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Virologic outcomes in early antiretroviral treatment: HPTN 052

Susan H. Eshleman, MD, PhD,

Dept. of Pathology, Johns Hopkins Univ. School of Medicine, Baltimore, MD, USA; 720 Rutland Ave, Ross Building, Room 646, Baltimore, MD 21205, USA; 410-614-4734

Ethan A. Wilson, MS,

Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; 1100 Fairview Ave N., M2-C200, PO Box 19024, Seattle, WA 98109 USA; 206-667-7207

Xinyi C. Zhang, PhD[*],

Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; One Microsoft Way, Redmond, WA 98052, USA; 425-421-6894

San-San Ou, MS[*],

Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; 22100 Bothell Everett Highway, PO Box 3003, Seattle, WA 98041, USA; 425-482-8950

Address correspondence and reprint requests to: Susan H. Eshleman, MD/PhD, Dept. of Pathology, The Johns Hopkins Medical Institutions, Ross Building, Room 646, 720 Rutland Avenue,, Baltimore, MD 21205, Phone: 410-614-4734; Fax: 410-502-9244; seshlem@jhmi.edu.

[*]Current affiliation: Xinyi Zhang: Microsoft Inc, Seattle, WA, USA; San-San Ou: Philips Healthcare, Bothell, WA, USA.

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Susan Eshleman : Virologist for HPTN 052; designed the study; analyzed the data; wrote the manuscript
Ethan Wilson : Performed statistical analysis
Xinyi Zhang : Performed statistical analysis
San-San Ou : Performed statistical analysis
Estelle Piwowar-Manning : HPTN Laboratory Center Quality Assurance/Quality Control Coordinator for HPTN 052
Joseph Eron : HPTN 052 Investigator
Marybeth McCauley : Senior Study Manager for HPTN 052
Theresa Gamble : Senior Study Manager for HPTN 052
Joel Gallant : HPTN 052 Investigator
Mina Hosseinipour : HPTN 052 Investigator, Lilongwe, Malawi
Nagalingeswaran Kumarasamy : HPTN 052 Investigator, Chennai, India
James Hakim : HPTN 052 Investigator, Harare, Zimbabwe
Ben Kalonga : HPTN 052 Clinician, Blantyre, Malawi
Jose Pilotto : HPTN 052 Investigator, HGNI, Rio de Janeiro, Brazil
Beatriz Grinsztejn : HPTN 052 Investigator, Fiocruz, Rio de Janeiro, Brazil
Sheela Godbole : HPTN 052 Investigator, Pune, India
Nuntisa Chotirosniramit : HPTN 052 Clinician, Chiang Mai, Thailand
Breno Santos : HPTN 052 Investigator, Porto Alegre RS, Brazil
Emily Shava : HPTN 052 Investigator, Gaborone, Botswana
Lisa Mills : HPTN 052 Investigator, Kisumu, Kenya
Ravindre Panchia : HPTN 052 Investigator, Soweto, South Africa
Noluthando Mwelase : HPTN 052 Clinician, Johannesburg, South Africa
Kenneth Mayer : HPTN 052 Investigator, Boston, USA
Ying Chen : Protocol Statistician for HPTN 052
Myron Cohen : Protocol Chair for HPTN 052
Jessica Fogel : Analyzed the data; wrote the manuscript

Estelle Piwowar-Manning, BS MT (ASCP),
Dept. of Pathology, Johns Hopkins Univ. School of Medicine, Baltimore, MD, USA; 600 North Wolfe Street, Pathology 306, Baltimore, MD 21287, USA; 410-614-6736

Joseph J. Eron, MD,
Dept. of Medicine, Univ. of North Carolina at Chapel Hill, Chapel Hill, NC, USA; 130 Mason Farm Road, CB# 7215, Chapel Hill, NC 27599, USA; 919-966-2536

Marybeth McCauley, MPH,
Science Facilitation Department, FHI 360, Washington, DC, USA; 1825 Connecticut Avenue NW, Washington, DC 20009, USA; 202-884-8340

Theresa Gamble, PhD,
Science Facilitation Department, FHI 360, Durham, NC, USA; 359 Blackwell Street, Suite 200, Durham, NC 27701, USA; 919-544-7040

Joel E. Gallant, MD, MPH,
Southwest CARE Center, Santa Fe, NM, USA; 649 Harkle Road, Ste E., P.O. Box 6880, Santa Fe, NM 87502-6880; 505-989-8200

Mina C. Hosseinipour, MD, MPH,
Univ. of North Carolina at Chapel Hill, Institute for Global Health and Infectious Diseases, Chapel Hill, USA; UNC Project-Malawi, Institute for Global Health and Infectious Diseases, Lilongwe, Malawi; Private Bag A104, Lilongwe, Malawi; 265-1-755-056

Nagalingeswaran Kumarasamy, MBBS, PhD,
YRGCARE Medical Centre, VHS, Chennai, India; Tidel Park Road, Taramani, Chennai, Tamil Nadu 600113, India; 91-93-8100-6962

James G. Hakim, MD,
Dept. of Medicine, Univ. of Zimbabwe, Harare, Zimbabwe; PO Box A178 Avondale, Harare, Zimbabwe; 263-4-885282

Ben Kalonga, Dipl. Clin. Med.,
College of Medicine-Johns Hopkins Project, Blantyre, Malawi; College of Med. JHU CRS, PO Box 1131, Chipatala Avenue, Blantyre, Malawi; 265-8841-875

Jose H. Pilotto, MD, Phd,
Hospital Geral de Nova Iguacu and Laboratorio de AIDS e Imunologia Molecular-IOC/Fiocruz, Rio de Janeiro, Brazil Av. Henrique Duque Estrada Mayer, 953, Alto da Posse, Nova Iguacu, RJ, 26030-380, Brazil; 55-21-98182-9797

Beatriz Grinsztejn, MD, PhD,
Instituto Nacional de Infectologia Evandro Chagas-INI-Fiocruz, Rio de Janeiro, Brazil; Av. Brasil, 4365, Manguinhos, Rio de Janeiro, 21040-900, Brazil; 55-21-2270-7064

