Published in final edited form as:
J Int Assoc Provid AIDS Care. 2013 ; 12(4): 270–277. doi:10.1177/1545109712469684.

Predictors of Clinical Progression in HIV-1-Infected Adults Initiating Combination Antiretroviral Therapy with Advanced Disease in the Asia-Pacific Region: Results from the TREAT Asia HIV Observational Database

H. Byakwaga, MBChB, PhD[1], **K. Petoumenos, BSc, MA, MPH, PhD**[1], **J. Ananworanich, MD, PhD**[2], **F. Zhang, MD**[3], **M. A. Boyd, MA, BA, BM, BS, MHID, DCTMandH**[1], **T. Sirisanthana, MD**[4], **P. C. K. Li, MD, MBBS**[5], **C. Lee, MD, MBBS**[6], **C. V. Mean, MD**[7], **V. Saphonn, MD, PhD**[7], **S. F. S. Omar, MD, MBBS**[8], **S. Pujari, MD, AAHIVS**[9], **P. Phanuphak, MD, PhD**[2], **P. L. Lim, MD, MPH, FAMS**[10], **N. Kumarasamy, MD, MBBS, PhD**[11], **Y. M. A. Chen, MD, MS, ScD**[12], **T. P. Merati, MD, PhD**[13], **S. Sungkanuparph, MD**[14], **R. Ditangco, MD**[15], **S. Oka, MD, PhD**[16], **G. Tau, MD**[17], **J. Zhou, BMed, MPH, PhD**[1], **M. G. Law, MG, MA, MSc, PhD**[1], and **S. Emery, BSC, PhD**[1]

[1]The Kirby Institute, University of New South Wales, Sydney, Australia [2]The HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT)/The Thai Red Cross AIDS Research Centre and South East Asia Research Collaboration, Bangkok, Thailand [3]Chinese Center for Disease Control and Prevention, Beijing Ditan Hospital, Beijing, China [4]Research Institute for Health Sciences, Chiang Mai, Thailand [5]Queen Elizabeth Hospital, Hong Kong, China [6]Hospital Sungai Buloh, Kuala Lumpur, Malaysia [7]National Center for HIV/AIDS, Dermatology & STDs, Phnom Penh, Cambodia [8]University of Malaya, Kuala Lumpur, Malaysia [9]Institute of Infectious Diseases, Pune, India [10]Tan Tock Seng Hospital, Singapore [11]YRG Centre for AIDS Research and Education, Chennai, India [12]Taipei Veterans General Hospital and AIDS Prevention and Research Centre, National Yang-Ming University, Taipei, Taiwan [13]School of Medicine Udayana University and Sanglah Hospital, Denpasar, Bali, Indonesia [14]Ramathibodi Hospital, Mahidol University, Bangkok, Thailand [15]Research Institute for Tropical Medicine, Manila, Philippines [16]International Medical Centre of Japan, Tokyo, Japan [17]Port Moresby General Hospital, Port Moresby, Papua New Guinea

Abstract

The majority of HIV-infected patients in developing countries commences combination antiretroviral therapy (cART) with advanced disease. We examined predictors of disease progression in patients initiating cART with CD4 count ≤200 cells/mm^3 in the TREAT Asia HIV Observational Database. The main outcome measure was progression to either an AIDS-defining illness or death occurring 6 months after initiation of cART. We used survival analysis methods. A total of 1255 patients contributed 2696 person years of follow-up; 73 were diagnosed with AIDS and 9 died. The rate of progression to the combined end point was 3.0 per 100 person years. The factors significantly associated with a higher risk of disease progression were Indian ethnicity, infection through intravenous drug use, lower CD4 count, and hemoglobin ≤130 g/dL at 6 months.

Corresponding Author: Helen Byakwaga, MBChB, PhD, The Kirby Institute, University of New South Wales, 45 Beach Street, Coogee NSW 2034, Sydney, Australia, hbyakwaga@nchecr.unsw.edu.au.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

In conclusion, measurements of CD4 count and hemoglobin at month 6 may be useful for early identification of disease progression in resource-limited settings.

Keywords

HIV; disease progression; antiretroviral therapy; resource-limited settings

Background

The increasingly widespread use of combination antiretroviral therapy (cART) since 1996 for the treatment of HIV infection has led to significant reductions in morbidity and mortality in HIV-infected patients. As a result, the prognosis of HIV-infected individuals has improved substantially.[1–4] In recent years, global efforts to expand access to cART have increased significantly. By the end of 2008, about 4 million people were receiving treatment with antiretroviral therapy (ART) in low-to middle-income countries, a 10-fold increase over the preceding 5 years.[5] However, in resource-limited settings in Africa, Asia, and South America, where 90%of the people with HIV/AIDS live, access to cART is still limited and the majority of the patients initiates therapy with advanced disease.[6,7] Although virologicl and immunologicl responses to ART observed among HIV-1-infected individuals treated in low-income and high-income countries are similar,[6–8] the mortality in low-income countries is approximately 4 times that observed in high-income countries.[6]

