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Virologic, Immunologic, and Clinical Response to Highly Active Antiretroviral Therapy: the Gender Issue Revisited

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Background: Highly active antiretroviral therapy (HAART) has dramatically improved the prognosis for patients with HIV. There is ongoing debate over a potential gender effect on patient outcome after HAART.

Methods: Individuals were from the EuroSIDA cohort, naive to protease inhibitors and nonnucleoside reverse transcriptase inhibitors, and had at least one viral load and CD4 measurement prior to starting HAART. Endpoints were virologic (time to <500 copies/mL, time to rebound [first of two consecutive viral loads >500 copies/mL]), immunologic (time to a 100/mm cell rise in CD4 count) and clinical (time to new AIDS and death).

Hazard ratios (HR), derived using Cox regression models, compared female to male rates of achieving endpoints.

Results: Of 2547 patients, 20% (511) were female. Significantly more females than males were nonwhite (24% vs. 10%, $p < .001$). Males were older (median age 39 vs. 35 years, $p < .0001$), had lower CD4 counts (211 vs. 240/mm, $p = .03$), higher viral loads (4.6 vs. 4.4 log copies/mL, $p < .0001$), were more likely to have a history of AIDS (26% vs. 18%, $p < .001$) and were more likely to be treatment-naive (34% vs. 29%, $p = .03$). Adjusted HR for association between gender (comparing females with males) and the outcomes studied were as follows: for reaching <500 copies/mL 0.91 (0.81–1.03, $p = .17$), rebound 1.17 (0.95–1.44, $p = .15$), for 100 cell CD4 count rise 1.02 (0.88–1.14, $p = .99$), for progression to new AIDS 1.12 (0.73–1.71, $p = .59$) and for time to death 1.15 (0.69–1.92, $p = .57$).

Conclusions: We found no significant evidence of a gender difference in virologic, immunologic, or clinical outcomes after starting HAART.

Key Words: Gender—HAART—Viral load—CD4 count—Clinical progression.

The widespread use of highly active antiretroviral therapy (HAART) has changed the face of the HIV epidemic in developed countries (1–3). Individuals with the disease are now able to realistically expect enhanced quality and duration of life in a way that would have been previously unimaginable. As the epidemic progresses,

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the demographic characteristics of those newly infected with HIV are altering, and the proportion of incident and prevalent cases that are in women increasing (4). Twenty percent of HIV-infected individuals in North America and Europe are female (5). It is important to ensure equal access to HAART and to understand whether there are any gender differences in response to treatment in order that HIV therapy can be used optimally. In the past, the majority of those infected were homosexual males and it was this group on whom clinical trials were based. As a consequence it has largely been the place of observational studies to assess the effect of treatment on women and to assess a possible gender effect (6). In the era of HAART (when clinical events [progression to new AIDS and death] are few) study endpoints in clinical trials are more usually based on surrogate marker responses to treatment and observational studies, which tend to be larger and have longer follow-up, now have an increasingly important role in assessing clinical response to therapy.

For some years there has been debate over a potential gender effect on the natural history of HIV and patient outcome after starting antiretroviral therapy. However, although in the majority of cases gender has not been found to be statistically significantly associated with outcome, in the pre-HAART era some studies suggested possible advantages for male patients (7–10), though others suggested that women might do better (11–14). In general it was felt that where females were found to progress at a faster rate than males, any inequality lay in access to care rather than in a fundamental biologic difference in response to (albeit suboptimal) treatment and that once this difference was accounted for, any discrepancy disappeared (15,16).

The surrogate markers CD4 count and viral load are both factors known to be strongly associated with clinical progression of HIV (17–20). In this study comparing males and females we examine virologic and immunologic response to HAART and clinical progression after HAART.