Sheela V. Godbole, MD, PGDEPI,
National AIDS Research Institute (ICMR), Pune, India; NARI, Plot No. 73, G Block, M.I.D.C. Bhosari, Pune, Maharashtra 411 026, India; 91-20-27331200

Nuntisa Chotirosniramit, MD,

Research Institute for Health Sciences, Chiang Mai University, Chiang Mai, Thailand; 110 Intavaroros Road, Chiang Mai, 50200, Thailand; 66-53-221-966

Breno Riegel Santos, MD,
Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil; Av. Francisco Trein, 596, Porto Alegre, RS 91350-200, Brazil; 55-51-3341-5316

Emily Shava, MBChB,MSc,
Botswana Harvard AIDS Institute, Gaborone, Botswana; Private Bag B0320, Gaborone, Botswana; 267-3392-2540

Lisa A. Mills, MD, MSc,
Centers for Disease Control and Prevention, Division of HIV/AIDS Prevention and Kenya Medical Research Institute (KEMRI)/CDC Clinical Research Site, Kisumu, Kenya; 2210 Kigali Place, Dulles, VA 20189, USA; 404-553-8587

Ravindre Panchia, MBBCh, BSc,
Univ. of the Witwatersrand, Perinatal HIV Research Unit, Soweto HPTN CRS, Soweto, South Africa; Chris Hani Baragwanath Hospital, Chris Hani Road, Soweto, South Africa; 27-11-9899711

Noluthando Mwelase, MBChB,
Clinical HIV Research Unit, Dept. of Medicine, Univ. of the Witwatersrand, Johannesburg, South Africa; Helen Joseph Hospital, Perth Road, Westdene, Johannesburg, Gauteng 2042, South Africa; 27 11 276 8800

Kenneth H. Mayer, MD,
The Fenway Institute, Fenway Health/Infectious Disease Division, Beth Israel Deaconess Medical Center/Department of Medicine, Harvard Medical School, Boston, MA, USA; 1340 Boylston St, 8th Floor, Boston, MA, 02215, USA; 617-927-6087

Ying Q. Chen, PhD,
Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; 1100 Fairview Avenue North, M2-C200, PO Box 19024, Seattle, WA, USA; 206-667-7051

Myron S. Cohen, MD, and
Dept. of Medicine, Univ. of North Carolina at Chapel Hill, Chapel Hill, NC, USA; 130 Mason Farm Road, Bioinformatics Bldg., Chapel Hill, NC, 27514, USA; 919-966-2536

Jessica M. Fogel, PhD
Dept. of Pathology, Johns Hopkins Univ. School of Medicine, Baltimore, MD, USA; 720 Rutland Ave, Ross Building, Room 646, Baltimore, MD 21205, USA; 410-614-6498

Abstract

INTRODUCTION—The HPTN 052 trial demonstrated that early antiretroviral therapy (ART) prevented 93% of HIV transmission events in serodiscordant couples. Some linked infections were observed shortly after ART initiation or after virologic failure.

OBJECTIVE—To evaluate factors associated with time to viral suppression and virologic failure in participants who initiated ART in HPTN 052.

METHODS—1,566 participants who had a viral load (VL) >400 copies/mL at enrollment were included in the analyses. This included 832 in the early ART arm (CD4 350–550 cells/mm^3 at ART initiation) and 734 in the delayed ART arm (204 with a CD4 <250 cells/mm^3 at ART initiation; 530 with any CD4 at ART initiation). Viral suppression was defined as two consecutive VLs ≤400 copies/mL after ART initiation; virologic failure was defined as two consecutive VLs >1,000 copies/mL >24 weeks after ART initiation.

RESULTS—Overall, 93% of participants achieved viral suppression by 12 months. The annual incidence of virologic failure was 3.6%. Virologic outcomes were similar in the two study arms. Longer time to viral suppression was associated with younger age, higher VL at ART initiation, and region (Africa vs. Asia). Virologic failure was strongly associated with younger age, lower educational level, and lack of suppression by 3 months; lower VL and higher CD4 at ART initiation were also associated with virologic failure.

CONCLUSIONS—Several clinical and demographic factors were identified that were associated with longer time to viral suppression and virologic failure. Recognition of these factors may help optimize ART for HIV treatment and prevention.

Keywords

HIV; HPTN 052; early ART; viral suppression; virologic failure; virologic outcomes; HIV prevention

INTRODUCTION

The risk of HIV transmission is correlated with HIV viral load.[1,2] Effective antiretroviral therapy (ART) inhibits viral replication and reduces HIV viral load to low or undetectable levels. In the multi-national HIV Prevention Trials Network (HPTN) 052 clinical trial, early ART initiation significantly reduced the risk of sexual HIV transmission in serodiscordant couples and improved the health of index participants.[3,4]

Results from HPTN 052 and other studies indicate that sexual transmission of HIV is very unlikely when the infected individual is virally suppressed. In HPTN 052, 78 partner infections were observed with 1,763 couples followed for >8,500 person-years.[4] Genetic linkage analysis was performed to determine the likely source of the partner's infection.[5,6] Over the course of the trial, eight linked infections were diagnosed after the index participant started ART.[6] Four of those infections occurred close to the time of index ART initiation (most likely before the index participant was virally suppressed) and four occurred after the index participant failed ART.[6,7] Linked partner infections were not observed when index participants were stably suppressed on ART. Partner infections have also been evaluated in observational studies of serodiscordant couples when the infected individual was on ART.[8–10] In a prospective cohort study with 168 person-years follow-up, three linked infections were observed within 6 months of ART initiation, before the index was virally suppressed.[11] In an observational study, no linked infections were observed during 1,238 couple-years of follow up when index participants were virologically suppressed on ART.[12]

In this report, we evaluated time to viral suppression and virologic failure among index participants who started ART in HPTN 052. These studies are relevant to use of ART for

HIV prevention, since viremia increases the risk of HIV transmission. The analysis in this report includes a comparison of these outcomes in the two study arms of HPTN 052 (early vs. delayed ART), and evaluates demographic and clinical factors associated with time to viral suppression and virologic failure. These analyses provide new information on clinical outcomes in the setting of early ART initiation and use of ART for HIV prevention.

