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Tolerability and Efficacy of PI Versus NNRTI-Based Regimens in Subjects Receiving HAART During Acute or Early HIV Infection

Linda G. Apuzzo, BS^{*}, Florin Vaida, PhD[†], Joel E. Gallant, MD, MPH^{*,‡}, Karin B. Ernststrom, MS[†], Susan J. Little, MD[†], Jean-Pierre Routy, MD[§], Ann C. Collier, MD^{||}, Brian Conway, MD[¶], Martin H. Markowitz, MD[#], Frederick M. Hecht, MD^{**}, Bruce D. Walker, MD^{††}, Elizabeth Connick, MD^{‡‡}, and Joseph B. Margolick, MD, PhD^{*}

^{*}Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

[†]Department of Family and Preventive Medicine, University of California San Diego, San Diego, CA

[‡]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

[§]Department of Medicine, McGill University, Montreal, Quebec, Canada

^{||}Department of Medicine, University of Washington School of Medicine, Seattle, WA

[¶]Department of Pharmacology and Therapeutics, University of British Columbia, Vancouver, British Columbia, Canada

[#]Aaron Diamond AIDS Research Center, New York, NY

^{**}Department of Medicine, University of California San Francisco, San Francisco, CA

^{††}Department of Medicine, Harvard Medical School, Boston, MA

^{‡‡}Department of Medicine, University of Colorado Denver, Denver, CO

Abstract

Background—Little is known about modifications to highly active antiretroviral therapy (HAART) initiated during acute or early HIV infection.

Methods—Reasons for first modifications of HAART regimens were recorded using the AIDS Clinical Trials Group form among 363 subjects who initiated HAART within 1 year of seroconversion from 2005 in the Acute Infection and Early Disease Research Program. Modifications recorded as due to “patient choice” or “physician choice” were clarified by query to the recording site. Times to events were analyzed by Kaplan–Meier methods; significance of differences was assessed by the log-rank test.

Results—Two hundred five of 363 (56%) subjects modified therapy, at a median of 425 days after initiation, by changing drugs, discontinuing treatment, or removing or adding drugs. Most modifications were attributed to toxicity ($n = 105$, 51%), most of which was low grade; regimen simplification ($n = 18$, 5%); and achievement of viral suppression ($n = 15$, 7%). Time to first modification was shorter for those with shorter time from infection to initiation ($P = 0.005$) and

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Correspondence to: Joseph B. Margolick, MD, PhD, Johns Hopkins, Bloomberg School of Public Health, Department of Molecular Microbiology, and Immunology, 615 North Wolfe Street, Baltimore, MD 21205, (e-mail: jmargoli@jhsph.edu).

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Data in this study were collected by sites participating in the Acute Infection and Early Disease Research Program.

those having higher CD4 lymphocyte count at initiation ($P = 0.06$). Modifications occurred sooner in subjects receiving regimens taken more than once daily ($P < 0.001$) or with more than 2 pills daily ($P < 0.001$). Most regimens were nonnucleoside reverse transcriptase inhibitor based or protease inhibitor based, and these did not differ significantly in rate and timing of modification.

Conclusions—HAART initiated early in HIV infection was modified in the majority of cases, usually due to minor toxicities whose incidence was similar for protease inhibitor–based and nonnucleoside reverse transcriptase inhibitor–based regimens. Convenience of regimens (lower pill burden and dosing frequency) was associated with a lower rate of modification.

Keywords

cohort studies; regimen modification; toxicity

INTRODUCTION

There is still no consensus on whether highly active antiretroviral therapy (HAART) should be instituted during primary or early HIV infection.^{1–5} Early initiation of HAART might minimize or prevent damage to the immune system and loss of anti-HIV immune responses^{6–8} but may increase the risk of drug toxicity and resistance.^{1,9,10} Because of these competing considerations, the Department of Health and Human Services guidelines continue to state that treatment in acute or early HIV infection is optional.¹

Initial HAART regimens in the mid 1990s were complex and relatively toxic, with high pill burdens and complex dosing schedules. Since 2002, HAART regimens have become considerably simpler. Nevertheless, toxicity is still common, nonadherence can still lead to treatment failure, and in a study of 51 people treated early in HIV infection, we found that modification or discontinuation of initial regimens was frequent (80%).¹¹ No large studies have examined the duration of the first regimen and the reasons for treatment changes or discontinuation in the setting of primary or early HIV infection.

