HIV Viral Load Response to Antiretroviral Therapy According to the Baseline CD4 Cell Count and Viral Load

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Context It is unclear whether delay in initiation of antiretroviral therapy (ART) may lead to a poorer viral load response for patients with human immunodeficiency virus (HIV).

Objective To characterize the relationship of viral load response to ART with baseline CD4 cell count and baseline viral load.

Design Inception cohort of 3430 therapy-naive patients with HIV, of whom 3226 patients had at least 1 viral load count after the start of ART.

Setting Three cohort studies of patients cared for in HIV clinics in Europe between 1996 and 2000.

Patients All patients initiating ART consisting of at least 3 drugs initiated in or after 1996 and for whom CD4 cell count and viral load were available in the prior 6 months (at most).

Main Outcome Measures Viral load decrease to below 500 copies/mL; viral load rebound to above 500 copies/mL (2 consecutive values).

Results Of 3226 patients during the median follow-up of 119 weeks, 2741 (85%) experienced viral suppression to less than 500 copies/mL by 32 weeks. Relative hazards (RHs) of achieving this were 1.08 (95% confidence interval [CI], 0.98-1.21) and 0.94 (95% CI, 0.84-1.04) for baseline CD4 cell counts between 200 and 349 $\times 10^6$/L and baseline CD4 cell counts lower than 200 $\times 10^6$/L, respectively, compared with baseline CD4 cell counts of 350 $\times 10^6$/L or higher, after adjustment for several factors including baseline viral load. For baseline viral load, the RHs were 0.95 (95% CI, 0.84-1.07) and 0.65 (95% CI, 0.58-0.74), for 10 000 to 99 999 and 100 000 copies/mL or greater, respectively, compared with less than 10 000 copies/mL, but the probability of viral load lower than 500 copies/mL at week 32 was similar in all 3 groups. Subsequent rebound above 500 copies/mL was no more likely with a lower baseline CD4 cell count or higher viral load.

Conclusion In this study, lower CD4 cell counts and higher viral loads at baseline were not associated with poorer virological outcome of ART. Those with baseline viral loads of greater than 100 000 copies/mL had a slower rate of achieving viral suppression.

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FOR MANY PATIENTS WITH chronic, asymptomatic, human immunodeficiency virus (HIV) infection who have not received antiretroviral therapy (ART), it is unclear whether such therapy should be initiated immediately or deferred until the CD4 cell count is lower, and/or the plasma viral load is higher. Viral load levels tend to change only moderately over time in untreated individuals, with at most approximately a 0.1 log copies/mL increase per year, although this rate of increase varies across individuals.[1-4] In untreated HIV infection, the risk of acquired immunodeficiency syndrome (AIDS) diseases is known to be small before the CD4 cell count has reached 200 $\times 10^6$/L[5,6] or the viral load has reached 10 000 copies/mL.[4] Early therapy brings immediate intervention against a virus known to be causing immune damage, provides the potential for preservation of HIV-specific CD4 cells and the microarchitecture of lymphoid organs, and lowers the viral load to reduce infectivity and prevent AIDS diseases with high case-fatality rates, such as lymphoma, which can occasionally occur at high CD4 cell counts and are refractory to therapy. Delaying therapy, on the other hand, means avoiding the risk of drug toxic effects, selection for drug resistance, and the inconve-

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nience of adhering to a complex regimen for an extended period. It also may mean that when therapy is finally initiated, it is with a more potent and/or more tolerable regimen developed in the intervening period. Furthermore, relatively complete immune reconstitution can be achieved with virologically suppressive therapy, even when initiated in people with very low CD4 counts.[7-9] There is no direct evidence from trials of when the optimum time is to initiate therapy in the highly active ART era. The lack of firm data on this issue is illustrated by the differences between various expert recommendations.[10-12]

Successful therapy requires a profound and prolonged virological response,[12] so a key consideration when deciding when to initiate therapy is whether the virological response is likely to be compromised by any delay. However, the relationship between baseline CD4 cell count, baseline viral load, and viral load response has not been characterized in detail. To address this, we have analyzed data from the databases of 3 large HIV cohort studies. We also included data on clinical events and deaths during follow-up.

