, 2010 [62]

**** At the time of the study, the World Health Organization (WHO) recommended ART for all patients with a CD4 cell count <200 cells/ml or an AIDS-defining illness

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2013 April 1.

Table 2

Characteristics of Patients Receiving Antiretroviral Therapy in the Caribbean

	Barbados (n=560)	DR (n=1207)	Haiti (n=4717)	Jamaica (n=476)	Martinique (n=325)	Trinidad (n=725)	PR (n=193)	Combined (n=8203)
Age*	39 (32, 46)	38 (32, 45)	38 (31, 45)	38 (31, 45)	41 (34, 49)	35 (28, 44)	41 (35, 47)	38 (31, 45)
Female gender – no. (%)	241 (43)	627 (52)	2566 (54)	229 (48)	120 (37)	344 (47)	64 (33)	4191 (51)
Education – no. (%)								
Missing**	26 (5)	493 (41)	39 (1)	***	10 (3)	164 (23)	3 (2)	1211 (15)
None or primary only	1 (0)	312 (44)	2366 (51)	***	149 (47)	111 (20)	31 (16)	2970 (42)
At least some secondary	487 (91)	342 (48)	2146 (46)	***	113 (36)	427 (76)	126 (66)	3641 (52)
At least some university	46 (9)	60 (8)	166 (4)	***	53 (17)	23 (4)	33 (17)	381 (5)
Income – no. (%)								
Missing**	23 (4)	***	45 (1)	***	***	71 (10)	7 (4)	2154 (26)
<365 USD/year	131 (24)	***	2961 (63)	***	***	228 (35)	117 (63)	3437 (57)
365 – 999 USD/year	157 (29)	***	1547 (33)	***	***	61 (9)	14 (8)	1779 (29)
1000 – 2999 USD/year	146 (27)	***	114 (2)	***	***	137 (21)	26 (14)	423 (7)
> 3000 USD/year	103 (19)	***	50 (1)	***	***	228 (35)	29 (16)	410 (7)
Current or past intravenous drug use – no. (%)								
Missing**	0 (0)	0 (0)	0 (0)	0 (0)	13 (4)	0 (0)	0 (0)	17 (0)
No intravenous drug use	560 (100)	1180 (98)	4717 (100)	453 (95)	275 (88)	725 (100)	91 (47)	7908 (97)
Intravenous drug use	0 (0)	27 (2)	0 (0)	23 (5)	37 (12)	0 (0)	102 (53)	278 (3)
Weight at ART initiation – no. (%)*								
Missing**	70 (13)	213 (18)	187 (4)	95 (20)	35 (11)	68 (9)	24 (12)	692 (8)
Median for females (pounds)	134 (112, 161)	121 (104, 140)	111 (98, 127)	131 (110, 154)	139 (121, 163)	128 (110, 151)	134 (115, 165)	116 (101, 136)
Median for males (pounds)	146 (127, 166)	136 (122, 152)	125 (111, 140)	141 (127, 157)	146 (130, 164)	139 (124, 155)	152 (134, 168)	131 (116, 148)
Baseline hemoglobin – no. (%)*								
Missing**	95 (17)	98 (8)	498 (11)	164 (34)	31 (10)	22 (3)	37 (19)	945 (12)

