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Early Versus Standard Antiretroviral Therapy for HIV Infected Adults in Haiti

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Abstract

Background—The optimal time to start antiretroviral therapy (ART) for HIV–infected adults in resource limited settings with a CD4⁺ T cell count of 200 – 350 cells per mm³ remains uncertain.

Methods—We conducted a randomized, open label, trial of early versus standard ART initiation in HIV–infected adults with no history of an AIDS illness and a confirmed CD4⁺ T cell count between 200 and 350 cells per mm³ in Haiti. The primary study end point was survival. Participants in both groups received monthly follow up, isoniazid and trimethoprim-sulfamethoxazole prophylaxis, and nutritional support. The early treatment group initiated zidovudine, lamivudine, and efavirenz within two weeks of enrollment. The standard group started the same ART regimen when participants developed a CD4⁺ T cell count < 200 cells/mm³ or clinical AIDS.

Results—Between 2005 and 2008, 816 participants, 408 per group, were enrolled and followed for a median of 21 months. The CD4 T cell count at enrollment was ~ 280 cells per mm³ in both groups. There were 23 deaths in the standard group and 6 in the early group, $p=0.0011$, hazards ratio 4.0, 95% CI 1.6 to 9.8. There were 36 incident tuberculosis cases in the standard group and 18 in the early group, $p = 0.0125$, hazard ratio 2.0, 95% CI 1.2 to 3.6.

Conclusions—Early ART decreased mortality and incident tuberculosis infection. Access to ART should be expanded to all HIV–infected adults with a CD4⁺ T cell count < 350 cells per mm³, including those from resource limited settings.

The optimal time to start antiretroviral therapy (ART) for human immunodeficiency virus (HIV)–infected individuals remains uncertain. There have been no randomized trials to

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determine the optimal time to start ART in adults with a CD4⁺ T cell count between 200 – 350 cells per mm³. Further, there are few data on the optimal time to start ART in resource poor settings where high rates of tropical co-infections, tuberculosis, and malnutrition may alter the natural history of HIV disease and the optimal time to initiate therapy. Therefore, international guidelines differ on when to start ART.¹²³⁴⁵⁶

In Haiti, following World Health Organization (WHO) guidelines, the first line ART regimen of zidovudine, lamivudine, and efavirenz is started when HIV-1 infected patients develop a CD4⁺ T cell count < 200 cells/mm³ or clinical AIDS.^{1, 2} In patients treated with this standard ART strategy, approximately 80% are alive at five years.⁷⁸ We hypothesized that starting ART earlier would further improve survival. We therefore conducted a randomized clinical trial in Haiti to determine whether early initiation of ART improves survival compared with standard ART.

METHODS

Design and Setting

We conducted a randomized, open-label controlled trial of early versus standard ART in HIV-infected adults with no history of an AIDS illness and a CD4⁺ T cell count between 200 and 350 cells per mm³. The primary study end point was survival.

The study was conducted at the Center of the Haitian Group for the Study of Kaposi's Sarcoma and Opportunistic Infections (GHESKIO) in Port au Prince, Haiti.⁹ The study was approved by institutional review boards at Weill Cornell Medical College and GHESKIO.

Inclusion and Exclusion Criteria

Enrollment inclusion criteria included HIV-infection; age ≥ 18 years, and a confirmed CD4⁺ T cell count between 200 and 350 cells per mm³ within 45 days of enrollment. Exclusion criteria included a history of an AIDS-defining illness (WHO stage 4)¹⁰ or prior ART use. Other criteria are detailed in Supplemental Table 1.

Recruitment and Randomization

Subjects were recruited at GHESKIO between August 2005 and July 2008. After subjects provided informed consent,¹¹ the study team performed a screening evaluation, and eligible subjects were enrolled. Participants were randomized by a computer-generated random numbers list in a 1:1 ratio to either the early or the standard group.

Study Intervention

Participants in both groups were seen monthly by a clinician and received a “package” of services provided to HIV-1 infected patients at GHESKIO. Participants were provided prophylaxis with trimethoprim-sulfamethoxazole,¹²¹³ and those with a positive purified protein derivative (PPD) skin test were provided isoniazid.¹⁴ Participants received nutritional support: daily multivitamins and monthly food basket with rice, beans, oil, and meat.¹⁵ Retention was encouraged by having field workers visit participants' residence at enrollment and at missed visits. Participants were counseled about adherence and to return to the clinic whenever they had symptoms.

