Effect of Persistent Moderate Viremia on Disease Progression During HIV Therapy

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Objective: Although highly active antiretroviral therapy has been shown to lower plasma HIV-1 RNA in HIV infection, many patients do not reach the target goal of undetectable viremia. We evaluated whether risk of clinical progression varies by level of viral suppression achieved.

Design: Patients in the Collaborations in HIV Outcomes Research/United States cohort who maintained stable HIV-1 RNA levels of either <400, 400 to 20,000, or >20,000 copies/mL during a run-in period of at least 6 months were studied. Baseline was the first day after this period.

Methods: Proportional hazards models were used to quantify the relation between baseline HIV-1 RNA levels and risk of a new AIDS-defining diagnosis or death after adjusting for CD4 count, age, gender, ethnicity, study site, prior AIDS-defining diagnosis, and antiretroviral therapy history.

Results: Patients (N = 3010) were followed for up to 4.3 years after the 6-month run-in period, with 343 deaths or AIDS-defining diagnoses reported. The risk of a new AIDS-defining diagnosis or death was not significantly different in the 400 to 20,000– and <400-copies/mL groups (6% vs. 7%, hazard ratio [HR] = 1.0, 95% confidence interval [CI]: 0.7–1.4; $P = 0.9$) but was significantly higher in the >20,000-copies/mL group (26%, HR = 3.3, 95% CI: 2.5–4.4; $P < 0.001$ vs. the <400-copies/mL group). Median CD4 count changes during the first year of follow-up showed increases of 75 and 13 cells/mm^3 for the <400- and 400 to 20,000–copies/mL groups, respectively, whereas the >20,000-copies/mL group had a decrease of 23 cells/mm^3.

Conclusions: Patients who maintained baseline HIV-1 RNA levels of 400 to 20,000 copies/mL for at least 6 months preserved immunologic status and were no more likely to die or develop a new AIDS-defining diagnosis in the time frame studied than those with baseline levels <400 copies/mL. Patients with HIV-1 RNA levels >20,000 copies/mL at baseline had greater clinical and immunologic deterioration. These data suggest that maintenance of moderate viremia may confer clinical benefit not seen when viremia exceeds 20,000 copies/mL, and this should be taken into account when considering the risks and benefits of continuing failing therapy.

Key Words: Collaborations in HIV Outcomes Research/United States, HIV disease progression, HIV viremia, plasma HIV-1 RNA

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Effective treatment of HIV infection is closely correlated with degree of viral suppression. Highly active antiretroviral therapy (HAART) has been shown to improve clinical outcomes in patients infected with HIV greatly, with decreased morbidity and mortality reported for successfully treated patients.[1–3] Although viral replication is thought to continue at extremely low levels in many successfully treated patients, the ultimate goal of therapy is still to suppress viral replication to below detectable levels.[4,5] Suppression of plasma HIV-1 RNA levels to less than 50 copies/mL has been associated with a more durable response to therapy.[6–8] Unfortunately, maximal suppression is not possible in all patients, with response rates varying from 30% to 80% in treatment-experienced patients.[1,2,9] Many patients show treatment-related decreases in baseline HIV-1 levels that do not reach undetectable levels.[10,11] Although such a partial response to HAART may reflect the maximal suppression now possible for many patients, limited data are available concerning the clinical outcome of partial suppression of viremia as compared with achieving greater suppression with sustained plasma HIV-1 RNA levels of <400 copies/mL.

This study was designed to evaluate the clinical course of HIV-infected patients in the Collaborations in HIV Outcomes Research/United States (CHORUS) cohort who maintained detectable plasma HIV-1 RNA levels for at least 6

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months and to compare the clinical outcomes in these patients with those of patients suppressed to undetectable plasma HIV-1 RNA levels (<400 copies/mL).