Guidelines and recommendations for commencement of ART are based mainly on CD4 T-lymphocyte count. In high-income countries, plasma HIV RNA load is also considered. These thresholds have been selected based on the risk of disease progression in both prospective and randomized controlled studies.[9–12] Although current ART guidelines recommend the initiation of therapy in patients with AIDS-defining illness, or CD4 count <500 cells/mm^3,[3,13] the majority of patients in low-income countries commences ART with advanced disease and with CD4 count <200 cells/mm^3.[6] Previous studies have shown that the risk of HIV disease progression for individuals commencing ART with CD4 count ≤200 cells/mm^3 is generally double the risk for those commencing at CD4 count of 350 cells/mm^3.[11]

Understanding the factors that predict disease progression in these patients commencing cART with advanced disease could facilitate therapeutic monitoring decisions especially in those settings where laboratory testing is not readily available. In this study, we aimed to determine the predictors of progression to either an AIDS-defining illness or death occurring between 6 months and 2 years after initiation of cART in patients initiating cART with CD4 count ≤200 cells/mm^3 in the TREAT Asia HIV Observational Database (TAHOD).

Methods

The TAHOD is a collaborative cohort study currently involving 17 sites in the Asia-Pacific region (see Appendix A). Details of the study methodology have been published elsewhere.[14] In brief, approximately 200 patients were recruited from each participating clinical site. These included both ART-naive patients and those receiving ART. Recruitment was based on a consecutive series of patients attending regularly at the given site from a particular start-up time. The study was approved by the University of New South Wales Human Research Ethics Committee and by a local ethics committee for each participating site. The data collected included patient demographics: age, sex, and ethnicity; clinical information: weight, height, exposure category, AIDS-defining illness, deaths, past and

present antiretroviral (ARV) regimen, and hepatitis status; laboratory measurements: CD4 counts and hemoglobin measurements.

Patients were included in this analysis if they started the first cART regimen after January 1, 1997 and had available CD4 count data at baseline and after 6 months of cART. We used a combined end point of progression to either a new AIDS-defining illness or death occurring between 6 months and 2 years after initiation of cART. We only considered the first AIDS illness that the patient developed during this period of analysis. A modified version of the 1993 US Centers for Disease Control and Prevention AIDS case definition[15] was adopted, in which a presumptive diagnosis was available for most illnesses. Deaths from all causes were included. We defined cART as the use of 3 or more ARV agents.

Covariates included patient characteristics at the start of cART: age, sex, exposure category, Hepatitis B surface antigen status (HBV), antihepatitis C virus (HCV) antibody status (note: patients were classified as HBV positive and or HCV positive if they ever had a positive test result), history of previous AIDS illness, body mass index (BMI; calculated as the weight in kilograms divided by the square of the height in meters), CD4 count, and hemoglobin level. We also examined the patient characteristics following 6 months of cART and these included BMI, CD4 count, hemoglobin level, development AIDS illness within the first 6 months of cART, CD4 level after 6 months of cART, and the absolute change in CD4 count within the first 6 months of cART. Because of the changes in trends of treatment, prophylaxis of opportunistic infections, choice of drugs, and diagnostic tests over the period of analysis, we stratified treatment periods into 2 periods: before the year 2000, to represent the period of early use of cART and the second period was >2000 to March 2007 to represent the later use of cART.

Predictors for progression to AIDS or death were assessed by univariable and multivariable analyses using survival analysis. We considered the follow-up as a period from the date cART was initiated (baseline) to the time of first diagnosis of new AIDS illness, and date of death from any cause or the last follow-up visit before 2 years for patients who did not experience clinical progression. The multivariable model was determined using both the forward stepwise and the backward stepwise approaches, considering only covariates that were significant at the 0.10 level in the univariable analysis. The final multivariable model included only covariates that remained significant at the 0.05 level. Analyses were performed using the statistical package STATA version 10 for Windows (StataCorp, College Station, Texas).