Participants with cough or symptoms suggestive of tuberculosis at any time during the study were screened with a chest radiograph and three sputum smears for acid fast bacilli (AFB) by Ziehl-Neelsen staining and *Mycobacterium tuberculosis* culture on Lowenstein Jensen media.¹⁶ Patients with active tuberculosis were treated using directly observed therapy (DOT) with four drugs daily for a 2 month initiation phase (isoniazid, rifampin, ethambutol,

and pyrazinamide) and then two-drugs daily for a four month continuation phase (isoniazid and rifampin).^{17,18} Patients with drug resistant tuberculosis were treated according to WHO guidelines.¹⁹

The early treatment group initiated lamivudine (150 mg every 12 hours) and zidovudine (300 mg every 12 hours) in a fixed dose combination and efavirenz (600 mg every 24 hours at bedtime) within two weeks of enrollment. The first two months of ART was provided under modified direct observation; the morning dose was observed at home by a GHESKIO field worker and the evening dose was left with the study participant and not observed.

For drug toxicities, the following single drug substitutions were possible: stavudine for zidovudine, nevirapine or lopinavir boosted by ritonavir for efavirenz. For participants on rifampin, efavirenz dosing was increased to 800 mg every 24 hours. ART failure was defined using WHO criteria: a confirmed decrease in CD4⁺ cell count 50% below peak or a decrease below baseline or a new AIDS illness while on ART.² Participants who failed first line therapy were changed to the second line regimen of abacavir, didanosine, and lopinavir boosted by ritonavir.

The standard treatment group started the same first line ART regimen as the early group (lamivudine, zidovudine, and efavirenz) when participants developed a single CD4⁺ T cell count measurement < 200 cells/mm³ or an AIDS defining illness. In addition, women in the standard group who became pregnant were initiated and maintained on ART to prevent vertical HIV transmission; nevirapine was substituted for efavirenz. Other drug substitutions and the second line regimen were the same as the early group.

Clinical Measurements

The primary study endpoint was death documented by one of the following: obituary, autopsy report, hospital death certificate, or contact report documenting verbal communication with subject's healthcare provider or family member.

Tuberculosis was a secondary study end-point. We used the case definition of the American Thoracic Society, as described previously.^{20,21}

Adherence to antiretroviral medications was measured using a previously described medication adherence questionnaire translated into Haitian Creole and administered every six months.²²

Serious adverse events and their relationship to antiretroviral medications were assessed, graded, and reported using the standard level of reporting in the National Institutes of Health, Division of AIDS manual for grading adverse events.²³ We report all severe (grade 3) and life-threatening (grade 4) suspected drug reactions.

Laboratory Measurements

Laboratory monitoring included baseline CD4 T cell count (Becton, Dickinson, Franklin Lakes New Jersey), complete blood count (CBC) (CellDyn, Abbott Laboratories, Abbott Park, Illinois), AST (SGOT), ALT (SGPT), and creatinine (VITROS, Ortho Clinical Diagnostics, Rariton, New Jersey). The CBC, liver function tests, and serum chemistries were repeated every three months for participants on antiretroviral drugs. The CD4 T cell count was repeated for all participants every six months or when requested by the primary care clinician.

Statistical Analysis

Clinical and laboratory case report forms were entered electronically in Haiti via an internet interface, and data were managed by Frontier Science and Technology Research Foundation, New York. Data were exported into SAS (SAS Institute, Cary North Carolina) for analysis.

The study was designed to achieve a fixed number of study endpoints. The target sample size was 794 participants, 397 per arm, in order to provide 80% power with two sided type I error of 5% to detect a hazards ratio of 2.0 in survival between the two groups when 65 deaths occurred. Three interim analyses were scheduled when 16, 32, and 48 deaths occurred. The blinded interim analyses were reviewed by the National Institutes of Health, Division of AIDS, Data Safety and Monitoring Board with pre-set stopping rules using the O'Brien-Fleming boundary for significance with Lan-DeMet's flexible spending function.²⁴

We hypothesized that early ART would improve survival compared to standard therapy. All analyses were based on the intention to treat principle. The primary study endpoint, mortality, was analyzed by standard Kaplan Meier survival methods, and differences between two survival curves were evaluated using the log-rank test as specified in the protocol.²⁵ Cox proportional hazards regression analysis was used to estimate the hazards ratio with 95% confidence intervals. We used the same survival methods to compare the secondary outcome of incident tuberculosis. For comparison of other proportions, we used Fisher's exact test. Two-sided hypotheses and tests were adopted for all statistical inferences.

