

Joanne Stekler¹, Sarah Holte^{1,2}, Janine Maenza¹, Claire E. Stevens¹, Ann C. Collier¹

¹University of Washington, Seattle, WA; ²Fred Hutchinson Cancer Research Center, Seattle, WA

Contact Information:
Joanne Stekler, MD, MPH
Box 359931, Harborview Medical Center
325 Ninth Avenue, Seattle, WA 98104
Phone: (206) 731-8312, Fax: (206) 731-5109
Email: jstekler@u.washington.edu



ABSTRACT

Background: It is controversial whether use of highly-active antiretroviral therapy (HAART) in primary HIV infection (PHI) has long-term benefit.

Methods: Since 1992, individuals with PHI were enrolled into an observational cohort study. After 1996, some subjects received HAART at discretion of their primary care provider. We evaluated the impact of HAART on clinical outcomes including AIDS-defining opportunistic infections (OIs), a pre-defined group of HIV-related diagnoses, and time to HAART-related adverse events (AEs). Treatment groups began HAART ≤ 30 days (group 1), 31-180 days (group 2), or >180 days (group 3) from the estimated HIV infection date and were compared to historical and contemporary controls. We analyzed time to first diagnosis ≤ 4 weeks from HIV infection. Cox proportional hazard models were adjusted for age, gender, race/ethnicity, acute retroviral symptom severity, baseline CD4 count and HIV level, and HAART regimen. **Results:** 243 men and 7 women contributed 925 person-years. Groups 1, 2, and 3 had 41, 82, and 35 subjects, respectively, and there were 29 historical and 63 contemporary control subjects. Group 1 subjects began HAART a median of 652 days (IQR 351-2533) from HIV infection; 17 subjects experienced a total of 16 OIs and 6 deaths during follow-up; 162 subjects reported 167 initial HIV-related diagnoses including herpesvirus infections (n=99), warts (n=26), sinusitis (n=23), seborrheic dermatitis (n=19), candidiasis (n=19), and bronchitis (n=13). Median time in years (IQR) to diagnosis was 3.8 (2.9-7.8) for group 1, 5.6 (3.9-6.6) for group 2, 7.3 (4.1-10.2) for group 3, 4.4 (3.4-6.7) for contemporary controls, and 1.8 (1.1-2.9) for historical controls. Compared to contemporary controls, adjusted hazard ratios were: 58 (95% CI 26-13, p=2) for group 1, 56 (30-10, p=0.7) for group 2, 27 (13-57, p=0.001) for group 3, and 3 (1.1-5.6, p=0.02) for historical controls. Groups 1 and 2 had an increased risk of grade 2-4 AEs compared to group 3.

Conclusions: The differing outcomes in historical versus contemporary controls underscores the need for understanding limitations of control groups. Subjects treated acutely did not have significantly less risk of HIV-related diagnoses compared to untreated contemporary controls, but this result may be biased by association of lower pre-treatment CD4 counts and higher HIV RNA levels with both use of HAART and poorer prognosis. Historical controls may be a more representative population for comparison, but differences in risk could be attributed to factors other than HAART.

BACKGROUND

- HAART initiated during primary HIV infection (PHI) has theoretical long-term benefits;
- No randomized clinical trial of HAART during PHI has been published;
- Observational cohorts show some benefit of treatment initiated during PHI;
- Benefits are likely to be greatest for those treated as early as possible after HIV acquisition.

METHODS: Patient Population

- Observational cohort at the University of Washington Primary Infection Clinic since 1992;
- Highly active antiretroviral therapy (HAART) available since February 1, 1996 through non-randomized protocols or primary care providers;
- HAART = ≥ 3 active agents from ≥ 2 classes of antiretrovirals (zidovudine, lamivudine, and abacavir included as HAART);
- Excluded: subjects who received hydroxyurea;
- Cohort was approved by the University of Washington Institutional Review Board. All subjects gave written consent.

METHODS: Data Collection and Definitions of Clinical Outcomes

- AIDS-defining opportunistic infections (OIs) = CDC Category C conditions;
- "HIV-related diagnoses" = CDC Category B and C conditions and other HIV-associated diagnoses: bacterial infections (pneumonia, bronchitis, and sinusitis) & mucocutaneous conditions (folliculitis, herpesvirus infections, genital and rectal warts, molluscum contagiosum, psoriasis, and seborrheic dermatitis);
- Adverse events and diagnoses self-reported and recorded prospectively;
- Adverse events unrelated, possibly, probably, or definitely related to HAART.

