

A Pilot Open-Label Phase II Trial of the Safety and Efficacy of a Compact 3-Drug Antiretroviral Treatment (ART) Regimen for Subjects with Acute or Recent Primary HIV-1 Infection (PHI)

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Abstract

Background: The optimal approach to ART for acute or recent primary HIV-1 infection (PHI) and its effect on immune function or disease progression are controversial.

Methods: We conducted a phase II, open-label, pilot study of the safety and efficacy of ART versus no treatment in patients with acute or recent PHI. Patients elected to start or not start ART (atazanavir 600mg + dd-EC + AZT). Substitution within the NRTI class, at the discretion of the clinician, was allowed. ART was continued for > 48 to 104 weeks. All patients were followed through week 104. The primary virologic endpoint was the % of treated patients who achieved and maintained HIV-1 RNA < 50 c/ml at week 48; the primary efficacy endpoint was the % of patients on assigned ART who achieved and maintained HIV-RNA < 50 c/ml at week 48 (IT, MuV).

Results: 55 patients enrolled: 95% men, 75% white, median age 33 years. 37 patients elected to start ART (12 acute/25 recent); 18 elected not to start ART (3 acute/15 recent). Median baseline (BL) CD4+ for acute treated (Gp 1A), acute untreated (Gp 1B), recent treated (Gp 2), and recent untreated patients (Gp 2R) were 478, 496, 605, and 826 cells/mm³, respectively. Median BL HIV-1 RNA was 146,900, 61,034, 91,756 and 4,289 c/ml, respectively. Genotypic resistance testing was performed at BL for 50 patients; mutations conferring ARV resistance were present in 25% of acute and 5% of recent PHI (Gp 1B). Fishers exact; those who started ART, 24/27 (60%; 95% CI 41.4, 73.8) met the primary virologic endpoint at week 48: 8/12 acute (97%; 95% CI 34.8, 90.1) and 16/25 recent PHI (64%; 95% CI 42.5, 81.1) (P=0.01). Fishers exact; 23/27 (85%; 95% CI 31.1, 72.3) (P=0.49). Median CD4+ at week 48 was 619 for Gp 1A, 243 for Gp 1B, 803 for Gp 2, and 522 for Gp 2R (P=0.009) for recent treated versus untreated. Median CD4+ at week 48 overall for treated versus untreated patients was 725 versus 496 (P=0.018). One patient (Gp 1A) had a rapid decline in CD4+ requiring ART before week 48. Treatment-limiting adverse effects were peripheral neuropathy (2/37) and hyperbilirubinemia (5/37).

Conclusions: Although there was a trend toward greater pre-ART drug resistance for acute versus recent PHI, virologic success was similar in both and comparable to rates in chronic HIV infection. AZT (600mg) plus 2 NRTIs was reasonably well tolerated in this setting. Patients treated during acute or recent PHI had higher CD4+ at week 48 than untreated patients.

Background

- Whether and when to treat acute or recent primary HIV-1 infection (PHI), and the optimal approach to antiretroviral therapy (ART) in individuals with PHI remain controversial.
- Previous retrospective, observational, prospective non-randomized, or case-control studies that have evaluated ART in patients with acute or recent PHI have produced conflicting results with regard to the influence of acute or early treatment on longer term virologic or immunologic outcomes.
- We and others have proposed that treatment of individuals with acute or early PHI with ART regimens that suppress HIV-1 replication to undetectable levels in plasma for periods of 1-2 years may reduce the viral set point, preserve immune function, and delay the progression of HIV-1 infection and the time to initiation of antiretroviral therapy.
- To test these hypotheses, we conducted a prospective, open-label pilot study comparing the safety and preliminary efficacy with respect to viral suppression and immune response at 48 weeks of ART compared with no ART in individuals with acute or early (< 3 months) PHI. Follow-up for an additional 48 weeks is ongoing.