RESULTS

Recruitment and Baseline Characteristics

One thousand sixty-six subjects were screened between August 2005 and July 2008, and 816 were successfully enrolled into the study, (Figure 1). There were 470 (58%) women. The median age was 40 years. The median CD4 T cell count was 281 per mm³. Baseline characteristics were comparable between the two arms, (Table 1).

Status at the time of Analysis

The DSMB reviewed the second interim analysis with data accumulated up to May 1, 2009 with 29 deaths. The trial crossed the pre-set stopping boundary for a survival difference between groups, and the DSMB recommended that the trial be stopped and all participants in the standard arm be provided ART.

The median length of follow up was 21 months with a range of 1 – 44 months. Of the 408 participants in the early group, 383 (94%) remained in follow up, 6 (1.5%) were deceased, and 19 (4.5%) were lost to follow-up. Of the 408 participants in the standard group, 367 (90%) remained in follow up, 23 (5.6%) were deceased, and 18 (4.4%) were lost to follow-up.

Of the 408 participants in the standard group, 160 (39%) reached criteria for ART initiation and started antiretroviral drugs. Of the 408 participants in the standard group, 118 (29%) received isoniazid prophylaxis for a positive tuberculin skin test and 400 (98%) received trimethoprim-sulfamethoxazole prophylaxis. Of the 408 in the early group, 99 (24%) received isoniazid prophylaxis and 388 (95%) received trimethoprim-sulfamethoxazole prophylaxis. Of the 327 participants in the early arm with at least 12 months of follow-up, 294 (90%) were ART adherent (receiving > 95% of antiretroviral medications in the first year on ART) versus 57 (95%) of 60 participants in the standard arm receiving ART for at least twelve months.

Survival

There were 29 deaths during the study, 23 deaths in the standard group and 6 in the early group, p -value=0.0011 by the log rank test. By Kaplan Meier analysis, 98 percent of the early group and 93 percent of the standard group were alive at 36 months, (Figure 2). The unadjusted hazards ratio comparing the risk of death in the standard arm to that in the early treatment arm was 4.0, with a 95% confidence interval of 1.6 to 9.8.

The causes of death in the 23 participants in the standard group who died were: gastroenteritis (7), tuberculosis (5), pneumonia (4), homicide (2), cancer (1), cardiomyopathy (1), cholangitis with sepsis (1), stroke (1), and suicide (1). The causes of death in the 6 participants in the early group who died were: burn injury (1), gastroenteritis (1), myocardial infarction (1), pulmonary embolism after gynecologic surgery (1), stroke (1), and gastrointestinal bleed (1). There was only one death from an infectious disease in the early group compared with seventeen in the standard group.

Of the 23 participants in the standard group who died, 7 initiated ART prior to death and 16 did not initiate therapy prior to death. The seven standard arm participants who initiated ART died a median of 2 months after starting therapy.

Incident Tuberculosis

Among 773 participants who were tuberculosis-free at enrollment, 54 participants were diagnosed with incident tuberculosis during follow up. Incident tuberculosis was a secondary study end-point. There were 36 incident tuberculosis cases in the standard group and 18 in the early group, p -value = 0.0125 by the log rank test. By Kaplan Meier survival analysis, 6 percent of the early group compared with 14 percent of the standard group developed tuberculosis by 36 months, (Figure 3). The hazards ratio comparing the risk of incident tuberculosis in the standard arm to that in the early treatment arm was 2.0, with a 95% confidence interval of 1.2 to 3.6.

Thirty one participants in the standard arm developed incident tuberculosis prior to initiating ART, and five participants in the standard arm developed tuberculosis a median of 6 months after initiating ART.

