Predictors of Virological Outcome and Safety in Primary HIV Type 1–Infected Patients Initiating Quadruple Antiretroviral Therapy: QUEST GW PROB3005

Bruno Hoen,[1] David A. Cooper,[4] Fiona C. Lampe,[6] Luc Perrin,[11] Nathan Clumeck,[13] Andrew N. Phillips,[6] Li-Ean Goh,[10] Stefan Lindback,[14] Daniel Sereni,[2] Brian Gazzard,[9] Julio Montaner,[15] Hans-Jurgen Stellbrink,[16] Adriano Lazzarin,[18] Diane Ponscarme,[3] Shlomo Staszewski,[17] Lars Mathiesen,[19] Don Smith,[4] Robert Finlayson,[5] Rainer Weber,[12] Laurence Wegmann,[11] George Janossy,[7] and Sabine Kinloch-de Loes,[8] for the QUEST Study Group[a]

Background. Initiation of antiretroviral therapy during primary human immunodeficiency virus (HIV)–1 infection may confer long-term benefit.

Methods. After initiation of zidovudine, lamivudine, abacavir, and amprenavir therapy in patients in the QUEST cohort, predictors of virological outcome, virological and immunological changes, and adverse events were evaluated over 48 weeks.

Results. One hundred forty-eight patients started antiretroviral therapy during primary HIV-1 infection with ≤3 bands on Western Blot (median plasma HIV-1 RNA load, 5.4 log copies/mL; median CD4 cell count, 517 cells/mm^3). By week 48, 36% of patients had stopped treatment or were lost to follow-up. Among the 115 patients receiving follow-up care at week 48 (102 of whom were receiving antiretroviral therapy), the median viral load decrease was −5.4 log copies/mL (interquartile range [IQR], −6.4 to −3.9 log copies/mL), and the median increase in CD4 cell count was 147 cells/mm^3 (IQR, −1 to 283 cells/mm^3); 84.2% of patients had a viral load ≤50 copies/mL, and 44.7% of patients had a viral load ≤3 copies/mL. The median cell-associated RNA level decreased from 3.4 log copies/million PBMCs (IQR, 2.9–4.1 log copies/million PBMCs) to 0.8 log copies/million PBMCs (IQR, 0.5–1.4 log copies/million PBMCs), and the median cell-associated DNA level decreased from 2.8 log copies/million PBMCs (IQR, 2.4–3.0 log copies/million PBMCs) to 1.6 log copies/million PBMCs (IQR, 1.2–1.9 log copies/million PBMCs); 33.3% of patients had an undetectable RNA level, and 9.5% of patients had an undetectable cell-associated DNA level. The median $CD8^+/CD38^{++}$ T cell count decreased from 459 cells/mm^3 (IQR, 208–974 cells/mm^3) to 33 cells/mm^3 (IQR, 19–75 cells/mm^3). Baseline $CD8^+/CD38^{++}$ T cell count and cell-associated DNA level were independent inverse predictors for reaching a viral load ≤3 copies/mL. Eighty-three patients experienced a serious adverse event (median duration of an adverse event, 15 days).

Conclusions. Initiation of antiretroviral therapy during primary HIV-1 infection was associated with very significant antiretroviral activity and a decrease in immune activation. Lower baseline $CD8^+/CD38^{++}$ T cell count and cell-associated DNA level were predictive of achieving a viral load ≤3 copies/mL.

It is unclear whether initiation of potent antiretroviral therapy (ART) during primary HIV-1 infection (PHI) can alter long-term prognosis [1–5]. Early ART can decrease HIV-1 load and cellular reservoirs, promote immune reconstitution, and limit viral heterogeneity [6–12]. Diagnosis of HIV infection during PHI and subsequent initiation of ART are for consideration as a public health strategy to decrease transmission of HIV infection [13, 14]. Arguments against early treatment include the risks of drug-induced toxicity and emer-

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Reprints or correspondence: Dr. Sabine Kinloch-de Loes, Royal Free Center for HIV Medicine, Dept. of Infection and Immunity, Royal Free Campus, Royal Free and University College Medical School, Rowland Hill St., London NW3 2QG, United Kingdom (sabine@kinloch.u-net.com).

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[a] Members of the study group are listed at the end of the text, as are author affiliations.

gence of resistance in noncompliant patients. Therefore, it is of interest to evaluate the parameters associated with optimal responses to early treatment and toxicity, which may affect responses to treatment.

Herein, we report the baseline characteristics, treatment continuation rates, virological and immunological responses, and safety parameters over 48 weeks after ART initiation, together with the predictors of virological control, in the largest therapeutic cohort of patients who were prospectively enrolled during PHI.

METHODS

Study patients. Patients aged ⩾18 years were recruited from 39 health care facilities in 10 countries (including Canada and Australia and European countries) if they had a negative HIV ELISA result or ⩽3 bands on Western Blot, in addition to one of the following characteristics: p24 antigenemia, a PCR result that was positive for HIV-1 RNA or DNA, or detectable viral activity by other RNA and DNA quantification methods.