Results

Of the 3516 patients recruited to the TAHOD by March 2007, 1664 initiated cART after January 1, 1997 and had available CD4 count data at baseline and after 6 months of therapy. A total of 1255 (75.4%) patients commenced cART with baseline CD4 count ≤200 cells/mm^3 were included in this analysis. Table 1 summarizes the characteristics of these patients at commencement of cART. The majority (886, 71%) of the patients were men, with a median age of 36 years (interquartile range [IQR], 32–42 years). The main populations were 527 (42%) Chinese, 310 (25%) Thai, and 193 (15%) Indian. Overall, the majority of patients, 1013 (81%), was infected through heterosexual contact. At initiation of cART, 638 (51%) of the patients had a history of prior AIDS-defining illness, the median CD4 count at commencement of cART was 63 (IQR, 25–130) cells/mm^3, the median hemoglobin was 120 (IQR, 106–133) mg/dL, and the median BMI was 19.9 (IQR, 17.8–22.1) kg/m^2. In all, 79% of the patients commenced cART after the year 2000. The median CD4 count after 6 months of cART was 175 (IQR, 106–268) with a mean CD4 count increase of 122 (standard

deviation, 105) cells/mm^3. In all, 76 (6%) patients developed a new AIDS-defining illness within the first 6 months of cART (Table 2).

During a follow-up period of 2696 person years, 73 patients were diagnosed with a new AIDS-defining illness and 9 died. Among the 73 new AIDS-defining illnesses, the most frequent diagnoses were *Mycobacterium tuberculosis* (either pulmonary or extra pulmonary) 25 (36%), chronic herpes simplex 8 (11%), and *Pneumocystis jiroveci* pneumonia 7 (10%).

The rate of progression to the combined end point (AIDS or death) was 3.0 per 100 person years. In multivariable analysis, a lower CD4 count at 6 months from the start of cART was significantly associated with a greater risk of disease progression (Table 3). Individuals with injection drug use as mode of HIV transmission were 3.31 times more likely to develop a new AIDS illness or die in comparison to those who acquired HIV infection through heterosexual transmission (95%confidence interval [CI], 1.33–8.24, $P = .01$), Indian patients were 2.64 times more likely to progress to AIDS or death compared to the Chinese (95% CI, 1.46–4.77, $P = .001$), and individuals with a hemoglobin level greater than 130 mg/dL at 6 months from the start of cART had a 27% lesser risk of clinical progression compared to those with a hemoglobin level less than 80 mg/dL (95% CI, 0.08–0.90, $P = .034$).

The CD4 count and hemoglobin level at the start of cART were not found to be associated with disease progression. In this study, there was no association found between HIV disease progression and other covariates that were examined; these included baseline BMI, history of AIDS illness prior to commencing cART, ART regimen, and AIDS illness occurring within the first 6 months.

Discussion

In this study of HIV-1-infected adults initiating cART with advanced disease, CD4 count and hemoglobin levels at month 6 were associated with disease progression. Individuals who acquired HIV through injection drug use were more likely to develop a new AIDS illness or die in comparison with those who acquired HIV infection through heterosexual transmission, and Indian patients had a greater risk of disease progression compared with Chinese patients. Patient characteristics at the commencement of cART, including BMI, hemoglobin, and CD4 count, were not found to be associated with disease progression.

The association of CD4 count with HIV disease progression was described early in the HIV epidemic[16] and its role in predicting HIV disease progression was defined by data from a number of prospective studies.[9–12] Baseline CD4 count has been shown to be the most significant predictor of HIV disease progression[2,17] and survival prior to the commencement of cART. Consequently, current ART guidelines recommend ART initiation based on CD4 count in preference to any single marker.[5,18] However, in the majority of patients, remarkable rises in CD4 count are observed within months following initiation of cART[19,20] and the predictive role of baseline CD4 count may perhaps decrease.[9,21–24] Data from the studies investigating specific AIDS-defining illnesses suggest that the current CD4 count compared with the CD4 count at the start of therapy is more useful in predicting the occurrence of clinical disease in HIV patients receiving cART.[25–27] Results from our study are similar to the findings from previous studies which showed that after starting cART, the CD4 count following 6 months of cART was a better prognostic factor for HIV clinical progression compared with baseline CD4 count.[9,23,28]

Despite increased access to HIV treatment in developing countries, the costs of CD4 count and HIV-RNA monitoring remain relatively high. Therefore, parameters that are easy to measure have been investigated as surrogate makers that may be useful in monitoring therapy in these countries. The decrease in hemoglobin levels has been correlated with

reducing CD4 counts, and monitoring hemoglobin levels has been shown to be useful in predicting disease progression.[29–34] Generally, initiation of cART is associated with an increase in hemoglobin levels.[29,32] Our findings are consistent with those of a previous report suggesting that in a patient population receiving cART, the most recent hemoglobin level is a stronger predictor of disease progression.[32] The BMI is a simple measure and has also been shown to predict disease progression in some studies.[33–35] A rapid decline in BMI is observed in the 6 months preceding AIDS[35] and a low BMI persistently less than 17 kg/m^2 6 months after the start of cART has been associated with a 2-fold increase in the risk of death.[36] Although BMI decline may be a useful marker of progression to AIDS, the sensitivity of this measure is only about 33%.[37] In other words, weight loss is only noted in about one-third of the HIV-infected individuals who develop AIDS; however, if weight loss is present, it is predictive for AIDS.

