

The Setpoint Study (ACTG A5217): Effect of Immediate Versus Deferred Antiretroviral Therapy on Virologic Set Point in Recently HIV-1–Infected Individuals

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(See the editorial commentary by Tossonian and Conway, on pages 10–12.)

Background. The benefits of antiretroviral therapy during early human immunodeficiency virus type 1 (HIV-1) infection remain unproved.

Methods. A5217 study team randomized patients within 6 months of HIV-1 seroconversion to receive either 36 weeks of antiretrovirals (immediate treatment [IT]) or no treatment (deferred treatment [DT]). Patients were to start or restart antiretroviral therapy if they met predefined criteria. The primary end point was a composite of requiring treatment or retreatment and the log₁₀ HIV-1 RNA level at week 72 (both groups) and 36 (DT group).

Results. At the June 2009 Data Safety Monitoring Board (DSMB) review, 130 of 150 targeted participants had enrolled. Efficacy analysis included 79 individuals randomized ≥ 72 weeks previously. For the primary end point, the IT group at week 72 had a better outcome than the DT group at week 72 ($P = .005$) and the DT group at week 36 ($P = .002$). The differences were primarily due to the higher rate of progression to needing treatment in the DT group (50%) versus the IT (10%) group. The DSMB recommended stopping the study because further follow-up was unlikely to change these findings.

Conclusions. Progression to meeting criteria for antiretroviral initiation in the DT group occurred more frequently than anticipated, limiting the ability to evaluate virologic set point. Antiretrovirals during early HIV-1 infection modestly delayed the need for subsequent treatment.

Clinical Trials Registration. NCT00090779.

The role of antiretroviral therapy (ART) during acute and early human immunodeficiency virus type 1 (HIV-1) infection has been an area of investigation for several years; however, the benefits of such treatment remain unproved, and best practice for clinical management of this unique stage of infection remains unknown [1]. The initiation of ART shortly after HIV-1 infection has been shown to preserve HIV-1–specific immune responses that could improve virologic control on discontinuation of treatment [2–4]. However, prospective observational

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studies have evaluated the effects of early ART followed by treatment cessation on subsequent virologic control with conflicting results [5–15], and few randomized clinical trials have been performed in the setting of acute and early HIV-1 infection [16–20]. We hypothesized that 36 weeks of ART administered to participants within 6 months of acquiring HIV-1 infection would lower the virologic set point after treatment discontinuation.

The AIDS Clinical Trials Group (ACTG) Setpoint Study (A5217) was a multicenter, randomized clinical trial during which individuals with recent but not acute HIV-1 infection were randomized to begin immediate treatment (IT) with a 36-week course of ART and then discontinue treatment, or to defer treatment (DT) until prespecified criteria for initiation of therapy were met. During a scheduled interim review, the Data and Safety Monitoring Board (DSMB) of the National Institute of Allergy and Infectious Diseases (NIAID) noted a higher than expected rate of disease progression and subsequent initiation of ART in the DT group, limiting the ability to compare the actual virologic set point between the 2 groups. As a result of these findings in June 2009, the DSMB stated that further enrollment and follow-up as designed could not be justified and recommended study discontinuation. We report here on the data collected through the time of the DSMB recommendations.

METHODS

Study Participants

The study enrolled men and nonpregnant women who were ≥ 18 years of age, were HIV-1 infected within the last 6 months but beyond the acute phase of infection (with a positive HIV-1 Western blot), and had no prior ART, acceptable laboratory parameters, and an HIV-1 RNA level ≥ 500 copies/mL. Recent infection was defined as a nonreactive detuned HIV-1 antibody test consistent with infection of < 6 months duration at the time of screening, or documented seroconversion (ie, a documented negative HIV-1 enzyme immunoassay [EIA] or a negative or indeterminate Western blot within 6 months before the study). We initially used the Vironostika HIV-1 detuned EIA, with recent infection defined as a standardized optical density measurement ≤ 0.75 [21]. In 2008, the Vironostika assay was no longer available, and the detuned Ora-Quick rapid test was used to confirm recent infection in the absence of documented seroconversion [22–24]. All detuned assays were performed at either the University of North Carolina at Chapel Hill or the Blood Systems Research Institute in San Francisco. We excluded participants who met immunologic or clinical criteria for treatment at entry [25], including the occurrence of Centers for Disease Control and Prevention (CDC) category B or C diagnoses, $CD4^+$ T-cell count < 350 cells/mm³, or $CD4^+$ T-cell percentage of $< 14\%$. Baseline genotypic resistance testing was performed on all participants, with therapy adjusted as necessary