METHODS

Patients

The EuroSIDA study is a prospective, European study of HIV infected patients in 63 centers across Europe (including Israel; see Appendix). From May 2, 1994 centers provided data on consecutive patients seen in the outpatient clinic until a predefined number of patients was enrolled from each center. The original cohort of 3118 patients was defined as the EuroSIDA I cohort. Enrollment of a second cohort of 1367 patients began in December 1995 (Eurosida II cohort), a third cohort of 2844 patients in April 1997 (EuroSIDA III cohort). A further cohort of 1227 patients was enrolled from March 1999 and forms the EuroSIDA IV cohort. Information from up to 13 follow-up visits is available from cohort I, up to 10 visits for cohort II, 7 visits for Cohort III, and 3 visits for Cohort IV; follow-up in this study is to Spring 2001. For Cohorts I–III, eligible patients were those with a CD4 lymphocyte count <500/mm, patients from Cohort IV had no restriction on their CD4 lymphocyte count at recruitment. Patients were aged older than 16 years at the time of enrollment. Information was collected from patient case notes onto a standardized data collection form at baseline and every 6 months thereafter. At each follow-up visit, details on all CD4 lymphocyte counts measured since last follow-up and viral load measurements, including the method used and the lower limit of detection, were collected. For each patient, the date of starting and stopping each antiretroviral drug was recorded, as was the use of drugs for prophylaxis against opportunistic infections. Dates of diagnosis of all AIDS-defining illnesses (ADIs) have also been recorded, using the 1993 clinical definition of AIDS from the Centers for Disease Control (21). Data on recurrence of diseases are collected for some diagnoses, but these data have not been included in the present analysis. Cause of death is collected wherever possible for patients who have died.

Information used in this analysis included demographic (date of birth, ethnic origin, gender, country of origin, risk group, height) and clinical factors (weight, hemoglobin, CD4 count, viral load, start date of each antiretroviral therapy, use of drug prophylaxis, dates and type of ADIs).

The various centers in the EuroSIDA study take part in their own local or national quality control schemes. There is no single scheme for the whole of Europe. Viral load methods differ with the Roche polymerase chain reaction (PCR) method the predominant one used in 64% of centers, NASBA in 16%, and Chiron branched DNA approach in 19%. Viral load levels from other methods than Roche PCR performed in EuroSIDA were not adjusted in this analysis.

Inclusion Criteria

Patients were 1) previously naive to protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs) and starting a HAART regimen including at least 2 nucleoside reverse transcriptase inhibitors and at least one PI or NNRTI; 2) had at least 1 viral load measurement (the most recent of which was >500 copies/mL) and 1 CD4 measurement in the 6 months preceding the start of HAART; and 3) had at least 1 CD4 count and viral load during follow-up. The small number of eligible individuals in the Eastern geographic region (74) were excluded. Data available until April 2001 was included in this analysis.

Endpoints

Endpoints considered were as follows: 1) the time to achievement of undetectable viral load (defined here as <500 copies/mL); 2) the time to rebound after achieving this (2 consecutive measurements >500 copies/mL, the date of the first being taken as the date of virologic failure); 3) the time to achieving a 100 cell rise in CD4 count; 4) the time to progression to a first or new AIDS diagnosis; and 5) the time to death.

Statistical Analysis

Analysis was performed using Stata software (version 6.0). Baseline demographic and clinical characteristics of males and females in the cohort were compared using χ^2 and Wilcoxon rank sum tests. Gender

comparisons were also made using Kaplan-Meier curves and differences tested for statistical significance using the log-rank test. Cox regression analysis provided hazard ratios (HR) comparing females with males. All endpoints were examined from time of starting HAART until first evidence of outcome (e.g., first RNA <500, first new AIDS diagnosis) except for virologic rebound (described above), those not achieving the endpoint being censored at the last viral load or CD4 measurement (for virologic and immunologic outcomes respectively) or at the last recorded clinic visit (for clinical outcomes). HRs for the outcomes, comparing female with male rates, were derived using the Cox proportional hazards model in univariate and multivariate analyses after testing the proportional hazards assumption using the χ^2 test for proportionality. All multivariate models included adjustment for CD4 count and RNA level at the time of starting HAART, previous AIDS diagnosis, treatment history (i.e., naive vs. non-naive, number of pre-HAART nucleosides, time on nucleosides pre-HAART, HAART combination, number of new nucleosides at the time of starting HAART, and calendar date of starting HAART), age, risk group, race, hemoglobin level, and geographic region. The analysis was based on intention to treat (i.e., treatment changes or stoppages were not adjusted for in the analysis), and treatment alterations are described separately.