METHODS

Study cohort

The HPTN 052 trial enrolled 1,763 HIV serodiscordant couples (≥18 years of age) at 12 sites in low- or middle-income countries (Botswana, Kenya, Malawi, South Africa, Zimbabwe, India, Thailand, Brazil); two additional couples were enrolled in the United States of America (NCT00074581; pilot enrollment from 2005–2007, full enrollment from 2007–2010). The trial design and results have been reported previously.[3,4] Couples were randomized to one of two study arms. In the early ART arm, index participants initiated ART immediately after enrollment (CD4 cell count between 350–550 cells/mm^3). In the delayed ART arm, ART was initiated after the CD4 cell count fell below 250 cells/mm^3 on two consecutive study visits, or when the index participant developed an AIDS-defining illness. At enrollment, HIV-infected index participants reported no prior ARV drug use with the exception of short-term ARV drug use for prevention of mother-to-child transmission. However, retrospective ARV drug testing revealed that some participants were on ART at the time of study enrollment.[13] The most common ART regimen was a combination of efavirenz (EFV), lamivudine (3TC), and zidovudine (ZDV); other drugs used for treatment included atazanavir, atazanavir/ritonavir, emtricitabine, lopinavir/ritonavir (LPV/r), nevirapine, stavudine, and tenofovir disoproxil fumarate.[3] The analyses in this report include data from the start of the trial through May, 2015 (end of study). In May 2011, participants were informed of interim study results that demonstrated that early ART prevented 96% of linked HIV transmissions.[3] After that date, all study participants were counseled on the personal and public health benefits of early ART, and ART was offered to all index participants regardless of CD4 cell count. In this report, virologic outcomes were evaluated in participants in the early and delayed ART arms. Participants in the delayed ART arm were also stratified into two groups based on whether they started ART before or after release of interim study results. Participants who had a viral load <400 copies/mL at study enrollment were excluded from analysis.

Laboratory and statistical methods

HIV viral load and CD4 cell count assays were performed at study sites.[3] Prior to November 2006, viral load testing was performed quarterly after ART initiation. Follow-up visits were allowed to occur within a 2-week window of the targeted visit dates. After November 2006, viral load testing was performed at an additional visit one month after ART initiation. The majority of participants were enrolled after this date and had a 1-month visit. Additional study visits with viral load assessments were permitted at the discretion of site investigators for clinical management of participants on ART. Viral suppression was defined as the first of two consecutive viral load measurements ≤400 copies/mL after ART initiation. Virologic failure was defined as the first of two consecutive viral load measurements >1,000

copies/mL after 24 weeks on ART. Potential ascertainment bias in determining the timing of a viral suppression due to variation in the timing of viral load measurements (interval censorship) was examined. Characteristics of study participants in different groups (early ART arm; delayed ART arm; delayed ART arm with ART initiation before vs. after May 2011) were analyzed using the Chi-square test (for categorical variables) and the Wilcoxon rank sum test (for continuous variables). Cox regression and Kaplan-Meier methods were used to analyze the association of demographic and other factors with time to viral suppression and virologic failure. The multivariate Cox regression model was created using a backward model selection method; $p<0.05$ was used to exclude variables in the backward selection model.

Ethical considerations

Institutional Review Boards/Ethics Committees at each participating institution approved the HPTN 052 trial. Written informed consent was obtained from all study participants.

RESULTS

Study cohort

We evaluated viral suppression and virologic failure outcomes in 1,566 index participants in HPTN 052 who had a viral load >400 copies/ml at study enrollment and initiated ART (Figure 1). Table 1 shows demographic and clinical characteristics of study participants at the time of ART initiation. At ART initiation, the median CD4 cell count was 439 cells/mm^3 in the early ART arm and 314 cells/mm^3 in the delayed ART arm. At the time of ART initiation, index participants in the early ART arm were younger and had higher CD4 cell counts and lower viral loads; they were also more likely to receive EFV/3TC/ZDV than other regimens, have a lower educational status, and have >1 sexual partner compared to participants in the delayed ART arm. In the delayed ART arm, index participants who started ART before release of interim study results in May 2011 had lower CD4 cell counts and higher viral loads at ART initiation; those participants also had a different regional distribution and were more likely to be male compared to index participants in the delayed ART arm who started ART after May 2011 (Table 1).

Analysis of viral suppression after ART initiation

Viral suppression was evaluated in 1,566 index participants (7,397 person-years of follow up on ART): 832 in the early ART arm and 734 in the delayed ART arm (Figure 1). In the delayed ART arm, 204 participants initiated ART before May 2011 and 530 initiated ART after May 2011 (Figure 1). Overall, 93% of the participants achieved viral suppression by 12 months after ART initiation. At 1, 3, 6, 9 and 12 months after ART initiation, the cumulative probabilities of viral suppression were 49%, 83%, 89%, 91%, and 92% in the early ART arm; 25%, 72%, 92%, 95%, and 96% in the delayed ART arm among participants who initiated ART before May 2011; and 43%, 77%, 87%, 90%, and 93% in the delayed ART arm among participants who initiated ART after May 2011.

In Kaplan-Meier analysis, there was no significant difference in time to viral suppression among participants in the following three groups: early ART arm; delayed ART arm with

ART initiation before May 2011; delayed ART with ART initiation after May 2011 (p=0.08, Figure 2A). Some differences were noted in the timing of viral load measurements in these three participant groups. More detailed analyses indicated that these differences were not likely to have impacted the analysis of time to viral suppression in these groups (Supplemental File 1). There was no difference in time to viral suppression between the two study arms (Table 2). Time to viral suppression was longer among participants in the delayed ART arm who initiated ART before May 2011 than in the early ART arm, but this difference was not statistically significant in the multivariate model (Table 2). In univariate analyses, the following variables were associated with a longer time to viral suppression: younger age, lower CD4 cell count at ART initiation, higher viral load at ART initiation, region, and regimen. However, only three of these factors were associated with longer time to viral suppression in the multivariate model: younger age (<25 years), higher viral load at ART initiation, and region (Africa, compared to Asia, Table 2). Kaplan-Meier plots were used to assess the proportional hazards assumption for these three variables (Supplemental File 2A); the plots indicate that the proportional hazards assumption is appropriate for the Cox model.