METHODS

Patients

The CHORUS project is an ongoing observational database designed to follow longitudinal clinical outcomes in a large cohort of HIV-infected patients. As previously described,[12] the CHORUS project was established in 1996 and has enrolled more than 5700 participants at 4 community-based clinical sites in the United States (Comprehensive Care Center, Nashville, TN; Liberty Medical Group, New York, NY; Pacific Horizon Medical Group, San Francisco, CA; and Pacific Oaks Medical Group, Los Angeles, CA). Patients are enrolled as part of their routine clinical care, and treatment decisions follow the community standard of care. All data elements (demographic, clinical, and laboratory) are retrieved from an electronic medical records system and transferred via a secure connection to an independent data aggregation facility. Confidentiality is maintained by using only aggregated nonidentifiable patient data. All patients provided institutional review board–approved informed consent before enrollment into the CHORUS project. An independent advisory board consisting of physicians and researchers from the participating sites, members of the HIV community, academic experts, and sponsor representatives oversees the CHORUS project and all data analyses.

Study Design

Patients were eligible for study if their plasma HIV-1 RNA level remained in the same virologic category as determined by at least 2 consecutive HIV-1 RNA polymerase chain reaction (PCR) measurements taken over a minimum period of 6 months. During this run-in period, eligible patients had to have at least 1 CD4 cell count and no new AIDS-defining illnesses. Patients were assigned to 1 of 3 groups based on their plasma HIV-1 RNA levels: <400, 400 to 20,000, and >20,000 copies/mL. If a subject had more than 1 period of sustained plasma HIV-1 RNA level, the latest period was used for analysis. Baseline was defined as the first day after the end of 6 months in the sustained plasma HIV-1 RNA level period, and this was also the beginning of the follow-up period for monitoring clinical and laboratory outcomes. All HIV-1 RNA PCR values were obtained between August 1996 and July 2001 and were transformed to the $\log_{10}$ scale for analysis. All HIV-1 RNA PCR values reported as undetectable or <400 copies/mL were set to 399 copies/mL for analysis. Laboratory determinations and diagnosis of new AIDS-defining conditions were performed as part of routine clinical care according to the discretion of the HIV care providers. All follow-up laboratory tests were included without regard to the number of tests per patient. Laboratory determinations were performed at licensed commercial laboratories.

Statistical Analysis

Demographic and baseline characteristics as well as changes in CD4 count and HIV-1 RNA level from baseline to last follow-up and number of antiretroviral regimen changes during follow-up were compared across the virologic groups. Comparisons were made between the 400 to 20,000–copies/mL and <400-copies/mL groups and between the >20,000-copies/mL and <400-copies/mL groups only, with statistical significance determined by the Fisher exact test or χ^2 tests for categoric variables and by Wilcoxon tests for continuous variables.

The primary outcome was death or development of a new AIDS-defining diagnosis during the follow-up period. Unadjusted comparisons of this outcome across the virologic groups were made using χ^2 tests. Adjusted comparisons were made using proportional hazards regression models, which included continuous variables for age and CD4 count and indicators for gender, ethnicity (white/other), study site, AIDS diagnosis before baseline, antiretroviral therapy (ART) before baseline, baseline protease inhibitor (PI) use, nucleoside reverse transcriptase inhibitor (NRTI) use, nonnucleoside reverse transcriptase inhibitor (NNRTI) use, virologic category, and terms for the interaction of CD4 count with virologic category. Hazard ratios (HRs) were generated to compare virologic groups at varying levels of baseline CD4 cell count. First, the model was run with patients followed in their baseline virologic category regardless of later changes. Second, the model was rerun with the data censored when a patient changed virologic category. Sensitivity analyses were conducted using different cut-off points for plasma HIV-1 RNA levels as follows: (1) <400, 400 to 5000, and >5000 copies/mL, (2) <400, 400 to 10,000, and >10,000 copies/mL, and (3) <400, 400 to 5000, 5000 to 20,000, 20,000 to 50,000, and >50,000 copies/mL. Analyses were completed using SAS, version 8.2.