METHODS

We considered all therapy-naive patients in the Swiss HIV Cohort Study (SHCS), Frankfurt HIV Clinic Cohort (FHCC), and EuroSIDA studies who initiated ART (1) consisting of at least 3 drugs in combination, (2) after January 1, 1996, (3) with a viral load and CD4 cell count measurement available 6 months before (at most), and (4) when the most recent viral load was greater than 500 copies/mL. For viral load outcomes, we required at least 1 measurement available after the start of therapy.

All 3 studies are clinic-based, capturing in a prospective fashion the ongoing clinical and laboratory marker status of complete populations of clinic patients (or, for EuroSIDA, a consecutive group of clinic attendees seen after a certain date). The SHCS is based in 5 university outpatient clinics and 2 outpatient clinics in Cantonal Hospitals in Switzerland, the FHCC is based at a single clinic, which is part of the J-W Goethe University, and EuroSIDA is based in 60 clinics in 20 European countries and coordinated in Copenhagen, Denmark. Details have been described elsewhere.[9,13-15] Viral load has been measured using the Roche PCR methods (Roche Molecular Systems, Branchburg, NJ) in the SHCS and FHCC. For EuroSIDA, the Amplicor HIV-1 monitory assay (Roche Molecular Systems) was used in 64% of the centers, NASBA HIV-1 RNA QT amplification system (Oganon Teknika Corp, Durham, NC) in 16%, and the branched DNA viral load test (Chiron Corp, Emeryville, Calif) in 19%.[16] Viral load levels from methods other than the Amplicor HIV-1 monitor assay performed in EuroSIDA were not adjusted in this analysis, but Cox models were stratified by clinic, minimizing any bias in the relationship between baseline CD4 cell count (viral load) and virological response resulting from use of different methods in different clinics. For the EuroSIDA and SHCS, viral load and CD4 cell counts were measured approximately every 3 months. In the Frankfurt HIV Clinic Cohort, viral load and CD4 cell counts were measured every 1 to 2 months. For these analyses, the assays were sensitive to a viral load above 500 copies/mL.[16] In a subset of patients (609 patients seen at 2 clinics in the SHCS and Frankfurt after January 1998), the ultrasensitive Amplicor HIV-1 monitor assay (detection limit, 50 copies/mL) was used. Due to some overlap between the EuroSIDA study and the other 2, all individuals from Swiss centers (SHCS) or Frankfurt (FHCC) were excluded from the EuroSIDA data for these analyses.

Statistical Methods

We used 3 main measures of virological response. The first measure was the time to viral load of less than 500 copies/mL. For those not achieving this by 32 weeks from start of therapy, this time was right-censored at 32 weeks, unless the last viral load was before 32 weeks, in which case the time was right-censored at the time of last viral load. Thirty-two weeks was chosen as a period over which, from previous experience, the viral load would be expected to have declined to below 500 copies/mL if it is going to do so.[7] Kaplan-Meier estimates of the proportion with viral loads lower than 500 copies/mL were calculated separately for those starting therapy with low ($<200\times10^6$/L), medium (200-349$\times10^6$/L), and high ($\geq350\times10^6$/L) CD4 cell count and with low (<10 000 copies/mL), medium (10 000-99 999 copies/mL), and high (≥100 000 copies/mL) viral load. The curves were compared using the log-rank test. We fitted Cox proportional hazards models including CD4 cell count and viral load (with categories as above), age at start of therapy, whether the regimen included saquinavir hard gel capsules as the only protease inhibitor or not (because such regimens have been found to be less virologically potent than other triple-drug regimens[9,13,15]), whether the initial antiretroviral regimen contained 3 or 4 or more drugs, sex, exposure category, and calendar year. These models estimate the relative hazard (RH) of viral load of less than 500 copies/mL by week 32. Since the majority of patients achieve this viral load level, the RH primarily reflects the speed with which this occurs—a lower RH indicating a longer time to suppression.

Second, we considered only those patients for whom there was at least 1 viral load measure available between weeks 24 and 40 and classified them according to whether the viral load measured closest to week 32 was below 500 copies/mL (ie, a binary response). We refer to this as the viral load at week 32. Here we fitted a logistic model to assess the factors associated with response.

The third measure of virological response—restricted to those patients who achieved a viral load of less than 500 copies/mL by 32 weeks—was the time from viral load first declining below 500 copies/mL to the time of

the first of 2 consecutive values above this level (ie, the time to viral load rebound). In those without rebound, the follow-up time was right-censored at the time of the last viral load measurement.