when data became available. Individuals with baseline resistance to > 1 component of the initial study regimen were excluded. The institutional review board at each participating site approved the study protocol, and written informed consent was obtained from all participants.

Study Design

ACTG 5217 was a 96-week, multicenter, randomized, open-label study that began in February 2005 and was performed at 25 sites in the United States and 2 in Peru. One hundred fifty recently HIV-1-infected adults were to be randomized 1:1 to the IT group versus the DT group. Participants in the IT group received 36 weeks of ART followed by treatment discontinuation. Participants in the DT group were followed up off treatment throughout the study; however, individuals in either group who met prespecified criteria for treatment initiation or reinitiation were advised to begin ART.

Screening evaluations included confirmation of recent HIV-1 infection as defined above, genotypic resistance testing, $CD4^+$ T-cell count, and HIV-1 RNA level. Baseline and on-study evaluations occurred at weeks 0, 1, 2, and 4 and every 4 weeks thereafter for the duration of the study and included $CD4^+$ T-cell count and HIV-1 RNA level, the latter measured using the Roche Amplicor Monitor assay, version 1.5, at a laboratory certified by Division of AIDS Virology Quality Assurance program.

Study Treatment

The study provided fixed-dose combination emtricitabine-tenofovir DF (one 200/300 mg tablet, once daily) and lopinavir-ritonavir (200/50 mg tablets, 2 tablets twice daily or 4 tablets once daily) for the first 36 weeks for individuals in the IT group and for the remaining duration of the study for individuals in either group who had met eligibility for initiation of ART. However, study participants were allowed to receive any alternative provider-prescribed potent ART regimen.

Criteria for Initiating ART

Participants in either arm who met protocol-specified criteria for treatment initiation or reinitiation were advised but not required to begin treatment. The prespecified criteria for initiating ART were designed to be consistent with treatment guidelines for chronic infection at the time [25] and included (1) $CD4^+$ T-cell count < 350 cells/mm³ at 2 consecutive determinations ≥ 4 weeks apart, ≥ 12 weeks into the study or ≥ 12 weeks after treatment discontinuation; (2) confirmed $CD4^+$ T-cell count < 200 cells/mm³ or $CD4^+$ T-cell percentage $< 14\%$ at any time during the study; (3) confirmed HIV-1 RNA level $> 750\,000$ copies/mL ≥ 4 weeks into the study or $> 200\,000$ copies/mL ≥ 12 weeks into the study; or (4) CDC category B or C diagnosis. The time requirements were to accommodate the fluctuations in $CD4^+$ T-cell counts and HIV-1 RNA levels characteristically seen with recent seroconversion.

Statistical Analysis

The primary end point was constructed as a composite measure that consisted of the average viral load at weeks 72 and 76 for study participants who continued to week 72 off treatment and an assigned viral load rank for those who met criteria for initiating ART before these study visits and thus could not contribute an off-treatment HIV-1 RNA assessment. Such individuals were considered to have experienced a poor outcome and were assigned an HIV-1 RNA rank. The assigned rank was either the last observed rank carried forward or the worst rank, according to an analysis plan that was designed to be, if anything, biased against finding a treatment effect; details of the algorithm for assigning ranks are provided in the Supplementary appendix. Differences in the primary end point between the 2 treatment groups at week 72 were then assessed using the Wilcoxon rank sum 1-sided test, use of which reflects the focus of interest in only the 1-sided alternative hypothesis that immediate short-term therapy is superior to delay in starting therapy. However, at 72 weeks, participants in the IT group would have been off therapy for 36 weeks, whereas those in the DT group would have been off therapy for 72 weeks. To provide additional insight about any benefits of treatment, a difference in virologic set point observed at 72 weeks would trigger an additional analysis: comparison of the end point at week 72 in the IT group (36 weeks after ART was interrupted) with the end point at week 36 in the DT group (detailed further in [26]). The secondary end point, time to meeting eligibility for initiating or reinitiating ART, was assessed via Kaplan-Meier plot and log-rank test.

