



Published in final edited form as:

N Engl J Med. 2011 October 20; 365(16): 1482–1491. doi:10.1056/NEJMoa1013607.

Timing of Antiretroviral Therapy for HIV-1 Infection and Tuberculosis

D. V. Havlir, M. A. Kendall, P. Ive, J. Kumwenda, S. Swindells, S. S. Qasba, A. F. Luetkemeyer, E. Hogg, J. Rooney, X. Wu, M. C. Hosseinipour, U. Lalloo, V. G. Veloso, F. F. Some, N. Kumarasamy, N. Padayatchi, B. R. Santos, S. Reid, J. Hakim, L. Mohapi, P. Mugenyi, J. Sanchez, J. R. Lama, J. W. Pape, F. R. Sattler, A. Asmelash, E. Moko, F. Sawe, J. Andersen, and I. Sanne for the AIDS Clinical Trials Group Study A5221

University of San Francisco, San Francisco, CA (DVH and AFL), Harvard School of Public Health, Boston, MA (MAK, XW, and JA), University of Witwatersrand, Johannesburg, South Africa (PI and IS), College of Medicine Johns Hopkins Project, Blantyre, Malawi (JK), University of Nebraska, Omaha, NE (SS), National Institutes of Health, Bethesda, MD (SSQ), Social & Scientific Systems, Silver Spring, MD (EH), Gilead Sciences, Foster City, CA (JR), Kamuzu Central Hospital, University of North Carolina Project, Lilongwe, Malawi (MCH) University of KwaZulu-Natal, Durban, South Africa (UL); Brazilian Ministry of Health/Fiocruz Institute, Rio de Janeiro, Brazil (VGV), Moi University Faculty of Health Sciences, Eldoret, Kenya (FFSome), YRG Centre for AIDS Research and Education, Voluntary Health Services, Chennai, India (NK), CAPRISA eThekweni Clinical Research Site, Durban, South Africa (NP), Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil (BRS), Centre for Infectious Disease Research in Zambia HIV/AIDS Clinical Trials Unit, Lusaka, Zambia (SR), Parirenyatwa CRS, Harare, Zimbabwe (JH), Chris Hani Baragwanath Hospital ACTG CRS, Soweto, South Africa (LM), Joint Clinical Research Centre, Kampala, Uganda (PM), Asociacion Civil Impacta Salud y Educacion – IMPACTA, Miraflores CRS, Lima, Peru (JS), Investigaciones Medicas en Salud - INMENSA. Lince CRS Lima, Peru (JRL), Les Centres GHESKIO, Port-au-Prince, Haiti (JWP), University of Southern California CRS, Los Angeles, California (FRSattler), Botswana Harvard Aids Institute CRSs, Gaborone and Molepolole, Botswana (AA and EM), Kenya Medical Research Institute/Walter Reed Project and U.S. Military HIV Research Program, Kericho, Kenya (FSawe)

Abstract

Background—Antiretroviral therapy (ART) is indicated during tuberculosis (TB) treatment of patients infected with HIV-1, but the urgency to start ART at TB diagnosis for patients of varying levels of immune compromise is not known.

Methods—We conducted an open label, randomized study comparing immediate (within 2 weeks of TB treatment initiation) to early (8–12 weeks) ART among HIV-1 infected patients with CD4+ lymphocytes < 250/mm³ and suspected TB. The primary study endpoint was proportion of patients who survived without an AIDS-defining illness at 48 weeks.

Results—809 patients with median baseline CD4+ lymphocytes of 77 cells/mm³ and HIV-1 RNA of 5.43 log₁₀ copies/mL were enrolled. In the immediate arm, 12.9% of patients experienced an AIDS-defining illness or death by 48 weeks compared to 16.1% in the early arm (p=0.45; 95% confidence interval (CI) for difference: –1.8%, 8.1%). In patients with screening CD4+ lymphocytes <50 cells/mm³, 15.5% of patients on the immediate arm vs. 26.6% on early ART experienced an AIDS defining illness or death (p=0.02; difference CI: 1.5%, 20.5%). TB immune

Address reprint requests to Dr. Havlir at University of California, San Francisco, 995 Potrero Avenue, Building 80, Ward 84, San Francisco, CA 94110-2897, dhavlir@php.ucsf.edu.

† Authors' full names and degrees, along with members of the A5221 study team, are listed in the Supplementary Appendix

reconstitution inflammatory syndrome (IRIS) was more common with immediate ART (11% vs. 5%; $p=0.002$). Viral suppression at 48 weeks was 74% and did not differ between arms ($p=0.38$).

Conclusion—Overall, immediate ART did not reduce AIDS-defining illnesses and death compared to early ART. For persons with CD4+ lymphocytes < 50 cells/mm³, immediate ART had 42% less AIDS defining illnesses and death compared to early ART. (ClinicalTrials.gov number NCT00108862.)