Table 1. Characteristics and Clinical Events, by Baseline CD4 Cell Count*

Variable	Baseline CD4 Cell Count, $\times 10^6$/L		
	<200 (n = 1666)	200-349 (n = 926)	≥350 (n = 838)
Women	421 (25)	238 (26)	202 (24)
HIV exposure			
Male who has had sex with another male	633 (38)	385 (42)	376 (45)
Injection drug use	408 (25)	206 (22)	172 (21)
Heterosexual	511 (31)	294 (32)	251 (30)
Other	114 (7)	41 (4)	39 (5)
HAART use began			
Median age, y	37	35	34
Median calendar year	1997	1997	1997
Previous AIDS	591 (36)	78 (8)	35 (4)
Baseline viral load, copies/mL			
<10 000	148 (9)	151 (16)	169 (20)
10000-99 999	470 (28)	418 (45)	386 (46)
>100 000	1048 (63)	357 (39)	283 (34)
Median (interquartile range)	5.2 (4.7-5.7)	4.8 (4.3-5.3)	4.6 (4.1-5.2)
Median (interquartile range) CD4 cell count, $\times 10^6$/L	78 (29-136)	274 (233-309)	467 (400-570)
Drugs in regimen			
≥4 Drugs	200 (12)	62 (7)	67 (8)
Saquinavir hard gel capsules (only protease inhibitor)	78 (5)	37 (4)	30 (4)
Zidovudine	979 (59)	546 (59)	525 (63)
Stavudine	655 (39)	346 (37)	279 (33)
Didanosine	280 (17)	178 (19)	158 (19)
Lamivudine	1341 (80)	740 (80)	689 (82)
Abacavir	88 (5)	58 (6)	46 (5)
Saquinavir hard gel capsules	193 (12)	80 (9)	53 (6)
Indinavir	598 (36)	301 (33)	296 (35)
Ritonavir	345 (21)	121 (13)	123 (15)
Nelfinavir	492 (30)	271 (29)	231 (28)
Nevirapine	99 (6)	82 (9)	86 (10)
Efavirenz	121 (7)	85 (9)	61 (7)
>1 Viral load available during follow-up	1574 (94)	864 (93)	788 (94)
Median (interquartile range) follow-up, wk	117 (57-169)	123 (63-161)	119 (69-161)
Viral load available between weeks 24 and 40	1296 (78)	695 (75)	646 (77)
Deaths during follow-up			
No./person-years of follow-up	104/3586	20/1982	13/1819
Rate (per 100 person-years)	2.9	1.0	0.7
P value for difference with baseline CD4 cell count ≥350 $\times 10^6$/L	<.001	.33	Referent
No. with CD4 cell count†	64	5	8
Percentage occurring at CD4 cell count >200 $\times 10^6$/L	12	100	62
AIDS diseases or death during follow-up			
No./person-years of follow-up	267/3217	44/1950	32/1785
Rate (per 100 person-years)	8.3	2.3	1.8
P value for difference with baseline CD4 cell count ≥350 $\times 10^6$/L	<.001	.32	Referent
No. with CD4 cell count†	237	29	23
Percentage occurring at CD4 cell count >200 $\times 10^6$/L	11	83	74

*Values are presented as number (percentage) unless otherwise indicated. HIV indicates human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; and HAART, highly active antiretroviral therapy.
†Closest CD4 cell count within 3 months before or after first new AIDS disease or before death.