Power calculations were based on a 1-sided, 2-sample *t* test at $\alpha = .05$, adjusted for the use of methods based on ranked data. The planned sample size of 75 individuals randomized to each group provided >90% power to detect a plasma HIV-1 RNA improvement of 0.6 log₁₀ copies/mL in the IT group compared with the DT group. This provided power of $\geq 80\%$ for the combined 2-step test, using Bonferroni inequality.

Study Monitoring

The initial monitoring plan included 2 interim safety reviews conducted by the NIAID Therapeutics DSMB. However, given slower than expected accrual, annual reviews of efficacy and futility analyses started in the summer of 2008. Subsequently, the DSMB performed an annual review of safety and efficacy data on 25 June 2009 and recommended premature discontinuation of the study.

RESULTS

Baseline Characteristics

We had enrolled 130 eligible of 150 targeted participants at the time of the June 2009 DSMB review. Baseline characteristics were well balanced between the groups (Table 1).

Study Status

At the time of the June 2009 DSMB review, 52 (40%) of 130 participants were still in the study, 52 (40%) had completed the protocol, 24 (18.5%) had left the study before week 96, and 2 in the DT group had died. One death was a suicide 14 weeks into the study, and the other occurred 8 weeks into the study and was of unknown cause. Reasons for going off study prematurely are shown in Table 2. Forty-five of 66 (68%) IT participants had completed 36 weeks of ART, 13 of 66 (20%) were in the midst of treatment when the study was stopped, 4 (6%) discontinued ART prematurely, and 4 (6%) discontinued the study before week 36. Fifty-five of 66 (83%) treated participants chose the study-provided ART regimen, and 88% of all participants randomized to the IT group achieved complete virologic suppression by week 24. One participant randomized to the IT group initiated study medications and was promptly discontinued and excluded from the efficacy analysis after review of the baseline *pol* sequence analysis showed multidrug resistance.

Eligibility for Initiation or Reinitiation of ART

When all 130 participants were included, regardless of length of time on protocol, 7 of 66 (11%) in the IT group and 23 of 64 (36%) in the DT group met eligibility for initiation/reinitiation of ART, with 13 (20%) of those in the DT group meeting criteria within the first 36 weeks. The majority of participants who met criteria for treatment initiation met immunologic criteria (6 in IT group, 14 in DT group), and a few met virologic criteria (5 in DT group). Five individuals met eligibility owing to the occurrence of a CDC category B or C event (4 in the DT group, 1 in the IT group) (Table 3). A total of 5 individuals, all in the DT group, progressed to AIDS—1 because of persistent herpes simplex infection, 1 because of CD4⁺ T-cell count <200 cells/mm³, and 3 because of CD4⁺ T-cell percentage <14%.

Primary Efficacy Analysis

Efficacy analysis was limited to 79 participants (39 and 40 from the IT and DT groups, respectively) who had been randomized ≥ 72 weeks before the DSMB review. By week 72, 50% of the 40 DT participants versus 10% of the 39 IT participants had met criteria for initiation/reinitiation of ART. At week 36, 27.5% of the 40 DT participants had met criteria for starting ART.