INTRODUCTION

Management of patients with tuberculosis (TB) and newly identified HIV-1 infection is one of the most challenging aspects of HIV medicine. Antiretroviral therapy (ART) must be started during TB treatment;^{1, 2} yet starting ART very early in the course of TB therapy increases pill burden, potential drug toxicity and the risk of TB immune reconstitution inflammatory syndromes (IRIS).^{3, 4} For these reasons, programs, providers, and patients are reluctant to start ART during the intensive eight-week induction phase of TB therapy where the burden and toxicity of TB medications are greatest. Conversely, delaying ART until after the completion of TB therapy increases AIDS-related morbidity and mortality.² The optimal timing of ART for patients during TB therapy is thus a critical question to address because over a half million persons die annually from HIV-associated TB.⁵

We designed a strategy trial to evaluate the optimal timing of ART during TB therapy that included subjects with both confirmed and suspected TB. This population reflects the common clinical situation where the decision to start or delay ART must be made before a definitive TB diagnosis is made, due to the current limitations of and access to TB diagnostics.⁶ We sought to include patients from a wide geographic spectrum to maximize generalizability of the findings and to inform policy.

METHODS

Study Population

The study population included HIV-1 infected persons 13 years of age and older with CD4+ lymphocytes < 250 cells/mm³, naïve to ART, with confirmed or probable TB. Confirmed TB was defined by demonstration of acid fast bacilli from sputum or lymph node or positive TB culture from sputum, lymph node, or other sterile site. Probable TB required clinician's assessment that signs and symptoms merited empiric TB therapy. Patients were required to have received 1 to 14 days of a rifamycin-based TB treatment. Entry criteria also included absolute neutrophil count ≥ 500 cells/mm³; hemoglobin ≥ 7 g/dL; platelet count $\geq 50,000$ /mm³; AST, ALT and bilirubin ≤ 5 times the upper limit of normal; Karnofsky status ≥ 20 ; and no known or suspected multidrug resistant (MDR) or extensively drug resistant TB. All participants gave written informed consent.

Study Design

This was a randomized, open-label, 48-week study comparing immediate and early ART in persons with HIV-1 infection initiating therapy for TB. Immediate ART was initiated within 2 weeks and early therapy between 8–12 weeks after initiation of TB treatment. Randomization was stratified by screening CD4+ < 50 vs. ≥ 50 cells/mm³ and balanced by site.

The study-provided ART regimen consisted of efavirenz 600 mg daily (Stocrin[®], provided by Merck) and a fixed-dose combination of emtricitabine (FTC) 200 mg daily and tenofovir disoproxil fumarate (TDF) 300 mg daily, formulated as Truvada[®] (provided by Gilead Sciences). Substitutions of antiretroviral drugs were permitted for toxicity management. TB

therapy was provided to the patients by the sites according to the country's national TB guidelines. The protocol was approved by the institutional review boards or ethics committees at all sites.

Clinical and laboratory evaluations were conducted at entry, weeks 4, 8, 12, 16 and every 8 weeks thereafter until 48 weeks. Plasma HIV-1 RNA (Roche Amplicor assay) and CD4+ counts were measured at Division of AIDS (DAIDS) certified laboratories. Adverse events were graded with the National Institute of Allergy and Infectious Diseases (NIAID) DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.⁷

Study Endpoints

The primary study endpoint was the proportion of participants who survived to week 48 without a new AIDS- defining event. An independent blinded reviewer assessed AIDS- defining events based on standardized ACTG definitions. Cause of death was reviewed by the study team. TB IRIS cases were classified by a blinded reviewer and required at least one major or two minor clinical criteria.⁸ Concurrent ART was not required to qualify as TB IRIS.³

Statistical Analysis

As this was a strategy study, all participants meeting clinical eligibility criteria were included in analyses. Participants were followed up to 48 weeks whether or not they started ART as scheduled. The target sample size of 400/arm would provide 90% power (two-sided $\alpha = 0.05$) to detect a difference of 15% failure in the immediate arm vs. 25% in the early arm, adjusted for 10% loss to follow-up and interim analyses. Treatment assignments were generated by a central computer using permuted blocks within strata.

Estimated proportions surviving without a new AIDS event at 48 weeks and failure-time plots were calculated using the Kaplan-Meier method.⁹ Failure was defined at the first qualifying event. Stratified tests and confidence intervals as well as interactions with respect to the primary endpoint were calculated by weighting by the inverse of the Greenwood's variance in each CD4+ stratum.¹⁰ Two pre-specified subgroup analyses of the primary endpoint by CD4 strata and TB confirmation level were performed and reported. Two post-hoc subgroup analyses of the primary endpoint by body mass index (BMI) and an analysis of mortality were performed; the BMI results were reported. These analyses were tested in the same manner as above. Unstratified log rank, Fisher's exact, Pearson chi-square, and Wilcoxon tests were used to assess between-group differences in secondary endpoints.

A NIAID DSMB monitored the trial annually. Pre-specified interim reviews of efficacy employed the O'Brien-Fleming method¹¹ with a Lan-Demets spending function.¹² Two efficacy analyses were presented to the DSMB. Adjusted for these analyses, *p*-values for the primary endpoint were required to be ≤ 0.0492 to be considered statistically significant. Confidence intervals related to the primary endpoint were similarly adjusted.

RESULTS

Study Subjects

From September 2006 to August 2009, 809 subjects enrolled (Figure 1) from 4 continents and 26 clinical research sites (Table 1). Three were medically ineligible, removed from the study, and excluded from the analysis. Subjects had a median (IQR) baseline CD4+ of 77 cells/mm³ (34, 146); 46% of subjects had confirmed TB. Among 120 subjects with baseline TB drug susceptibility testing, 8 had isoniazid resistance, 5 had MDR TB, and 3 had single-

drug resistance to rifampin, pyrazinamide, or ethambutol. Trimethoprim-sulfa prophylaxis was used in 94% of subjects.