Duration of pre-HAART nucleoside exposure was treated as cumulative months on treatment. Hemoglobin levels were categorized as 'low' if <14.0g/dL in males and <12.5g/dL in females. HAART regimen was categorized as one of eight possibilities: ritonavir, indinavir, nelfinavir or saquinavir (hard- or soft-gel) with at least 2 nucleoside agents; boosted PI (with ritonavir) or double PI regimens with at least 2 nucleosides; and either efavirenz or nevirapine with at least 2 nucleosides. Changes in HAART regimen during follow-up were assessed and categorized according to the first change in regimen if one occurred. Thus patients either "stopped" (stopped one or all their antiretrovirals without starting new ones), "added" (one or more agents without stopping their originals) or "swapped" (stopped some or all of the originals and started new agents on the same date).

RESULTS

Patient Characteristics

Of the 8556 patients in the data set, 2547 (30%) were eligible for inclusion in this analysis (Table 1). Eighty percent (2036) of the patients were male. The majority of patients were white but significantly more of the females were nonwhite (128 [25.1%] females vs. 215 [10.6%] males, $p < .001$). Males were significantly older than females (median age 39 vs. 35 years, $p < .0001$). CD4 counts were lower in males than females at the time of starting of HAART (211 vs. 240/mm, $p = .03$), viral

TABLE 1. *Patient characteristics*

	Male (n = 2037)	Female (n = 511)	*p*
Age*	38.8 (34.0–46.2)	35.0 (31.1–40.7)	<.0001
White race	1821 (89.4)	383 (75.0)	<.001
Homosexual	1233 (60.6)	0 (0)	<.001
Injection drug user	380 (18.7)	153 (29.9)	
Heterosexual	297 (14.6)	304 (59.5)	
Other	126 (6.2)	54 (10.6)	
History of AIDS	530 (26.02)	90 (17.6)	<.001
CD4 ($\times 10^6$/L)*	211 (98–336)	240 (125–339)	.03
RNA (log copies/mL)*	4.6 (4.0–5.2)	4.4 (3.7–5.0)	<.0001
NRTIs pre-HAART			
0	696 (34.2)	148 (29.0)	<.001
1	82 (4.0)	37 (7.2)	
2	656 (32.2)	146 (28.6)	
≥3	602 (29.5)	180 (35.2)	
NRTI (months pre-HAART)*	46.0 (22.0–81.1)	55.0 (28.0–85.0)	.02
Indinavir-based HAART	845 (41.5)	212 (41.5)	.07
Ritonavir-based HAART	316 (15.5)	58 (11.4)	
Boosted/dual PI HAART	594 (29.1)	168 (32.9)	
Efavirenz-based HAART	78 (3.9)	13 (2.5)	
Nevirapine-based HAART	203 (10.0)	60 (11.7)	
New nucleosides			
0	572 (28.1)	163 (31.9)	.07
1	454 (22.3)	127 (24.9)	
2	996 (48.9)	219 (42.9)	
3	14 (0.7)	2 (0.4)	
First change to HAART during follow-up[a]			
No change	452 (22.2)	98 (19.2)	.01
Add agent	473 (22.2)	115 (22.5)	
Stop agent	471 (23.1)	141 (27.6)	
Swap agent	640 (31.4)	157 (30.7)	

[a] Stop, stopped one/all antiretrovirals; Add, added one/more antiretrovirals; Swap, stopped some/all & also added new antiretrovirals.

* Numbers = n(%), except where asterisk indicates median (interquartile range).

HAART, highly active antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

loads higher (4.6 vs. 4.4 log copies/mL, $p < .0001$), and a history of previous AIDS more likely (26% vs. 18%, $p < .001$). Among the males 1354 (66.5%) had normal hemoglobin measurements and among the females 354 (69.3%, $p = .23$). Males were more likely to be naive to antiretrovirals when starting HAART (34% vs. 29%, $p = .03$), the median number of nucleosides in treatment-experienced males and females was 2 (range 1–5). Twenty-seven percent of the males and 37% of the females came from southern Europe, 31% and 29% respectively from central Europe, the remainder coming from the west, $p < .001$.

Median HAART start date was in May 1997 in males (range October 1994–January 2001) and August 1997 in females (range May 1995–August 2000; $p < .001$). EuroSIDA dates are recorded to the nearest month.