The present study was designed to determine the duration of the HAART regimen initiated during the early course of infection and to identify determinants for regimen modification or discontinuation. To this end, we analyzed first modifications of initial HAART regimens, including both drug switches and discontinuation, in subjects who initiated HAART between 2002 and 2005 in the Acute Infection and Early Disease Research Project (AIEDRP).

METHODS

Subjects

The study population was enrolled in the AIEDRP CORE01 Database Protocol. AIEDRP was a North American, multicenter, network studying primary and early HIV infection.^{12–14} Subjects were eligible for enrollment in the CORE01 Database Protocol if they met one of the following criteria for acute or early infection: (1) documented negative or indeterminate HIV antibody test and plasma HIV-1 RNA ≥ 5000 copies/mL or a positive p24 antigen test; (2) documented positive HIV antibody test and a negative less sensitive (detuned) HIV antibody test, indicating a low antibody titer suggestive of recent infection (standardized optical density < 1.0),^{15–20} or (3) a documented positive HIV antibody test preceded by a documented negative HIV antibody test within 365 days of study entry.

The CORE01 Database includes subjects who elected to begin HAART immediately, subjects who declined HAART at study entry but later began it, subjects whose treatment

was mandated by a specific study protocol, and subjects who did not start therapy. It also includes a small number of subjects in parent protocols evaluating investigational medications and/or immune-based therapies. Data were collected at baseline, weeks 2, 4, and 12 after entry into the CORE01 protocol, then every 12 weeks through week 168, and finally every 24 weeks for the duration of the study. At each visit, subjects were evaluated for interim medical events, HIV-related adverse events, and laboratory and clinical toxicities of antiretroviral medications. Participating centers included the following: Baltimore, MD; Boston, MA; Montreal, PQ; New York, NY; Vancouver, BC; San Diego, CA; San Francisco, CA; and Seattle, WA. Subjects receiving antiretroviral therapy were asked to complete an adherence questionnaire every 12 weeks for the first 48 weeks and every 24 weeks thereafter. Absolute CD4⁺ and CD8⁺ T-cell counts and subset percentages and plasma HIV-1 RNA levels were obtained at each study visit, using site laboratories certified by appropriate quality assurance programs.

For the present analysis, we included subjects who: (1) enrolled in CORE01 between January 2002 and December 2005; (2) received therapy that did not include protocol-mandated treatment interruptions; and (3) received HAART, defined as one of the following types of regimens: (a) 2 or more nucleoside analog reverse transcriptase inhibitors (NRTIs) and 1 nonnucleoside reverse transcriptase inhibitor (NNRTI), (b) 2 or more NRTIs and 1 unboosted protease inhibitor (PI), (c) 2 or more NRTIs and 1 ritonavir-boosted PI (PI/r), or (d) 2 NRTIs, 1 or more PIs, and 1 NNRTI.

Classification of Changes in HAART Regimens

In 2001, questions concerning reasons for modification of HAART regimens were added to the AIEDRP master protocol. Every change in the original HAART regimen was classified as either drug switch (substitution of one drug for another), discontinuation (of all drugs), reduction (discontinuation of 1 or more drugs), or addition (addition of 1 or more agents) and was attributed to 1 of the following reasons using the format developed by the AIDS Clinical Trials Group (www.aactg.org): (1) treatment completion or initiation, (2) laboratory or clinical toxicity, (3) clinical events or progression (includes physician-assessed virologic failure), (4) toxicity decreased or resolved, (5) clinician or subject request, (6) noncompliance, or (7) other.