Study design. The design, methods, and outcome measures of the study have been described previously [15]. Eligible patients initiated therapy with the following drugs, which were administered twice daily: 300 mg of zidovudine plus 150 mg of lamivudine, 300 mg of abacavir, and 1200 mg of amprenavir. Alteration to this initial regimen was allowed for treatment-limiting toxicities or compliance issues.

Ethics. All patients provided signed informed consent prior to study enrollment. Independent local ethics committees reviewed and approved the study protocol and its amendments. An independent data safety and monitoring board monitored the progress of the trial.

Measurements and evaluations. At enrollment, physicians recorded the patient's medical history, risk factors for HIV acquisition, and symptoms and signs of PHI (with date of onset) and performed a clinical examination. Baseline blood sample examination included safety parameters and immunological and virological studies. After enrollment, clinical status and adverse events were recorded. Safety parameters, plasma HIV-1 RNA load, and CD4, CD8, and $CD8^+/CD38^{++}$ T cell counts were obtained at regular intervals. Cell-associated DNA and RNA levels were determined for European and Australian patients at baseline and at weeks 4, 12, 24, 36, and 42.

Laboratory methods. Routine complete blood cell counts, biochemistry values, HIV-1 loads, and CD4 and CD8 cell counts were measured at central laboratories. The Amplicor Monitor (Roche Molecular Diagnostics; lower limit of detection, 400 copies/mL) was used to quantify HIV-1 load. Samples with HIV-1 loads <400 copies/mL were reanalyzed with the Ultrasensitive Monitor assay, version 1.5 (limit of detection, 50 copies/mL). The Ultraboosted assay was used to determine viral loads <3 copies/mL at strategic time points, when the viral load was <50 copies/mL [7]. $CD8^+/CD38^{++}$ T cell counts were quantitated at the HIV Immunology Unit at the Royal Free Hospital (London, United Kingdom) and at the Centre for Immunology at National Centre in HIV Epidemiology and Clinical Research (Sydney, Australia), as previously described [7]. A normal $CD8^+/CD38^{++}$ T cell count was defined as a count <20 cells/mm^3 [16]. Cell-associated HIV-1 DNA and RNA assays were performed at the Central Virology Laboratory at Geneva University Hospital (Geneva, Switzerland) (limit of detection, 3 copies/million PBMCs) [7].

Genotypic analysis. Sequence analysis of HIV-1 *gag* region and protease coding region and RT-PCR were performed at baseline (VircoGEN HIV-1 report; Virco).

Statistical methods. Virological and immunological parameters during follow-up and changes from baseline were summarized by median and interquartile range (IQR) values, using data from all patients with measurements available, regardless of whether the patient was receiving ART. Kaplan-Meier analysis was used to assess changes from baseline in $\log_{10}$ HIV-1 load and cell-associated DNA and RNA levels to account for the lower limit of detection of assays [17]. Additional analyses of the proportion of patients over time with HIV-1 loads ⩽50 copies/mL, ⩽10 copies/mL, or ⩽3 copies/mL used (1) an intention-to-treat approach and (2) a "receiving ART" analysis. Associations between variables were assessed using Spearman's rank correlation coefficients. Continuous variables were compared between subgroups using the Mann-Whitney *U* test. Kaplan-Meier estimates were used to examine the probability of ART discontinuation and change according to various end points, including the time to achieve an HIV-1 load ⩽3 copies/mL and the occurrence of a serious or grade 3 or 4 adverse event. Cox proportional hazards regression (stratified by country) was used to investigate factors associated with these end points. Results are presented as hazard ratios (HRs) with 95% CIs.

RESULTS

Patient population and baseline characteristics. From February 1998 through October 1999, 148 enrolled patients started ART. The demographic and baseline characteristics of the patients are shown in table 1. The majority of the patients were men who had sex with men and were symptomatic during PHI (90% of patients; fever was reported for 66% of these patients, malaise for 54%, lethargy for 53%, headache for 44%, myalgia for 42%, rash for 40%, gastrointestinal symptoms for 39%, and weight loss for 37%). Treatment was initiated within 1 and 2 weeks of diagnosis in 64% and 83% of patients, respectively.

Patient follow-up and treatment changes. Thirty-three patients (22.3%) withdrew from follow-up prior to week 48 (12 patients withdrew by choice, 8 withdrew because of adverse events, 6 were lost to follow-up, and 7 withdrew because of

Table 1. Demographic and baseline characteristics of 148 patients with primary HIV-1 infection (PHI).

Baseline characteristics	Patients
Recruiting countries	
Australia	31 (20.9)
Belgium	4 (2.7)
Canada	10 (6.8)
Denmark	4 (2.7)
France	32 (21.6)
Germany	7 (4.7)
Italy	9 (6.1)
Sweden	7 (4.7)
Switzerland	23 (15.5)
United Kingdom	21 (14.2)
Sex	
Male	133 (89.9)
Female	15 (10.1)
Age, mean years (range)	34.6 (20.6–58.7)
Ethnicity	
White	140 (94.6)
Asian	2 (1.4)
Black	3 (2.0)
Hispanic	1 (0.7)
Other	2 (1.4)
HIV-1 risk group (n = 146)	
Men who have sex with men	105 (71.9)
Heterosexual contact	34 (23.3)
Drug user	5 (3.4)
Occupational	1 (0.7)
Other	1 (0.7)
Symptomatic PHI	132 (89.9)
Duration of symptoms, median days (range)	21 (2–168)
Time from symptoms to initiation of ART, median days (range)	18 (−8 to 111)
Time from diagnosis to initiation of ART, median days (range)	6 (−6 to 111)