First HAART regimens were PI-based in 1755 males and 438 females (86% of both genders) and NNRTI-based in 281 males and 73 females (14%). Only 452 (22%) males and 98 (19%) females remained on their original HAART regimen throughout the period of follow-up (Table 1). Overall, in those who did alter their therapy, females first changed their original regimen at an earlier stage of follow-up (median 10.0 months vs. 13.0 months [males], $p < .0001$). Among those whose original HAART was PI-based, similar proportions of males and females as the cohort as a whole first added (25.1% of males and 24.9% of females), stopped (23.7% of males and 25.6% of females) or swapped (32.7% in males and females), the remainder staying on their original regimen during the period of follow-up. Those males and females who did change their PI-based regimen first altered it at similar stages (11.3 months in females vs. 13.1 months in males, $p < .001$) to the cohort as a whole. In those whose HAART regimen was initially NNRTI-based (354 patients, 74% taking nevirapine), the percentage adding was 11.4% in males and 8.2% in females, stopping 19.2% and 39.7% respectively, whereas 23.8% of males and 19.2% of females swapped, the remainder remaining on the original combination throughout the period of study. The median number of months until a change was sooner than for those taking PIs and, again, earlier in females (3.2 months) than males (7.9 months, $p < .0001$).

TABLE 2. *Hazard ratios for virologic, immunologic, and clinical outcomes*

	All	Males	Females
HIV RNA <500 copies/mL			
Number (%) achieving success	2259 (89)	1810 (89)	449 (88)
Median months to success	4.01	4.01	4.96
Crude HR (95% CI, *p*)		0.93 (0.84–1.03, $p = .19$)	
Adjusted HR (95% CI, *p*)		0.91 (0.81–1.03, $p = .17$)	
Rebound after <500 copies/mL			
Number (%) rebounding	708 (33)	538 (31)	170 (40)
% rebounded at 6 months	18	17	21
Crude HR (95% CI, *p*)		1.40 (1.18–1.67, $p < .001$)	
Adjusted HR (95% CI, *p*)		1.17 (0.95–1.44, $p = .15$)	
100 cell rise in CD4 count			
Number (%) achieving success	2113	1702 (84)	411 (80)
Median months to success	9.01	9.07	9.00
Crude HR (95% CI, *p*)		0.96 (0.86–1.70, $p = .47$)	
Adjusted HR (95% CI, *p*)		1.02 (0.88–1.14, $p = .99$)	
Development of new AIDS			
Number (%) developing new AIDS	201 (9.8)	164 (8)	37 (7)
% with new AIDS at 12 months	4.5	4.7	3.6
Crude HR (95% CI, *p*)		0.93 (0.65–1.33, $p = .59$)	
Adjusted HR (95% CI, *p*)		1.12 (0.73–1.71, $p = .59$)	
Death			
Number (%) dying	133 (%)	109 (5)	24 (5)
% dead at 12 months	1.5	0.8	1.7
Crude HR (95% CI, *p*)		0.94 (0.60–1.46, $p = .79$)	
Adjusted HR (95% CI, *p*)		1.15 (0.69–1.92, $p = .57$)	

All multivariate models include adjustment for CD4 and RNA at the time of starting HAART, previous AIDS diagnosis, treatment history (i.e., naive vs. non-naive, number of pre-HAART nucleosides, time on nucleosides pre-HAART, HAART combination, number of new nucleosides at the time of starting HAART and calendar date of starting HAART), age, risk group, race, hemoglobin level, and geographic region.

HAART, highly active antiretroviral therapy; HR, hazard ratio.