Analysis of virologic failure

Virologic failure was evaluated in 1,528 index participants with 6,662 person-years of follow up on ART (Figure 1). The annual incidence of virologic failure was 3.6% (95% confidence intervals [CI]: 3.1%–4.1%) overall; 3.4% (95% CI: 2.9%–4.0%) in the early ART arm, and 3.8% (95% CI: 3.1%–4.7%) in the delayed ART arm (p=0.37). In the delayed ART arm, the annual incidence of virologic failure was 2.9% (95% CI: 1.9%–4.3%) among participants who initiated ART before May 2011 and 4.4% (95% CI: 3.4%–5.6%) among participants who initiated ART after May 2011 (p=0.08).

In Kaplan-Meier analysis, there was no significant difference in virologic failure among participants in the three study groups described above (p=0.32, Figure 2B). In univariate analyses, there was also no significant difference in virologic failure in the early vs. delayed ART arms or in the early ART arm compared to either delayed ART group (before vs. after May 2011, Table 3). Other factors were associated with a higher risk of virologic failure, including younger age (<25 years), female gender, higher CD4 cell count at ART initiation, lower education level, marital status (married), and lack of viral suppression by 3 months. All of these variables were independently associated with virologic failure in the multivariate model with the exception of gender. In addition, lower viral load at ART initiation was associated with virologic failure in the multivariate model (Table 3). Kaplan-Meier plots were used to assess the proportional hazards assumption for variables that were associated with virologic failure in the multivariate model (see Supplemental File 2B); the plots indicate that the proportional hazards assumption is appropriate for the Cox model.

Overall (in both study arms), only 16 (6.7%) of the 238 virologic failures occurred after four years on ART. To explore whether the findings were affected by late failure events, the analysis shown in Table 3 was repeated using the same methods after censoring data from study visits more than 4 years after ART initiation. In the multivariate model that included censoring, the same variables were significantly associated with virologic failure with the

exception of CD4 cell count. Furthermore, the hazard ratios for all variables analyzed were similar with and without censoring; the p-values for these variables were similar with and without censoring with one exception: the p-value for viral load at ART initiation was lower with censoring (p=0.0035).

DISCUSSION

Achieving and maintaining viral suppression after ART initiation directly benefits those on ART and has public health benefits by reducing HIV transmission.[4,14] The HPTN 052 trial identified two risk periods for HIV transmission when ART is used for HIV prevention: near the time of ART initiation (before the index was virally suppressed) and after virologic failure (when the index was viremic).[6] Overall, 93% of the participants included in this report were virally suppressed by 12 months after ART initiation. The time to viral suppression was similar between the two study arms (early ART arm vs. delayed ART arm, p=0.06). We did observe a longer time to viral suppression for participants in the delayed ART arm who initiated ART before May 2011, compared to those in the early ART arm (p=0.038, univariate analysis); this subset of participants in the delayed ART arm started ART at lower CD4 cell counts than the participants in the other two groups (early ART arm, delayed ART arm with ART initiation after May 2011). This difference was not observed in the multivariate model where the analysis was adjusted for other factors. There was also no significant difference when time to viral suppression was compared across all three participant groups (p=0.095). CD4 cell count at ART initiation was highly associated with time to viral suppression in the univariate model, but was not significantly associated with time to viral suppression in the multivariate model that adjusted for other variables.

In this cohort, three factors were independently associated with longer time to viral suppression: higher viral load at ART initiation, younger age (<25 years), and geographic region (Africa compared to Asia). Higher viral load at ART initiation was also associated with a longer time to viral suppression in studies where ART was initiated at lower CD4 cell counts.[15] Younger age has been associated with lack of viral suppression[16,17] and poor ART adherence[18,19] in previous studies. In HPTN 052, self-reported ART adherence was higher among older participants in the early ART arm, but this association was not statistically significant in multivariate analysis.[20] The regional differences in time to viral suppression observed in HPTN 052 may reflect differences in HIV subtype or other factors, such as adherence. Regional differences in adherence were observed in the early ART arm in HPTN 052.[20] Previous studies have reported more rapid viral suppression in individuals with certain HIV subtypes.[21,22]

We did not find an association between ART regimen (EFV/3TC/ZDV vs. other) and time to viral suppression in HPTN 052. Other studies have demonstrated that the rate of viral load decline varies with different ARV drug regimens.[23,24] For example, shorter time to viral suppression has been observed using EFV-based ART compared to LPV/r-based ART[25] and with regimens that include an HIV integrase strand transfer inhibitor (INSTI).[26,27] In HPTN 052, 72% of the index participants on ART were on EFV/3TC/ZDV; the remaining participants were on a variety of different ART regimens;[3] none received an INSTI-based regimen.

Among the HPTN 052 participants in this report, virologic failure was uncommon, with an annual incidence of 3.6%. Three factors were strongly associated with virologic failure in multivariate analyses: younger age (<25 years, compared to ≥40 years), a lower level of education, and lack of viral suppression by 3 months; lower viral load and higher CD4 cell count at ART initiation were also associated with virologic failure. An association between younger age and virologic failure was observed in a previous study.[28] An association between lower educational level and virologic failure was not observed in previous studies performed in the US and Southern Africa;[29,30] further studies are needed to determine whether the association observed in this study is due to lower adherence or other factors. We did observe a weak association between a higher CD4 cell count at ART initiation and virologic failure. A possible explanation for this finding is that participants who had higher CD4 cell counts at the time of ART initiation may have had lower adherence to ART because they were in better health. Of note, the incidence of virologic failure was similar in the two study arms in the interim analysis of the HPTN 052 trial (data through February 2011)[3] and in this extended analysis (data through May 2015). This may have reflected the fact that the interim analysis included a shorter follow-up period with fewer virologic failure events, and that in the extended analysis, the delayed ART arm included two distinct participant groups: (1) before May 2011, participants initiated ART when their CD4 cell count fell below 250 cells/mm^3 or they developed an AIDS defined illness; (2) after May 2011, participants started ART at higher CD4 cell counts and were aware of the benefits of early ART. Interestingly, participants in the latter group had a higher annual incidence of virologic failure than those who started ART before May 2011 (2.9% vs. 4.4%, p=0.08). This indicates that knowledge of the beneficial effects of early ART did not improve treatment outcomes.