For the present study, we queried the staff at the pertinent study site regarding changes that were initially attributed to “clinician/subject request” or “other” for more detail. For treatment modifications categorized as “subject’s request,” sites were asked to select from the following the reason that best described why the modification was made: (1) toxicity (including grades of side effects that led to the subject’s request to change antiretroviral agents), (2) pill burden (the subject requested a regimen containing fewer pills), or (3) adherence (the subject was unable to adhere to the initial regimen). For treatment modifications categorized as “clinician request,” the sites were asked to choose from the following possible reasons: (1) clinician decision to switch subject from a twice-daily to a once-daily regimen, (2) virologic failure on initial regimen (subjects who achieved viral suppression but later rebounded), (3) change in therapy after achievement of viral suppression (including subjects whose therapy was stopped once viral suppression was achieved), (4) structured treatment interruption, (5) baseline genotype results (subjects who initiated treatment before receipt of genotype results), (6) regimen intensification, or (7) induction-maintenance strategy (the use of aggressive initial regimens that were later simplified). Treatment modifications that were classified as “other” were assigned to one of the categories above or as participation in a protocol. Modifications that occurred within 5 days of each other were considered as a single modification. The following were not considered HAART modifications: increase in nevirapine dose from 200 mg to 400 mg, reduction in didanosine dose from 400 mg to 250 mg, protocol-mandated modifications,

switches from pills containing a single agent to combined formulations [eg, tenofovir plus emtricitabine to Truvada (Gilead Sciences, Foster City, CA)], switches from lamivudine to emtricitabine, and interleukin-2 cycles. Toxicities were graded using the Division of AIDS Table for Grading Severity of Adult Adverse Experiences.²¹

Virologic Failure

For the analysis of the ability of study subjects to achieve and maintain virologic suppression, virologic failure was defined as follows: (a) for patients with 24 weeks or more of follow-up, the definition was 2 consecutive values of plasma HIV-1 viral load above 500 copies/mL, after achieving a viral load below 500 copies/mL, or failure to achieve a viral load below 500 copies/mL after 24 weeks of therapy; (b) for patients with 12–24 weeks of therapy, the definition was failure to achieve a 10-fold reduction in viral load from start of treatment by week 12.

Statistical Analysis

The initial regimens, the reasons for changing them, and the types of changes made were categorized by year of initiation of therapy. The predictors of time to first change in regimen (overall and for changes due to laboratory and clinical toxicities alone) were analyzed using the log-rank test (univariate) and Cox proportional hazards models (multivariate). The factors considered were year of therapy initiation, sex, race, age, injection drug use (never, currently, or previously), presence or absence of hepatitis C coinfection, time from infection to initiation of therapy (categorized into quartiles), baseline CD4⁺ lymphocyte count (categorized into quartiles), antiretroviral medication class, daily number of pills taken, and frequency of dosing. Times to events were analyzed by Kaplan–Meier methods, and significance of differences was assessed by the log-rank test. Time from infection was estimated from the tests documenting acute or early HIV infection using a network-wide algorithm based on studies of early HIV infection in plasma donors.²² This algorithm correlates the date(s) of HIV exposure(s) (if known) with the results of both HIV antibody (HIV enzyme-linked immunosorbent assay, Western blot, and detuned antibody test) and viral load (HIV RNA) tests and the onset of symptoms related to acute antiretroviral syndrome.

The influence of changing therapy on the time to virologic failure was analyzed using Cox proportional hazards models, with the changing of therapy as a time-dependent indicator variable.

RESULTS

Study Population and HAART Regimens

During the study period, 697 subjects were enrolled in the CORE01 Database Protocol, and 433 of these initiated therapy. We excluded from the analysis 35 subjects participating in a 6-month treatment protocol, 21 subjects who received antiretroviral regimens that did not meet criteria for HAART, and 12 subjects who received blinded treatment regimens. Also excluded were 1 subject who interrupted treatment after 1 day and 1 whose treatment records were inconsistent. Thus, the study included 363 patients who initiated therapy. The median time from infection to initiation of therapy was estimated to be 89 days [interquartile range (IQR) = 47–187 days]; median CD4⁺ cell count and plasma HIV RNA concentration at initiation of therapy were 448 (range 124–1321) cells/ μ L and 5.0 (range 1.7–7.5) log₁₀ copies/mL, respectively. Follow-up was censored at February 07, 2007. The median follow-up was 701 days (IQR = 454–906 days).