Primary Outcome

There were 26 AIDS and 26 death events in the immediate arm and 37 AIDS and 27 death events in the early arm (Table 2) with no difference between the arms (12.9% in immediate ART versus 16.1% in early; 95% CI for difference: -1.8%, 8.1%; stratified $p=0.45$; Figure 2). In pre-specified analyses of the primary endpoint within CD4+ strata, the rate of AIDS or death was significantly lower in subjects in the <50 cells/mm³ CD4+ stratum in the immediate compared to the early arm (15.5% versus 26.6%; CI for difference: 1.5%, 20.5%; $p=0.02$); there was no difference within the ≥ 50 cells/mm³ CD4+ stratum ($p=0.67$). There was no interaction between CD4+ stratum and arm ($p=0.13$). When the analysis was performed within subgroups defined by confirmed or probable TB, there were no differences between the arms (stratified $p=0.21$ and 0.35 , respectively); results by CD4+ stratum within these subgroups were consistent with the primary result. Within those with low BMI at baseline (≤ 18.5 kg/m²), there were fewer events in the immediate arm (stratified $p=0.06$), largely driven by results in the <50 cells/mm³ CD4+ stratum, with significantly fewer events in the immediate arm (15.2% vs. 38.2%; CI for difference: 8.0%, 37.8%; $p=0.003$).

The most common AIDS events for the primary outcome were extrapulmonary cryptococcal disease, candida esophagitis and Kaposi's sarcoma (Table 3). Overall, there were 31 and 37 deaths in the immediate and early arms, respectively. Sixty-eight percent (21/31) of deaths in the immediate arm and 57% (21/37) in the early arm were attributed to HIV-related disease including progression of TB. The 21 deaths attributed to HIV-related disease included: bacterial infection or sepsis (10), cryptococcal meningitis (5), cytomegalovirus disease (2), Mycobacterium avium complex (2), toxoplasmosis (1), lymphoma (1). Among the 21 deaths attributed to TB, there were 14 in the immediate and 7 in the early arm; $p=0.18$. Twelve of these deaths were ascribed to pulmonary TB, and 8 deaths to extra pulmonary TB, including 4 cases of reported central nervous system tuberculosis.

In a sensitivity analysis including 23 patients with a single-bacterial pneumonia episode as primary endpoints, results of the study did not change (14.6% in immediate vs. 19.7% in early arms; CI for difference: -0.2%, 10.4%; stratified $p=0.14$). However, the difference between the arms among subjects in the <50 cells/mm³ CD4+ stratum was amplified (16.2% versus 31.0; CI for difference: 4.9%, 24.6%; $p=0.003$).

HIV RNA and CD4 Response to Antiretroviral Therapy

Suppression of plasma HIV RNA ≤ 400 copies/mL was achieved in 95% of 663 subjects with available data by 48 weeks (Table 4). In all 806 subjects, 74% achieved viral suppression at the end of 48 weeks, with no difference between arms ($p=0.38$). Thirty-five subjects met the definition of virologic failure with no difference between arms. The median change in CD4+ lymphocytes at 48 weeks was 156/mm³ in 666 subjects and was not different between arms ($p=0.49$).

TB Immune Reconstitution Inflammatory Syndrome

Sixty-two (8% of 806) subjects met the criteria for the TB IRIS, 43 (11%) subjects on the immediate and 19 (5%) on the early arms at a median of 4.6 and 11.7 weeks from TB treatment start in subjects randomized to the immediate versus early arms, respectively ($p<0.001$). Four events in the early arm occurred in patients prior to ART initiation. Median times to resolution of symptoms were 75 and 69 days in the immediate versus early arms. Prednisone was utilized in 29 of the 62 subjects for a median duration of 15 days. No deaths were associated with patients classified as having TB IRIS.

Adverse Events

Grade 3 or 4 signs or symptoms were reported in 18% of subjects and were comparable between study arms. Constitutional symptoms including fever and weight loss were the most common grade 3 or 4 event occurring in 8% of patients. Grade 3 or 4 laboratory abnormalities were reported in 46% of patients and were comparable between study arms; the notable exceptions were neutropenia (36 versus 69 subjects, $p=0.0004$) and thrombocytopenia (3 versus 13 subjects, $p=0.01$), with fewer events in the immediate arm than in the early arm. Twenty-one of 783 subjects who started ART changed regimen, 14 on the immediate and 7 on the early arm. Fifty six percent of patients completed TB treatment without TB regimen modification or interruption, with no difference between the arms.

DISCUSSION

Our study demonstrates ART can be safely administered early in the onset of TB treatment and that the urgency of starting ART during the course of TB therapy is dependent on the immune status of the patient. For patients with CD4+ counts below 50 cells/mm³, AIDS-related illnesses and mortality were reduced by 42% from 26.6% to 15.5% in those who started ART two weeks after start of TB treatment compared to those who started 8 to 12 weeks after initiation of TB therapy. That such a small delay in time to initiate ART for those with low CD4+ T lymphocytes would have such a detrimental effect on AIDS and mortality highlights the vulnerability and suppression of the host immune system to AIDS complications in the setting of TB, and the remarkable capacity for ART to abrogate this effect rapidly.