another or unknown reason). Thirty of the patients who withdrew from follow-up had stopped ART at the last recorded follow-up visit. Among 115 patients still receiving follow-up care at week 48, 13 (11.3%), 23 (20%), 78 (67.8%), and 1 (1%) were receiving 0, 3, 4, and 5 drugs (excluding ritonavir, given as protease inhibitor booster), respectively, with the following regimens: nucleoside reverse-transcriptase inhibitors and a protease inhibitor (administered to 93 patients), a nucleoside reverse-transcriptase inhibitor and nonnucleoside reverse-transcriptase inhibitors (administered to 2 patients), and nucleoside reverse-transcriptase inhibitors alone (administered to 7 patients). Fifty-eight patients continued to receive their initial ART regimen, and 86, 85, and 73 patients continued to receive abacavir, zidovudine plus lamivudine, and amprenavir, respectively. At week 48, 20 (17.4%) of 115 patients had discontinued ART for ⩾7 days (8 patients discontinued ART because of noncompliance, 5 because of adverse events, 2 by choice, and 5 because of an other or unknown reason), and 62 (53.9%) of 115 patients had changed their initial regimen (defined as discontinuation of any drug for ⩾7 days or addition of a new drug).

Figure 1 shows Kaplan-Meier cumulative proportions over time for 3 outcomes, including study withdrawal (outcome A; 33 patients), study withdrawal or discontinuation of ART for ⩾7 days (outcome B; 53 patients), and study withdrawal or regimen change (outcome C; 95 patients), with percentages at week 48 of 22.3%, 35.8%, and 64.2%, respectively. The rate of discontinuation or change of ART was high during the first 2 months and decreased over time ($P = .22$, $P = .006$, and $P < .001$, by Poisson regression for linear trend in rate of outcomes A, B, and C, respectively, over four 12-week periods). In a Cox model of the association of baseline factors with outcome B, stratified by country of recruitment, older age, being a man who has sex with men, and higher baseline viral load were independently associated with a lower risk of study withdrawal and/or ART discontinuation (adjusted HR, 0.93 [95% CI, 0.88–0.97; $P < .001$], for every year older in age; adjusted HR, 0.76 [95% CI, 0.59–0.98; $P = .036$], for every log higher in viral load; adjusted HR, 0.47 [95% CI, 0.23–0.99; $P = .046$], for being a man who has sex with men vs. other sexual preferences); no association was found between study withdrawal and/or discontinuation of ART and baseline CD4 cell count or presence of symptoms of PHI ($P > .5$, for adjusted HRs).

Baseline plasma viral load and immunological parameters. The median HIV-1 load was 5.4 log copies/mL (range, 2.1–7.9 log copies/mL), and the median CD4 cell count was 514 cells/mm^3 (range, 162–1380 cells/mm^3) (table 2). Plasma viremia was inversely correlated with CD4 cell count (Spearman's correlation: $r = -0.41$; $P < .001$). Patients with symptoms tended to have higher viral loads than did patients who did not have symptoms (5.5 log copies/mL vs. 4.9 log copies/mL; $P = .13$, by Mann-Whitney U test). More recent symptom onset was associated with higher viral load and lower CD4 cell count. Correlations of time since symptom onset with viral load and CD4 cell count were -0.35 ($P < .001$) and 0.17 ($P = .052$), respectively.

Baseline cell-associated RNA and DNA levels and correlation with viral load and CD4 cell counts. Cell-associated HIV-1 RNA and DNA levels were measured in 114 patients. The median HIV-1 RNA level was 3.4 log copies/million PBMCs (range, 0.9–5.9 log copies/million PBMCs), and the median cell-associated HIV-1 DNA level was 2.8 log copies/million PBMCs (range, 1.2–4.0 log copies/million PBMCs) (table 2); these levels strongly correlated with HIV-1 load (Spearman's correlation: $r = 0.88$ and $P < .001$, for RNA; $r = 0.64$