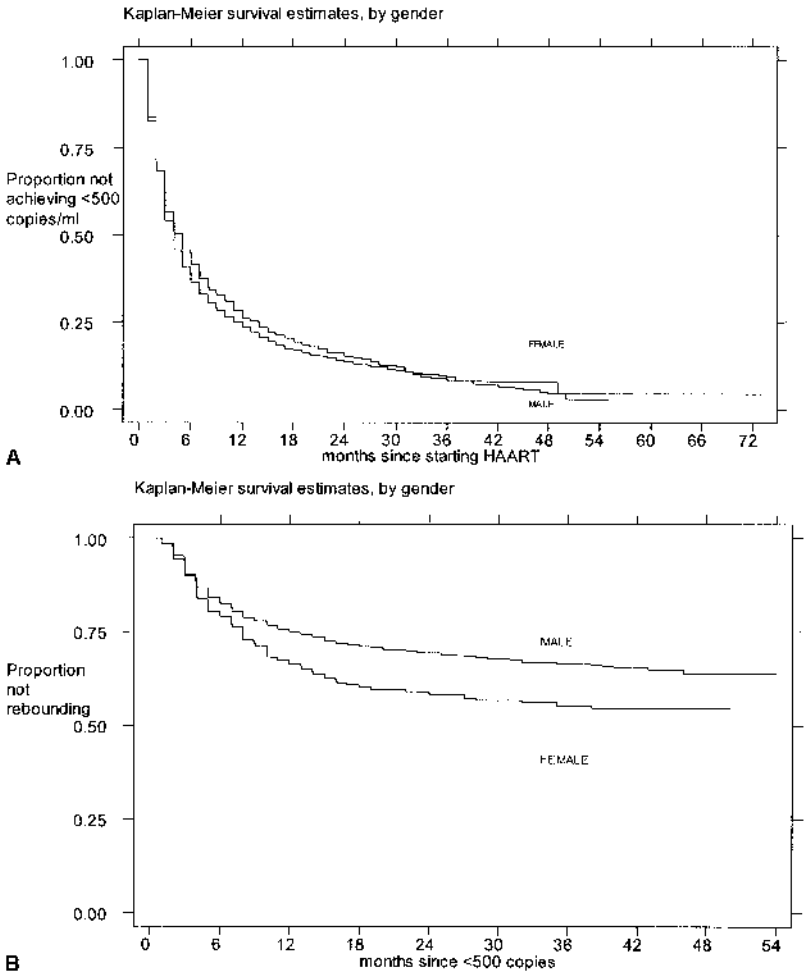

FIG. 1. Kaplan-Meier graph showing time to virologic outcomes. **(A)** achievement of <500 copies; **(B)** rebound after <500 copies.

Virologic Outcomes

Achievement of <500 copies/mL

Two thousand and fifty-nine (89%) males and 1810 (88%) females achieved a viral load <500 copies/mL on their first HAART regimen during a total of 1877 person-years of follow-up (last follow-up date being the first viral load <500 copies/mL or the last viral load measurement if this was not achieved) (Table 2, Fig. 1). Median time to reaching <500 copies/mL was 4.0 months in males and 5.0 months in females. By 1 year 76.1% (Kaplan-Meier) of all patients (76.6% of males and 73.9% of females) had reached this level or below (Fig. 1). Rates were similar in males and females, crude HR 0.93 (95% CI 0.84–1.03, $p = .19$—comparing females with males). Factors independently associated with an increased hazard of becoming undetectable were higher baseline CD4 count and later HAART start date, while a previous history of AIDS and a higher baseline viral load were associated with a lower hazard. In the multivariate analysis, the HR showed females having a nonsignificant 9% lower probability of achieving <500 copies/mL, HR 0.91 (95% CI 0.81–1.03, $p = .17$).

Virologic Rebound

Ninety-six percent of those achieving undetectable viral load had further follow-up and of these, 708 patients (33%) experienced virologic rebound (31% of the males and 40% of the females, [Table 2, Fig. 1]). Within 6 months, 17% of males and 21% females had rebounded, and after 2 years 31% and 42%, respectively. Univariate analysis suggested an increased hazard of rebound in females, crude HR 1.40 (95% CI 1.18–1.67, $p = .15$). Factors independently associated with rebound were higher baseline CD4 count, being treatment-naïve, and greater age (lesser probability), and greater number of pre-HAART nucleosides (greater probability). The ad-