For the primary end point, the IT group at week 72 had a better outcome than the DT group at 72 weeks ($P = .005$; 1-sided Wilcoxon test) or 36 weeks ($P = .002$; 1-sided Wilcoxon test). The outcome was the same when the analysis was based on available data for all enrolled participants (ie, including an additional 50 participants) instead of being restricted only to 79 who were randomized ≥ 72 weeks before the DSMB recommendations. Thus, superiority was demonstrated for the IT group. Because of the higher-than-expected number of individuals meeting criteria for initiating ART, the primary

Table 1. Baseline Characteristics

Characteristic	All Eligible Subjects			Subjects Included in Primary Analysis		
	IT Group (n = 66)	DT Group (n = 64)	Total (n = 130)	IT Group (n = 39)	DT Group (n = 40)	Total (n = 79)
Sex						
Male	58 (88)	59 (92)	117 (90)	34 (87)	40 (100)	74 (94)
Female	8 (12)	5 (8)	13 (10)	5 (13)	0 (0)	5 (6)
Age, median (IQR), y	34 (25–40)	33 (27–42)	33 (26–42)	37 (23–42)	36.0 (28.5–42.5)	36 (26–42)
Race						
White	49 (74)	56 (88)	105 (81)	31 (79)	38 (95)	69 (87)
Black/African American	10 (15)	3 (5)	13 (10)	6 (15)	2 (5)	8 (10)
Other/unknown	7 (11)	5 (8)	12 (9)	2 (5)	0 (0)	2 (3)
Ethnicity						
Hispanic or Latino	14 (21)	9 (14)	23 (18)	7 (18)	1 (3)	8 (10)
Not Hispanic or Latino	52 (79)	55 (86)	107 (82)	32 (82)	39 (98)	71 (90)
Transmission risk						
MSM	52 (79)	55 (86)	107 (82)	31 (79)	36 (90)	67 (85)
Heterosexual	10 (15)	7 (11)	17 (13)	8 (21)	3 (8)	11 (14)
IVDU	1 (2)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
MSM and IVDU	3 (5)	1 (2)	4 (3)	0 (0)	1 (3)	1 (1)
Unknown	0 (0)	1 (2)	1 (1)	0 (0)	0 (0)	0 (0)
CD4 ⁺ T-cell count, median (IQR), cells/mm ^{3a}	514 (415–671)	557 (441–721)	540 (435–697)	488 (402, 671)	552 (435–704)	534 (415–697)
CD4⁺ T-cell count, cells/mm³						
201–350	4 (6)	2 (3)	6 (5)	3 (8)	2 (5)	5 (6)
351–500	26 (39)	24 (38)	50 (38)	17 (44)	14 (35)	31 (39)
>500	36 (55)	38 (59)	74 (57)	19 (49)	24 (60)	43 (54)
HIV-1 RNA, median (IQR), log ₁₀ copies/mL ^a	4.4 (3.9–4.8)	4.4 (4.0–4.7)	4.4 (4.0–4.7)	4.4 (3.9–4.8)	4.4 (4.1–4.9)	4.4 (4.0–4.9)
HIV-1 RNA, copies/mL						
<10 000	17 (26)	16 (25)	33 (25)	10 (26)	8 (20)	18 (23)
≥10 000	49 (74)	48 (75)	97 (75)	29 (74)	32 (80)	61 (77)

Except where otherwise indicated, data represent No. (%) of subjects. $P > .05$ for all comparisons between treatment groups.

Abbreviations: DT, deferred treatment; HIV-1, human immunodeficiency virus, type 1; IQR, interquartile range; IT, immediate treatment; IVDU, intravenous drug use; MSM, men who have sex with men.

^a Baseline CD4⁺ T-cell counts and baseline HIV-1 RNA levels were the values at study entry.

analysis was highly influenced by the higher rate of progression in the DT group. Because off-treatment HIV-1 RNA levels were unobserved for all participants who met criteria for initiating ART, we were unable to make conclusions regarding the actual virologic set point.