	Barbados (n=560)	DR (n=1207)	Haiti (n=4717)	Jamaica (n=476)	Martinique (n=325)	Trinidad (n=725)	PR (n=193)	Combined (n=8203)
Median for females	11.3 (10.3, 12.3)	11.1 (9.9, 12.0)	10.0 (8.9, 11.0)	10.2 (9.1, 11.3)	11.1 (10.1, 12.0)	10.0 (9.0, 11.0)	11.8 (10.2, 13.1)	10.3 (9.1, 11.4)
Median for males	12.5 (11.3, 13.7)	12.0 (10.5, 13.2)	11.0 (9.6, 12.2)	11.8 (10.4, 13.0)	12.6 (11.3, 13.7)	11.0 (10.0, 13.0)	13.2 (11.5, 14.9)	11.4 (10.0, 12.9)
Baseline CD4 Cell Count – no. (%)*								
Missing**	94 (17)	211 (17)	423 (9)	124 (26)	10 (3)	19 (3)	10 (5)	891 (11)
Median CD4 cell count	128 (42, 221)	96 (33, 175)	122 (49, 192)	123 (47, 230)	196 (47, 333)	85 (32, 173)	221 (72, 340)	118 (44, 196)
Baseline CD4 Cell Count – no. (%)								
Missing**	94 (17)	211 (17)	423 (9)	124 (26)	10 (3)	19 (3)	10 (5)	891 (11)
< 50 cells/mm3	133 (29)	321 (32)	1074 (25)	92 (26)	79 (25)	255 (36)	34 (19)	1988 (27)
50 to 99 cells/mm3	72 (15)	192 (19)	776 (18)	62 (18)	31 (10)	133 (19)	19 (10)	1285 (18)
100 to 199 cells/mm3	109 (23)	302 (30)	1501 (35)	91 (26)	49 (16)	201 (28)	31 (17)	2284 (31)
200 to 349 cells/mm3	117 (25)	163 (16)	827 (19)	85 (24)	90 (29)	117 (17)	55 (30)	1454 (20)
>/= 350 cells/mm3	35 (8)	18 (2)	116 (3)	22 (6)	66 (21)	0 (0)	44 (24)	301 (4)
WHO Stage – no. (%)								
Missing**	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	***	0 (0)	725 (9)
Stage I	156 (28)	223 (18)	366 (8)	75 (16)	198 (61)	***	91 (47)	1109 (15)
Stage II	107 (19)	439 (36)	0 (0)	134 (28)	12 (4)	***	54 (28)	746 (10)
Stage III	99 (18)	359 (30)	3080 (65)	160 (34)	28 (9)	***	4 (2)	3730 (50)
Stage IV	198 (35)	186 (15)	1271 (27)	107 (22)	87 (27)	***	44 (23)	1893 (25)
Year of ART Initiation – no. (%)								
Missing**	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
1998–2002	152 (27)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	127 (66)	280 (3)
2003–2004	250 (45)	76 (6)	1414 (30)	65 (14)	97 (30)	355 (49)	39 (20)	2296 (28)
2005–2006	158 (28)	562 (47)	1128 (24)	336 (71)	109 (34)	369 (51)	24 (12)	2686 (33)
2007–2008	0 (0)	569 (47)	2175 (46)	75 (16)	119 (37)	0 (0)	3 (2)	2941 (36)
First ART Regimen – no. (%)								
Missing**	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
NNRTI-containing regimen	486 (87)	1192 (99)	4475 (95)	458 (96)	25 (8)	718 (99)	30 (16)	7384 (90)

	Barbados (n=560)	DR (n=1207)	Haiti (n=4717)	Jamaica (n=476)	Martinique (n=325)	Trinidad (n=725)	PR (n=193)	Combined (n=8203)
PI-containing regimen	67 (12)	14 (1)	181 (4)	16 (3)	271 (83)	6 (1)	156 (81)	711 (9)
Other regimen	7 (1)	1 (0)	61 (1)	2 (0)	29 (9)	1 (0)	7 (4)	108 (1)
Tuberculosis – no. (%)****								
Missing**	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
No TB and ART Co-Treatment	558 (100)	1155 (96)	4235 (90)	469 (99)	321 (99)	707 (98)	193 (100)	7638 (93)
TB and ART Co-Treatment	2 (0)	52 (4)	482 (10)	7 (1)	4 (1)	18 (2)	0 (0)	565 (7)

* Continuous variables are reported as medians (interquartile range)

** Percentages are computed using the number of patients with non-missing values

*** Data not collected at site

**** TB and ART co-treatment was defined as any overlap of treatment with these two therapies.

Table 3

Mortality and Loss to Follow-up during the Study Period (per 100 person-years in care)