We observed that patients with injection drug use as mode of HIV transmission had a greater risk of disease progression compared with those who acquired HIV through heterosexual transmission. This finding is similar to findings from previous studies which showed that the rate of clinical progression was higher in patients infected through injection drug use compared with those infected through other routes.[2,23] Independent of HIV infection, these patients are known to have increased risk of death from other causes including overdose and violent causes.[38,39]

Similar to previous reports from studies of HIV-infected patients in the Asia-Pacific region, tuberculosis was the most frequently occurring AIDS-defining diagnosis.[14,40,41] The risk and prognostic significance of tuberculosis for patients enrolled in TAHOD has been published elsewhere.[40] In a report of HIV-infected patients receiving cART in programs in sub-Saharan Africa, it accounted for up to 21% of all the deaths.[42] Other commonly occurring AIDS-defining illnesses in this study were chronic herpes simplex and *P jiroveci* pneumonia. Although there was a high occurrence of AIDS-defining illnesses within the first 6 months of commencing cART in this cohort of patients, it was not significantly associated with an increased risk of subsequent disease progression. This may in part be due to the fact that by month 6, 42% of the patients had achieved a CD4 count greater than 200 cells/mm^3 and 22% of the patients had a CD4 count less than 100 cells/mm^3 compared with 64% at the start of cART. The cause of the greater morbidity and mortality observed within the first 6 months after initiation of ART[6,42] is not fully known but immune restoration disease is postulated to play a significant role.[42–44] Immune restoration disease is particularly common in low-income countries, where HIV-infected individuals have a higher prevalence of comorbidities; yet, resources for diagnostic facilities, prophylaxis, and effective treatment of opportunistic infections are limited. Moreover, individuals who have high immunodeficiency at the start of cART, as included in this study, are at a greater risk of developing immune restoration disease.[45]

This study has a number of possible limitations. First, some of the factors that have been associated with HIV disease progression in the previously published literature were not found to be associated with disease progression in this study. This may be due to the limited power of this analysis as a result of the small number of participants and end points. Second, we were not able to examine the effect of opportunistic infection prophylaxis on clinical progression because prophylaxis information was not regularly documented in this cohort. Third, viral load measurements, an important prognostic factor of disease progression, were not consistently available and therefore were not incorporated in this analysis.

In conclusion, results from this study suggest that measurement of the CD4 count and hemoglobin level after the first 6 months of cART may be useful for early identification of subsequent risk of HIV clinical progression in patients who commences cART with

advanced disease. Our findings contribute to data in the Asia-Pacific region and are especially important in resource-limited settings where the majority of patients commences cART with advanced disease and routine plasma HIV viral and CD4 count monitoring are not readily available.

Acknowledgments

The TREAT Asia HIV Observational Database is part of the Asia-Pacific HIV Observational Database and is an initiative of TREAT Asia, a program of amfAR, The Foundation for AIDS Research, with support from the National Institute of Allergy and Infectious Diseases (NIAID) of the US National Institutes of Health (NIH) as part of the International Epidemiologic Databases to Evaluate AIDS (IeDEA; grant No. U01AI069907), and from the Dutch Ministry of Foreign Affairs through a partnership with Stichting Aids Fonds. The National Centre in HIV Epidemiology and Clinical Research is funded by the Australian Government Department of Health and Ageing, and is affiliated with the Faculty of Medicine, The University of New South Wales. The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of any of the institutions mentioned above.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Egger M, Hirschel B, Francioli P, et al. Impact of new antiretroviral combination therapies in HIV infected patients in Switzerland: prospective multicentre study. Swiss HIV Cohort Study. BMJ. 1997; 315(7117):1194–1199. [PubMed: 9393221]
2. Egger M, May M, Chene G, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. Lancet. 2002; 360(9327):119–129. [PubMed: 12126821]
3. Mocroft A, Vella S, Benfield TL, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. Lancet. 1998; 352(9142):1725–1730. [PubMed: 9848347]
4. Sterne JA, Hernan MA, Ledergerber B, et al. Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: a prospective cohort study. Lancet. 2005; 366(9483):378–384. [PubMed: 16054937]
5. Towards Universal Access: scaling up priority HIV/AIDS interventions in the health sector. Progress Report. 2009. http://www.who.int/hiv/pub/tuapr_2009_en.pdf
6. Braitstein P, Brinkhof MW, Dabis F, et al. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. Lancet. 2006; 367(9513):817–824. [PubMed: 16530575]
7. Nash D, Katyal M, Brinkhof MW, et al. Long-term immunologic response to antiretroviral therapy in low-income countries: a collaborative analysis of prospective studies. AIDS. 2008; 22(17):2291–2302. [PubMed: 18981768]
8. Ivers LC, Kendrick D, Doucette K, et al. Efficacy of antiretroviral therapy programs in resource-poor settings: a meta-analysis of the published literature. Clin Infect Dis. 2005; 41(2):217–224. [PubMed: 15983918]
9. Grabar S, Le Moing V, Goujard C, et al. Clinical outcome of patients with HIV-1 infection according to immunologic and virologic response after 6 months of highly active antiretroviral therapy. Ann Intern Med. 2000; 133(6):401–410. [PubMed: 10975957]
10. Mellors JW, Munoz A, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. Ann Intern Med. 1997; 126(12):946–954. [PubMed: 9182471]
11. Phillips A, Collaboration C. Short-term risk of AIDS according to current CD4 cell count and viral load in antiretroviral drug-naive individuals and those treated in the monotherapy era. AIDS. 2004; 18(1):51–58. [PubMed: 15090829]
12. Volberding PA, Lagakos SW, Grimes JM, et al. A comparison of immediate with deferred zidovudine therapy for asymptomatic HIV-infected adults with CD4 cell counts of 500 or more per