Our study shows that for those with CD4+ lymphocytes greater than 50 cells/mm³, waiting 8–12 weeks after the initiation of TB therapy did not confer any increased risk of an AIDS-defining illness or death and was associated with less TB IRIS. For several reasons including TB IRIS, this brief delay in starting ART may simplify TB management, although TB IRIS still occurred in the early treatment arm. Our study should not be interpreted to indicate that there is no urgency to starting ART in this group of patients; indeed, delaying ART until after completion of TB therapy increased mortality in a concurrent randomized study.²

Results from this trial complement and extend findings from other concurrent randomized studies of ART among HIV-1 infected persons with TB. Mortality in the CAMELIA study (median entry CD4+ lymphocyte counts of 25 cells/mm³(IQR,10,56)) and death or AIDS defining illness in the low CD4+ strata (<50 cells/mm³) of our study and in the SAPIT study were all significantly reduced among patients starting immediate vs early ART.^{13, 14} Our study also extends the generalizability of prior studies through its inclusion of these patients from four continents and those with either confirmed or probable TB.

Clinicians are often hesitant to start ART because of potential medication toxicity and laboratory abnormalities that may occur when ART and TB therapy are started in close proximity. Overall, there was no difference in these events between the immediate and early ART strategies; interestingly, there was a higher frequency of neutropenia and thrombocytopenia in the early as compared to the immediate arm. The explanation for the difference is likely multi-factorial, although immediate ART could have exerted a more rapid effect on reversing bone marrow suppression characteristic of untreated HIV disease.

Consistent with earlier studies, there was a higher rate of TB IRIS in the immediate compared to early ART arm of the study.⁸ However, the more frequent and earlier occurrence of these events did not lead to worse overall outcomes. Prednisone was used to alleviate symptoms by about half of the subjects with TB IRIS in our study; the optimal use

of prednisone in this setting to reduce symptoms without increasing susceptibility to masking other complications is an area of active study.¹⁵

Assessment of optimal ART strategies must take into account rates of plasma HIV-1 RNA suppression and CD4+ lymphocyte response. Starting ART early could potentially jeopardize adherence and lead to higher rates of virologic failure, development of viral resistance and worse immune response. Patients simultaneously treated for both TB and HIV-1 have an extremely high pill burden and side effects of the antimicrobial agents are overlapping with not only each other but also with the clinical manifestations of TB. Thus, it is reassuring that despite the additional burden to adhere to a complex treatment regimen with the immediate start of ART, participants on the immediate arm achieved similar rates of viral suppression at 48 weeks on study compared those who delayed treatment until at least 8 weeks of TB treatment. Similar results were observed in ACTG A5164, an ART strategy study for patients with AIDS conditions other than TB.¹⁶

Patients with known drug-resistant TB were ineligible for our study; thus results here may not be applicable to this population.¹⁷ For patients with TB meningitis where TB IRIS can lead to inflammation in the central nervous system, our study does not provide definitive guidance. A recent randomized study of adults exclusively with TB meningitis in Viet Nam reported extraordinary high mortality rates in both arms and no benefit of immediate versus early ART.¹⁸ These exceptions withstanding, our study provides evidence that it is feasible and safe to start ART within 2 weeks of TB treatment start, and that for individuals with CD4+ lymphocytes <50 cells/mm³, it significantly reduces morbidity and mortality.

Applying the findings of this study to the clinical setting will require a concerted and coordinated effort on behalf of TB and HIV programs worldwide. Prompt HIV testing among TB patients is critical to the application of our findings.¹⁹ Although progress is visible on this front, less than half of patients in sub-Saharan Africa who reported to TB control programs had HIV testing in 2008.⁵ Implementation of these findings also means that ART services must either be available at the TB clinic or there must be a seamless referral to HIV clinics that can rapidly absorb patients and initiate ART.^{20, 21} Time requirements for HIV and ART adherence counseling prior to ART initiation will need to be balanced with the substantial risk of morbidity and mortality with treatment delay. Training for TB IRIS identification and treatment may need to be increased. Implementation studies that identify barriers to adaptation of the clinical practice of immediate ART for patients with low CD4 cell counts newly diagnosed with TB are clearly warranted to ensure the benefits of this research are realized.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We express our deep gratitude to the study participants. We also would like to acknowledge the exceptional efforts by the site principal investigators and staff to conduct the study, to coordinate efforts with the in country TB Control programs and to help build capacity of integrated HIV-TB services. We thank Constance Benson, MD for her pivotal contributions and ACTG leadership, our data managers Carol Suckow BSN and Lynne Jones BS, DAIDS pharmacist Ana Martinez R Ph, protocol pharmacist Francesca Aweeka Pharm D, field representative Janet Nicotera RN BSN, laboratory technologist Patty Anthony BS CLS, laboratory data coordinator, Travis Behm BS, community representative Martha Tholanah Mensah-King, and our sponsors from the National Institute of Allergy and Infectious Diseases Division of AIDS, the members of the Data, Safety and Monitoring Board and Gilead Sciences and Merck Pharmaceuticals.