Other studies have shown that HIV subtype is associated with virologic failure. HIV subtypes were not available for all participants in this study; however the prevalent HIV subtypes are different in the Americas (mostly B and F in Brazil), Africa (mostly C in sub-Saharan Africa). In the ACTG 5175 study (PEARLS), which was performed at many of the same study sites as HPTN 052, subtype C infection was associated with a higher rate of virologic failure compared to subtype B infection.[31] The frequency of ART failure was also higher in subtype C compared to subtype B in a cohort study from Sweden.[32]

The findings from HPTN 052 and other studies provide strong support for universal HIV treatment where HIV-infected individuals are eligible to start ART early regardless of CD4 cell count,[4,33] which is now recommended for all HIV-infected individuals.[34] Community randomized trials are underway to determine the best way to deliver universal ART and assess the impact of universal ART on HIV incidence at a population level. Additional interventions (e.g., use of pre-exposure prophylaxis in couples at the start of ART until viral suppression is well-established, and use of INSTI-based ART regimens) may help reduce transmission risk. This study identified several clinical and demographic factors associated with time to viral suppression after ART initiation and virologic failure. Recognition of these factors may help to optimize ART for HIV treatment and prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Biographies

Susan Eshleman : Professor of Pathology at Johns Hopkins Univ. School of Medicine; Director of the HIV Prevention Trials Network Laboratory Center

Ethan Wilson : Statistical Research Associate at Fred Hutchinson Cancer Research Center

Xinyi Zhang : Staff Scientist at Fred Hutchinson Cancer Research Center*

San-San Ou : Staff Scientist at Fred Hutchinson Cancer Research Center*

Estelle Piwowar-Manning : HIV Prevention Trials Network Laboratory Center Deputy Director

Joseph Eron : Professor of Medicine and Director, Clinical Core, UNC Center for AIDS Research at Univ. of North Carolina at Chapel Hill

Marybeth McCauley : HIV Prevention Trials Network Leadership and Operations Center Senior Clinical Program Manager

Theresa Gamble : HIV Prevention Trials Network Leadership and Operations Center Senior Clinical Program Manager

Joel Gallant : Medical Director of Specialty Services at Southwest CARE Center; Adjunct Professor of Medicine at Johns Hopkins Univ. School of Medicine; Clinical Professor of Medicine at Univ. of New Mexico School of Medicine

Mina Hosseinipour : Professor of Medicine at Univ. of North Carolina at Chapel Hill; Scientific Director, UNC Project-Malawi

Nagalingeswaran Kumarasamy : Chief Medical Officer at YRGCARE Medical Centre

James Hakim : Professor of Medicine at Univ. of Zimbabwe; Director of the UZ Clinical Research Centre

Ben Kalonga : Clinician and investigator at the College of Medicine-Johns Hopkins Project

Jose Pilotto : Principal Investigator at Hospital Geral de Nova Iguacu and Laboratorio de AIDS e Imunologia Molecular-IOC

Beatriz Grinsztejn : Director of the STD/AIDS Clinical Research Laboratory at IPEC/ FIOCRUZ

Sheela Godbole : Scientist D in Epidemiology and Biostatistics at the National AIDS Research Institute (ICMR)

Nuntisa Chotirosniramit : Clinician and investigator at the Research Institute for Health Sciences, Chiang Mai University

Breno Santos : Clinician and investigator at the Hospital Nossa Senhora da Conceição

Emily Shava : Study physician and coordinator at the Botswana Harvard AIDS Institute, Gaborone, Botswana

Lisa Mills : Director, HIV Research Branch CDC Kenya

Ravindre Panchia : Clinician and investigator at the Univ. of the Witwatersrand, Perinatal HIV Research Unit

Noluthando Mwelase : Clinician and investigator at the Univ. of the Witwatersrand, Clinical HIV Research Unit

Kenneth Mayer : Co-Chair and Medical Research Director of The Fenway Institute; Director of HIV Prevention Research at the Beth Israel Deaconess Medical Center; Professor of Medicine at Harvard Medical School

Ying Chen : Full Member of Biostatistics at Fred Hutchinson Cancer Research Center

Myron Cohen : Associate Vice Chancellor for Global Health and Yeargan-Bate Distinguished Professor of Medicine, Microbiology and Immunology, and Epidemiology at

Univ. of North Carolina at Chapel Hill; Co-Principal Investigator of the HIV Prevention Trials Network