cubic millimeter. AIDS Clinical Trials Group. N Engl J Med. 1995; 333(7):401–407. [PubMed: 7616988]

13. US Department of Health and Human Services. [Accessed January 13, 2011] Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. http://www.aidsinfo.nih.gov/guidelines/
14. Zhou J, Kumarasamy N, Ditangco R, et al. The treat Asia HIV observational database: baseline and retrospective data. J Acquir Immune Defic Syndr. 2005; 38(2):174–179. [PubMed: 15671802]
15. Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. Morb Mortal Wkly Rep. 1992; 41:1–19.
16. Lane HC, Masur H, Gelmann EP, et al. Correlation between immunologic function and clinical subpopulations of patients with the acquired immune deficiency syndrome. Am J Med. 1985; 78(3):417–422. [PubMed: 3872068]
17. Bonnet F, Thiébaut R, Chêne G, et al. Determinants of clinical progression in antiretroviral-naive HIV-infected patients starting highly active antiretroviral therapy. Aquitaine Cohort, France. HIV Med. 2005; 6(3):198–205. [PubMed: 15876287]
18. World Health Organisation. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach. 2010 Revision. http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf
19. Kaufmann G, Perrin L, Pantaleo G, et al. CD4 T-lymphocyte recovery in individuals with advanced HIV-1 infection receiving potent antiretroviral therapy for 4 years: the Swiss HIV Cohort Study. Arch Intern Med. 2003; 163(18):2187–2195. [PubMed: 14557216]
20. Smith C, Sabin C, Lampe F, et al. The potential for CD4 cell increases in HIV-positive individuals who control viraemia with highly active antiretroviral therapy. AIDS. 2003; 17(7):963–969. [PubMed: 12700445]
21. Mocroft A, Katlama C, Johnson AM, et al. AIDS across Europe, 1994–98: the EuroSIDA study. Lancet. 2000; 356(9226):291–296. [PubMed: 11071184]
22. Lundgren JD, Mocroft A, Gatell JM, et al. A clinically prognostic scoring system for patients receiving highly active antiretroviral therapy: results from the EuroSIDA study. J Infect Dis. 2002; 185(2):178–187. [PubMed: 11807691]
23. Chene G, Sterne JA, May M, et al. Prognostic importance of initial response in HIV-1 infected patients starting potent antiretroviral therapy: analysis of prospective studies. Lancet. 2003; 362(9385):679–686. [PubMed: 12957089]
24. Antiretroviral Therapy Cohort Collaboration. Importance of baseline prognostic factors with increasing time since initiation of highly active antiretroviral therapy: collaborative analysis of cohorts of HIV-1-infected patients. J Acquir Immune Defic Syndr. 2007; 46(5):607–615. [PubMed: 18043315]
25. CASCADE Collaboration. Systemic non-Hodgkin lymphoma in individuals with known dates of HIV seroconversion: incidence and predictors. AIDS. 2004; 18(4):673–681. [PubMed: 15090773]
26. Ledergerber B, Egger M, Erard V, et al. AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy: the Swiss HIV Cohort Study. JAMA. 1999; 282(23): 2220–2226. [PubMed: 10605973]
27. Ledergerber B, Mocroft A, Reiss P, et al. Discontinuation of secondary prophylaxis against Pneumocystis carinii pneumonia in patients with HIV infection who have a response to antiretroviral therapy. Eight European Study Groups. N Engl J Med. 2001; 344(3):168–174. [PubMed: 11188837]
28. Duncombe C, Kerr SJ, Ruxrungtham K, et al. HIV disease progression in a patient cohort treated via a clinical research network in a resource limited setting. AIDS. 2005; 19(2):169–178. [PubMed: 15668542]
29. Mocroft A, Kirk O, Barton SE, et al. Anaemia is an independent predictive marker for clinical prognosis in HIV-infected patients from across Europe. EuroSIDA study group. AIDS. 1999; 13(8):943–950. [PubMed: 10371175]
30. Anastos K, Shi Q, French AL, et al. Total lymphocyte count, hemoglobin, and delayed-type hypersensitivity as predictors of death and AIDS illness in HIV-1-infected women receiving

highly active antiretroviral therapy. J Acquir Immune Defic Syndr. 2004; 35(4):383–392. [PubMed: 15097155]