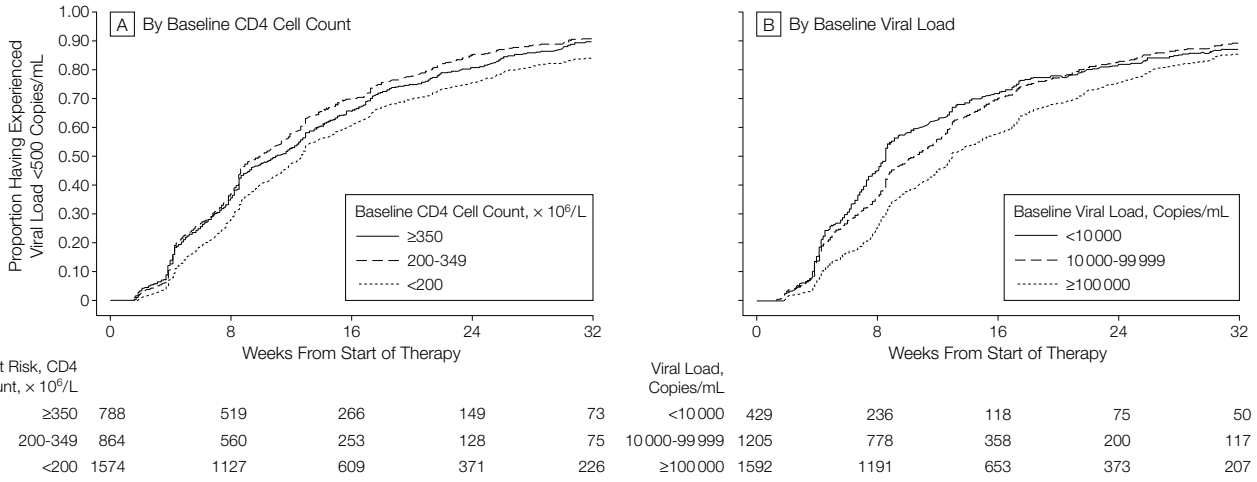
We also used a combined time to virological failure end point. Failure was defined as failure to reach a viral load of less than 500 copies/mL by 32 weeks (in which case the time to failure was 32 weeks or, if the time of last viral load was before week 32, the failure time was right-censored at this time) or, in those in whom such a low viral load was achieved, time to rebound above 500 copies/mL (in which case the time to failure was the time from start of therapy to the date of rebound).

Cox models were also fitted for these latter 2 end points. These were stratified by clinic and hence by cohort also. For the proportional hazard models for the time to suppression and time to rebound, there was no evidence of nonproportionality of hazards for the CD4 cell count or viral load groups, except between the baseline viral load greater than 100 000 copies/mL and less than 10 000 copies/mL for the time to suppression. For all the main analyses, we used an intent-to-treat type approach so changes in ART were ignored, but we also performed an analysis restricted to those with no change in therapy up to week 40. The analysis cutoff dates were October 2000 for the FHCC and December 2000 for the SHCS and EuroSIDA. Statistical software was used to perform data analyses (SAS Version 6.12, SAS Institute Inc, Cary, NC).

RESULTS

Of the 3430 patients, 807 were from EuroSIDA, 813 from the FHCC, and 1810 from the SHCS. Details according to CD4 cell count categories are given in TABLE 1. There was a greater tendency for prior AIDS diagnosis and a higher average viral load in those with lower CD4 cell counts. Our viral load response analysis included the 3226 patients with at least 1 viral load value available during follow-up. Overall, there was a median of 3 and mean of 3.4 viral load measures between baseline and week 32 (SHCS, median 3 and mean 2.7; FHCC, median 6 and mean 5.6; EuroSIDA, median 2 and mean 2.3) and this did not differ between the baseline CD4 cell

Figure 1. Proportion of Patients Who Achieved a Viral Load of Less Than 500 Copies/mL



No. at Risk, CD4 Cell Count, × 10^6/L

≥350	788	519	266	149	73
200-349	864	560	253	128	75
<200	1574	1127	609	371	226

Viral Load, Copies/mL

<10 000	429	236	118	75	50
10 000-99 999	1205	778	358	200	117
≥100 000	1592	1191	653	373	207

count groups (<200 × 10^6/L, median 3 and mean 3.4; 200-349 × 10^6/L, median 3 and mean 3.4; ≥350 × 10^6/L, median 3 and mean 3.2). Ninety-two of the 3226 patients were lost to follow-up in the first 32 weeks (defined as not seen for 1 year before the analysis cutoff). There was a median of 119 weeks of follow-up from start of therapy, with 10% followed up for more than 189 weeks. Overall, viral load was measured with a median interval of 11 weeks.

Of the 3226 patients, 2741 (85%) experienced a viral load of less than 500 copies/mL by 32 weeks. FIGURE 1A shows Kaplan-Meier estimates of the percentage achieving such viral suppression, according to baseline CD4 cell count. Those with low baseline CD4 cell counts (<200 × 10^6/L) showed a slightly lesser tendency to achieve viral suppression, but there was no apparent difference between the 2 higher CD4 cell count categories (global log-rank test, P<.001). TABLE 2 shows results from the corresponding Cox model, before and after adjustment. After adjustment, the observed lower RH for those with low baseline CD4 cell counts was not significantly less than 1.