RESULTS

Baseline Characteristics

As of July 5, 2001, data were available for 5574 patients. Of these, 3010 met entry criteria and were included in the analysis. Compared with the rest of the CHORUS population, patients in the analysis cohort had lower CD4 counts and higher plasma HIV-1 RNA levels at study consent as well as significantly greater exposure to ART (data not shown). Table 1 shows baseline (day 1 after the 6-month run-in period) characteristics for the 3 virologic groups. In the >20,000-copies/mL category, half the patients had a baseline viral load >82,000 (median $\log_{10}$ RNA = 4.9). Compared with those in the <400-copies/mL group, patients in the >20,000-copies/mL category were more likely to be nonwhite, have a lower CD4

TABLE 1. Baseline* Characteristics of the <400-, 400–20,000– and >20,000-HIV-1 RNA Copies/mL Groups

	<400 HIV-1 RNA (N = 1299)	400–20,000 HIV-1 RNA (N = 989)†	>20,000 HIV-1 RNA (N = 722)†
White (%)	79	74 ($P = 0.001$)	69 ($P = 0.001$)
Male (%)	92	86 ($P = 0.001$)	91 ($P = 0.7$)
Median age (y)	39	39 ($P = 0.08$)	38 ($P = 0.01$)
AIDS at baseline (%)	25	25 ($P = 0.9$)	44 ($P = 0.001$)
Median CD4 count at baseline (cells/mm^3)	443	405 ($P = 0.001$)	205 ($P = 0.001$)
Median $\log_{10}$ HIV-1 RNA at baseline (copies/mL)	2.60	3.48 ($P = 0.001$)	4.92 ($P = 0.001$)
Any ART use before baseline (%)	99	97 ($P = 0.001$)	93 ($P = 0.001$)
Prior NRTI use (%)	97	88 ($P = 0.001$)	90 ($P = 0.001$)
Prior PI use (%)	84	64 ($P = 0.001$)	80 ($P = 0.02$)
Prior NNRTI use (%)	28	33 ($P = 0.009$)	47 ($P = 0.001$)
Any ART use at baseline (%)	96	81 ($P < 0.0001$)	70 ($P < 0.0001$)
NRTI use at baseline (%)	93	79 ($P = 0.001$)	65 ($P = 0.001$)
PI use at baseline (%)	76	48 ($P = 0.001$)	51 ($P = 0.001$)
NNRTI use at baseline (%)	13	14 ($P = 0.3$)	4 ($P = 0.6$)

*Baseline is defined as the first day after the 6-month run-in period.
†*P* values shown for a test between the <400- and 400–20,000–copies/mL and <400 and >20,000 copies/mL groups.

count, and have a prior diagnosis of AIDS. Patients in the middle and high virologic groups had significantly less prior exposure to NRTIs and PIs but greater prior exposure to NNRTIs.

Frequency of Clinical Events

Patients were followed up to 4.3 years, with a median of 3 years in the <400-copies/mL group (N = 1299) and approximately 2 years in the 400 to 20,000–copies/mL group (N = 989) and the >20,000-copies/mL group (N = 722; Table 2). Overall, 343 patients were diagnosed with new AIDS-defining conditions or died. The incidence of events was similar in the 400 to 20,000– and <400-copies/mL groups (6% vs. 7%; $P = 0.5$) but was significantly higher in the >20,000-copies/mL group (26%; $P = 0.001$ compared with the <400-copies/mL group).

TABLE 2. Follow-up, Regimen Changes, CD4/HIV-1 RNA Change From Baseline, and Number of Deaths/AIDS-Defining Events in the <400–, 400–20,000– and >20,000-HIV-1 RNA Copies/mL Groups

	<400 HIV-1 RNA (N = 1299)	400–20,000 HIV-1 RNA (N = 989)*	>20,000 HIV-1 RNA (N = 722)*
Median time to event or censor (d)	1114	894 ($P < 0.001$)	687 ($P < 0.001$)
Median change in CD4 count from baseline (median % change)	91 (21)	9 (3) ($P < 0.001$)	−19 (−13) ($P < 0.001$)
Median change in CD4 count during first year of follow-up	75 (N = 966)	13 (N = 602)	−23 (N = 390)
Median $\log_{10}$ HIV-1 RNA change from baseline	0	0.07 ($P = 0.3$)	−0.08 ($P < 0.001$)
Median change in $\log_{10}$ HIV-1 RNA during first year of follow-up	0 (N = 709)	0.06 (N = 547)	−0.06 (N = 374)
Median no. regimen changes (range)†	1 (0, 12)	1 (0, 14) ($P = 0.04$)	2 (0, 20) ($P < 0.001$)
No. patients discontinuing antiretrovirals for ≥3 months during follow-up (%)	41 (3)	80 (8) ($P < 0.001$)	183 (25) ($P < 0.001$)
Deaths (%)	26 (2)	21 (2) ($P = 0.8$)	68 (9) ($P < 0.001$)
AIDS-defining diagnoses (%)	66 (5)	42 (4) ($P = 0.4$)	120 (17) ($P < 0.001$)
Total AIDS diagnoses and deaths (%)	92 (7)	63 (6) ($P = 0.5$)	188 (26) ($P < 0.001$)