REFERENCES

1. Sterling TR, Pham PA, Chaisson RE. HIV infection-related tuberculosis: clinical manifestations and treatment. *Clin Infect Dis*. 2010; 50 Suppl 3:S223–S230. [PubMed: 20397952]
2. Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med*. 2010; 362(8):697–706. [PubMed: 20181971]
3. Breen RA, Smith CJ, Bettinson H, et al. Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection. *Thorax*. 2004; 59(8):704–707. [PubMed: 15282393]
4. Burman W, Weis S, Vernon A, et al. Frequency, severity and duration of immune reconstitution events in HIV-related tuberculosis. *Int J Tuberc Lung Dis*. 2007; 11(12):1282–1289. [PubMed: 18229435]
5. Global Tuberculosis Control: A short update to the 2009 report. 2009. (Accessed at http://whqlibdoc.who.int/publications/2009/9789241598866_eng.pdf)
6. Pai M, Minion J, Sohn H, Zwerling A, Perkins MD. Novel and improved technologies for tuberculosis diagnosis: progress and challenges. *Clin Chest Med*. 2009; 30(4):701–716. viii. [PubMed: 19925962]
7. Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. NIAID.NIH.gov. 2004. (Accessed at <http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/daidaegradingtable.pdf>)
8. Meintjes G, Lawn SD, Scano F, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis*. 2008; 8(8):516–523. [PubMed: 18652998]
9. Kaplan E, Meier P. Nonparametric estimation of incomplete observations. *J Am Stat Assoc*. 1958; (53):457–481.
10. Kalbfleisch, J.; Prentice, R. *The Statistical Analysis of Failure Time Data*. New York, NY: John Wiley and Sons; 1980.
11. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics*. 1979; 35(3): 549–556. [PubMed: 497341]
12. Lan K, DeMets D. Discrete sequential boundaries for clinical trials. *Biometrika*. 1983; 70(3):659–663.
13. Abdool Karim, S.; Naidoo, K.; Padayatchi, N., et al. *Optimal Timing of ART during TB Therapy: Findings of the SAPiT Trial*; 18th Conference on Retroviruses and Opportunistic Infections; Boston, MA: 2011.
14. Blanc, FX.; Sok, T.; Laureillard, D., et al. *AIDS 2010. Austria: Vienna; 2010. Significant enhancement in survival with early (2 weeks) vs late (8 weeks) initiation of highly active antiretroviral treatment (HAART) in severely immunosuppressed HIV-infected adults with newly diagnosed tuberculosis.*
15. Meintjes G, Wilkinson RJ, Morroni C, et al. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. *Aids*. 2010; 24(15):2381–2390. [PubMed: 20808204]
16. Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS One*. 2009; 4(5):e5575. [PubMed: 19440326]
17. Dheda K, Shean K, Zumla A, et al. Early treatment outcomes and HIV status of patients with extensively drug-resistant tuberculosis in South Africa: a retrospective cohort study. *Lancet*. 2010; 375(9728):1798–1807. [PubMed: 20488525]
18. Torok, ME.; Yen, NTB.; Chau, TTH., et al. *Randomised Controlled Trial of Immediate Versus Deferred Antiretroviral Therapy in HIV-Associated Tuberculous Meningitis*; 49th ICAAC; San Francisco, CA: 2009.
19. Getahun H, Gunneberg C, Granich R, Nunn P. HIV infection-associated tuberculosis: the epidemiology and the response. *Clin Infect Dis*. 2010; 50 Suppl 3:S201–S207. [PubMed: 20397949]

20. Havlir DV, Getahun H, Sanne I, Nunn P. Opportunities and challenges for HIV care in overlapping HIV and TB epidemics. *Jama*. 2008; 300(4):423–430. [PubMed: 18647985]
21. Howard AA, El-Sadr WM. Integration of tuberculosis and HIV services in sub-Saharan Africa: lessons learned. *Clin Infect Dis*. 2010; 50 Suppl 3:S238–S244. [PubMed: 20397954]