We next considered those 2637 patients with a viral load available at week 32 (ie, between weeks 24-40). The proportions below 500 copies/mL were 78% (1014/1296), 86% (596/695), and 83% (536/646) for those with low–, medium–, and high–baseline CD4 cell counts, respectively. Table 2 shows the odds ratios (ORs) of achieving such suppression, before and after adjustment. After adjustment, there were no significant differences across the groups. When we used smaller ranges for CD4 cell count categories, the proportions with viral loads less than 500 copies/mL at 32 weeks were 86%, 80%, 84%, 86%, 78%, and 78% for baseline CD4 cell counts greater than 500, or of between 400 and 499, 300 and 399, 200 and 299, 100 and 199, and less than 100 × 10^6/L, respectively.

Figure 1B shows Kaplan-Meier estimates of the percentage achieving a viral load of less than 500 copies/mL from start of therapy, according to baseline

Table 2. Viral Load and Rebound According to Baseline CD4 Cell Count and Viral Load*

	CD4 Cell Count, × 10^6/L			Viral Load, copies/mL		
	≥350	200-349	<200	<10 000	10 000-99 999	≥100 000
Relative Hazard of Viral Load <500 copies/mL by 32 wk (2741/3226)						
Univariate	1.00	1.06 (0.95-1.17)	0.80 (0.73-0.88)	1.00	0.95 (0.84-1.07)	0.62 (0.55-0.70)
P value		.32	<.001		.39	<.001
Adjusted	1.00	1.08 (0.98-1.21)	0.94 (0.84-1.04)	1.00	0.95 (0.84-1.07)	0.65 (0.58-0.74)
P value		.14	.20		.40	<.001
Odds Ratio of Viral Load <500 copies/mL at 32 wk (2146/2637)†						
Univariate	1.00	1.24 (0.92-1.66)	0.74 (0.58-0.94)	1.00	1.46 (1.07-1.99)	1.10 (0.82-1.47)
P value		.16	.01		.02	.53
Adjusted	1.00	1.32 (0.97-1.79)	0.81 (0.62-1.07)	1.00	1.45 (1.05-2.01)	1.21 (0.89-1.67)
P value		.08	.14		.02	.22
Relative Hazard of Viral Rebound to >500 copies/mL in Those With Initial Suppression Below This Level (649/2741)						
Univariate	1.00	1.02 (0.69-1.06)	0.96 (0.78-1.19)	1.00	1.00 (0.77-1.30)	1.10 (0.85-1.41)
P value		.81	.20		>.99	.48
Adjusted	1.00	0.86 (0.69-1.06)	0.96 (0.78-1.19)	1.00	1.02 (0.79-1.33)	1.12 (0.86-1.45)
P value		.16	.73		.87	.40

*Values are expressed as odds ratio or relative hazard (95% confidence interval) unless otherwise indicated. Adjusted for viral load and CD4 cell count as well as age, sex, exposure category, whether taking 3 drugs or 4 or more drugs, previous acquired immunodeficiency syndrome, use of saquinavir hard gel capsules, and stratified for cohort (logistic model) or clinic (Cox model: 60 in EuroSIDA, 7 in Swiss HIV Cohort Study, and 1 in Frankfurt HIV Clinic Cohort).
†Between weeks 24 and 40.

viral load. At 16 weeks, those with a high–baseline viral load (≥100 000 copies/mL) experienced a lower probability of suppression to less than 500 copies/mL than those with low viral load (<10 000 copies/mL). However, after this period the curves begin to close, reflecting a higher probability of suppression in the former group, such that the overall percentage with suppression to less than 500 copies/mL by 32 weeks is similar in the 2 groups (global log-rank test, $P<.001$). In the Cox model (Table 2), there is a lower RH of viral suppression in the high–viral load group (RH, 0.65; 95% confidence interval [CI], 0.58-0.74) compared with the group with low–baseline viral load. As described above, this RH is an overall value based on the entire 32 weeks. When broken down into the first 16 weeks and weeks 16 through 32, the RHs were 0.50 and 1.52, respectively.

Considering the patients with viral load levels available at week 32, the proportions below 500 copies/mL were 79% (263/335), 84% (815/968), and 80% (1068/1334), for those with low–, medium–, and high–baseline viral load, respectively. The adjusted ORs of achieving viral loads of less than 500 copies/mL at 32 weeks are shown in Table 2. Using a finer classification of baseline viral load, the proportions with viral load less than 500 copies/mL at 32 weeks were 79%, 85%, 84%, 81%, 79%, and 80% for viral loads of less than 10 000, 10 000 to 29 999, 30 000 to 99 999, 100 000 to 299 999, 300 000 to 749 000, and 750 000 copies/mL or higher, respectively.