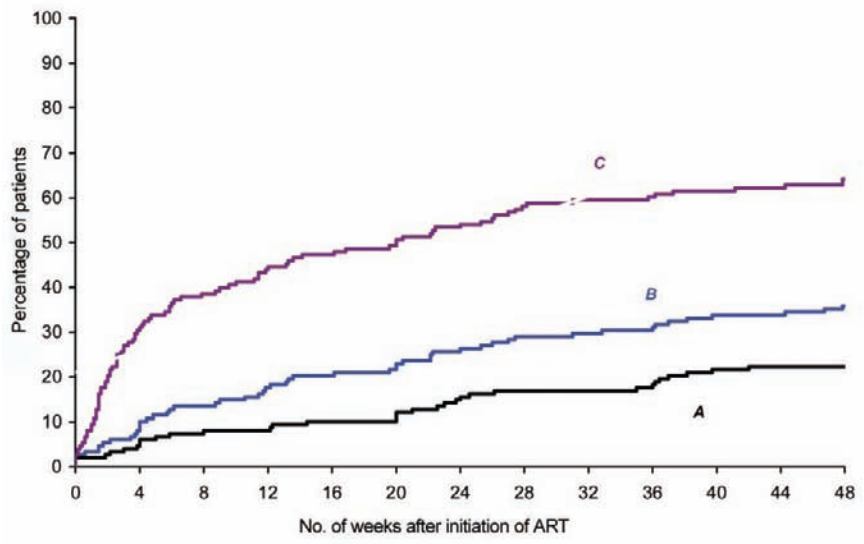


Figure 1. Cumulative percentage of patients according to study withdrawal *(A),* study withdrawal or discontinuation of all antiretroviral therapy (ART) for ⩾7 days *(B),* and study withdrawal or discontinuation of any ART drug for ⩾7 days or addition of a new drug *(C),* by number of weeks after initiation of ART.

and $P < .001$, for DNA). CD4 cell count was inversely correlated with cell-associated RNA level ($r = -0.44$; $P < .001$) and cell-associated DNA level ($r = -0.31$; $P = .001$).

Baseline genotypic resistance. Genotyping performed for 132 patients revealed thymidine-associated mutations in 5 patients (4%), and 9 patients (7%) harbored other nucleoside reverse-transcriptase inhibitor–associated mutations (3 patients had mutations in codon 215, 3 had mutations in codon 184, and 3 had mutations in codon 41). One patient had a primary protease inhibitor–associated mutation, and none had nonnucleoside reverse-transcriptase inhibitor–associated mutations.

Changes in plasma viral load and immunological parameters after initiation of ART. HIV-1 load decreased over 48 weeks after ART initiation (table 2 and figure 2). Median changes adjusted for the limit of detection were −1.8 log copies/mL (IQR, −2.5 to −1.4 log copies/mL) at week 2, −3.4 log copies/mL (IQR, −4.2 to −2.7 log copies/mL) at week 12, and −5.4 log copies/mL (−6.4 to −3.9 log copies/mL) at week 48. Corresponding changes unadjusted for the limit of detection at weeks 2, 12, and 48 were −1.8 log copies/mL, −3.2 log copies/mL, and −4.7 log copies/mL, respectively. At week 48, 96 (84.2%) of 114 patients had a viral load ⩽50 copies/mL, 71 (62.3%) of 114 patients had a viral load ⩽10 copies/mL, and 51 (44.7%) of 114 patients had a viral load ⩽3 copies/mL. CD4 cell count increased rapidly during the first 2 weeks of treatment, with little further increase at week 2. The median change in CD4 cell count at week 2 was +124 cells/mm^3 (IQR, −25 to +267 cells/mm^3), at week 12 was +152 cells/mm^3 (IQR, 0 to +275 cells/mm^3), and at week 48 was +147 cells/mm^3 (IQR, −1 to +283 cells/mm^3), at which time the median CD4 cell count was 677 cells/mm^3 (IQR, 520–843 cells/mm^3). CD4 percentage also increased. Median changes in CD4 percentage from baseline were +9% (IQR, +3% to +14%) at week 2, +9% (IQR, +4% to +17) at week 12, and +12% (IQR, +6% to +19%) at week 48 (table 2). The median CD8$^+$/CD38^{++} T cell count decreased to 33 cells/mm^3 (IQR, 19–75 cells/mm^3) at week 48 (table 2).

Changes in cell-associated HIV-1 RNA and DNA levels after initiation of ART. Changes of cell-associated HIV-1 RNA and DNA levels are shown in table 2 and figure 2. The cell-associated RNA level decreased rapidly during the first 4 weeks in parallel with HIV-1 load, with little further decrease thereafter. At week 42, the median RNA level was 0.8 log copies/million PBMCs (IQR, 0.48–1.43 log copies/million PBMCs) among 63 patients. The cell-associated DNA level decreased gradually over 42 weeks to reach a median level of 1.58 log copies/million PBMCs (IQR, 1.18–1.90 log copies/million PBMCs) among 63 patients. At week 42, levels <3 log copies/million PBMCs were noted in 21 (33.3%) of 63 patients and 6 (9.5%) of 58 patients for cell-associated RNA and DNA, respectively. Levels of cell-associated RNA and DNA at week 42 were associated with the viral load at week 48 ($r = 0.42$, for cell-associated RNA level, and $r = 0.43$, for cell-associated DNA level; $P < .001$). Baseline cell-associated DNA levels were also associated with cell-associated DNA levels at week 42 ($r = 0.43$; $P = .001$). Two patients achieved undetectable levels according to all 3 measures (cell-associated RNA and DNA levels <3 log copies/million PBMCs and viral load ⩽3 copies/mL) at week 42.

Baseline factors and time to achieve an HIV-1 load ⩽3 copies/mL. Cumulative proportions of 78 patients with an

Table 2. Baseline values, week 48 values, and changes from baseline to week 48, for virological and immunological parameters among all patients who continued to receive follow-up care.