The demographic characteristics of the study population are shown in Table 1. The population was composed predominately of men ($n = 356$, 98%) and whites ($n = 304$, 84%); few had a self-reported history of injection drug use ($n = 18$, 5%). These characteristics did not differ significantly between those who modified initial HAART regimens and those who did not. The study subjects received 50 different initial HAART regimens, almost all of which were NNRTI based ($n = 183$, 50%) or PI based ($n = 172$, 48%). Triple class regimens accounted for only 2% ($n = 8$) of initial regimens. The NRTI backbones changed over time, reflecting an increased use of agents that can be given once a day (data not shown). Ninety-one percent of PI-based regimens were boosted with ritonavir.

Rates of Treatment Modification

The initial regimen was modified in 205 (56%) study subjects during the follow-up period. Sixty-five modifications (32%) were initially classified as “clinician decision” or “subject decision,” but 46 (71%) of these were reclassified after additional inquiry to the study sites. Modifications were finally classified as drug switches ($n = 121$, 59%), treatment discontinuation ($n = 46$, 22%), reductions ($n = 27$, 13%) or additions ($n = 10$, 5%) of drugs, or dose changes ($n = 1$, <1%). The reasons for regimen modification are shown in Table 2. The majority ($n = 105$, 51%) of the modifications were attributed to toxicity (discussed below). Other important reasons were regimen simplification ($n = 18$, 9%), achievement of viral suppression ($n = 15$, 7%), induction-maintenance ($n = 10$, 5%), and decisions that were not further clarified and remained attributed to “clinician” or “subject” decision ($n = 11$, 5% and $n = 8$, 4%, respectively). However, only 2% ($n = 5$) of modifications were due to virologic failure. The overall rate of modification was 0.51 per person-year of follow-up, with a 95% confidence interval (0.44 to 0.59). The reasons for treatment modification were similar among those who modified HAART within 90 days of initiation and those who modified later.

Reasons for Treatment Discontinuation

Overall, toxicity was the leading reason for treatment discontinuation ($n = 23$, 50%), followed by subject decision ($n = 7$, 15%), and virologic failure ($n = 3$, 7%); all other reasons were less than 5% each. The median time to treatment discontinuation was 40 (range, 2 to 822) days. Reasons for treatment discontinuation did differ as a function of time since initiation of treatment. Of the 27 subjects who discontinued HAART within 90 days of initiation of therapy, 81% ($n = 22$) did so because of toxicity. Other reasons included subject decision ($n = 2$, 7%) and baseline resistance, noncompliance, and death (each $n = 1$, 4%). In contrast, among the 19 subjects who discontinued HAART more than 90 days after treatment initiation, subject decision was the most prevalent reason ($n = 5$, 26%), followed by clinician decision ($n = 4$, 21%), virologic failure ($n = 3$, 16%), viral suppression and other (each $n = 2$, 11%), and pill burden, toxicity, and completed treatment (each $n = 1$, 5%).

Timing of Treatment Modifications

The median time from initiation of therapy to the first modification was 425 days. The median CD4⁺ cell count and plasma HIV RNA concentration at time of the first modification were 648 cells/ μ L (IQR = 510–822 cells/ mm^3) and 2.2 log₁₀ copies/mL (IQR = 1.7–3.2 log₁₀ copies/mL), respectively. Shorter time to first modification was significantly related to shorter time from infection to initiation ($P = 0.005$) in a direct relationship, although the third and fourth quartiles did not diverge until after the median time to modification (Fig. 1). Those with baseline CD4⁺ lymphocyte cell count below the median maintained their initial regimens longer than those whose CD4 counts were above the median, and this was of borderline statistical significance ($P = 0.063$; Fig. 2). Drug class was associated with time to modification, with NNRTI- or PI-based dual class regimens being modified later than triple class regimens ($P < 0.001$; Fig. 3). However, there was no

significant difference in time to first modification between PI- and NNRTI-based HAART regimens. Pill burden and dosing frequency were both significantly associated with time to modification: subjects taking regimens consisting of 1–2 pills modified later than those with higher pill burdens, ($P < 0.001$; Fig. 4) and those taking once a day regimens modified later than those taking regimens given more often ($P < 0.001$; Fig. 5).