We repeated the above analyses after excluding those with a previous AIDS diagnosis at the time of starting therapy. The findings were similar. The adjusted ORs of achieving a viral load of less than 500 copies/mL at week 32 were 1.35 (95% CI, 0.98-1.85) and 0.80 (95% CI, 0.60-1.07) for those with medium– and low–baseline CD4 cell count, respectively, compared with those with high–baseline CD4 cell count; and 1.39 (95% CI, 0.98-1.99) and 1.20 (95% CI, 0.84-1.72) for those with medium– and high–baseline viral load, respectively, compared with those with low–baseline viral load. Similarly, the association between baseline CD4 cell count and viral load response and baseline viral load and viral load response did not differ significantly by sex.

Changes to the initial regimen were made during the first 40 weeks in 1329 (41%) patients. For the low–, medium–, and high–baseline CD4 cell count groups, the proportions were 43%, 38%, and 40%, respectively (χ^2 $P=.04$), while for the low–, medium–, and high–baseline viral load categories, the proportions were 41%, 38%, and 44%, respectively (χ^2 $P=.005$). When we restricted the analysis to patients who did not change therapy within the first 40 weeks (and who had a viral load value between weeks 24 and 40), the proportions below 500 copies/mL at 32 weeks were 91%, 91%, and 85% for high–, medium–, and low–baseline CD4 cell count, respectively, and 88%, 90%, and 87% for low–, medium–, and high–baseline viral load, respectively. For 14% of patients, the first change in therapy within the first 40 weeks involved stopping all drugs, typically for a few days or weeks but sometimes for longer. This was the case for 13%, 14%, and 16% of those in the low–, medium–, and high–baseline CD4 cell count groups, respectively, and 15%, 14%, and 14% of those in the low–, medium–, and high–baseline viral load groups, respectively. Sixty-six percent of those stopping therapy achieved viral loads below 500 copies/mL by 32 weeks, either before or after stopping.

In the 609 patients who had viral load results using the ultrasensitive Amplicor HIV-1 monitor assay, the proportions with viral loads below 50 copies/mL at week 32 were 74%, 75%, and 62%, with adjusted ORs of 1.00, 1.13 (95% CI, 0.65-1.97), and 0.81 (95% CI, 0.48-1.37) for high–, medium–, and low–baseline CD4 cell count, respectively. For viral load, the proportions were 71%, 74%, and 62%, with adjusted ORs of 1.00, 1.24 (95% CI, 0.69-2.23), and 0.66 (95% CI, 0.37-1.20) for low–, medium–, and high–baseline viral load, respectively.

Of the 2741 patients with initial suppression below 500 copies/mL by 32 weeks, confirmed viral rebound to above 500 copies/mL was observed in 649 patients, during a median 81 weeks follow-up after the initial value of less than 500 copies/mL. FIGURE 2 indicates that there was little difference in rebound rate according to baseline CD4 cell count. This also is reflected in Table 2, where the RHs indicate no significant difference according to baseline CD4 cell count. There were also no differences according to baseline viral load.

When we assessed the effect of baseline CD4 cell count on time to virological failure (1023 failures out of 3226 patients), the adjusted RHs were 1.00, 0.88 (95% CI, 0.73-1.05), and 1.09 (95% CI, 0.92-1.29) for high–, medium–, and low–baseline CD4 cell count, respectively, and 1.00, 0.95 (95% CI, 0.78-1.17), and 1.06 (95% CI, 0.86-1.30) for low–, medium–, and high–baseline viral load, respectively.

Table 1 also shows the rate of death and disease progression (development of a new AIDS disease or death). For both end points, the rates are significantly higher in those with a low–baseline CD4 cell count compared with those with a high–baseline CD4 cell count ($P<.001$). While there is a tendency for slightly higher rates in those with medium– vs high–baseline CD4 cell counts, this was not statistically significant for the end points of disease progression ($P=.32$) or death alone ($P=.33$). For those with low–baseline CD4 cell count, a large proportion of the clinical events that occurred during follow-up were during the time the CD4 cell count remained below 200×10^6/L. On the other hand, for those with higher baseline CD4 cell counts, the majority of events occurred at CD4 cell counts above 200×10^6/L.