Time to Meeting Eligibility Criteria for Initiating or Reinitiating ART

A secondary end point was time to meeting eligibility criteria for initiating or reinitiating ART, which was significantly shorter in the DT group than in the IT group using data up to 76 and 96 weeks ($P < .001$ for both, by log-rank test). Figure 1 shows the time to meeting eligibility criteria for starting ART over the 96 weeks of the study. In a different analysis that compared the first 36 weeks of the study for participants in the DT group and the period from weeks 36 to 72 for participants in the IT group,

the time to meeting criteria for initiating ART remained shorter in the DT group than in the IT group (Figure 2). Using the time when ART was interrupted (week 36) as the time origin for the IT group and week 0 as the time origin for the DT group, the curves remain significantly different ($P = .035$; log-rank test), but the analysis includes only those in the IT group who continued ART through week 36 ($n = 49$), compared with all in the DT group ($n = 64$), and therefore it is not a randomized comparison. Treated participants experienced an additional delay (~16 weeks) beyond the 36 weeks of treatment before failures began to occur.

Proportional hazard models adjusted for treatment group were used to evaluate whether any of the baseline characteristics predicted time to meeting criteria for initiating ART. Baseline CD4⁺ T-cell count <540 cells/mm³ and baseline viral load ≥ 4.4

Table 2. Summary of Study Status at the Time of Data and Safety Monitoring Board Recommendations

Status	Treatment Group, No. (%)		
	Immediate (n = 66)	Deferred (n = 64)	Total (n = 130)
In study	29 (44)	23 (36)	52 (40)
Died	0 (0)	2 (3)	2 (2)
Completed protocol	26 (39)	26 (41)	52 (40)
Premature discontinuation ^a	11 (17)	13 (20)	24 (18)
Subject refused further participation	4 (36)	2 (15)	6 (25)
Nonadherence to study requirements	0 (0)	1 (8)	1 (4)
Subject relocated, no remote follow-up planned	2 (18)	8 (62)	10 (42)
Subject could not be contacted	3 (27)	2 (15)	5 (21)
Investigator/clinician decision	1 (9)	0 (0)	1 (4)
Other (pregnancy)	1 (9)	0 (0)	1 (4)

^a Four subjects (all in the deferred treatment group) met criteria for initiation of antiretroviral therapy before prematurely leaving the study.

log₁₀ copies/mL were associated with shorter time to meeting criteria for starting ART (hazard ratio, 4.49 [*P* = .0003] and 3.99 [*P* = .0007], respectively). No significant interaction effect was found between treatment group and baseline CD4⁺ T-cell count or baseline HIV-1 RNA value.

Observed HIV-1 RNA Values

Among participants who contributed an observed week 72 and/or week 76 HIV-1 RNA value (26 of 39 [67%] in the IT group and 11 of 40 [27.5%] in the DT group), the mean HIV-1 RNA levels at weeks 72 and 76 were similar between the 2 treatment groups (3.99 log₁₀ copies/mL in the IT group and 4.15 log₁₀ copies/mL in the DT group). Among participants (26 in the IT group and 22 in the DT group) who contributed an observed week 72 and/or week 76 HIV-1 RNA value (IT group) or an

observed week 36 and/or week 40 HIV-1 RNA value (DT group), the point estimate for the mean HIV-1 RNA level at week 36 in the DT group was higher than that measured at week 72 in the IT group (4.37 log₁₀ copies/mL vs 3.99 log₁₀ copies/mL), but this finding must be interpreted with caution, given that the confidence intervals overlap and the remaining individuals were a selected subgroup of the original participants. The mean log₁₀ copies/mL change in HIV-1 RNA from baseline was -0.29 at 72 weeks in the IT group and 0.07 at 36 weeks in the DT group (Table 4).