31. Costello C, Nelson KE, Suriyanon V, et al. HIV-1 subtype E progression among northern Thai couples: traditional and non-traditional predictors of survival. Int J Epidemiol. 2005; 34(3):577–584. [PubMed: 15737969]
32. Kowalska JD, Mocroft A, Blaxhult A, et al. Current hemoglobin levels are more predictive of disease progression than hemoglobin measured at baseline in patients receiving antiretroviral treatment for HIV type 1 infection. AIDS Res Hum Retroviruses. 2007; 23(10):1183–1188. [PubMed: 17961102]
33. Zhou J, Kumarasamy N. Predicting short-term disease progression among HIV-infected patients in Asia and the Pacific region: preliminary results from the TREAT Asia HIV Observational Database (TAHOD). HIV Med. 2005; 6(3):216–223. [PubMed: 15876289]
34. Srasuebkul P, Lim PL, Lee MP, et al. Short-term clinical disease progression in HIV-infected patients receiving combination anti-retroviral therapy: results from the TREAT Asia HIV observational database. Clin Infect Dis. 2009; 48(7):940–950. [PubMed: 19226231]
35. Maas JJ, Dukers N, Krol A, et al. Body mass index course in asymptomatic HIV-infected homosexual men and the predictive value of a decrease of body mass index for progression to AIDS. J Acquir Immune Defic Syndr Hum Retrovirol. 1998; 19(3):254–259. [PubMed: 9803967]
36. Mekonnen Y, Dukers NH, Sanders E, et al. Simple markers for initiating antiretroviral therapy among HIV-infected Ethiopians. AIDS. 2003; 17(6):815–819. [PubMed: 12660528]
37. Badri M, Wood R. Usefulness of total lymphocyte count in monitoring highly active antiretroviral therapy in resource-limited settings. AIDS. 2003; 17(4):541–545. [PubMed: 12598774]
38. Eskild A, Magnus P, Samuelsen SO, Sohlberg C, Kittelsen P. Differences in mortality rates and causes of death between HIV positive and HIV negative intravenous drug users. Int J Epidemiol. 1993; 22(2):315–320. [PubMed: 8505190]
39. Selwyn PA, Hartel D, Wasserman W, Drucker E. Impact of the AIDS epidemic on morbidity and mortality among intravenous drug users in a New York City methadone maintenance program. Am J Public Health. 1989; 79(10):1358–1362. [PubMed: 2782502]
40. Zhou J, Elliott J, Li PC, et al. Risk and prognostic significance of tuberculosis in patients from The TREAT Asia HIV Observational Database. BMC Infect Dis. 2009; 9:46. [PubMed: 19383122]
41. Kumarasamy N, Solomon S, Flanigan TP, Hemalatha R, Thyagarajan SP, Mayer KH. Natural history of human immunodeficiency virus disease in southern India. Clin Infect Dis. 2003; 36(1): 79–85. [PubMed: 12491206]
42. Lawn SD, Myer L, Orrell C, Bekker LG, Wood R. Early mortality among adults accessing a community-based antiretroviral service in South Africa: implications for programme design. AIDS. 2005; 19(18):2141–2148. [PubMed: 16284464]
43. Etard JF, Ndiaye I, Thierry-Mieg M, et al. Mortality and causes of death in adults receiving highly active antiretroviral therapy in Senegal: a 7-year cohort study. AIDS. 2006; 20(8):1181–1189. [PubMed: 16691070]
44. Lortholary O, Fontanet A, Mémain N, Martin A, Sitbon K, Dromer F. Incidence and risk factors of immune reconstitution inflammatory syndrome complicating HIV-associated cryptococcosis in France. AIDS. 2005; 19(10):1043–1049. [PubMed: 15958835]
45. French MA, Lenzo N, John M, et al. Immune restoration disease after the treatment of immunodeficient HIV-infected patients with highly active antiretroviral therapy. HIV Med. 2000; 1(2):107–115. [PubMed: 11737333]

Appendix A

The TREAT Asia HIV Observational Database

C. V. Mean, V. Saphonn,* and K. Vohith, National Center for HIV/AIDS, Dermatology & STDs, Phnom Penh, Cambodia; F. J. Zhang,* H. X. Zhao, and N. Han, Beijing Ditan Hospital, Beijing, China; P. C. K. Li*† and M. P. Lee, Queen Elizabeth Hospital, Hong Kong, China; N. Kumarasamy* and S. Saghayam, YRG Centre for AIDS Research and