Methods

Study Design: Pilot prospective open-label study of treatment of acute or recent PHI with ART

Study Population: 55 treatment-naïve subjects with acute (N=15; defined as 1) a negative ELISA or a positive ELISA with a negative or indeterminate WB within 14d of entry, or 2) a positive ELISA and a WB within 14d but documented negative ELISA or plasma HIV-1 RNA within 30d prior to study entry; or recent (N=40; defined as 1) positive ELISA and WB within 14d of entry but with a

Methods (cont'd)

documented negative ELISA or plasma HIV-1 RNA within 31-90 days prior to entry; or 2) positive ELISA and WB with a non-reactive retested ELISA within 14d of entry; plasma HIV-1 RNA \geq 2,000 copies/ml.

Treatment regimens: Group 1 = Atazanavir 600 mg p.o. QD + 2 NRTIs (the study supplied d4T 40 mg BID + dd-EC 400 mg QD [doses adjusted by weight] but substitution of alternative non-study supplied NRTIs allowed) versus Group 2 = no treatment

Primary Endpoints: 1) The proportion of treated pts who achieved and maintained plasma HIV-1 RNA < 50 copies/ml at 48 weeks; 2) safety and tolerability of ART in pts with acute or recent PHI

Statistical Analyses: Intent-to-treat/missing-failure, Fisher's exact tests, and time-to-event methods (Kaplan-Meier and logrank)

Table 1. Baseline Characteristics

Characteristic	Total	Acute Treated	Acute Untreated	Recent Treated	Recent Untreated
N	55	12	3	25	15
Follow-up (wks)	104	103.5	77	104	104
Baseline CD4+ (cells/mm ³)	567 (174-1194)	478 (56-104)	496 (0-77)	605 (4-104)	826 (32-104)
Baseline VL (copies/ml)	50,950 (226-3,670,000)	146,500 (3,870,000)	61,634	59,756 (50,950-1,050,000)	4,280 (226-135,000)
Risk**					
MSM	32 (58.2%)	9	0	12	11
IDU	1 (1.8%)	0	0	0	1
MSM + IDU	1 (1.8%)	0	0	0	1
Other	2 (3.6%)	1	0	1	0
Unknown	19 (34.6%)	2	3	2	12
Male	52 (94.5%)	12	1	14	14
Age (yrs)	33 (19-59)	34 (21-47)	35 (32-39)	31 (20-59)	32 (19-38)
Race					
White	41 (74.5%)	11	0	19	11
Black	3 (5.5%)	0	1	2	0

Table 2: Baseline Antiretroviral Drug Resistance

Resistance Patterns	Overall (N=50)	Acute Treated (N=10)	Acute Untreated (N=2)	Recent Treated (N=24)	Recent Untreated (N=14)
NNRTI	2	1	0	1	0
NNRTI + 3TC + PI	1	0	1	0	0
NRTI	1	0	0	1	0
PI	1	1	0	0	0
No Resistance	45	8	1	22	14

Resistance to antiretroviral drugs was defined as detection of known primary drug resistance mutations by genotype analysis and decreased susceptibility to one or more drugs in that class by the Phenosense assay at study entry; P=0.08 for comparison of the proportion of Acute and Recent subjects with antiretroviral drug resistance at study entry.

Table 3. Week 48 VL and CD4+ Results

Week 48 Endpoint	Overall (N=55)	Acute Treated (N=11)	Acute Untreated (N=1)	Recent Treated (N=18)	Recent Untreated (N=10)
Median CD4+ (cells/mm ³)	N/A	619	243	763	577
Median VL	N/A	< 50 c/ml	336 c/ml	< 50 c/ml	17,911 c/ml
No. Virologic Failure (%)	13/37 (35%)	4 (33%)	N/A	9 (36%)	N/A
No.** Treatment Success (%)	21/37 (57%)	8 (67%)	N/A	13 (52%)	N/A