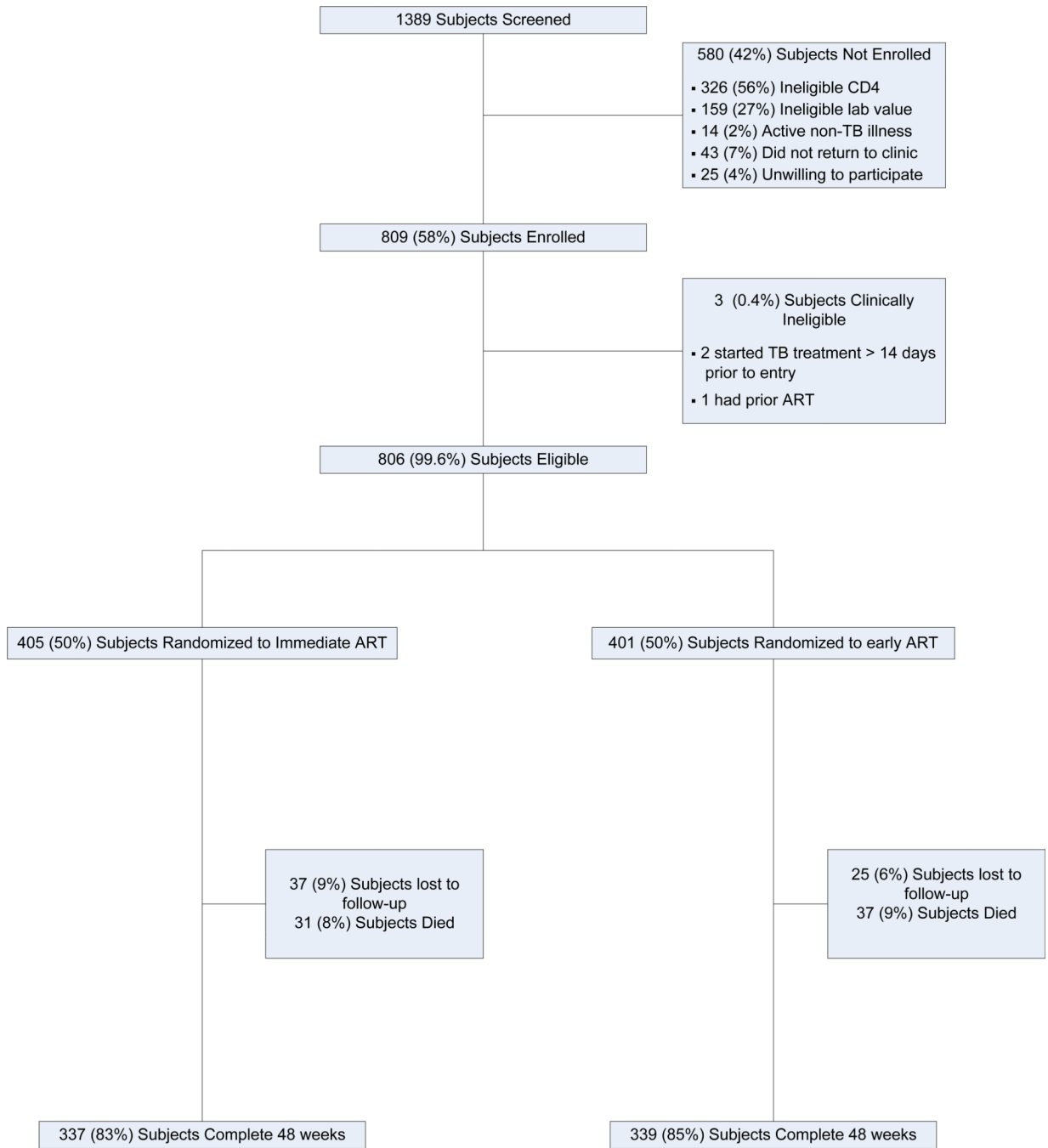
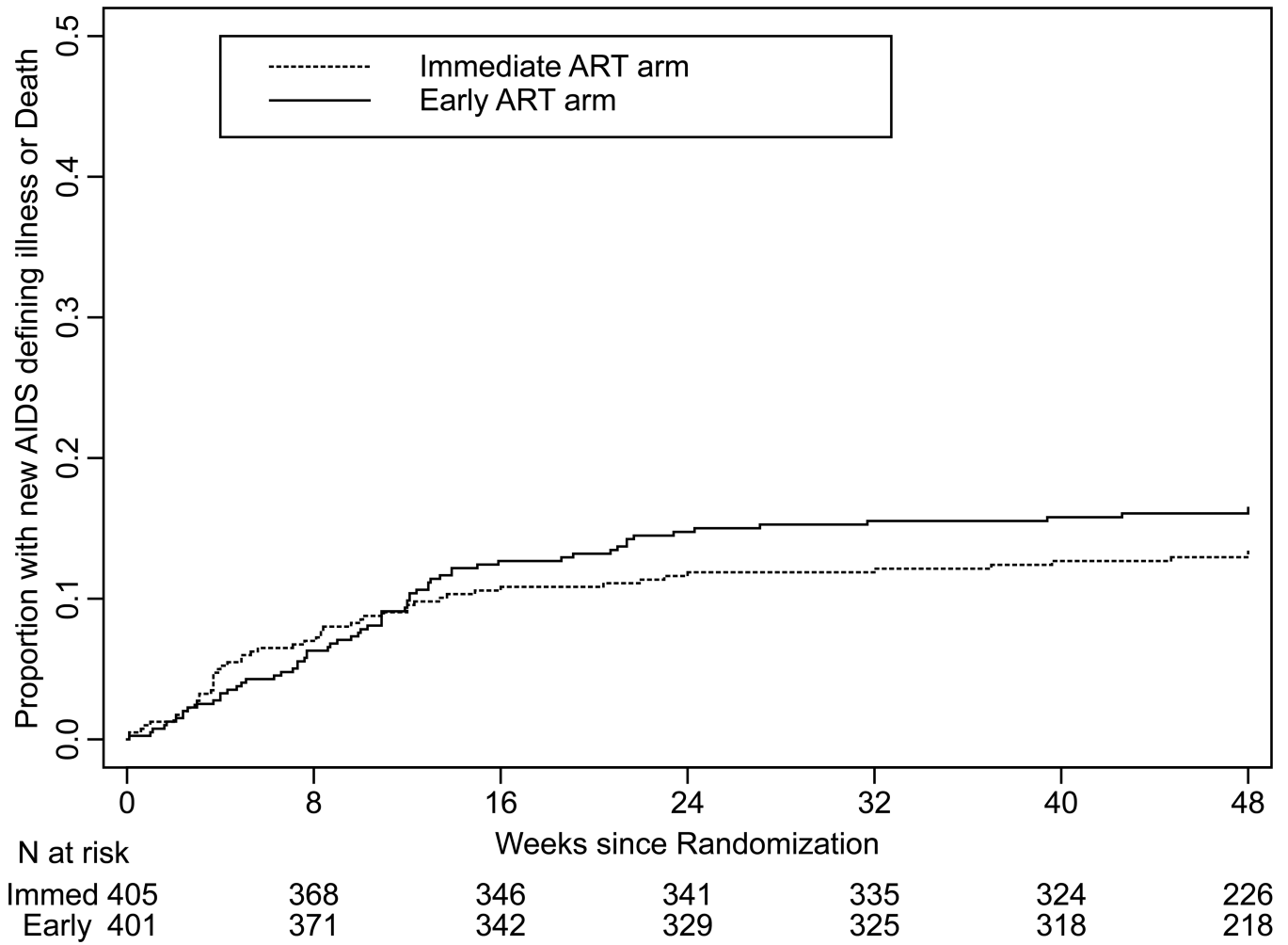


Figure 1. Enrollment and Follow-up of Study Subjects

The disposition of the subjects from screening tuberculosis suspects to study completion is shown.