Education, Chennai, India; S. Pujari* and K. Joshi, Institute of Infectious Diseases, Pune, India; T. P. Merati* and F. Yuliana, Faculty of Medicine Udayana University & Sanglah Hospital, Bali, Indonesia; E. Yunihastuti* and O. Ramadian, Working Group on AIDS Faculty of Medicine, University of Indonesia/Ciptomangunkusumo Hospital, Jakarta, Indonesia; S. Oka* and M. Honda, International Medical Centre of Japan, Tokyo, Japan; J. Y. Choi* and S. H. Han, Division of Infectious Diseases, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea; C. K. C. Lee* and R. David, Hospital Sungai Buloh, Kuala Lumpur, Malaysia; A. Kamarulzaman* and A. Kajindran, University of Malaya Medical Centre, Kuala Lumpur, Malaysia; G. Tau,* Port Moresby General Hospital, Port Moresby, Papua New Guinea; R. Ditangco* and R. Capistrano, Research Institute for Tropical Medicine, Manila, Philippines; Y. M. A. Chen,* W. W. Wong, and Y. W. Yang, Taipei Veterans General Hospital and AIDS Prevention and Research Centre, National Yang-Ming University, Taipei, Taiwan; P. L. Lim,* O. T. Ng, and E. Foo, Tan Tock Seng Hospital, Singapore; P. Phanuphak* and M. Khongphattanayothin, HIV-NAT/Thai Red Cross AIDS Research Centre, Bangkok, Thailand; S. Sungkanuparph* and B. Piyavong, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; T. Sirisanthana*‡ and W. Kotarathititum, Research Institute for Health Sciences, Chiang Mai, Thailand; A. H. Sohn,* L. Messerschmidt,* and B. Petersen, The Foundation for AIDS Research, Bangkok, Thailand; J. Chuah,* Gold Coast Sexual Health Clinic, Miami, Queensland, Australia; D. A. Cooper, M. G. Law,* K. Petoumenos, and J. Zhou,* National Centre in HIV Epidemiology and Clinical Research, The University of New South Wales, Sydney, Australia. *TAHOD Steering Committee member; †Steering Committee Chair; ‡co-Chair.

Table 1

Patient Characteristics at the Start of Combination Antiretroviral Therapy

	No. of Patients	%
Total	1255	100.0
Sex		
Male	886	70.6
Female	369	29.4
Ethinicity		
Chinese	527	42.0
Indian	193	15.4
Thai	310	24.7
Other	225	17.9
Mode of infection		
Heterosexual	1,013	80.7
Homosexual	125	10.0
IDU only	27	2.2
Other	90	7.2
Prior AIDS illness		
No	617	49.2
Yes	638	50.8
Year of cART start		
≤2000	264	21.0
>2000	991	79.0
HBsAg		
Negative	660	52.6
Positive	102	8.1
Not tested	493	39.3
HCV antibody		
Negative	641	51.1
Positive	70	5.6
Not tested	544	43.4
Median age, y (IQR)		36 (31–42)
Median CD4 count, cells/mm^3 (IQR)		63 (25–130)
Median BMI,[a] kg/m^2 (IQR)		19.9 (17.8–22.1)
Median hemoglobinears,[a] mg/dL (IQR)		120 (106–133)

Abbreviations: IDU, intravenous drug use; cART, combination antiretroviral therapy; HbSAg, Hepatitis B surface antigen; HCV, hepatitis C virus; IQR, interquartile range; BMI, body mass index.

[a]Number of patients (%) missing body mass index and hemoglobin measurements at baseline: 610 (48.6%) and 256 (20.4%), respectively.

Table 2

Patient Characteristics 6 Months after Initiation of Combination Antiretroviral Therapy

	No. of Patients	%
AIDS event in first 6 months		
No	1179	93.9
Yes	76	6.1
CD4 count after 6 months of cART, cells/mm^3		
≤50	74	5.9
51–100	205	16.3
101–200	451	35.9
>200	525	41.8
CD4 change from baseline at month 6, cells/mm^3		
≤50	286	22.8
51–100	347	27.7
101–200	398	31.7
>200	224	17.9
Hemoglobin after 6 months of cART, mg/dL		
≤80	14	1.1
81–130	508	40.5
>130	502	40.0
Missing	231	18.4

Abbreviation: cART, combination antiretroviral therapy.