P=0.099 for Week 48 CD4+ recent PHI treated vs. recent PHI untreated; **Treatment success is defined as the number/percent of treated subjects who achieved and maintain plasma HIV-1 RNA levels < 50 copies/ml through week 48

Fig. 2a-d: Week 48 Virologic and Immunologic Responses Acute vs. Recent PHI

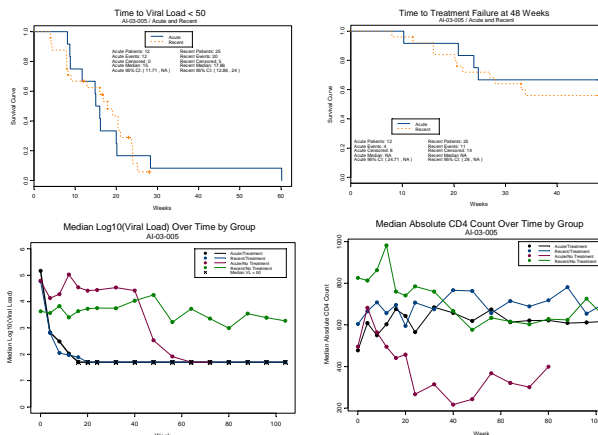
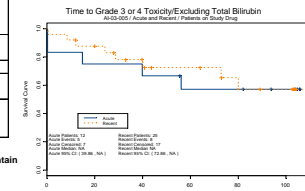


Fig. 1: Time to Grade 3 or 4 Toxicity



Results

- Overall at Week 48:**
- 24/37 treated subjects (65%) met the definition of virologic response (defined as those who achieved and maintained VL < 50 copies/ml at week 48) (95% CI = 64.9% [47.4%, 78.8%]; 8/12 acute PHI (95% CI 66.7% [34.8%, 90.1%]) and 16/25 recent PHI (95% CI 64% [42.5%, 82.1%] (P=1.0; Fisher's Exact test).
 - 13/37 (35.1%) met the definition of virologic failure (defined as failure to reach VL < 50 copies/ml by week 24 or a confirmed rise in VL to \geq 200 copies/ml at any time after achieving a VL of < 50 copies/ml) by week 48; 4/12 (33%) in the acute PHI treated group and 9/25 (36%) in the recent PHI treated group.
 - 29/37 treated subjects (78.4%) developed grade 3 or 4 elevations of total bilirubin; 24 responded to dose reduction while 5/37 (13.5%) discontinued atazanavir due to elevated bilirubin levels.
 - 7/37 treated subjects (18.9%) were diagnosed with possible or confirmed peripheral neuropathy; 2/37 (5.4%) discontinued ddI and/or d4T due to peripheral neuropathy.
 - Median CD4+ T cell count was 725 cells/mm³ overall for treated pts with PHI versus 496 cells/mm³ for untreated pts with PHI (P=0.018).
 - One pt with acute PHI and 2-class drug resistance at baseline elected not to be treated; this subject experienced a rapid decline in CD4+ count to 243, and was started on treatment prior to the Week 48 endpoint.

Conclusions

- We observed a trend toward greater pre-treatment drug resistance for subjects with acute versus recent PHI.
- Virologic response (intent-to-treat, missing=failure) was similar in subjects with acute and recent PHI treated with atazanavir + 2 NRTIs, and was comparable to rates reported in studies of chronic HIV infection using similar definitions and statistical analyses.
- Atazanavir (600mg) plus 2 NRTIs was reasonably well tolerated in this setting; although grade 3 or 4 hyperbilirubinemia was common at this dose, most subjects responded to a subsequent dose reduction to 400 mg daily. Hyperbilirubinemia resulted in atazanavir treatment discontinuation in only 5/37 subjects.
- Patients treated during acute or recent PHI had higher CD4+ T cell counts at week 48 than untreated patients with acute or recent PHI. Whether this difference will be sustained over time or whether the improved immunologic response will result in a delay in disease progression remains to be established with further follow-up.

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