There was no significant relationship between calendar year of initiation of therapy and rate of modification (Table 3) by Kaplan–Meier analysis (data not shown). Furthermore, time to first modification was not significantly related to variables such as age, race, gender, hepatitis C virus coinfection (although this information was available for only 61 study participants), or injection drug use.

Toxicities That Induced Modifications

To assess the types of toxicity that led to treatment modification, we analyzed both clinical and laboratory toxicities and their severity. Among 105 modifications due to toxicity, 82 (78%) were due to clinical toxicities and 21 (20%) were due to laboratory toxicities and “other” toxicity. Of note, the majority of modifications due to toxicity ($n = 63$, 60%) occurred within the first 90 days after initiation of therapy. This included 57% ($n = 47$) of all clinical toxicities and 71% ($n = 15$) of all laboratory toxicities.

Sixty-eight of the 82 clinical toxicities (83%) were graded. Most were grade 1 (56%) or grade 2 (37%), few were grade 3 (7%), and none were grade 4. Patients receiving NNRTI-based HAART regimens had a higher rate of clinical toxicity than those receiving PI-based regimens (55% vs. 45%, respectively), but this was not statistically significant ($P = 0.46$). Table 4 shows the specific clinical toxicities that were cited as reasons for treatment modification. The most common were gastrointestinal and neuropsychiatric, followed by allergy/rash and fatigue. Among those receiving NNRTIs, the most common clinical toxicities were neuropsychiatric; in the PI group, gastrointestinal events were most common. Among those experiencing clinical toxicity, subjects taking NNRTIs or PIs did not differ significantly in the time to first modification.

Subjects whose treatment was modified due to laboratory toxicity ($n = 21$) had a somewhat more severe spectrum of toxicity. Of 19 graded laboratory toxicities, 12 (63%) were graded 0, 1, or 2 (5%, 37%, and 21%, respectively), but more than one-third were graded as serious (grade 3, 26%) or life threatening (grade 4, 11%). The most prevalent laboratory toxicity was hepatotoxicity, which was observed in 11 of 21 cases (52%) and was equally distributed between patients receiving NNRTI- and PI-based regimens. Anemia (6/21, 29%) and hyperlipidemia (3/21, 5%) were also reported as reasons for regimen modification.

Modification of the initial HAART regimen, for any reason, was a predictor of future virologic failure. Sixty-five of 361 subjects experienced virologic failure at some time during the observation period, including 11 who were taking their original treatment and 54 taking regimens which had been modified at least once, representing, respectively, 12% and 32% patients failed among those at risk. Thus, the hazard of virologic failure was 2.1 times higher (95% confidence interval 1.4 to 3.2, $P < 0.001$) in those who modified therapy than in those who did not.

Five of 6 patients whose regimens were changed due to baseline resistance were successfully suppressed on their new regimen.

DISCUSSION

This study evaluated the duration of initial HAART regimens in a large cohort of subjects with acute or early HIV infection. We found that modifications were (1) frequent, usually consisting of medication switches rather than discontinuation of therapy altogether; (2) most commonly due to toxicity, which was usually minor; and (3) rarely due to virologic failure. We found no difference in overall duration of NNRTI-based vs. PI-based regimens, nor did we find such differences based on age, race, gender, injection drug use, or hepatitis C virus coinfection. Time to modification was significantly shorter in those who received less convenient regimens, that is, those requiring >2 pills or more than 1 dose per day. Despite changes in HAART regimens during the study period, the frequency of regimen modification did not change significantly over time, although there were relatively fewer observations in the last year studied. Most modifications due to toxicity occurred within 90 days of initiation of HAART, which was earlier than modifications for other reasons. Overall, modification of therapy was more often related to clinical than to laboratory toxicity. High-grade toxicities were rare but were somewhat more common among laboratory than clinical events. However, no toxicity-related deaths were observed.

Modifications occurred with equal frequency among subjects receiving NNRTI- and PI-based HAART. The same was true when the modifications were subdivided according to laboratory vs. clinical toxicity. The most common events in the NNRTI group were neuropsychiatric side effects related to efavirenz, whereas gastrointestinal effects were most prevalent in the PI group.