None of the participants in the early arm died from incident tuberculosis compared with five of the participants in the standard treatment arm.

Median CD4 T cell counts

The median CD4 T cell count of the early group increased from 280 cells per mm^3 at enrollment to 520 cells per mm^3 at month 36. The median CD4 T cell count of the standard group declined from 282 cells per mm^3 at baseline to 270 cells per mm^3 at month 36.

Estimated Time to Requiring ART in the Standard Group

Of the 408 participants in the standard group, 160 (39%) started ART; 147 developed a CD4 T cell count < 200 cells per mm^3 , 7 developed an AIDS- defining illness, 3 developed both an AIDS-defining illness and a CD4 T cell count < 200 cells per mm^3 , and 3 pregnant women started ART to prevent mother to child HIV transmission. The median CD4 T cell count of the 160 participants in the standard group at the time of initiating ART was 166 cells per mm^3 , (interquartile range 130 – 190 cells per mm^3).

An additional 16 participants in the standard group died before ART could be initiated. By Kaplan Meier survival analysis, the estimated median ART-free survival in the standard group was 24 months, (Figure 4).

Drug reactions and toxicities

Of the 408 participants in the early group, 32 (8%) had a severe or life-threatening drug reaction. Of the 160 participants in the standard group who initiated ART, 18 (9%) had a severe or life-threatening drug reaction. These are detailed in Supplemental Table 2. Zidovudine related anemia was the most common toxicity and occurred in 13 of the 160 (8.1%) participants in the standard group who initiated ART and in 14 of 408 (3.4%) participants in the early group.

DISCUSSION

The results of this randomized controlled trial demonstrate that in HIV -1 infected adults with a CD4 T cell count between 200 and 350 cells per mm³ in a resource poor setting, early ART reduces mortality by 75% and decreases the incidence of tuberculosis by 50% when compared with deferring ART until the CD4 T cell count falls to 200 cells per mm³ or an AIDS-defining illness occurs.

Our finding that early ART improves survival are consistent with data from observational cohorts.²⁶²⁷ The “When To Start Consortium” examined outcomes of more than 24,000 HIV infected patients in 15 cohorts in Europe and North America and found an increased hazard ratio for death of 1.4 – 2.0 when ART was initiated at a threshold lower than 350 cells per cells per mm³.²⁶ Our prospective study validates these observational findings with a randomized controlled trial. Further, the effect size found in our trial with a hazards ratio of 4.0 was larger than the effect size seen in the observational cohorts. Importantly, our study was conducted in a resource poor setting where high rates of tuberculosis, malnutrition, and tropical co-infections may exacerbate the effect of deferred therapy.

Early ART for HIV-1 infected participants also decreased tuberculosis incidence by 50%. This is consistent with observational studies from Africa showing a decrease in TB incidence after ART is started.²⁸²⁹³⁰ TB is a leading cause of death in HIV-1 infected patients in developing countries,³¹ and the effect of early ART upon TB in part explains the decreased mortality seen in our trial. Further, the HIV epidemic has dramatically increased the incidence of active tuberculosis in resource poor countries and is overwhelming tuberculosis control programs.³² Provision of early ART on a large scale in resource poor settings has the potential to decrease the incidence of active tuberculosis at a population level.

The World Health Organization has promoted a public health approach in its ART guidelines, emphasizing feasibility, cost effectiveness, and large scale implementation.³³ Starting ART earlier at a CD4 T cell count of 350 cells per mm³ is likely to be consistent with this approach.³⁴ The median time to ART in the standard arm was 2 years. At current pricing two years of ART drugs will cost ~ \$400 per person. For this price, mortality is cut by 75% and active tuberculosis by 50%. Further, the standard group had higher rates of infectious diseases, treatment-limiting drug toxicities, and required frequent CD4 T cell count monitoring. This complex medical care consumed resources and the time of highly trained health care workers and may in part offset the cost of starting ART earlier.

The study was not blinded. This would not affect the primary study endpoint, mortality, but we cannot exclude the possibility that detection bias influenced secondary endpoints. The equal and high rates of retention argue that both groups were followed with the same intensity.