Table 3

Univariable and Multivariable Predictors of AIDS or Death Using Cox Proportional Hazards Model

				Univariable		Multivariable	
	No. of events	**Person Years**	**Rate,/100 pys**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
Total	82	2696					
Sex							
Male	64	1920.0	3.33	1.00			
Female	18	776.1	2.32	0.69 (0.41–1.17)	.168	0.74 (0.44–1.25)	.260
Age, y							
≤35	35	1307.0	2.68	1.00			
>35	47	1389.1	3.38	1.26 (0.82–1.96)	.295	1.25 (0.80–1.93)	.326
Ethinicity							
Chinese	32	1191.9	2.68	1.00			
Indian	20	418.3	4.78	1.83 (1.05–3.19)	.034	2.64 (1.46–4.77)	.001
Thai	16	695.6	2.30	0.87 (0.48–1.58)	.648	0.90 (0.49–1.63)	.720
Other	14	390.3	3.59	1.26 (0.67–2.37)	.469	1.34 (0.71–2.51)	.370
Mode of infection							
Heterosexual	63	2196.1	2.87	1.00			
Homosexual	11	272.6	4.03	1.14 (0.74–2.68)	.292	1.59 (0.83–3.03)	.160
IDU only	5	46.5	10.76	3.64 (1.46–9.07)	.005	3.31 (1.33–8.24)	.010
Other	3	180.9	1.66	0.56 (0.18–1.80)	.334	0.58 (0.18–1.83)	.350
Prior AIDS illness							
No	40	1305.7	3.06	1.00			
Yes	42	1390.5	3.02	0.99 (0.64–1.52)	.956	0.90 (0.58–1.39)	.629
Year of cART start							
≤2000	19	629.4	3.02	1.00			
>2000	63	2066.8	3.05	0.99 (0.59–1.66)	.983	1.10 (0.65–1.84)	.723
CD4 count before start of cART, cells/mm^3							
≤50	42	1182.2	3.55	1.00			
51–100	17	569.9	2.98	0.85 (0.48–1.49)	.561	1.06 (0.59–1.91)	.837
101–200	23	944.0	2.44	0.69 (0.42–1.15)	.154	1.08 (0.59–1.98)	.798

	No. of events	Person Years	Rate,/100 pys	Univariable HR (95% CI)	P	Multivariable HR (95% CI)	P
Baseline hemoglobin, mg/dL							
≤80	4	64.7	6.18	1.00			
81–130	43	1453.1	2.96	0.49 (0.17–1.35)	.167	0.53 (0.19–1.480	.225
>130	17	609.0	2.79	0.45 (0.15–1.35)	.156	0.52 (0.17–1.55)	.241
Missing	18	569.3	3.16	0.53 (0.18–1.56)	.250	0.64 (0.21–1.90)	.419
BMI before start of cART, kg/m^2							
≤18.5	15	462.3	3.24	1.00			
18.6–24.9	20	760.1	2.63	0.82 (0.42–1.61)	.567	0.86 (0.44–1.68)	.662
>24.9	1	111.4	0.90	0.28 (0.04–2.14)	.221	0.30 (0.04–2.28)	.245
Missing	46	1362.3	3.38	1.06 (0.59–1.90)	.842	1.12 (0.62–2.00)	.707
Antiretroviral treatment (ARV)							
2 NRTIs + PI	19	618.5	3.07	1.00			
2 NRTIs + NNRTI	60	2024.8	2.96	0.96 (0.57–1.61)	.874	1.02 (0.61–1.71)	.942
Others	3	52.9	5.67	1.83 (0.54–6.20)	.329	1.67 (0.50–5.70)	.401
CD4 count after 6 months of cART, cells/mm^3							
≤50	13	152.4	8.53	1.00			
51–100	15	454.3	3.30	0.38 (0.18–0.81)	.012	0.38 (0.18–0.81)	.012
101–200	29	972.4	2.98	0.35 (0.18–0.67)	.002	0.35 (0.18–0.67)	.002
>200	25	1117.1	2.24	0.26 (0.14–0.52)	.001	0.26 (0.14–0.52)	.001
Hemoglobin after 6 months of cART, mg/dL							
≤80	3	25.0	12.02	1.00			
81–130	35	1065.8	3.28	0.27 (0.08–0.89)	.032	0.32 (0.10–1.05)	.059
>130	30	1088.6	2.76	0.23 (0.07–0.76)	.016	0.27 (0.08–0.90)	.034
Missing	14	516.7	2.71	0.23 (0.07–0.80)	.021	0.29 (0.08–1.03)	.056
AIDS event in first 6 months							
No	73	2535.4	2.88	1.00			
Yes	9	160.8	5.60	1.97 (0.99–3.94)	.055	1.76 (0.88–3.54	.111

Abbreviations: IDU, intravenous drug use; cART, combination antiretroviral therapy; HbSAg, Hepatitis B surface antigen; HCV, hepatitis C virus; IQR, interquartile range; BMI, body mass index; ART, antiretroviral therapy; CI, conficence interval; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.