**P* values shown for a test between the <400- and 400–20,000–copies/mL and <400 and >20,000 copies/mL groups.
†Defined as a change in any single drug.

A detailed review of deaths was performed using a methodology developed and currently employed by the CHORUS project.[13] Deaths occurred in 2% of patients in the <400- and 400 to 20,000–copies/mL groups ($P = 0.8$ compared with the <400-copies/mL group) groups and in 9% of the >20,000-copies/mL group ($P < 0.001$ compared with the <400-copies/mL group). Comorbid (non-AIDS) conditions were determined to be the immediate cause for 77% of deaths in the <400-copies/mL group and 83% of deaths in the 400 to 20,000–copies/mL group. Comorbid conditions were the immediate cause for only 44% of deaths among patients in the >20,000-copies/mL group, whereas 56% of deaths were attributed to AIDS-defining diagnoses.

Risk Analyses

After adjusting for demographic variables, prior AIDS diagnosis, prior ART use, study site, baseline CD4 cell count, and baseline ART use, no statistically significant difference in the risk of events was detected between patients in the 400 to 20,000– and <400-copies/mL groups (overall HR = 1.0, 95% confidence interval [CI]: 0.7–1.4; $P = 0.9$). There was no indication of any significant difference in this relation for patients with varying baseline CD4 counts (Table 3). In contrast, compared with patients in the <400-copies/mL group, those in the >20,000-copies/mL group were at increased risk of a new AIDS-defining diagnosis or death (overall HR = 3.3, 95% CI: 2.5–4.4; $P < 0.001$). This risk varied depending on baseline CD4 count, with estimated HRs ranging from 1.7 to 5.6 for patients with baseline counts of ≤500 cells/mm^3. No significant difference was detected for patients with baseline CD4 cell counts ≥600 cells/mm^3.

The analysis was repeated using follow-up information only, with patients remaining in their original virologic category. Follow-up time was reduced to between 8 and 11 months in each virologic group, and 144 events occurred. Again, no significant difference was detected in the risk of a new AIDS-defining diagnosis or death for patients in the 400 to 20,000–copies/mL group compared with those in the <400-copies/mL group ($P = 0.1$). A significant difference remained between the >20,000- and <400-copies/mL groups depending on baseline CD4 count. Patients with HIV-1 RNA levels of >20,000 copies/mL and baseline CD4 counts of 300 cells/mm^3 or less were significantly more likely to have an event, but no difference was found for those with higher baseline CD4 counts (data not shown).

Changes in CD4/HIV-1 RNA Levels, Treatment Regimens, and Virologic Categories

The number of antiretroviral regimen changes, defined as a change in any single drug, was comparable in the <400- and 400 to 20,000–copies/mL groups but higher in the >20,000-copies/mL group (see Table 2). A significantly higher percentage of patients in the >20,000-copies/mL group discontinued ART for 3 or more months during follow-up. Median CD4 counts increased 21% between baseline and last follow-up in the <400-copies/mL and 3% in the 400 to 20,000–copies/mL groups and decreased (−13%) in the >20,000-copies/mL group. Median $\log_{10}$ HIV-1 RNA levels showed no change in the <400-copies/mL group, increased slightly in the <400 to 20,000–copies/mL group, and decreased slightly in the >20,000-copies/mL group. During the first year of follow-up, median CD4 counts increased by 75 and 13 cells/mm^3 in the <400- and 400 to 20,000–groups and decreased by 23 cells/mm^3 in the >20,000-copies/mL group. During this same period, median $\log_{10}$ HIV-1 RNA level showed no change in the <400-copies/mL group, increased 0.06 in the 400 to 20,000–copies/mL group, and decreased 0.06 in the 20,000-copies/mL group.