In conclusion, early ART decreased mortality by 75% in HIV-infected adults with a CD4⁺ T cell count between 200 and 350 cells per mm³. Access to ART should be expanded to all

HIV-infected adults with a CD4⁺ T cell count less than 350 cells per mm³, including those from resource limited settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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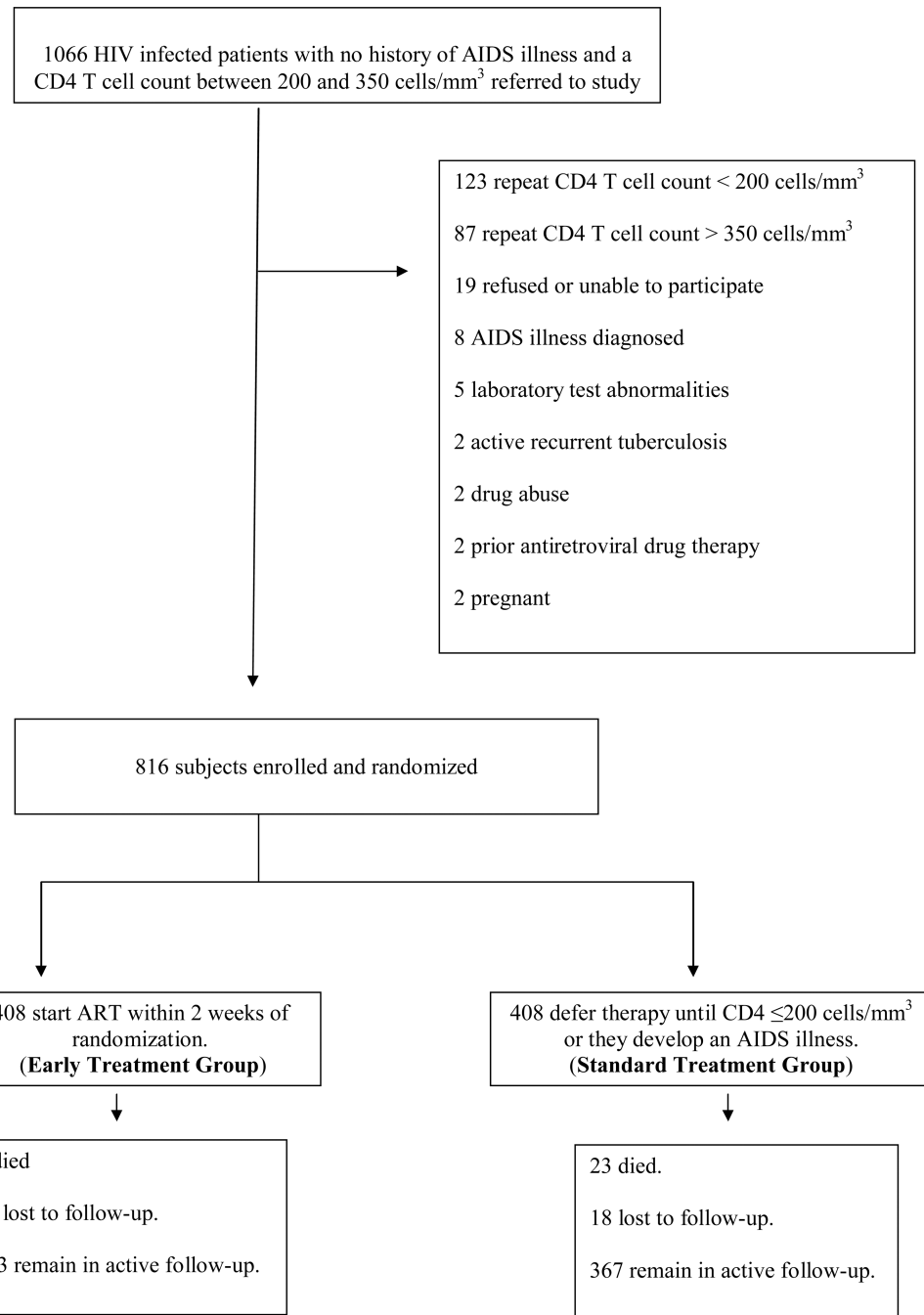
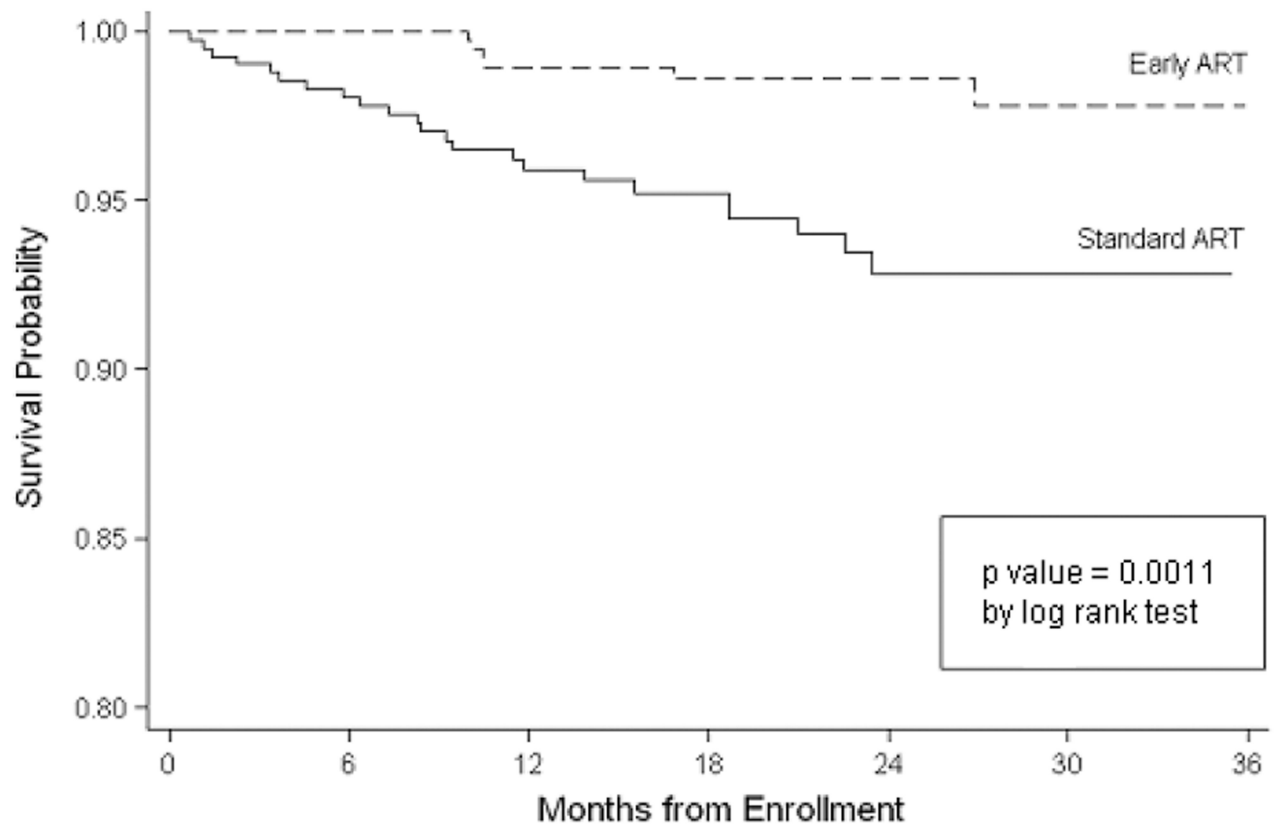