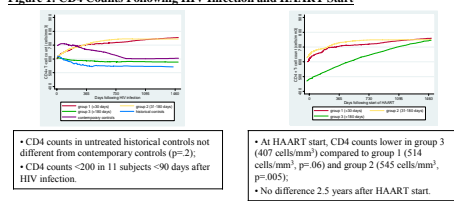
METHODS: Statistical Analysis

- Primary objective: compare HAART initiated ≤ 30 days after HIV infection (group 1), 31-180 days after HIV infection (group 2), & >180 days after HIV infection (group 3);
- Untreated subjects = historical or contemporary control subjects (by enrollment date);
- Analyses: time to 1) HIV-related diagnosis, & 2) treatment-related adverse events (AEs);
- Excluded: conditions occurring ≤ 4 weeks from HIV infection;
- Adjustment for age, gender, race/ethnicity, severity of seroconversion symptoms, baseline CD4 and HIV RNA levels, and initial HAART regimen;
- Viral "set point" = HIV RNA level @ 180 days (range 120-240 days) after infection;
- Treatment success = <500 copies/mL;
- Statistical tests: two-sample t-tests, Wilcoxon-Rank-sum, chi-square tests, ANOVA, Kruskal-Wallis, linear or logistic regression, and generalized estimating equations.

Table 1: Demographic and Subject Characteristics, by Study Group

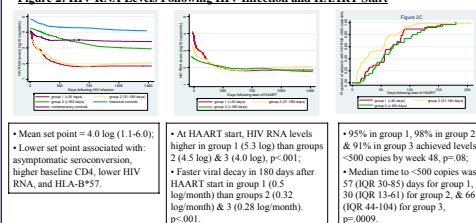
	group 1 1-30 days (n=41)	group 2 31-180 days (n=82)	group 3 >180 days (n=35)	historical controls (n=29)	contemporary controls (n=63)	All subjects (n=200)
Age (mean, range)	36 (22-53)	34 (21-51)	34 (24-55)	28 (19-53)	34 (18-56)	34 (18-56)
Male	95%	95%	100%	95%	95%	97%
Race/ethnic non-Hispanic	95%	95%	95%	95%	95%	95%
HIV risk factor	MSM (95%)	MSM (95%)	MSM (95%)	MSM (95%)	MSM (95%)	MSM (95%)
Sexual partner in 4 wks before HIV infection (median, range)	2 (0-5)	3 (0-8)	3 (0-8)	1 (0-4)	2 (0-5)	2 (0-5)
Severity of acute retroviral syndrome	moderate (24%)	moderate (24%)	moderate (24%)	moderate (24%)	moderate (24%)	moderate (24%)
Baseline CD4 ≥ 500 cells/mm ³ (range)	48% (23-100)	57% (18-100)	62% (17-100)	60% (29-100)	60% (29-100)	60% (29-100)
Days from HIV infection to study (median, range)	33 (0-40)	34 (13-156)	99 (31-391)	92 (17-280)	92 (0-213)	92 (0-213)
Days of baseline (median, range)	5 (0-20)	10 (0-30)	13 (0-40)	5 (0-20)	10 (0-30)	10 (0-30)
Baseline HIV RNA $\geq 10^5$ copies/mL (range)	83% (40-100)	83% (40-100)	83% (40-100)	83% (40-100)	83% (40-100)	83% (40-100)
Days from HIV infection to study (contemporary controls)	33 (0-40)	34 (13-156)	99 (31-391)	92 (17-280)	92 (0-213)	92 (0-213)
Days of baseline (contemporary controls)	5 (0-20)	10 (0-30)	13 (0-40)	5 (0-20)	10 (0-30)	10 (0-30)
Baseline HIV RNA $\geq 10^5$ copies/mL (contemporary controls)	83% (40-100)	83% (40-100)	83% (40-100)	83% (40-100)	83% (40-100)	83% (40-100)
Days from HIV infection to study (historical controls)	33 (0-40)	34 (13-156)	99 (31-391)	92 (17-280)	92 (0-213)	92 (0-213)
Days of baseline (historical controls)	5 (0-20)	10 (0-30)	13 (0-40)	5 (0-20)	10 (0-30)	10 (0-30)
Baseline HIV RNA $\geq 10^5$ copies/mL (historical controls)	83% (40-100)	83% (40-100)	83% (40-100)	83% (40-100)	83% (40-100)	83% (40-100)

Figure 1: CD4 Counts Following HIV Infection and HAART Start



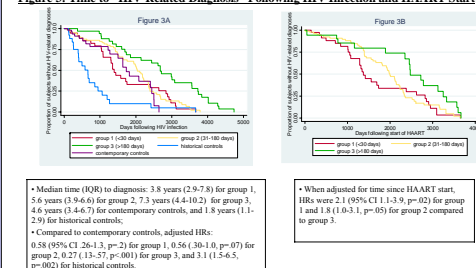
- CD4 counts in untreated historical controls not different from contemporary controls (p=2);
- CD4 counts <200 in 11 subjects <90 days after HIV infection;
- At HAART start, CD4 counts lower in group 3 (407 cells/mm³, p=.06) and group 2 (545 cells/mm³, p=.05);
- No difference 2.5 years after HAART start.