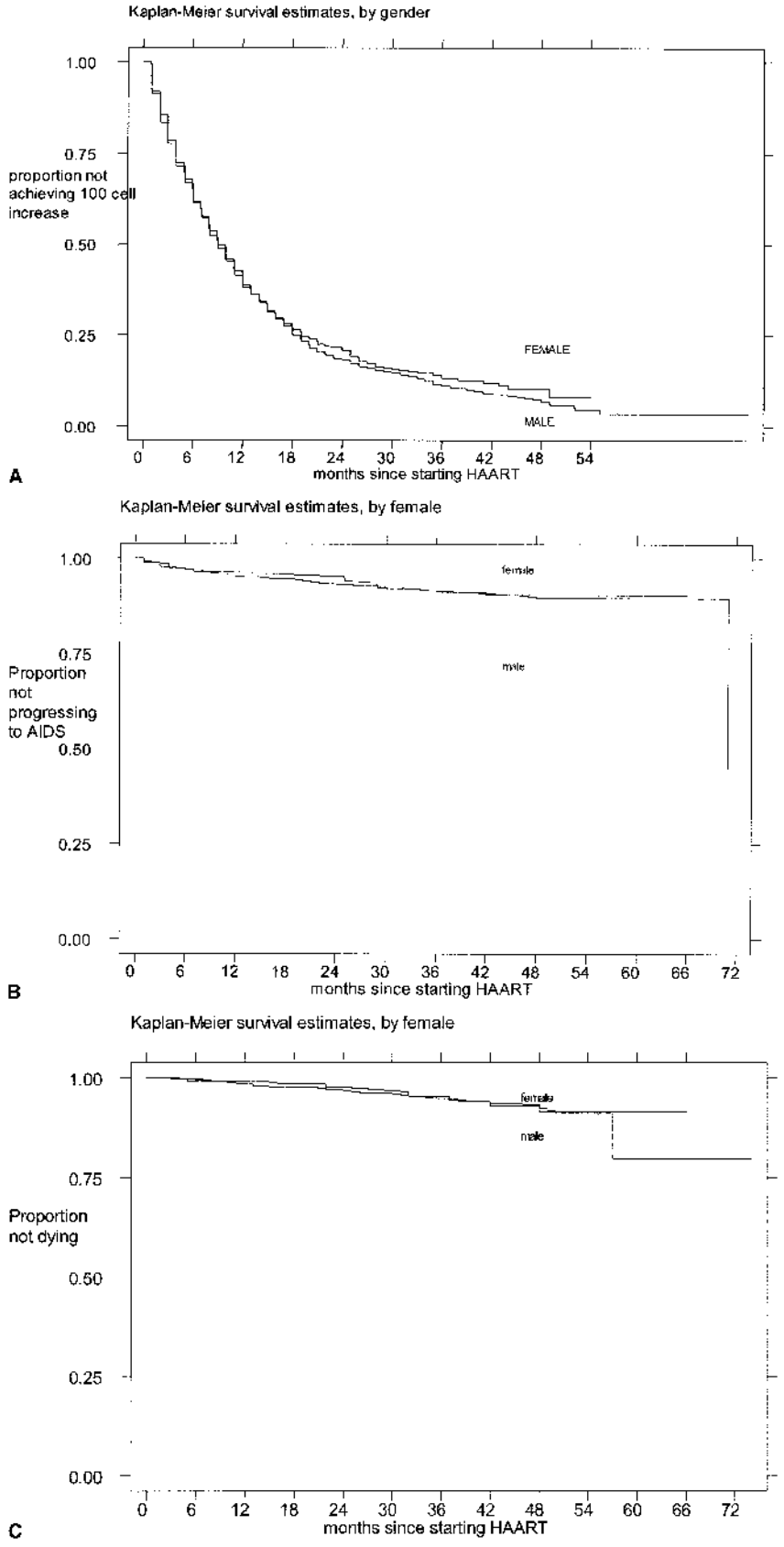

FIG. 2. Kaplan-Meier graph showing time to immunologic and clinical outcomes. **(A)** achievement of 100 cell/mm rise in CD4 count; **(B)** clinical progression to new AIDS; **(C)** time until death.

justed HR was 1.17 (95% CI 0.95–1.44, $p = .15$), showing a nonsignificant 17% increased probability of virologic failure in women.