Jessica Fogel : Research Associate at Johns Hopkins Univ. School of Medicine

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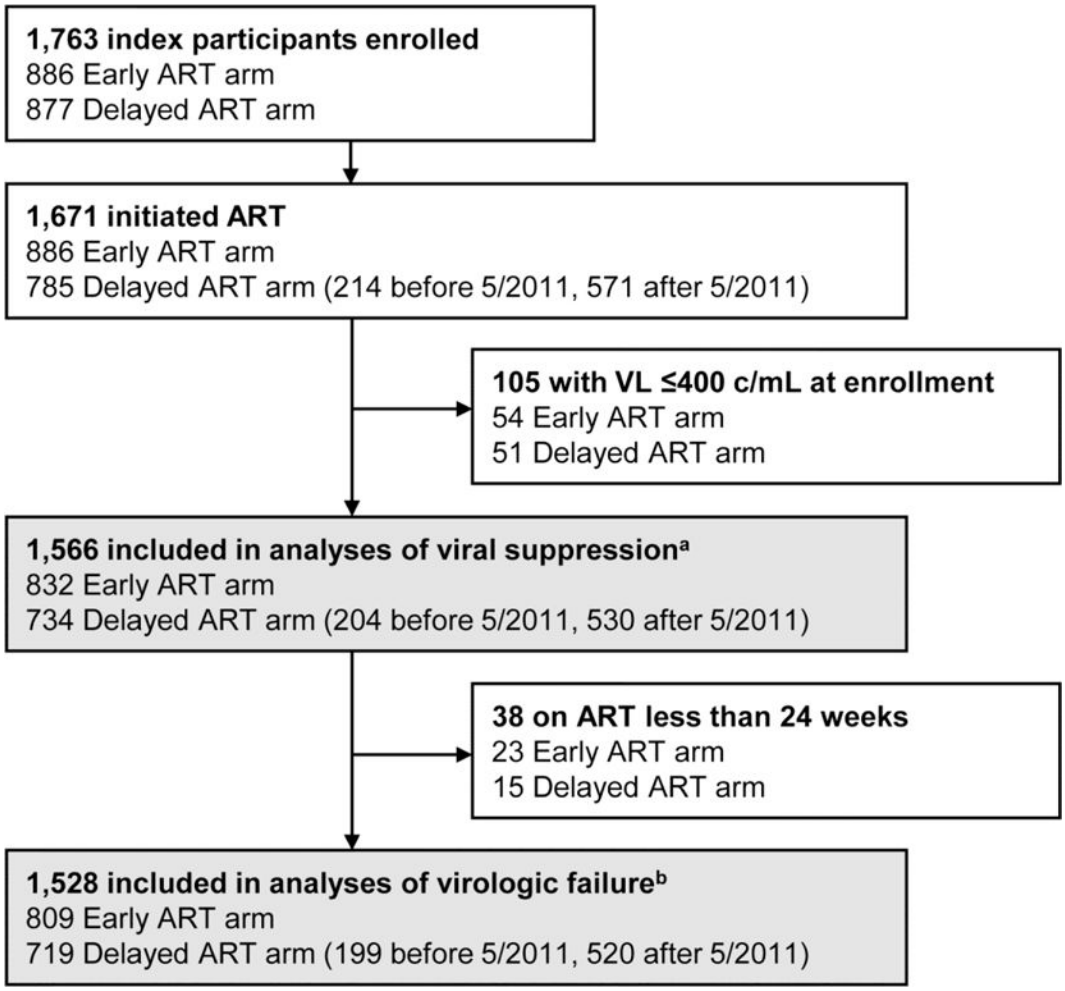

Figure 1.

Study cohort for virologic outcomes analysis.

The figure shows the number of participants in the early ART arm and delayed ART arm (stratified by whether or not ART was initiated before or after May, 2011) included in the analyses of viral suppression and virologic failure. Abbreviations: ART: antiretroviral therapy, VL: viral load; c/mL: copies/milliliter.

[a] The 1,566 participants included in the viral suppression analysis were followed for 4722.4 person-years in the early ART arm and 2674.8 person-years in the delayed ART arm (977.4 person-years in the delayed ART arm before May, 2011 and 1697.4 person-years in the delayed ART arm after May, 2011).

[b] The 1,528 participants included in the virologic failure analysis were followed for 4216.1 person-years in the early ART arm and 2445.8 person-years in the delayed ART arm (893.1 person-years in the delayed ART arm before May, 2011 and 1552.7 person-years in the delayed ART arm after May, 2011).

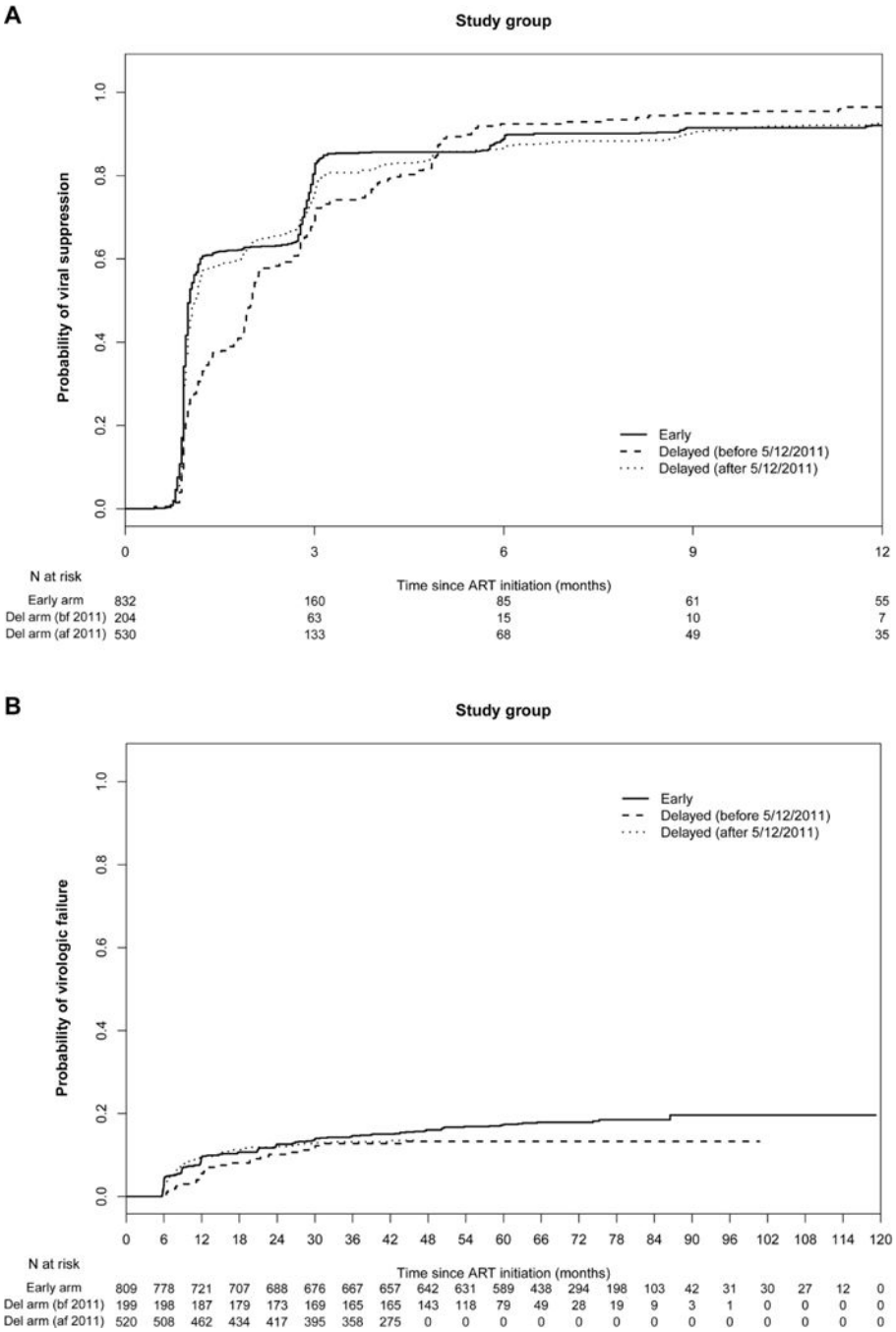

Figure 2.