COMMENT

When initiating ART, sustained virological suppression is the goal because it leads to CD4 cell count increases,[7,17] and hence markedly reduced risk of

clinical events,[8,9,18] and reduces the risk of developing resistance. There is consensus that therapy should be initiated before the CD4 cell count has declined below 200×10^6/L, but views differ widely on how close to this value the CD4 cell count should be permitted to decrease. In this analysis, we found no evidence to suggest that viral load responses were worse in those with CD4 cell counts between 200 and 349×10^6/L compared with those with counts of 350×10^6/L or greater, in either the short-term or the long-term. Considering the baseline viral load, we found no evidence that those with viral loads between 10 000 and 100 000 copies/mL experienced a worse response than those with lower baseline levels. Those with viral loads greater than 100 000 copies/mL at baseline tended to experience a significantly slower rate of initially achieving a viral load of less than 500 copies/mL. Although, this greater duration of time with high–viral load levels in the presence of ART theoretically could lead to a greater risk of evolution of drug resistance, there was a similar OR of achieving less than 500 copies/mL at 32 weeks (1.21; 95% CI, 0.89-1.67; P=.22) and a similar rate of subsequent viral rebound above 500 copies/mL between the groups with 100 000 copies/mL or greater and less than 10 000 copies/mL (OR, 1.12; 95% CI, 0.86-1.45; P=.40). Around 40% of the patients in our analysis experienced some change in their ART during the first 40 weeks, but this differed only slightly by baseline CD4 cell count and viral load group. It previously has been shown that most early changes are due to toxicity.[19,20] When we restricted our analysis to those with no change in therapy, the results were consistent with our overall findings.

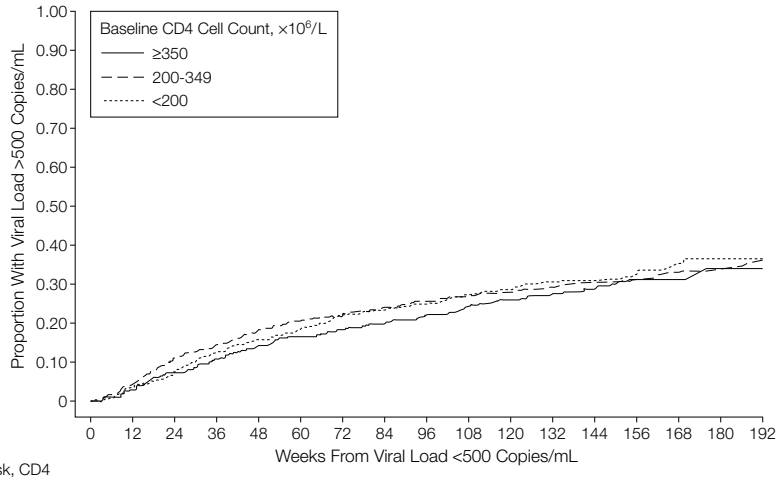
The association of virological response with both the baseline CD4 cell count and baseline viral load frequently has been assessed in patients starting triple- or quadruple-drug therapy for the first time.[9,15,21-35] Our results make a distinct new contribution because few previous trials or cohorts have studied the relationship in analyses restricted to previously drug-naive patients (in whom the relationship between baseline CD4 cell count and/or viral load and viral load response would be expected to be different than that in patients treated with mono- or dual-nucleoside reverse transcriptase inhibitor therapy before starting a triple- or quadruple-drug regimen),[22-26] few have followed patients for more than 2 years, have determined the shape of this relationship, or have studied such a large cohort. A recent report from Cozzi Lepri et al,[35] which was based on a large Italian cohort of patients starting ART, found results broadly consistent with our own.

The findings are of key practical relevance. They do not indicate, for example, that the virological response to therapy will be compromised in a patient with a CD4 cell count of 340×10^6/L and a viral load of 40 000 copies/mL—a person in whom guidelines would suggest treatment should be started[11]—if therapy initiation is delayed until the CD4 cell count has decreased to 220×10^6/L. However, there are other issues that a clinician and patient would wish to take into account when deciding on initiation of therapy, so these results should not be considered in isolation. These issues include the possibly lower potential for complete immune recovery if therapy is started at a lower CD4 cell count[35] and the factors, such as younger age, which appear to be associated with a more rapid CD4 cell count increase.[36]

Individuals who started therapy at lower CD4 cell counts are more likely to have presented later for care and perhaps are reluctant to start therapy or may be perceived by their clinician to be less likely to be able to adhere to therapy.[37] Greater problems with toxicity or due to concomitant HIV-related symptoms might also be expected to lead to less complete adherence. However, despite these concerns, we found little evidence that even those with a baseline CD4 cell count of less than 200×10^6/L experienced an inferior virological response.