Immunologic Response

Median time to improvement in CD4 count by at least 100×10^6 cells/L was 9 months after starting treatment of both males and females (Table 2, Fig. 2). Overall, females appeared to achieve this at the same rate as males, crude HR 0.96 (95% CI 0.86–1.07, $p = .47$) and adjusted 0.99 (95% CI 0.88–1.14, $p = .99$). Factors independently associated with increased hazard of achieving a 100 cell/mm CD4 rise were higher baseline RNA and later HAART start date, higher baseline CD4 count was associated with a lesser probability of a rise.

For those with CD4 counts recorded within the 6 months preceding a new AIDS diagnosis or death, females (n = 34) had higher CD4 counts than males (n = 145), but not significantly so (103 vs. 100×10^6/L $p = .09$) and at death females (n = 7) had lower counts than males (n = 41) (18 vs. 68, $p = .13$).

Clinical Outcomes

AIDS

During a total of 6872 person-years of follow-up there were 201 AIDS diagnoses. Thirty-seven (7.2%) of the females and 164 (8.1%) of the males were affected (Table 2, Fig. 2), and 1 year after starting HAART 4.7% of the males and 3.6% of the females had developed a new ADIs. Univariate analysis suggested a similar rate of progression to first /new AIDS diagnosis in males and females, crude HR 0.93 (95% CI 0.65–1.33, $p = .59$) though adjustment reversed the HR leading to the suggestion of a slightly increased hazard for females to progress to new ADI compared with males, HR 1.12 (95% CI 0.73–1.71, $p = .59$). Pre-HAART AIDS diagnosis and higher baseline RNA were associated with increased probability of developing a new ADI and higher CD4 count with a lesser probability of new ADI. Repeating the analysis excluding Kaposi sarcoma (KS) (20 cases) and replacing these cases with a subsequent diagnosis if one existed did not alter the adjusted HR.

Death

During 7203 person-years of follow-up 133 patients died, 24 (4.7%) females and 109 (5.4%) males. Nine (37.5%) of the females and 44 (40.4%) of the males who died had also had a new ADI (Table 2, Fig. 2). Univariate analysis showed similar rates of death in males and females, crude HR 0.94 (95% CI 0.60–1.46, $p = .79$), but adjustment reversed this, suggesting a possibly increased hazard of death in females, adjusted HR 1.15 (95% CI 0.69–1.92, $p = .57$). In univariate analysis, higher CD4 count, being treatment-naive at the start of HAART, greater number of new nucleosides started, and having a normal hemoglobin at the time of starting HAART were all significantly associated with a lesser chance of death while history of an ADI, greater number of pre-HAART nucleosides, and higher baseline viral load were all associated with a greater chance of death.

Repeating all the analyses excluding males in the homosexual risk group category did not significantly alter the results (not shown).

DISCUSSION

In the EuroSIDA study commencement of HAART resulted in virologic suppression to undetectable levels in the majority of patients. There was no significant difference in median time to achievement of <500 copies in males and females and time taken to achieve suppression was similar to that found in previous studies (22,23). Confidence intervals for adjusted HRs for virologic rebound, however, show that we cannot exclude a fairly substantial disadvantage for women (results similar to those found in other studies examining durability of virologic response) (24). Indeed, previous analysis of this cohort showed that females had a significantly higher rate of hospital admission than males (25).

There are definite differences in men and women in terms of viral load (which is known to be lower in women than men in the early stages of infection, the gender difference decreasing and in fact disappearing later in the course of the disease) (9,26) and some studies have suggested that for equivalent viral loads women may progress at a faster rate than males (9). Our results show similar rates of virologic suppression and rebound to those previously reported in other observational studies (22,24) but less favorable results than in clinical trials (27–29). Despite females having lower viral loads, higher CD4 counts, and less likelihood of having had an AIDS diagnosis at the time of starting HAART, there was no evidence of a significant gender difference in subsequent rates of virologic outcome or clinical events. It should be noted that the standard of care regarding viral load is to achieve "undetectable" levels, often in current clinical practice a level <50 copies/mL (30,31). Just as antiretroviral therapies change rapidly, our ability to monitor therapeutic response mirrors this, and it is possible that if a lower virologic cut-off point were used,

our findings would alter. The virologic cut-off points are essential for use in clinical trials where more rapid measures of outcome are necessary but are imperfect surrogates for predicting clinical response (19) and this again highlights the need for large studies based on long follow-up to more accurately assess clinical outcomes.