	Baseline		Week 48[a]		Change from baseline to week 48[b]	
Variable	No. of patients for whom data were available	Median (IQR)	No. of patients for whom data were available	Median (IQR)	No. of patients for whom data were available	Median (IQR)
Plasma HIV-1 RNA load, log copies/mL	146	5.4 (4.9–6.2)	114	0.7 (0.5–1.5)	112	−5.4[c] (−6.4 to −3.9)
CD4 cell count, cells/mm^3	139	514 (399–674)	110	677 (520–843)	104	+147 (−1 to +283)
CD4 percentage	139	26 (19–35)	110	40 (32–43)	104	+12 (+6 to +19)
CD8 cell count, cells/mm^3	139	1035 (657–1620)	110	647 (447–924)	104	−389 (−987 to −35)
CD4:CD8 cell count	139	0.5 (0.3– 0.8)	110	1.0 (0.8–1.4)	104	+0.5 (+0.2 to +0.8)
CD8$^+$/38^{++} cell count, cells/mm^3	127	459 (208–974)	101	33 (19–75)	92	−410 (−933 to −136)
Cell-associated RNA level, log copies/million PBMCs	114	3.4 (2.9–4.1)	63	0.8 (0.5–1.4)	55	−2.6[c] (−3.3 to −2.0)
Cell-associated DNA level, log copies/million PBMCs	113	2.8 (2.4–3.0)	63	1.6 (1.2–1.9)	54	−1.1[c] (−1.6 to −0.8)

NOTE. IQR, interquartile range.

[a] Cell-associated RNA and DNA levels were measured at week 42.

[b] $P < .001$ for all.

[c] Adjusted for assay limit of detection.

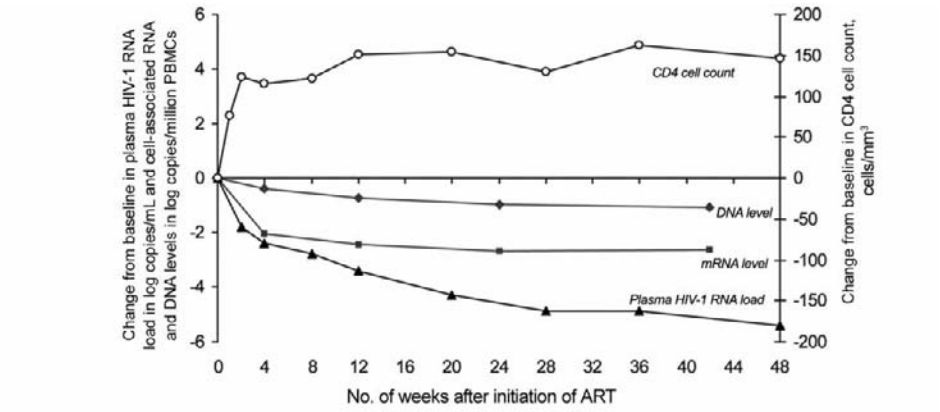
HIV-1 load ⩽3 copies/mL were 1.5%, 11.1%, 32.8%, 55.2%, and 63.4% by weeks 12, 20, 28, 36, and 48, respectively. In univariable Cox models stratified by country, baseline viral load, cell-associated RNA level, cell-associated DNA level, and CD8$^+$/CD38^{++} T cell count were each inversely associated with time to achieve a viral load ⩽3 copies/mL (HRs for every 1 log higher value for each parameter were 0.79 [95% CI, 0.64–0.98] for viral load, 0.29 [95% CI, 0.17–0.50] for cell-associated DNA level, 0.60 [95% CI, 0.44–0.80] for cell-associated RNA level, and 0.55 [95% CI, 0.32–0.94] for CD8$^+$/CD38^{++} T cell count); CD4 cell count was not inversely associated with time to achieve a viral load ⩽3 copies/mL (HR for every 100 cells higher, 1.04; 95% CI, 0.94–1.15). In a multivariable model, baseline CD8$^+$/CD38^{++} T cell count and cell-associated DNA level were independent predictors of a viral load ⩽3 copies/mL among 103 patients (adjusted HR for every 1 log higher, 0.30 [95% CI, 0.18–0.51]; $P < .001$, for cell-associated DNA; HR, 0.47 [95% CI, 0.25–0.86]; $P = .016$, for CD8$^+$/CD38^{++} T cell count).

Suppression of plasma viremia according to "intention-to-treat" and "receiving ART" analyses. Figure 3 shows the proportion of patients with viral loads ⩽50 copies/mL, ⩽10 copies/mL, and ⩽3 copies/mL, by week of follow-up, using (1) an "intention-to-treat" analysis, in which all 148 patients were included at each time point, with missing data counted as "failure;" and (2) a "receiving ART" analysis, in which only patients receiving any type of ART were included at the time of viral load measurement. Using an intention-to-treat analysis, 64.9% (95% CI, 57.2%–72.6%), 48.0% (95% CI, 39.9%–56.0%), and 34.5% (95% CI, 26.8%–42.1%) of all 148 patients had viral loads ⩽50 copies/mL, ⩽10 copies/mL, and ⩽3 copies/mL at week 48, respectively. Corresponding percentages for the receiving ART analysis were 94.0% (95% CI, 87.4%–97.8%), 69.05 (95% CI, 59.0%–77.9%), and 49.0% (95% CI, 38.9%–59.2%) among 100 patients. Overall, only 5 patients reached a viral load >400 copies/mL during weeks 28–48 while receiving ART.