One of the limitations of our analysis was that different viral load assays were used within the EuroSIDA clinics. However, Cox models were stratified by clinic and results were consistent in analyses restricted to the SHCS

Figure 2. Proportion of Patients With Viral Rebound Greater Than 500 Copies/mL on 2 Consecutive Occasions, According to Baseline CD4 Cell Count



No. at Risk, CD4 Cell Count, ×10⁶/L					
≥350	692	485	319	143	10
200-349	767	521	344	157	18
<200	1282	791	527	300	59

Results are from patients who initially achieved such a level of viral suppression by 32 weeks.

and FHCC cohorts alone (data available from corresponding author on request), for which only the Amplicor HIV-1 monitor assay was used. Another drawback is that our threshold for viral load suppression was 500 copies/mL for most analyses. In current clinical practice, a viral load less than 50 copies/mL is the aim, but assays measuring down to such low levels were not consistently available in our cohorts during the period covered by these analyses. Our results indicate that even if there were differences (according to baseline CD4 cell count and viral load) among those achieving less than 500 copies/mL in the proportion achieving less than 50 copies/mL, these do not translate into differences in the subsequent rate of rebound greater than 500 copies/mL because we found no differences in rebound rate according to baseline CD4 cell count or viral load. In analyses restricted to clinics and periods in which assays with a lower limit of 50 copies/mL were available, our findings regarding the probability of reaching less than 50 copies/mL by 32 weeks were similar. There was a lower OR of achieving viral load of less than 50 copies/mL at 32 weeks in the group with high–baseline viral load than in the main analysis (although this result was not statistically significant). This could indicate that 32 weeks is insufficient time for this level to be achieved and a measurement to be made.

While individual values vary over time due to laboratory and biological variability, there is only a slight underlying trend for increasing viral load over time in untreated patients.[1-4] The question of timing of therapy for an individual patient thus largely depends on the degree of CD4 cell count depletion one is willing to tolerate, with the knowledge that the rate of such depletion tends to be greater in those with higher viral load levels.[38,39] Nonetheless, viral load can show a marked increase over time in some patients, and our results suggest that if viral load is allowed to increase from less than 100 000 copies/mL to above this level before therapy is initiated there may be a slower initial response to therapy, and (based on our subanalysis) a decreased probability of viral load decreasing to a level below 50 copies/mL at 32 weeks. However, we found no evidence that a response, once achieved, was less durable. It would be useful in future studies to assess the association between CD4 cell count and viral load changes before therapy and the viral load response.

We also considered incidence of new AIDS diseases and death during follow-up according to baseline CD4 cell count and viral load. This showed a tendency for higher event rates with lower baseline CD4 cell count category, although the difference between rates in the 2 higher CD4 cell count categories was not statistically significant. Interpretation of such results is not straightforward because of lead-time bias. Clinical event rates by baseline CD4 cell count mainly reflect the status of the patient before starting therapy, not the effect of therapy (unlike the viral load end point, in which changes to below 500 or 50 copies/mL can be almost entirely attributed to the effect of therapy). Because of lead-time bias, the higher event rate in the group with CD4 cell counts between 200 and 350×10^6/L than in the group with CD4 cell counts greater than 350×10^6/L does not mean that therapy has less effect in the lower CD4 cell count group, nor that therapy should necessarily be initiated at CD4 cell counts above 350×10^6/L. The low event rates experienced indicate that a randomized trial of immediate vs deferred therapy would likely have to be very large and last several years.

In conclusion, in our study, there was no strong evidence that lower CD4 cell counts and higher viral loads at baseline are associated with poorer virological outcome of ART. Nevertheless, there is a slower rate of achieving viral suppression in those with a baseline viral load greater than 100 000 copies/mL. The decision of when to initiate therapy is complicated, and many factors must be taken into account. We have provided information concerning only 1 issue, albeit an important one. Until firm evidence from randomized trials is available, it is pieces of evidence such as this study that clinicians and patients must refer to when deciding on when to initiate therapy.

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