Kaplan-Meier estimates for virologic outcomes after ART initiation by study group. Kaplan-Meier plots show the relationship of study group (early ART arm, delayed ART arm with ART initiation before May 2011, and delayed ART arm with ART initiation after May 2011) with time to viral suppression (Panel A) and virologic failure (Panel B) after ART initiation. The numbers below each graph show the number of participants who were at risk of viral suppression or virologic failure at each time point.

Abbreviations: ART: antiretroviral therapy; c/mL: copies/milliliter.

Table 1

Characteristics of participants at the time of ART initiation (N=1,566).

Variables	Early ART (N=832)	Delayed ART (N=734)	p-value	Delayed ART (Before 5/2011) (N=204)	Delayed ART (After 5/2011) (N=530)	p-value
Median age (IQR)	33 (28–39)	35 (29, 41)	<**0.001**	36 (31–42)	34 (29–40)	0.07
Gender			0.63			**0.042**
Male	433 (52.0%)	373 (50.8%)		116 (56.9%)	257 (48.5%)	
Female	399 (48.0%)	361 (49.2%)		88 (43.1%)	273 (51.5%)	
Median CD4 cell count (IQR)	439 (371–518)	314 (239–421)	<**0.0001**	228 (196–246)	365 (291–462)	<**0.001**
Median $\log_{10}$ viral load (IQR)	4.5 (3.9–4.9)	4.8 (4.2, 5.3)	<**0.0001**	5.1 (4.6–5.5)	4.6 (4.1–5.1)	<**0.001**
Median time to ART initiation (IQR)	0 (0–0)	2.3 (1.7, 3.0)	<**0.0001**	1.6 (0.9–2.3)	2.5 (2.0–3.2)	<**0.001**
Region			0.98			<**0.001**
Americas	136 (16.3%)	119 (16.2%)		54 (26.5%)	65 (12.3%)	
Asia	257 (30.9%)	230 (31.3%)		85 (41.7%)	145 (27.4%)	
Africa	439 (52.8%)	385 (52.5%)		65 (31.9%)	320 (60.4%)	
Regimen			**0.006**			0.13
EFV/3TC/ZDV	605 (72.7%)	487 (66.3%)		144 (70.6%)	343 (64.7%)	
Other[a]	227 (27.3%)	247 (33.7%)		60 (29.4%)	187 (35.3%)	
Education			**0.019**			0.90
None	96 (11.5%)	54 (7.4%)		15 (7.4%)	39 (7.4%)	
Primary or secondary schooling	660 (79.3%)	613 (83.5%)		172 (84.3%)	441 (83.2%)	
Post-secondary-schooling	76 (9.1%)	67 (9.1%)		17 (8.3%)	50 (9.4%)	
Marital status			0.78			0.97
Married	784 (94.2%)	694 (94.6%)		193 (94.6%)	501 (94.5%)	
Not married	48 (5.8%)	40 (5.4%)		11 (5.4%)	29 (5.5%)	
Number of sex partners[b]			<**0.001**			0.81
0–1	777 (93.4%)	721 (98.2%)		200 (98.0%)	521 (98.3%)	
>1	53 (6.4%)	13 (1.8%)		4 (2.0%)	9 (1.7%)	

Abbreviations: ART: antiretroviral therapy; IQR: interquartile range; EFV: efavirenz; 3TC: lamivudine; ZDV: zidovudine.

P-values <0.05 are bolded. Chi-square test was used for categorical variables and Wilcoxon rank sum test was used for continues variables.

[a]Other ART regimens were: 14% protease inhibitor-based ART, 13% EFV-based ART, and 3% nevirapine-based ART.

[b] Number of sex partners in the 3 months prior to ART initiation.

Table 2

Factors associated with time to viral suppression after ART initiation (censored at 12 months after ART initiation).

			Univariate		Multivariate	
	Total, N	**VS, N (%)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Study arm				0.06		
Early ART arm	832	748 (89.9)	Ref			
Delayed ART arm	734	680 (92.6)	0.91 (0.82, 1.01)			
Study group[a]				0.095		
Early ART arm	832	748 (89.9)	Ref			
Delayed ART arm (ART start before 5/2011)	204	194 (95.1)	0.85 (0.72, 0.99)	**0.038**		
Delayed ART arm (ART start after 5/2011)	530	486 (91.7)	0.93 (0.83, 1.05)	0.23		
Age at ART initiation				**0.0026**		**0.0007**
<25 years	147	120 (81.6)	Ref		Ref	
25–39 years	992	905 (91.2)	1.39 (1.15, 1.69)	**0.0006**	1.40 (1.16, 1.70)	**0.0006**
≥40 years	427	403 (94.4)	1.38 (1.13, 1.69)	**0.0020**	1.49 (1.21, 1.83)	**0.0002**
Gender				0.44		
Male	806	747 (92.7)	Ref			
Female	760	681 (89.6)	0.96 (0.87, 1.06)			
CD4 at ART initiation (per 100 CD4 increment)	1560	1422 (91.2)	1.07 (1.03, 1.11)	**0.0007**		
VL at ART initiation (per unit $\log_{10}$ VL increment)	1563	1425 (91.2)	0.73 (0.68, 0.78)	<**0.0001**	0.71 (0.66, 0.76)	<**0.0001**
Time to ART initiation (years)[b]	1566	1428 (91.2)	0.98 (0.95, 1.02)	0.38		
Region				0.07		**0.015**
Africa	824	749 (90.9)	Ref		Ref	
Asia	487	444 (91.2)	1.14 (1.02, 1.28)	**0.027**	1.19 (1.05, 1.34)	**0.0046**
Americas	255	235 (92.2)	1.00 (0.86, 1.15)	0.96	1.02 (0.88, 1.19)	0.74
Regimen				**0.015**		
Other	474	442 (93.2)	Ref			