Safety and adverse events. Eighty-three clinical adverse events classified as grade 3 or 4 or serious adverse events occurred among 49 patients during the 48 weeks after ART initiation. The most common clinical adverse events were depression and/or attempted suicide (accounting for 11% of all serious adverse events or grade 3 or 4 clinical adverse events), rash (9%), vomiting (8%), nausea (7%), fever (6%), diarrhea (6%), and hypersensitivity to abacavir (6%). Of these 83 adverse events, 38 were considered to be related to study drug. One death due to gastrointestinal hemorrhage was considered to be unrelated to study drug. Ninety-three grade 3 or 4 laboratory abnormalities occurred among 45 patients (increased alanine aminotransferase [accounting for 19% of all grade 3 or 4 laboratory adverse events], amylase [19%], aspartate aminotransferase [12%], and creatine phosphokinase levels [15%] and neutropenia [11%]). Cumulative percentages of patients having a serious or grade 3 or 4 adverse event during 4, 12, 24, and 48 weeks of ART initiation were 23.9%, 38.0%, 45.6%, and 58.5%, respectively. The median duration of an adverse event was 15 days, with 90% of adverse events occurring for <65 days. Thirty-two adverse events (in 22 patients) resulted in interruption (14 patients) or discontinuation (18 patients) of a drug. No patient developed AIDS during the study period.

DISCUSSION

Herein, we report the largest prospective therapeutic study of PHI. The majority of patients were men who have sex with



Denominators for differences:

Week	0	1	2	4	8	12	20	24	28	36	42	48
HIV-1 RNA load	146		133	138	128	127	121		115	117		112
CD4 cell count	139	129	118	131	118	117	112		104	100		104
cell-associated RNA level	114			83		66		83			55	
cell-associated DNA level	114			83		66		83			55	

Figure 2. Median changes from baseline in plasma HIV-1 RNA load, cell-associated RNA and DNA levels, and CD4 cell count, by number of weeks after initiation of antiretroviral therapy (ART). Data include all patients who continued to receive follow-up care. Changes in plasma HIV-1 RNA load were adjusted for assay limit of detection.

men and were symptomatic during PHI. By week 48, 36% of the patients who had started receiving ART were either not receiving treatment or lost to follow-up, with an initial high rate of treatment change, which stabilized later during the study. The vast majority of patients who stopped receiving ART prematurely had undetectable HIV-1 loads when therapy was interrupted. ART initiation was associated with decreases in HIV-1 load and cell-associated RNA and DNA levels and an improvement in immunological parameters. Baseline $CD8^{+}$/$CD38^{++}$ T cell count and cell-associated DNA level were independent predictors for achieving a viral load $\leqslant$3 copies/mL. Toxicity was generally reversible.

This study provides important information regarding the feasibility of starting quadruple ART in a large cohort of patients with PHI. Previous studies, which generally used 3 drugs, have shown treatment discontinuation rates of 19%–50% at 1 year [18–21]. A recent diagnosis of HIV infection, a rapid life-changing decision, clinical symptoms, and future rather than immediate administration of ART may compound the problems of treatment-related toxicity and high pill burden when comparing treatment discontinuation rates between patients with acute infection and those with chronic infection [22]. Kost et al. [22] revealed a higher number of patients stopping a similar ART regimen when they were treated during early infection, compared with those treated during chronic infection. Among newly infected patients, nonadherence and intolerance to adverse effects of therapy were the main reported reasons for stopping treatment. The availability of newer drugs with lower toxicities and pill counts may positively impact patients' adherence in future studies.

Our results confirm those from previous smaller studies of PHI that reveal the possibility of achieving an undetectable HIV-1 load [18–24]. The extent of virological control after ART initiation was further exemplified by the percentages of patients receiving ART at week 48 who had HIV-1 loads $\leqslant$50 copies/mL, $\leqslant$10 copies/mL, and $\leqslant$3 copies/mL, a median decrease in HIV-1 load of 5.4 log copies/mL, and an HIV-1 load of 0.7 log copies/mL. Even during a conservative intention-to-treat analysis (with missing data counted as "failure"), 64% of the patients had an HIV-1 load $\leqslant$50 copies/mL at week 48—a result comparable to that found during chronic infection [25].

Baseline parameters were helpful in forecasting virological outcome. Cell-associated HIV-1 RNA and DNA levels are indirect markers of treatment efficacy [7, 18]. Previous studies, including a study by Garrigue et al. [26], have revealed a median HIV-1 mRNA level of 1.7 log copies/million PBMCs and detectable mRNA levels after 12 months of ART in some aviremic patients with PHI who received ART and in all patients with chronic infection who received ART [7, 20, 27–29]. We extend these results by revealing that plasma replication was dramatically decreased overall, because 33% of the patients had viral loads $\leqslant$3 copies/mL, and that the overall cell-associated RNA level decreased from 2.6 log copies/million PBMCs to 0.8 log copies/million PBMCs.