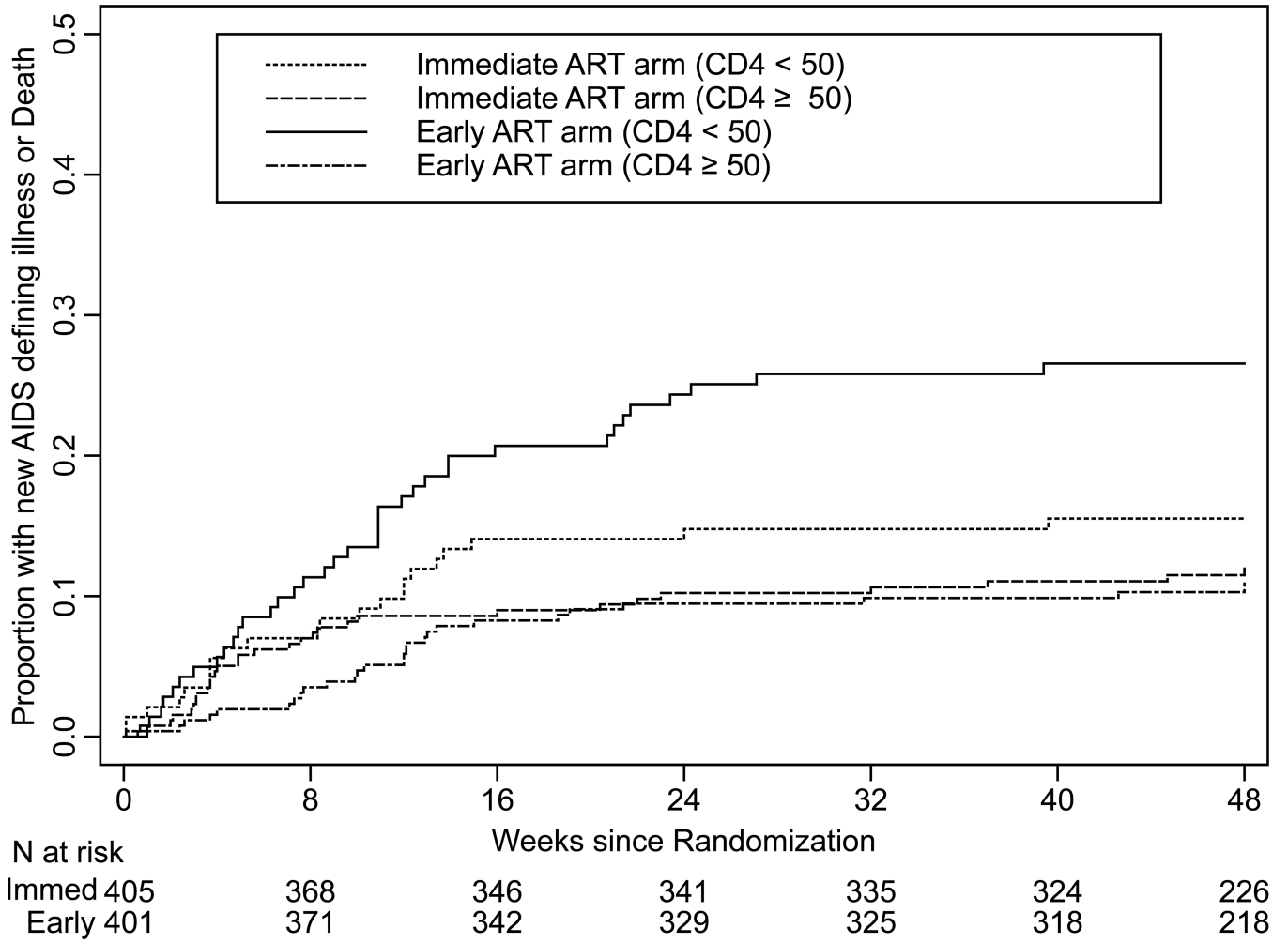


Figure 2. Time to New AIDS Defining Illness or Death

Shown are the times to the primary endpoint of AIDS defining illness or death for the entire study population (Panel A) and for the study population by CD4+ lymphocyte stratum (Panel B).