DISCUSSION

This is the largest randomized controlled trial designed to assess whether ART initiated during early but not acute HIV-1

Table 3. Summary of Eligibility Criteria Met for Initiation of Antiretroviral Therapy (ART)

Criteria	Treatment Group, No.	
	Immediate (n = 66)	Deferred (n = 64)
Total meeting ART criteria	7 (11%)	23 (36%)
CD4 ⁺ T-cell percentage <14% and HIV-1 RNA >200 000 copies/mL ^a	0	1
CD4 ⁺ T-cell count <350 cells/mm ³ (2 consecutive visits)	6	10
CD4 ⁺ T-cell percentage <14%	0	2
CD4 ⁺ T-cell count <200 cells/mm ³	0	1
HIV-1 RNA >750 000 copies/mL (2 consecutive visits)	0	1
HIV-1 RNA >200 000 copies/mL (2 consecutive visits)	0	4
CDC category B or C disease	1	4
Herpes simplex for >1 month	0	1
Oral hairy leukoplakia	0	1
Fatigue	1	0
Idiopathic thrombocytopenic purpura	0	2

Abbreviations: CDC, Centers for Disease Control and Prevention; HIV-1, human immunodeficiency virus, type 1.

^a Only the first criterion that study participants met was counted in the summary of eligibility for ART initiation. One individual met 2 eligibility criteria simultaneously. Laboratory values meeting eligibility criteria were confirmed over 2 consecutive visits.

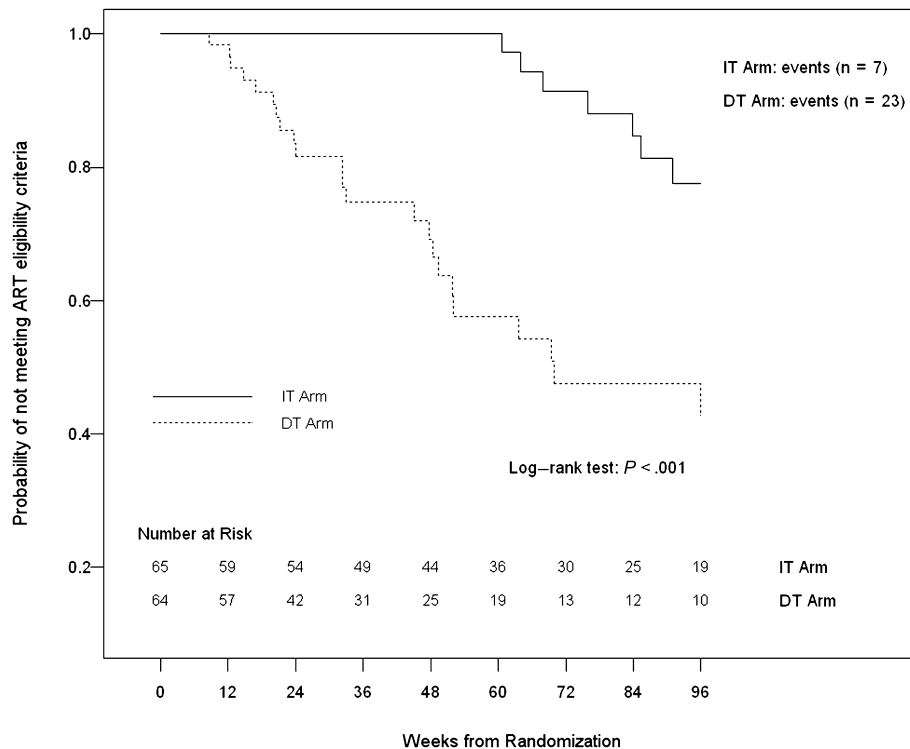


Figure 1. Time to meeting eligibility criteria for initiation or reinitiation of antiretroviral therapy (ART) for the immediate treatment (IT) and deferred treatment (DT) groups over the 96 weeks of the study; times were significantly longer in the IT group ($P < .001$; log-rank test).

infection is associated with better virologic outcomes than deferred ART. The study demonstrated a better outcome in the IT group, as measured by the composite end point at week 72 as well as at week 36 for the DT group versus week 72 for the IT group. Owing to the higher-than-anticipated rates of progression and, consequently, initiation of therapy, the difference in virologic set points between the 2 groups could not be statistically evaluated. In addition, participants in the IT group took significantly longer to meet the criteria for starting ART. Treated participants appear to have been protected not only while on treatment but also for a brief period of time thereafter. Thus, a limited period of ART during early HIV-1 infection delayed the need for subsequent initiation of long-term ART.