When looking at cell-associated DNA level, which reflects

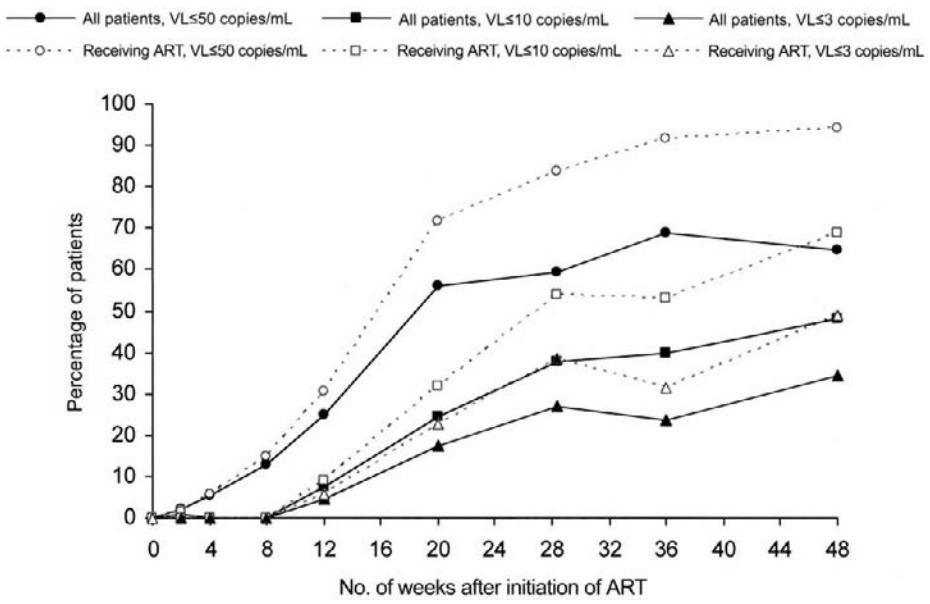


Figure 3. Percentage of patients with plasma HIV-1 RNA loads (VL) ⩽50 copies/mL, ⩽10 copies/mL, and ⩽3 copies/mL. The solid line represents data according to an intention-to-treat analysis, with missing data counting as "failure." The dotted line represents a "receiving antiretroviral therapy (ART)" analysis. The numbers of patients in the "receiving ART" analysis were 146, 133, 126, 120, 113, 104, 111, and 100 at weeks 0, 4, 8, 12, 20, 28, 36, and 48, respectively.

the reservoir size, we found a median decrease of the cell-associated DNA level of 1.1 log copies/million PBMCs and a cell-associated DNA level of 1.6 log copies/million PBMCs at the end of year 1. Previous studies of PHI have described a decrease of the cell-associated DNA level of ~1.0 log after 18 months of ART, compared with the one-half log decrease and absence of undetectable levels during chronic infection [7, 20, 26, 27, 30–32]. Garrigue et al. [26] reported that, after 1 year of ART, cell-associated DNA levels were 2.0 log copies/million PBMCs, with 1 of 22 patients having a cell-associated DNA level <10 copies/million PBMCs; these findings contrast our figure of 6 patients (9.5%) with cell-associated DNA levels ⩽3 copies/million PBMCs. Five of these 6 patients had a viral load <10 copies/mL at the time of proviral measurement. These patients did not differ in terms of baseline CD4 cell count and HIV-1 load from those who had detectable cell-associated DNA levels. Our results suggest that lower levels of cell-associated DNA are achievable with ART initiation during PHI than with ART initiation during chronic infection [7, 31, 32].

Our data also illustrate the changes in immune activation. Normalization of the $CD8^+/CD38^{++}$ T cell count occurred in 28 (27.7%) of 101 patients at week 48. These cell counts decreased initially in parallel with viral load and continued to decrease in patients achieving a viral load ⩽50 copies/mL—but not in patients with a viral load ⩾3 copies/mL—and could, therefore, represent a sensitive indicator of residual viral replication [33, 34]. Patients with an undetectable cell-associated RNA level at week 42 indeed had lower $CD8^+/CD38^{++}$ T cell counts at weeks 36 and 48, compared with those who had a detectable cell-associated RNA level at week 42. The initial follow-up of 6 patients who had stopped treatment prematurely suggested that the $CD8^+/CD38^{++}$ T cell count tended to increase with subsequent viral load rebound (data not shown).

Safety is an important factor to consider when initiating early treatment. Grade 3 or 4 clinical and laboratory severe adverse events occurred in a substantial proportion of patients but were generally reversible, as previously reported [22]. The incidence of hypersensitivity to abacavir (3%) was comparable to that in other studies. The rate of severe adverse events in our study compares with that in a previous study in which 17 of 39 patients with acute and chronic infection experienced 19 severe adverse events; significant depression accounted for 2 severe adverse events [22]. In a French cohort study of PHI, 124 patients (51%) described having experienced at least 1 adverse event, and 19% of these events were reported as mood disorder [35]. The 14 psychiatric severe adverse events in our study were not considered to be related to study medication. Strong past confounding factors were present in 11 of 13 patients, revealing the potential for serious psychiatric events during the immediate postseroconversion phase in patients with a previous psychiatric history.