Several limitations apply to this study. It should be noted that nearly one third of the treatment changes were initially attributed to either “clinician decision” or “subject decision”. More than two-thirds of these changes could be classified more precisely on further investigation and were in fact due to low-level toxicities. The option to code the reason for treatment modification as “clinician decision” or “subject decision” may have led to underreporting of other events. We found that likelihood of virologic failure was significantly higher in those who modified their HAART regimens than in those who did not. This finding was not due to virologic failure before modifying regimens because virologic failure was a very uncommon reason for such modification. The association between regimen modification and virologic failure may reflect difficulty in finding a tolerable regimen for certain patients.

This study extends the findings of an earlier study, 11 which looked at treatment modification in 51 subjects at the Baltimore site of the AIEDRP network who initiated therapy between 1998 and 2002. That study had a median follow-up of 1549 days, as compared with 701 days in the present study, which may have contributed to the lower prevalence of treatment modification in the present study (56% vs. 80%). However, even after adjustment for length of follow-up, the modification rate was lower in the present study: 0.51 modifications per person-year of follow-up vs. 0.72 in the earlier study ($P = 0.049$). The earlier study also reported higher proportions of therapy modifications due to poor adherence (20% vs. 2% in the present study) and discontinuations (71% vs. 22%) and a lower prevalence of “drug switches” (27% vs. 59%). These differences could be not only due to the differing lengths of follow-up but also due to differing cohort composition: the earlier cohort, unlike the present one, included significant percentages of people who acquired HIV through heterosexual contact (43%) and of nonwhites (53%) and injection drug users (15%). Other possible explanations include differing sample size, calendar time, and improved tolerability of HAART regimens; in the present study, there was greater use of coformulated medications and HAART regimens which can be given once a day and have better tolerability.

The proportion of discontinuations in the present study is similar to or slightly greater than those that have been observed in studies of discontinuation of initial HAART regimens in large numbers of chronically infected subjects.^{23–25} The prevalence of treatment modification in our study was higher (56% vs. 44%) than that seen by Mocroft et al²³ in a study of treatment modifications in initial HAART regimens among 556 chronically infected patients at a single site in London. That study had shorter mean follow-up time (14.2 months) than the present study. The finding of equal efficacy and tolerability of PI- and NNRTI-based HAART contrasts with recently presented data from studies of early²⁶ and chronic^{27,28} HIV infection, in which tolerability of PI- and NNRTI-based regimens differed. These data are limited by differences in regimens used and lack of standardized rates of modification per person-year of follow-up.

Our finding that time to first treatment modification was directly related to shorter time from seroconversion to initiation suggests that treatment of early HIV seroconverters may pose a greater challenge than that of chronically infected patients. This finding was not due to intentional interruption of HAART as a treatment strategy for long-term control of viremia—a common strategy in this population—because we excluded protocol-driven modifications from our analysis. Possibly, symptoms of acute retroviral symptoms may interfere with adherence to HAART or may be taken as adverse effects of therapy. Those possibilities are supported by the higher rate of modification in those who started therapy within 30 days of study entry. Other aspects of early HIV infection that could reduce adherence include psychological instability due to the recent diagnosis of HIV and a patient–physician relationship of shorter duration, which may make it harder for the patient to express reluctance to be treated. However, the presence of such symptoms was not significantly associated with time to changing therapy, in either univariate or multivariate analyses (data not shown). Because time to first treatment modification was related to higher CD4⁺ cell count at initiation of therapy, it is also possible that clinicians and patients have a lower threshold for changing a regimen when treatment is not clinically mandated. The finding of more frequent changes among patients with higher CD4⁺ cell counts is probably not related to the use of nevirapine because this drug was used in only 6 of the 105 HAART regimens that were changed due to toxicity. In interpreting these data, it should be kept in mind that the frequency of follow-up in the present study exceeded that of standard clinical practice, thus affording more opportunities to alter therapy.