During the follow-up period, some patients had a change in viral categories (Table 4). In all 3 viral groups, most patients

TABLE 3. CD4 Stratification and Risk of Disease Progression

Baseline CD4 Count (cells/mm^3)	400–20,000 vs. <400 HIV-1 RNA			>20,000 vs. <400 HIV-1 RNA		
	HR*	95% CI	*P*	HR*	95% CI	*P*
50	1.5	0.8, 2.7	0.2	5.6	3.7, 8.6	<0.001
100	1.4	0.8, 2.5	0.2	4.9	3.2, 7.5	<0.001
150	1.3	0.7, 2.4	0.3	4.3	2.8, 6.6	<0.001
200	1.2	0.7, 2.3	0.3	3.8	2.5, 5.8	<0.001
300	1.1	0.6, 2.0	0.6	2.9	1.9, 4.4	<0.001
400	1.0	0.5, 1.8	0.9	2.2	1.4, 3.4	<0.001
500	0.9	0.5, 1.6	0.6	1.7	1.1, 2.6	0.04
600	0.8	0.4, 1.4	0.4	1.3	0.8, 2.0	0.4
700	0.7	0.4, 1.3	0.3	1.0	0.7, 1.5	0.9

*HRs were adjusted for age, gender, ethnicity, prior AIDS diagnosis, prior ART use, baseline ART use, baseline CD4 count, and study site.

TABLE 4. Patients with a Change in Viral Category From Baseline to End of Study

Virologic Group at Baseline	Final Virologic Category at End of Study [N (%)]		
	<400 HIV-1 RNA	400–20,000 HIV-1 RNA	>20,000 HIV-1 RNA
<400 HIV-1 RNA	1107 (85)	144 (11)	48 (4)
400–20,000 HIV-1 RNA	125 (13)	731 (74)	133 (13)
>20,000 HIV-1 RNA	57 (8)	134 (18)	534 (74)

remained in their baseline viral categories. A small percentage of patients in the <400-copies/mL group showed an increase in viremia, whereas some patients in the >20,000-copies/mL group became aviremic. In the 400 to 20,000–copies/mL group, an equal percentage of patients improved or showed deterioration in their viremic status.

Sensitivity Analyses

Sensitivity analyses were performed using 3 alternative HIV-1 RNA level stratifications (Table 5). Compared with patients in the <400-copies/mL group, those in the highest virologic groups were consistently at significantly higher risk for a new AIDS-defining diagnosis or death. The increased risk associated with a baseline HIV-1 RNA of >50,000 copies/mL (HR = 3.7, 95% CI: 2.7–5.1) but not with 20,000 to 50,000 copies/mL (HR = 1.6, 95% CI: 0.8–3.0) suggests that clinical progression is most likely with high-level virologic failure.

DISCUSSION

Since effective therapy for HIV became available in the late 1990s, various studies have linked successful clinical outcomes with virologic and immunologic markers. Cohort studies have demonstrated a marked decrease in morbidity and mortality in patients receiving effective therapy,[3,14,15] and initial clinical trials have reported virologic response rates of 70% to 90% in treatment-naive patients receiving HAART.[2,16,17] In subsequent studies, virologic response was correlated with baseline HIV-1 RNA levels, baseline CD4 cell counts, prior treatment status, and individual components of treatment regimens.[18–23] As experience with new antiretroviral agents accumulates, however, it has become apparent that the target goal of undetectable viremia is not always possible.[10,24] Heavily treatment-experienced patients have rates of attaining undetectable levels of HIV-1 RNA that are much lower than those reported for treatment-naive patients.[25–27] Even cohorts of treatment-naive patients show significant rates of virologic failure.[11] Patient tolerability and adherence, development of drug-resistant strains, and long-term toxicities have all become key issues in the determination of the best treatment option and may limit the number of effective drug regimens for an individual patient.[28–36]