It is known that in the HIV-negative population early in HIV infection women have higher CD4 counts than men (approximately 100 cells higher in females than males in HIV-negative individuals and in HIV-positive individuals for up to 5 years after infection) (11,32–36). Previous studies have also shown evidence that this gender difference in CD4 count presents no functional benefit (16)—women seroconverting, progressing to AIDS, and dying at slightly higher counts than their male counterparts (11,32). The results from this cohort show similar gender differences in CD4 count at diagnosis of AIDS though at death females had lower counts. The number of events that these CD4 counts are based on are, however, small. In fact, the "normal range" for CD4 count may continue to be gender-specific throughout the course of HIV infection. Parallels with hemoglobin [Hb] level may be drawn here. The normal range of Hb varies according to gender and it is established that a lower absolute level is associated with less favorable clinical outcome in patients with HIV (37). If treated as a continuous variable in analysis, even if it is adjusted for, residual confounding will result because of the gender-specific normal ranges. For this reason in this analysis Hb was treated as a categorical variable (with the lower limit of the normal range being the cut-off point for males and females). It may be that CD4 count should be treated in a similar way to more accurately capture its effect, but its level is dynamic and in the absence of knowledge regarding the "normal" range during HAART-treated HIV, this factor must be acknowledged as a potential limitation of the analysis. More importantly, this again raises the issue regarding the use of a single treatment guideline for males and females. Furthermore, the analyses presented show multivariate models in which adjustment for many factors including viral load, CD4 count as well as hemoglobin level is made. As we have discussed, hemoglobin and potentially CD4 and viral load have gender-specific normal ranges and adjustment for these factors may actually introduce residual confounding into the model. Analyses for all outcomes were therefore also performed excluding these three factors and the results were not significantly altered (not shown).

Recently updated British HIV Association guidelines (30) and current US guidelines suggest commencement of HAART at CD4 counts of between 200 and 350 $\times$ 10^6/L (31). In this study only 22% of males and 23% of females had CD4 counts of $>350 \times 10^6$/L at baseline (when starting HAART), 48% of the males and 41% of the females having counts of $<200 \times 10^6$/L.

Two possibilities for gender bias arise when assessing the clinical outcome disease progression. Cervical cancer (added as an ADI in 1993) (21) can be diagnosed only in women, whereas KS has been found to occur relatively early in the disease and most commonly in homosexual males (38,39). However, there were no new cases of cervical cancer in the cohort during the study, and when substitution of KS for a subsequent diagnosis was performed the results were unchanged. In terms of comparison with other published work this alteration is probably unnecessary.

Another important factor is the accuracy of the collected death data. While within EuroSIDA every attempt is made to collect accurate death data, without cross-referencing with national statistics there can be no certainty that ascertainment of death is complete. In the era of HAART as the HIV-positive population ages, more cases of death will begin to be attributable to other, non–HIV-related causes and methods of ensuring even more accurate data will be necessary if we are accurately to monitor the effect of HAART on HIV-related death rates. While any gender-specific effect on the analyses is uncertain, more complete data is certainly desirable.

Differences in adherence to treatment are likely to also play a role and this cohort currently has no data on this. Our results, in line with previous studies (40,41), showed that females altered their original HAART therapy earlier than males. Dosing regimens of antiretrovirals are not gender-specific and it may be that gender differences in circulating blood volume and body mass index result in different levels of efficacy, toxicity, tolerance, and adherence. Changes in the initial HAART regimen were not adjusted for in this study, the analysis being based on intention-to-treat.

Notably, no data was collected on socioeconomic status or education level—shown in some studies to be associated with survival (15,40,42). Gender differences in health-seeking behavior and access to care and treatment would also certainly impact on outcomes but no measures of these factors were available for this study.

Observational studies such as cohort studies are a unique "real life" source of information for the investigation of clinical outcomes in HIV in the era of HAART where the incidence rate of clinical outcomes is low. In terms of the effect of gender on clinical progression of HIV in the era of HAART, it is likely that the definitive answer will be reached only with a still larger cohort and still more follow-up data. To date, however, the weight

of evidence suggests that there is no significant effect of gender on virologic, immunologic, or clinical outcome.

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