Figure 2: HIV RNA Levels Following HIV Infection and HAART Start



- Mean set point = 4.0 log (1.1-6.4);
- Lower set point associated with: asymptomatic seroconversion, higher baseline CD4, lower HIV RNA, and HLA-B*57;
- At HAART start, HIV RNA levels higher in group 1 (5.3 log) than groups 2 (4.5 log) & 3 (4.0 log), p<.001;
- Faster viral decay in 180 days after HAART start in group 1 (0.5 log/month) than groups 2 (0.32 log/month) & 3 (0.28 log/month), p<.001;
- 95% in group 1, 98% in group 2, & 91% in group 3 achieved levels <500 copies by week 48, p<.08;
- Median time to <500 copies was 57 (IQR 30-85) days for group 1, 30 (IQR 13-61) for group 2, & 66 (IQR 40-104) for group 3, p<.009.

Figure 3: Time to "HIV-Related Diagnosis" Following HIV Infection and HAART Start



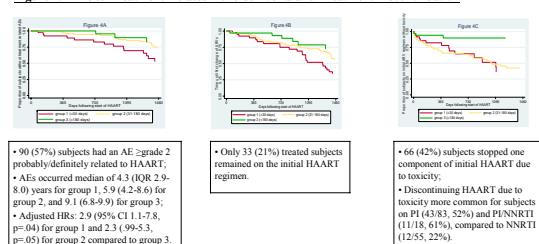
- Median time (IQR) to diagnosis: 3.8 years (2.9-7.8) for group 1, 5.6 years (3.9-6.6) for group 2, 7.3 years (4.1-10.2) for group 3, 4.6 years (3.4-6.7) for contemporary controls, and 1.8 years (1.1-2.9) for historical controls;
- Compared to contemporary controls, adjusted HRs: 0.58 (95% CI 26-13, p=2) for group 1, 0.56 (30-10, p=0.7) for group 2 (1.3-57, p<.001) for group 3, and 3.1 (1.5-6.5, p=.002) for historical controls;
- When adjusted for time since HAART start, HRs were 2.1 (95% CI 1.1-3.9, p=.02) for group 1 and 1.8 (1.0-3.1, p=.05) for group 2 compared to group 3.

Table 2: First HIV-Related Diagnoses in 162 Subjects

Diagnosis	n
Bacterial infections	13
Herpesvirus infections	13
Mucocutaneous conditions	13
Opportunistic infections	13
Seborrheic dermatitis	13
Sinusitis	13
Warts	13
Other HIV-related diagnoses	13
Total	162

- Overall, 16 OIs and 6 deaths occurred among 17 subjects; 3 deaths occurred only after HIV-related diagnoses.
- Deaths not HIV-associated and were due to subarachnoid hemorrhage, motor vehicle accident, and suicide.
- Five individuals reported two HIV-related diagnoses with concurrent start dates.

Figure 4: Time to Treatment-Related Adverse Events and Treatment Discontinuation



- 90 (57%) subjects had an AE \geq grade 2 probably/definitely related to HAART;
- AEs occurred median of 4.3 (IQR 2.9-8.0) years for group 1, 5.9 (4.2-8.6) for group 2, and 9.1 (6.8-9.9) for group 3;
- Adjusted HRs: 2.9 (95% CI 1.1-7.8, p=.04) for group 1 and 2.3 (99-5.3, p=.05) for group 2 compared to group 3.
- Only 33 (21%) treated subjects remained on the initial HAART regimen.
- 66 (42%) subjects stopped one component of initial HAART due to toxicity;
- Discontinuing HAART due to toxicity more common for subjects on PI (45/83, 52%) and PNNRTI (11/18, 61%), compared to NNRTI (12/55, 22%).

LIMITATIONS

- Non-randomized cohort design led to significant differences in baseline characteristics of groups;
- Variable length of follow-up after HIV acquisition;
- The cohort at the University of Washington Primary Infection Clinic may not be representative of all individuals who acquire HIV infection worldwide.

CONCLUSIONS

- 1) Differing outcomes in historical versus contemporary controls underscores the need for understanding limitations of control groups and the potential impact on results of observational analyses.
- 2) Subjects treated acutely did not have significantly less risk of HIV-related diagnoses compared to untreated contemporary controls, but this result may be biased by association of lower pre-treatment CD4 counts and higher HIV RNA levels with both use of HAART and poorer prognosis.
- 3) Historical controls may be a less selected population for comparison, but differences in risk could be attributed to factors other than HAART (e.g. increases in prescribing of prophylactic medications over time).
- 4) A randomized treatment study is needed to determine the long-term impact of HAART for individuals with acute HIV infection.

Acknowledgments

We would like to thank the subjects who participated in the cohort, current members of the Seattle Primary Infection Program, and Larry Corey, Tim Schacker, Michelle Berrey, Bob Geise, and Theresa Shea for their previous work with the cohort. Funding was provided by NIH K23 A65243, U01 A141535 and P01 A07500, and the UW Center for AIDS and STDS A1-27757. Pharmaceutical support was provided by Bristol Myers Squibb (formerly DuPont Pharmaceuticals Co.), GlaxoSmithKline and Merck.