Table 1

Characteristics of the Patients

Characteristic	Immediate ART Arm (N=405)	Early ART Arm (N=401)	All Patients (N=806)
Continent – no. (%)			
Africa	275 (68)	279 (70)	554 (69)
Asia	29 (7)	23 (6)	52 (6)
North America	21 (5)	18 (4)	39 (5)
South America	80 (20)	81 (20)	161 (20)
Gender			
Male – no. (%)	266 (66)	235 (59)	501 (62)
Median (IQR) age at enrollment (yr)	34 (29, 40)	34 (29, 42)	34 (29, 41)
Tuberculosis – no. (%)			
Confirmed	193 (48)	181 (45)	374 (46)
Probable	208 (51)	218 (54)	426 (53)
Not TB	4 (1)	2 (1)	6 (1)
Median (IQR) CD4 Count (cells/mm ³)	70 (34, 146)	82 (40, 144)	77 (36, 145)
Median (IQR) HIV-1 RNA (log ₁₀ copies/mL)	5.39 (4.94, 5.79)	5.50 (5.03, 5.79)	5.43 (5.00, 5.79)
Prior AIDS diagnosis – no. (%)	26 (6)	29 (7)	55 (7)
Median (IQR) Body Mass Index (kg/m ²)	19.1 (17.3, 21.1)	19.4 (17.7, 21.8)	19.2 (17.5, 21.4)
Initial ART Regimen – no. (%) [*]			
EFV, TDF, FTC	394 (98)	368 (97)	762 (97)
Median (IQR) days of tuberculosis therapy at time of ART start	10 (7, 12)	70 (66, 75)	14 (10, 70)

* Percentage based on number of subjects who started ART in this study.

Table 2

Proportions of AIDS or Death at 48 weeks

Study Population	Immediate ART Arm		Early ART Arm	P Value
	N	Proportion with AIDS or death by 48 weeks		
All Patients	806	12.9%	16.1%	0.45*
Within CD4 Stratum:				
< 50 cells/mm ³	285	15.5%	26.6%	0.02
≥ 50 cells/mm ³	521	11.5%	10.3%	0.67
Subsets:				
Confirmed TB at Entry	374	13.8%	19.7%	0.21*
Within CD4 Stratum:				
< 50 cells/mm ³	151	17.9%	31.4%	0.06
≥ 50 cells/mm ³	223	10.8%	12.1%	0.77
Suspected TB at Entry	432	15.4%	19.7%	0.35*
Within CD4 Stratum:				
< 50 cells/mm ³	134	14.1%	30.5%	0.02
≥ 50 cells/mm ³	298	15.9%	14.5%	0.75
Low BMI (≤18.5 kg/m ²) at Entry	332	16.3%	26.5%	0.06*
Within CD4 Stratum:				
< 50 cells/mm ³	130	15.2%	38.2%	0.003
≥ 50 cells/mm ³	202	16.9%	17.8%	0.88

* Stratified by CD4 stratum

Table 3

Frequency of AIDS-Defining Illnesses in the Primary Study Endpoint

AIDS-Defining Illness	Immediate ART Arm	Early ART Arm	Total Patients
Extrapulmonary cryptococcus	6	7	13
Esophageal candidiasis	4	8	12
Kaposi's sarcoma	3	8	11
Pneumocystis pneumonia	3	3	6
Toxoplasma ncephalitis	2	3	5
Cytomegalovirus disease	2	2	4
Mycobacteria, non TB, disseminated	2	1	3
Chronic or visceral herpes simplex	1	2	3
Chronic intestinal cryptosporidiosis	1	1	2
Histoplasmosis	1	1	2
Recurrent bacterial pneumonia	1	0	1
HIV associated cardiomyopathy	0	1	1

Table 4

HIV RNA and CD4 Response to Antiretroviral therapy

Variable	Week 8*		Week 16		Week 24		Week 32		Week 48	
	N#		N		N		N		N	
HIV RNA < 400 cp/mL; N (%)										
Immediate ART	370	273 (74)	361	314 (87)	355	320 (90)	349	312 (89)	331	293 (89)
Early ART	380	4(1)	365	237 (65)	349	295 (85)	347	313 (90)	332	301 (91)
CD4 cells/mm ³ ; median(IQR)										
Immediate ART	368	200(121,275)	357	207(134,279)	350	218(145,294)	346	219(154,305)	333	246(169,352)
Early ART	379	77(34,140)	364	193(113,289)	347	207(130,296)	343	221(150,308)	333	250(173,343)
CD4 cells/ mm ³ change from entry: median(IQR)										
Immediate ART	368	93(48,172)	357	107(65,168)	350	124(72,189)	346	132(77,198)	333	160(91,240)
Early ART	379	-2(-23, 14)	364	95 (43,165)	347	104(60,173)	343	124(71,204)	333	151(94, 228)

* Weeks denote the duration of the patient on the study;

denotes ---

Table 5

Grade 3 or 4 Clinical Events or Laboratory Abnormalities

Event –no(%)	Immediate (n=405)	Early (n=401)	Total (n=806)
Grade 3 or 4 Clinical Event			
Constitutional	31 (8)	31 (8)	62 (8)
Respiratory	17 (4)	16 (4)	33 (4)
Cardiac/Circulatory	11 (3)	7 (2)	18 (2)
Gastrointestinal	17 (4)	20 (5)	37 (5)
Skin	11 (3)	11 (3)	22 (3)
Neurological	22 (5)	28 (7)	50 (6)
Grade 3 or 4 Laboratory Abnormality			
Absolute Neutrophil count <750/mm ³ †	36 (9)	69 (17)	105 (13)
Hemoglobin	28 (7)	22 (5)	50 (6)
Platelets†	3 (<1)	13 (3)	16 (2)
Hepatic aminotransferases >5 times ULN‡	26 (6)	41 (10)	67 (8)
Creatinine >1.9 times ULN	12 (3)	7 (2)	19 (2)
Chemistry, general	65 (16)	55 (14)	120 (15)
Any 3 or 4 Adverse Event	177 (44)	190 (47)	367 (46)

†P<0.05

‡Included in this category were aspartate aminotransferase, alanine aminotransferase, or both.