	Barbados (n=560)	DR (n=1207)	Haiti (n=4717)	Jamaica (n=476)	Martinique (n=325)	Trinidad (n=725)	Puerto Rico (n=193)	Combined (n=8203)
Median Follow-up Time and Patient Status								
Median Follow-up (Months)	52 (33, 70)	20 (9, 33)	27 (13, 49)	40 (28, 47)	39 (21, 60)	48 (37, 59)	35 (10, 63)	31 (14, 50)
Alive or Transferred	434 (78)	871 (72)	3517 (75)	361 (76)	290 (89)	593 (82)	56 (29)	6122 (75)
Deceased	85 (15)	181 (15)	598 (13)	38 (8)	21 (6)	78 (11)	47 (24)	1048 (13)
Lost to Follow-up	41 (7)	155 (13)	602 (13)	77 (16)	14 (4)	54 (7)	90 (47)	1033 (13)
Mortality								
3 months	13.9	34.2	21.8	10.8	3.8	17.2	6.8	20.9
6 months	10.8	23.8	15.7	6.4	5.1	10.8	8.3	14.8
1 year	8.1	15.5	10.1	3.8	3.6	6.5	7.0	9.6
3 years	4.6	8.9	5.9	3.2	2.3	3.2	6.7	5.5
5 years	3.8	8.4	5.0	2.7	2.1	2.8	6.9	4.7
Loss to Follow-up								
6 months	1.1	15.1	16.7	16.1	3.8	3.5	39.1	14.0
1 year	1.3	10.5	10.7	10.6	2.6	3.7	26.8	9.3
3 years	2.1	7.2	6.1	6.5	1.6	2.1	15.7	5.5
5 years	1.7	7.2	5.1	5.5	1.3	2.0	14.6	4.7

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2013 April 1.

Table 4

Risk Factors for Mortality by Cox Proportional Hazards Regression

Variable	Reference Group	Univariate			Multivariate		
		Hazard Ratio (95% CI)	p-value	p-value for Variable	Hazard Ratio	p-value	p-value for Variable
Year of ART initiation							
1998–2000	2007–2008	3.21 (2.17 – 4.73)	<0.0001	<0.0001	2.17 (0.92 – 5.15)	0.0781	0.1794
2001–2002	2007–2008	1.27 (0.88 – 1.84	0.1942		0.87 (0.47 – 1.62)	0.6634	
2003–2004	2007–2008	1.54 (1.30 – 1.82)	<0.0001		0.94 (0.75 – 1.18)	0.6013	
2005–2006	2007–2008	1.24 (1.04 – 1.47)	0.0151		1.05 (0.85 – 1.31)	0.6240	
ART regimen							
PI regimen	NNRTI	0.88 (0.71 – 1.10)	0.2675	0.3164	N/A	N/A	N/A
Other regimen	NNRTI	1.24 (0.81 – 1.92)	0.3259		N/A	N/A	N/A
Site							
Barbados	Haiti	0.91 (0.72 – 1.14)	0.4209	<0.0001	1.95 (1.37 – 2.76)	0.0002	<0.0001
Dominican Republic	Haiti	1.40 (1.18 – 1.66)	<0.0001		1.72 (1.34 – 2.21)	<0.0001	
Jamaica	Haiti	0.58 (0.42 – 0.80)	0.0010		0.88 (0.52 – 1.47)	0.6183	
Martinique	Haiti	0.43 (0.28 – 0.67)	0.0002		1.03 (0.63 – 1.70)	0.8936	
Puerto Rico	Haiti	1.59 (1.17 – 2.18)	0.0033		2.25 (1.04 – 4.87)	0.0389	
Trinidad	Haiti	0.68 (0.53 – 0.86)	0.0013		0.82 (0.60 – 1.12)	0.2060	
Age at ART initiation	Unit = 10 years	1.13 (1.07 – 1.20)	<0.0001		1.19 (1.11 – 1.28)	<0.0001	
Gender	Female	1.22 (1.08 – 1.38)	0.0014		1.58 (1.33 – 1.87)	<0.0001	
Intravenous drug use	None	1.40 (1.05 – 1.86)	0.0220		1.32 (0.85 – 2.05)	0.2119	
Baseline weight	Unit = 10 pounds	0.84 (0.82 – 0.87)	<0.0001		0.85 (0.82 – 0.89)	<0.0001	
Baseline hemoglobin	Unit = 1 g/dl	0.82 (0.79 – 0.85)	<0.0001		0.84 (0.80 – 0.88)	<0.0001	
Baseline CD4 cell count	Unit = 50 cells/ml	0.88 (0.85 – 0.91)	<0.0001		0.90 (0.86 – 0.93)	<0.0001	
TB and ART Co-Treatment	No TB	1.84 (1.53 – 2.21)	<0.0001		1.58 (1.25 – 2.01)	0.0002	

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2013 April 1.