Figure 1.
Trial profile

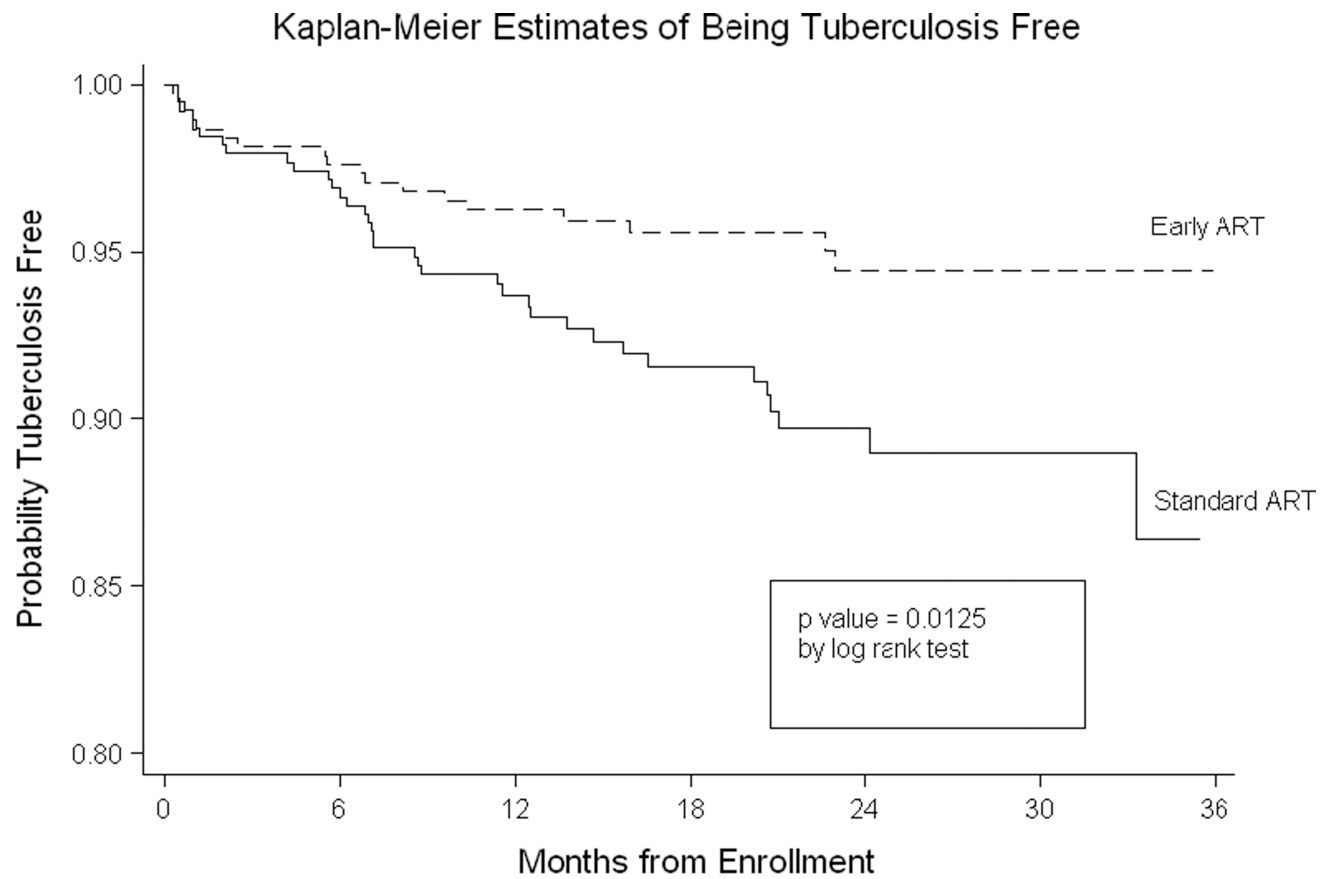
Kaplan-Meier Estimates of Survival



No at risk:

Early	408	327	153	25
Standard	408	309	137	22

Figure 2.



No at risk :

Early	380	302	140	20
Standard	393	288	122	16

Figure 3.