TABLE 5. Sensitivity Analysis Results: Risk of Death or an AIDS-Defining Event From Models Using Different Cut-Off Points

Virologic Group Compared With <400-HIV-1 RNA Group	Overall HR*	95% CI	*P*
Original groups			
400–20,000	1.0	0.7, 1.4	0.9
>20,000	3.3	2.5, 4.4	0.001
Alternative groups			
400–5000	0.7	0.4, 1.1	0.2
>5000	2.2	1.7, 2.9	0.001
400–10,000	1.0	0.7, 1.5	0.9
>10,000	2.7	2.1, 3.6	0.001
400–5000	0.8	0.5, 1.2	0.2
5000–20,000	0.7	0.4, 1.3	0.3
20,000–50,000	1.6	0.8, 3.0	0.2
>50,000	3.7	2.7, 5.1	0.001

*HRs were adjusted for age, gender, ethnicity, prior AIDS diagnosis, prior ART use, baseline ART use, baseline CD4 count, and study site.

The present study demonstrates that patients who maintained an HIV-1 RNA plasma level between 400 and 20,000 copies/mL over a 6-month baseline period had no significantly higher risk for clinical disease progression over a 3-year period than patients with an HIV-1 RNA level <400 copies/mL during the baseline period. Patients with baseline HIV-1 RNA plasma levels exceeding 20,000 copies/mL had a significantly increased risk for disease progression at baseline CD4 cell counts of 500 cells/mm^3 or less. CD4 cell counts increased between baseline and last follow-up in the <400-copies/mL group and to a lesser extent in the 400 to 20,000–copies/mL group but decreased among patients with >20,000 copies/mL at baseline.

Few data are available on the clinical outcomes of patients who maintain detectable virus. Plasma viremia was first associated with survival in untreated patients, with a significantly decreased 10-year survival in patients whose baseline viremia was in the highest quartile.[18] Subsequently, levels of plasma viremia became accepted as surrogate markers for therapeutic response, and the goal of ART became an undetectable level of plasma HIV in treated patients. More recent studies have examined surrogate markers and disease progression in patients who are either failing or discontinuing therapy.

Ledergerber and colleagues[10] compared disease progression in patients who initiated HAART and never achieved undetectable viremia, patients who achieved undetectable levels, and patients who had viral rebound after achieving undetectable plasma viremia. An increased risk of clinical progression was found only in patients who had never reached undetectable levels, although the risk of clinical progression was less than that previously reported for patients receiving mono- and dual-drug therapy. In another study,[37] a similar cohort was analyzed to evaluate the association of prior nadir CD4 count with disease progression. Patients with baseline CD4 cell counts less than 50 cells/mm^3 had an increased risk of clinical progression, as did patients with higher CD4 cell counts, who had substantially lower nadir CD4 counts. Stratification by viral load was not performed. A short-term study[38] examined the clinical outcomes of patients initiating HAART based on their 6-month virologic and immunologic responses. Patients not responding virologically and immunologically and those patients with only a virologic response had significantly higher risk for clinical progression compared with complete responders. Immunologic response in the absence of virologic response was not associated with an increased risk for clinical progression.

Deeks and colleagues[39] have examined the immunologic course of patients who have developed detectable plasma viremia after initiating HAART. Sustained elevations in CD4 counts were reported in patients who failed to achieve and maintain an undetectable plasma viral load while receiving PI-based therapy. An analysis of extended follow-up data[40] showed that CD4 cell counts do decrease in patients failing therapy but only after an extended period. The median time to return to pretherapy CD4 cell counts was 3 years in failing patients, which is in good agreement with the preservation of immunologic status reported in the 400 to 20,000–HIV-1 RNA copies/mL group described in the current study. Several other more recent reports[41–46] have linked disease progression with baseline CD4 cell count and viral load, latest cell CD4 count, age, injection drug use, previous diagnosis of AIDS, hemoglobin level, body mass index, adherence with prophylactic medications, and intensity of treatment.