Our findings are reminiscent of the tolerability of HAART used as postexposure prophylaxis.^{29,30} For example, in a study of 492 health care workers participating in the HIV postexposure prophylaxis registry, 76% reported adverse events of HAART, mostly low-grade clinical toxicities.²⁹

Recent evidence indicates that the period of acute and early HIV infection is a time of high HIV transmission rates, and increased screening for recent infection (eg, by use of pooled plasma RNA testing^{31–33}) may lead to identification of more individuals with primary or early HIV infection who may be considered for antiretroviral therapy. The higher prevalence of modifications of initial HAART regimens in our study compared with studies of chronically infected individuals suggests that these groups may tolerate treatment differently. In addition to establishing whether early treatment is clinically beneficial for people with acute or early HIV infection, defining these differences will be important in the establishment of guidelines for the treatment of this group. It will also be important to define the rate at which development of drug resistance occurs in this population. In the present study, there were insufficient data to address this question. As early treatment may lead to reduction in HIV transmission,³⁴ there may be a renewed interest in initiating HAART early after infection. Our data show that current treatments are generally well tolerated but

suggest that close monitoring of mild toxicities during the first 90 days of treatment may be beneficial.

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FIGURE 1.

Kaplan–Meier estimates for the proportion of subjects remaining on their initial HAART regimen, as a function of the time from infection to initiation of HAART. The dashed vertical line denotes the overall median time to treatment modification.

FIGURE 2.

Kaplan-Meier estimates for the proportion of subjects remaining on the initial HAART regimen, as a function of CD4⁺ lymphocyte count (per μ L) at initiation of HAART. The dashed vertical line is defined as in the legend to Figure 1.

FIGURE 3.

Kaplan–Meier estimates for proportion of subjects remaining on their initial HAART regimens, as a function of class of initial HAART regimen. The vertical dashed line is defined as in the legend of Figure 1.

FIGURE 4.

Kaplan–Meier estimates for proportion of subjects remaining on their initial HAART regimens, as a function of number of pills per day in initial HAART regimen. The vertical dashed line is defined as in the legend of Figure 1.

FIGURE 5.

Kaplan–Meier estimates for proportion of subjects remaining on their initial HAART regimens, as a function of frequency of dosing of initial HAART regimen. The vertical dashed line is defined as in the legend of Figure 1.

TABLE 1

Selected Demographic Characteristics of the Cohort

	Initiated HAART, n (%)	Modified HAART, n (%)	Did Not Modify HAART, n (%)
Sex			
Male	356 (98)	202 (99)	154 (97)
Female	7 (2)	3 (1)	4 (2)
Age median, (range)	37 (19–65)	37 (19–64)	37 (20–65)
Risk factor			
MSM	343 (94)	196 (96)	147 (93)
Heterosexual contact	10 (3)	4 (2)	6 (4)
IDU	7 (2)	3 (1)	4 (3)
Other/unknown	3 (1)	2 (1)	1 (1)
Race			
White	304 (84)	177 (86)	127 (80)
African American	16 (4)	7 (3)	9 (6)
Asian	17 (5)	9 (4)	8 (5)
Other/Unknown	26 (7)	12 (6)	14 (9)
IDU			
No history of IDU	345 (95)	195 (95)	150 (95)
History of IDU	18 (5)	10 (4)	8 (5)
HAART regimens			
NNRTI	183 (50)	100 (49)	83 (52)
PI	172 (48)	97 (47)	75 (48)
NNRTI + PI	8 (2)	8 (4)	—
Median CD4 count (cells/ μ l) *	448	480	410
Median log10 HIV RNA *	5.0	5.2	4.8
Symptoms of acute infection *			
Yes	98 (27)	65 (66)	33 (34)
No	265 (73)	140 (53)	125 (47)
Time of HAART initiation relative to study entry			
<30 days of study entry	249 (69)	161 (65)	88 (35)
$\geq$ 30 days after study entry [†]	114 (31)	44 (39)	70 (61)
Days from infection to initiation of HAART (median, (IQR)) = 89 (47–187)			

* At initiation of HAART.