			Univariate		Multivariate	
	Total, N	**VS, N (%)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
EFV/3TC/ZDV	1092	986 (90.3)	0.87 (0.78, 0.97)			
Education				0.20		
None	150	129 (86.0)	Ref			
Primary or secondary schooling	1273	1162 (91.3)	1.10 (0.92, 1.32)	0.29		
Post-secondary schooling	143	137 (95.8)	1.24 (0.98, 1.58)	0.08		
Marital status				0.16		
Married	1478	1344 (90.9)	Ref			
Not married	88	84 (95.5)	1.17 (0.94, 1.46)			
Number of sex partners[c]				0.08		
0–1	1498	1363 (91.0)	Ref			
>1	66	63 (95.5)	1.25 (0.97, 1.61)			

Abbreviations: N: number; VS: virally suppressed; HR: hazards ratio; CI: confidence interval; ART: antiretroviral therapy; ref: reference group; VL: HIV viral load; EFV: efavirenz; 3TC: lamivudine; ZDV: zidovudine.

P-values <0.05 are bolded. Hazard ratios (HR) were calculated using Cox regression model. HR >1 indicates higher risk of viral suppression at any time, thereby shorter time to viral suppression. The mulitvariate model was created using a backward model selection method; p<0.05 was used to exclude variables in this model. Results for the variables that remained significant in the multivariate model are shown.

[a]Median (interquartile range) days to viral suppression was 30 (28–88) days for participants in the early ART arm, 60 (30–107) days for participants in the delayed ART arm who started ART before May 2011, and 33 (28–91) days for participants in the delayed ART who started ART after May 2011).

[b]Time to ART initiation indicates the time between study enrollment and treatment initiation.

[c]Number of sex partners in the 3 months prior to ART initiation.

Table 3

Factors associated with virologic failure.

				Univariate		Multivariate	
	N	**Virologic failure, N (%)**	**Median days to failure (IQR)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Study arm					0.18		
Early ART arm	809	144 (17.8)	361 (184–899)	Ref			
Delayed ART arm	719	94 (13.1)	279 (202–465)	0.83 (0.64, 1.09)			
Study group					0.31		
Early ART arm	809	144 (17.8)	361 (184–899)	Ref			
Delayed ART arm (ART start before 5/2011)	199	26 (13.1)	397 (336–686)	0.75 (0.49, 1.13)	0.17		
Delayed ART arm (ART start after 5/2011)	520	68 (13.1)	245 (187–443)	0.87 (0.65, 1.17)	0.37		
Age at ART initiation					**<0.0001**		**0.0018**
<25 years	141	40 (28.4)	356 (238–800)	Ref		Ref	
25–39 years	969	157 (16.2)	356 (197–723)	0.55 (0.39, 0.78)	**0.0007**	0.78 (0.55, 1.11)	0.17
≥40 years	418	41 (9.8)	270 (182–619)	0.32 (0.21, 0.50)	**<0.0001**	0.46 (0.29, 0.72)	**0.0007**
Gender					**0.025**		
Male	784	106 (13.5)	357 (193–719)	Ref			
Female	744	132 (17.7)	344 (194–721)	1.34 (1.04, 1.73)			
CD4 at ART initiation (per 100 CD4 increment)	1522	237 (15.6)	353 (193–720)	1.10 (1.00, 1.20)	**0.047**	1.11 (1.00, 1.22)	**0.044**
VL at ART initiation (per unit $\log_{10}$ VL increment)	1525	237 (15.5)	353 (193–720)	1.05 (0.89, 1.25)	0.56	0.81 (0.67, 0.98)	**0.026**
Time to ART initiation (years)[a]	1528	238 (15.6)	354 (193–720)	0.97 (0.88, 1.07)	0.51		
Region					0.16		
Africa	803	123 (15.3)	350 (198–721)	Ref			
Asia	472	65 (13.8)	297 (190–646)	0.88 (0.65, 1.19)	0.41		
Americas	253	50 (19.8)	373 (237–911)	1.26 (0.91, 1.75)	0.17		
Regimen					0.33		
Other	464	65 (14.0)	361 (241–724)	Ref			

				Univariate		Multivariate	
	N	**Virologic failure, N (%)**	**Median days to failure (IQR)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
EFV/3TC/ZDV	1064	173 (16.3)	350 (185–719)	1.15 (0.87, 1.53)			
Education					**0.0019**		**0.0007**
None	145	33 (22.8)	244 (182–636)	Ref		Ref	
Primary or secondary schooling	1244	195 (15.7)	357 (200–724)	0.66 (0.46, 0.96)	**0.029**	0.62 (0.43, 0.89)	**0.018**
Post-secondary schooling	139	10 (7.2)	314 (180–641)	0.29 (0.14, 0.58)	**0.0005**	0.27 (0.15, 0.54)	**0.0004**
Marital status					**0.049**		
Married	1440	231 (16.0)	353 (193–723)	Ref			
Not married	88	7 (8.0)	360 (181–630)	0.47 (0.22, 1.00)			
Number of sex partners[b]					0.62		
0–1	1462	228 (15.6)	352 (192–719)	Ref			
>1	64	9 (14.1)	619 (261–903)	0.85 (0.43, 1.65)			
Lack of viral suppression by 3 months					<**0.0001**		<**0.0001**
No	1182	107 (9.1)	239 (181–359)	Ref			
Yes	346	131 (37.9)	633 (358–977)	5.53 (4.28, 7.14)		6.65 (5.04, 8.76)	

Abbreviations: N: number; IQR: interquartile range; HR: hazard ratio; CI: confidence interval; ART: antiretroviral therapy; ref: reference group; VL: HIV viral load; EFV: efavirenz; 3TC: lamivudine; ZDV: zidovudine; mo: months.

P-values <0.05 are bolded. Hazard ratios (HR) were calculated using Cox regression model. HR >1 indicates higher risk of virologic failure. The multivariate model was created using a backward model selection method; p<0.05 was used to exclude variables in this selection model. Results for the variables that remained significant in the multivariate model are shown.

[a] Time to ART initiation indicates the time between study enrollment and treatment initiation.

[b] Number of sex partners in the 3 months prior to ART initiation.