This large observational study demonstrates the utility of efforts directed at controlling HIV-1 plasma viremia in patients who may not attain undetectable levels. Despite the complex issues and factors involved in determining virologic response in patient populations, experienced HIV providers at 4 large outpatient treatment centers were able to delay disease progression in patients who, for whatever reason, could not achieve or maintain maximal viral suppression. Immunologic response was closely tied to clinical failure in the most highly viremic patients but not among patients who maintained HIV-1 RNA levels below 20,000 copies/mL. Analysis of causes of death confirmed what has been suggested by other mortality studies: patients on effective antiretroviral regimens are more likely to die of non–AIDS-related causes than patients who are not receiving suppressive therapy. Again, a difference was seen only in patients who had high levels of persistent viremia, who were more likely to die of AIDS-related than non–AIDS-related causes.

Although this study was not limited to only patients receiving ART, most patients did receive treatment during the study period. The observation that nonmaximal suppressive therapy resulted in a clinically and immunologically stable disease state similar to maximal suppressive therapy over a 2- to 3-year period highlights 2 important issues to consider. First, the effect seen in this study could be a result of reduced virulence caused by altered replicative capacity or viral fitness. The fact that standard-of-care treatment practices resulted in stable disease in all but the most highly viremic patients suggests that maintaining selective pressure results in decreased viral fitness, immunologic stability, and increased survival. Second, the immunologically and clinically stable disease state in the 2 groups that maintained a plasma HIV-1 RNA level below 20,000 copies/mL suggests that the definition of failure may need to be reconsidered to include the immune status and a stepwise consideration of the plasma HIV-1 RNA level. When the 400 to 20,000–copies/mL group was compared with the <400-copies/mL group, there was a trend but no statistically significant difference between the groups at all CD4 strata. When this same comparison was made between the >20,000- and <400-copies/mL groups, however, a statistically significant difference was seen at CD4 strata of 500 cells/mm^3 and below, with a 70% increase in risk of clinical events observed at 500 cells/mm^3. The stratification of viral load and CD4 count seems to identify patients at the highest risk for disease progression accurately.

Strengths of this study include the large number of patients per exposure arm, the number of events, and a 2- to 3-year follow-up period. The success of current management of HIV patients may mean that more follow-up is needed to identify long-term consequences of persistent viremia, however, and the CHORUS project will be able to update these findings. Patients with persistent viremia who are maintained on ART may accumulate mutations associated with antiretroviral drug resistance, thereby limiting future treatment options. Plasma HIV-1 RNA levels and CD4 cell counts before the start of the baseline period were not included in this analysis. The change from pretreatment plasma HIV-1 RNA levels may be a significant predictor of time to immunologic and, subsequently, clinical progression.[40] Because patients were not randomized to different arms, selection bias may have occurred, with more complicated and effective regimens given to patients perceived as more likely to be adherent. Patients with extremely high levels of viremia could have been identified as less than ideal candidates for treatment and received less effective therapies. Nevertheless, we found that patients with the highest levels of baseline viremia were treated with a greater

number of antiretroviral regimens when compared with patients in the other 2 categories. Known differences between the groups that could have influenced progression rates, including baseline CD4 count and antiretroviral exposure, were taken into account in the analysis. As with all observational studies, however, the possibility remains that unknown and uncontrolled factors influenced the results. Finally, the public health impact of patients with persistently elevated levels of plasma HIV-1 was not evaluated. Such patients may represent a population at increased risk of transmission compared with patients maintaining undetectable viremia.

This study provides important information that can be used when a patient and a clinician are attempting to determine the best strategic course of treatment of HIV. Although persistent viremia may promote the development of clinically significant resistance mutations,[36,47–49] a treatment regimen that only provides partial virologic suppression may still offer immunologic and clinical benefits. The decision about when to switch drug regimens may thus vary depending on immunologic status, prior treatment experience, and remaining drug options. This study did not examine whether drug-resistant virus with decreased replication capacity contributed to the findings. Further study of this issue as well as when to switch therapy in treatment-experienced patients is needed.

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APPENDIX

Collaborations in HIV Outcomes Research/United States Sites

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