Table 5

Sensitivity Analyses Examining the Effect of Loss to Follow-up on Mortality Rates at each Site

	Barbados (n=560)	DR (n=1207)	Haiti (n=4717)	Jamaica (n=476)	Martinique (n=325)	Trinidad (n=725)	Puerto Rico (n=193)	Combined (n=8203)
Total Patient Months of Follow-up	27951	25843	150722	17037	13078	32918	7759	275308
Loss to Follow-up – Number (%)	41 (7)	155 (13)	602 (13)	77 (16)	14 (4)	54 (7)	90 (47)	1033 (13)
Unadjusted Deaths – Number (%)	85 (15)	181 (15)	598 (13)	38 (8)	21 (6)	78 (11)	47 (24)	1048 (13)
LTFU Per 100 Person-Years of Follow-up	1.8	7.2	4.8	5.4	1.3	2.0	13.9	4.5
Unadjusted Mortality Per 100 Person-Years	3.6	8.4	4.8	2.7	1.9	2.8	7.3	4.6
Sensitivity Analyses – Effect of LTFU on Mortality – Number (Percentage) of Deaths								
Assume Death in 27% of Patients LTFU – No. (%)*	96 (17)	223 (18)	761 (16)	59 (12)	25 (8)	93 (13)	71 (37)	1327 (16)
Assume Death in 40% of Patients LTFU – No. (%)**	101 (18)	243 (20)	839 (18)	69 (14)	27 (8)	100 (14)	83 (43)	1461 (18)
Assume Death in 87% of Patients LTFU – No. (%)*	121 (22)	316 (26)	1122 (24)	105 (22)	33 (10)	125 (17)	125 (65)	1947 (24)
Assume Death if LTFU and CD4 <50 Cells/ mm^3	95 (17)	230 (19)	734 (16)	57 (12)	24 (7)	90 (12)	59 (31)	1289 (16)
Assume Death if LTFU and CD4 <100 Cells/ mm^3	99 (18)	253 (21)	834 (18)	66 (14)	24 (7)	100 (14)	70 (36)	1446 (18)
Sensitivity Analyses – Effect of LTFU on Mortality – Mortality Rates Per 100 Person-Years of Follow-up								
Assume Death in 27% of Patients LTFU – No. (%)*	4.1	10.3	6.1	4.1	2.3	3.4	11.0	5.8
Assume Death in 40% of Patients LTFU – No. (%)**	4.4	11.3	6.7	4.8	2.4	3.6	12.8	6.4

	Barbados (n=560)	DR (n=1207)	Haiti (n=4717)	Jamaica (n=476)	Martinique (n=325)	Trinidad (n=725)	Puerto Rico (n=193)	Combined (n=8203)
Assume Death in 87% of Patients LTFU – No. (%)*	5.2	14.7	8.9	7.4	3.0	4.6	19.4	8.5
Assume Death if LTFU and CD4 <50 Cells/ mm^3	4.1	10.7	5.8	4.0	2.2	3.3	9.1	5.6
Assume Death if LTFU and CD4 <100 Cells/ mm^3	4.3	11.7	6.6	4.6	2.2	3.6	10.8	6.3

* The lowest mortality rate in the published literature from low and middle-income countries from tracking studies of ART patients presumed LTFU is 27% and the highest mortality is 87% [39, 40].

** In a meta-analysis of 17 studies from low and middle-income countries by Brinkhof et al. [41] the combined mortality of ART patients from tracking studies of patients presumed LTFU was 40% (95% CI: 33–48%).