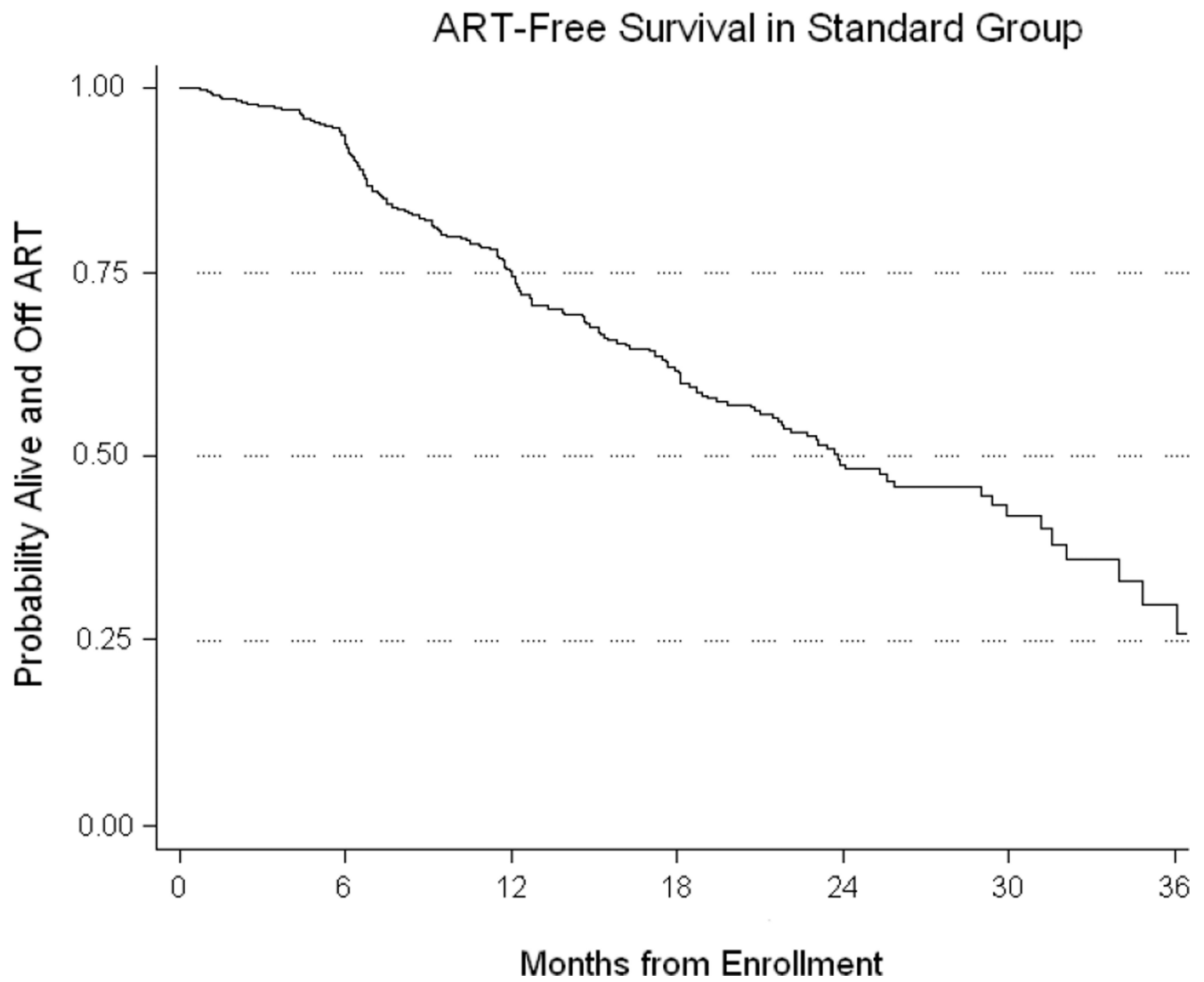


Figure 4.

Table 1

Baseline Characteristics of Participants

Characteristics	Early Group N = 408	Standard Group N = 408
Age – years		
Median	40	40
(Interquartile range)	(34 – 46)	(32 – 47)
Female – no. (%)	241 (59)	229 (56)
Education – no. (%)		
Never went to school	133 (33)	120 (29)
Primary school	122 (30)	124 (30)
Secondary school or more	153 (38)	164 (40)
Annual wage less than \$100/year – no. (%)	259 (63)	254 (62)
Living with spouse or partner – no. (%)	177 (43)	164 (40)
WHO HIV clinical stage – no. (%)		
Stage 1, no symptoms	135 (33)	126 (31)
Stage 2	199 (49)	219 (54)
Stage 3	74 (18)	63 (15)
Pulmonary tuberculosis – no. (%)	28 (7)	15 (4)
CD4 T-cell count – per mm ³		
Median	280	282
Interquartile range)	(250 – 305)	(250 – 310)
Body mass index – kg/m ²		
Median	21.3	21.0
(Interquartile Range)	(19.6 – 23.7)	(19.2 – 23.4)
Hemoglobin – g/dl		
Median	11.5	11.4
Interquartile range	(10.3 – 12.6)	(10.3 – 12.5)