The best practice for the clinical management of primary HIV-1 infection remains unknown. Although prospective observational data from the HIV-CAUSAL Collaboration demonstrated the lowest mortality rate (6/1000 person-years) in seroconverters who started ART, compared with the overall mortality rate of 10/1000 person-years among individuals with established infection who started ART [27], no randomized clinical trials to date provide definitive recommendations for ART use in this patient population [16–20]. Efforts to evaluate the potential effect of ART on virologic set point in recently infected individuals have been limited, in part because of the challenges involved in identifying recently infected persons [5–15].

A study comparing 58 individuals who received ART during primary HIV-1 infection with 116 who remained untreated found no differences in virologic set point 12 months after withdrawal of effective ART [6]. Among the very few randomized clinical trials evaluating the impact of ART on virologic set point in recently infected persons, no persistent significant differences have been observed in HIV-1 RNA levels [16, 17, 20]. Like our study, a recently completed randomized controlled trial of temporary treatment versus no treatment during acute HIV-1 infection in the Netherlands observed a delay in the need for long-term ART in the immediate treatment group, although the delay appeared to be longer in the Dutch study [20]. However, whether such a delay in treatment yields durable or substantial clinical benefits remains unknown. A substudy of A5217 is underway to address whether immediate versus deferred treatment during primary infection results in improvements in markers of inflammation and immune activation, which may provide further insight into the potential benefits of treating primary infection.

Perhaps the most compelling finding of the A5217 study is that the time between the diagnosis of early infection and the need for initiation of ART was shorter than anticipated in the DT group. Investigators from the CASCADE study evaluated 14 387 individuals with well-estimated dates of HIV seroconversion to predict the proportion of participants with CD4⁺

inconsistent with this hypothesis, the relatively small number of participants is insufficient to support or refute the possibility of changing virulence in the epidemic.

Recently revised treatment guidelines recommend treatment initiation at higher CD4⁺ T-cell count thresholds [36, 37]. These guidelines consider emerging data highlighting the consequences of untreated HIV-1 infection and the potential role of ART in preventing serious non-AIDS conditions, which may result from the persistent immune activation and systemic inflammation associated with uncontrolled viral replication [27, 38–41]. The results of our current study may be of interest to clinicians and patients struggling with the decision of whether to initiate ART during recent HIV infection. Our results suggest that if immediate therapy is not begun, progression to meeting standard criteria for ART initiation may occur more rapidly than expected, especially with changing treatment paradigms.

Limitations of the study include the methods currently available for classifying study participants as having recent HIV infection. Detuned assays, used to confirm early infection for 78% of the participants, are limited in precision [42, 43]. The potential errors in disease stage classification were thought to favor exclusion of those with recent infection rather than inappropriate inclusion of participants with advanced HIV. We are unable to exclude, however, the possibility of this latter type of misclassification contributing to the more rapid rate of progression. Another possible contribution to a selection bias favoring rapid progression for this cohort may result from oversampling of individuals with symptomatic seroconversion syndromes (55% overall), who are more likely to seek medical attention and may experience more rapid disease progression [44, 45]. Finally, it is not possible to extrapolate the observed study results to individuals who present with acute HIV infection (HIV-1 RNA positive, HIV-1 antibody negative), because our study enrolled only participants with recent but not acute infection.

In conclusion, this randomized, controlled trial of immediate versus deferred ART in the setting of recent HIV-1 infection demonstrated a treatment effect in favor of immediate treatment. A limited period of ART during early HIV-1 infection modestly delayed the need for subsequent initiation of long-term ART. The study was unable to answer the initial question regarding virologic set point, and durable clinical benefits of this strategy remain unproved. However, the higher than anticipated rate of disease progression among untreated individuals, which prevented us from drawing conclusions regarding the virologic set point, is a compelling finding of this study and contributes to the growing body of evidence favoring earlier treatment.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://www.oxfordjournals.org/our_journals/jid/). Supplementary

materials consist of data provided by the authors that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the authors.

Notes

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