[†] Eighty-six subjects had HIV RNA or CD4⁺ cell count measured within 30 days before starting HAART, and 51 (59%) of these had CD4 <350 cells per microliter or HIV RNA >100,000 copies per milliliter.
IDU, injection drug use; MSM, men who have sex with men.

TABLE 2**Reasons for First Modification of Initial HAART Regimen**

Reason	Overall (n = 205) n (%)	NNRTI (n = 99) n (%)	PI (n = 98) n (%)	NNRTI + PI (n = 8) n (%)
Toxicity	105 (51)	56 (57)	46 (47)	3 (37)
Regimen simplification	18 (9)	3 (3)	14 (14)	1 (13)
Achievement of viral suppression	15 (7)	2 (2)	11 (11)	2 (25)
Clinician decision	11 (5)	4 (4)	7 (7)	—
Induction maintenance	10 (5)	9 (9)	1 (1)	—
Subject decision	8 (4)	2 (2)	4 (4)	2 (25)
Initial dose	7 (3)	3 (3)	4 (4)	—
Baseline drug resistance	6 (3)	5 (5)	1 (1)	—
Nonadherence	5 (2)	3 (3)	2 (2)	—
Virologic failure	5 (2)	4 (4)	1 (1)	—
Other	4 (2)	4 (4)	—	—
Avoid toxicity	3 (1)	1 (1)	2 (2)	—
Pill burden	2 (1)	—	2 (2)	—
Completed treatment	1 (<1)	—	1 (1)	—
ddI/TDF interaction	1 (<1)	1 (1)	—	—
Death	1 (<1)	—	1 (1)	—
Intensify regimen	1 (<1)	1 (1)	—	—
New drug approval	1 (<1)	—	1 (1)	—
Pharmacy error	1 (<1)	1 (1)	—	—

ddI, didanosine; TDF, tenofovir.

TABLE 3

Modification of Initial HAART Regimen by Year of Initiation of Therapy

Year	Subjects Who Initiated Therapy, n	Subjects Who Modified Therapy, n (%)
2002	46	30 (65)
2003	141	95 (67)
2004	135	67 (50)
2005	41	13 (32)
Total	363	205 (56)

P value for time trend: 0.22.

TABLE 4

Clinical Toxicities Leading to Treatment Modification, Stratified by Drug Class

	NNRTI n = 45 (%)	PI n = 3 (%)	Boosted PI n = 32 (%)	NNRTI + Boosted PI n = 2 (%)	Total n = 82 (%)
Neuropsychiatric					
Abnormal feeling	1 (2)	—	—	—	1 (1)
CNS-related symptoms	9 (20)	—	—	1 (50)	10 (12)
Dizziness, anxiety	1 (2)	—	—	—	1 (1)
Depression	2 (4.5)	—	—	—	2 (2)
Insomnia/irritability	2 (4.5)	—	1 (3)	—	3 (4)
Nightmares	1 (2)	—	—	—	1 (1)
Neuropsychiatric/mood	7 (16)	—	—	—	7 (9)
Subtotal	23 (51)	0	1 (3)	1 (50)	25 (30)
Gastrointestinal					
Abdominal pain	—	—	1 (3)	—	1 (1)
Diarrhea	1 (2)	1 (33)	10 (31)	1 (50)	13 (16)
GI disruption	4 (9)	—	3 (9)	—	7 (9)
Nausea	7 (16)	1 (33)	7 (22)	—	15 (18)
Subtotal	12 (27)	2 (66)	21 (65)	1 (50)	36 (44)
Other					
Abacavir hypersensitivity	—	—	1 (3)	—	1 (1)
Allergy/rash	3 (7)	1 (33)	2 (6)	—	6 (8)
Dark spots on hands	—	—	1 (3)	—	1 (1)
Fatigue	4 (9)	—	2 (6)	—	6 (8)
Lethargy	—	—	1 (3)	—	1 (1)
Headache	3 (7)	—	1 (3)	—	4 (5)
Scleral jaundice	—	—	1 (3)	—	1 (1)
Tingling finger	—	—	1 (3)	—	1 (1)
Subtotal	10 (23)	1 (33)	10 (31)	—	21 (26)
Total	45	3	32	2	82

CNS, central nervous system.