In conclusion, we have described the first-year outcome of a large cohort of patients who initiated a protease inhibitor–based, 4-drug ART regimen during PHI. Our results are very

encouraging for achieving a very low HIV-1 load, considering the virological parameters in patients receiving ART, undetectable cell-associated RNA and DNA levels in a substantial proportion of patients and predictive value of proviral DNA, and $CD8^{+}/CD38^{++}$ T cell count. This cohort data may serve as reference when using newer, simpler regimens with lower acute toxicity and activity during the preintegration stage. Future studies may also explore whether long-term treatment is associated with a continuous decrease of the viral reservoir and a potential absence of viral rebound after very prolonged ART.

QUEST STUDY GROUP

Recruiting centers. D. Baker, M. Bloch, D. Smith, R. Finlaysson, P. Grey, D. Smith, and D. A. Cooper (Sydney, Australia); P. Hermanns, K. Kabeya, and N. Clumeck (Brussels, Belgium); M. Harris and J. Montaner (Vancouver, Canada); C. Tsoukas (Montreal, Canada); L. Mathiesen and J. Gerstoft (Hvidovre, Denmark); B. Hoen (Besancon, France); P. M. Girard, J. Modai, A. G. Saimot, D. Sereni, J. F. Delfraissy, and C. Katlama (Paris, France); F. Raffi (Nantes, France); C. Aquilina (Toulouse, France); F. Caron (Rouen, France); P. Canton and T. May (Nancy, France); J. M. Chennebault (Angers, France); S. Staszewski (Frankfurt, Germany); H. J. Stellbrink (Hamburg, Germany); G. Tambussi and A. Lazzarin (Milan, Italy); S. Lindback, A. Blaxhult, and H. Gaines (Stockholm, Sweden); M. C. Bernard, B. Hirschel, and L. Perrin (Geneva, Switzerland); P. Vernazza (St. Gallen, Switzerland); K. Wolf and M. Battegay (Basel, Switzerland); R. Weber (Zurich, Switzerland); S. Kinloch-de Loes, M. Youle, M. Tyrer, S. Bhagani, M. A. Johnson, C. Higgs, D. Hawkins, and B. Gazzard (London, United Kingdom); M. J. Fisher (Brighton, United Kingdom); and A. Friedman (Cardiff, United Kingdom).

GlaxoSmithKline QUEST team. V. Mallet, S. Turkish, S. Fortes, H. Maseruka, H. McDade, H. Steel, and L.-E. Goh (Greenford, United Kingdom).

GlaxoSmithKline monitors. M. Haberl and J. Young (Australia); D. Luyts and I. van Steenberg (Belgium); S. Pratt and T. Russell (Canada); L. Beauvais and J. M. Vauthier (France); M. Sikora (Germany); C. Gussetti, C. M. Anghileri, V. Piva, and D. Fendt (Italy); G. Larsson (Sweden); C. Python, I. Schauwecker, and E. Gremlich (Switzerland); and K. Studdard, P. Humphreys, and U. Loughrey (United Kingdom).

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Virco. W. Verbiest and P. Stoffels (Mechelen, Belgium).

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Data safety and monitoring board. M. Schechter (Canada), I. Weller (United Kingdom), R. Luethy (Switzerland), and J. M. Molina (France).

Statistical analysis. F. C. Lampe and A.N. Phillips.

QUEST core group (steering committee). S. Kinloch-de Loes, L. Perrin, D. Cooper, B. Hoen, B. Autran, A.N. Phillips, J. Andersson, A. Sonneborg, and C. Tsoukas.

AUTHOR AFFILIATIONS

[1]Department of Infectious Diseases, University Medical Centre, Besancon, and [2]Department of Internal Medicine, St. Louis Hospital, and [3]Service des Maladies Infectieuses et Tropicales, Centre Hospitalier Universitaire Saint-Louis, Paris, France; [4]National Centre in HIV Epidemiology and Clinical Research, University of New South Wales and St. Vincent's Hospital, Sydney, New South Wales, and [5]Taylor Square Private Clinic, Surry Hills, Sydney, Australia; Departments of [6]Primary Care and Population Sciences, [7]Immunology and Molecular Pathology, and [8]Infection and Immunity, Royal Free Center for HIV Medicine, Royal Free and University College Medical School, and [9]Kobler Centre, Chelsea & Westminster Hospital, London, and [10]GlaxoSmithKline Research and Development, Greenford, United Kingdom; [11]Laboratory of Virology, Division of Infectious Diseases, Geneva University Hospital, Geneva, and [12]Division of Infectious Diseases, Department of Internal Medicine, University Hospital, Zurich, Switzerland; [13]Department of Infectious Diseases, St. Pierre Hospital, Brussels, Belgium; [14]Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden; [15]John Ruedy Immune Deficiency Clinic, St. Paul's Hospital, University of British Columbia, Vancouver, Canada; [16]IPM Study Center, Hamburg, and [17]Klinikum der JW Goethe Universitat, Zentrum der Inneren Medizin, Frankfurt, Germany; [18]Clinic of Infectious Diseases, San Raffaele Scientific Institute, Milan, Italy; and [19]Hvidovre Hospital, Hvidovre, Denmark.

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