VIROLOGICAL, IMMUNOLOGICAL AND CLINICAL RESPONSE TO HAART:
THE GENDER ISSUE REVISITED

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Abstract

Background: Highly active antiretroviral therapy (HAART) has dramatically improved the prognosis for patients with HIV. With the number of HIV-infected women infected rising, there is ongoing debate over a potential gender effect on patient outcome after HAART.

Methods: Individuals were from the EuroSIDA cohort, naïve to PI & NNRTI, starting HAART and had at least one viral load and CD4 measurement. Endpoints were virological (time to <500 copies/ml, time to rebound [first of two consecutive viral loads >500 copies/ml] and failure [failure to reach <500 copies/ml by 32 weeks or subsequent rebound]), immunological (time to a 100/mm³ cell rise in CD4 count) and clinical (time to progression). Hazard ratios (HR), derived using Cox regression models, compared female to male rates of achieving endpoints.

Results: Of 2547 patients, 80% (2036) were male. Significantly more females than males were non-Caucasian (24% v 10%, P<0.001). Males were older (median age 39 v 35 years, P<0.0001), had lower CD4 counts (211 v 240/mm³, P=0.03), higher viral loads (4.6 v 4.4 log copies/ml, P<0.0001), were more likely to have a history of AIDS (26% v 18%, P<0.001) and were more likely to be treatment-naïve (34% v 29%, P=0.03). Adjusted hazard ratios for association between gender (comparing females to males) and the outcomes studied were: for reaching <500 copies/ml 0.91 (0.81-1.03, P=0.17), rebound 1.17 (0.95-1.44, P=0.15), failure 1.15 (0.98-1.33, P=0.10), for 100 cell CD4 count rise 1.02 (0.88-1.14, P=0.99) and for clinical progression 1.11 (0.77-1.58, P=0.59).

Conclusions: Whilst we have no significant evidence of a gender difference, there is trend towards virological responses being poorer overall in women. It is likely that the definitive answer will only be reached with a still larger cohort and longer follow up.

Keywords: gender, HAART, viral load, CD4 count, clinical progression
Introduction

The widespread use of HAART has changed the face of the HIV epidemic in developed countries [1,2,3]. 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, the demographic characteristics of those newly infected with HIV is 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] and it is important that we ensure that they have equal access to HAART and that we understand if there are any differences in their response to treatment compared with men. In the past, the majority of those infected were homosexual males and it was this group that largely took part in and contributed to clinical trials. 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. In the pre-HAART era some studies showed survival benefits for male patients [7,8,9,10] though others suggested that women might do better [11,12,13,14] In general it was felt that any inequality lay in access to care rather than in a fundamental biological difference in response to (albeit sub-optimal) 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. [17,18,19,20] and in this study comparing males
and females we examine virological and immunological response to HAART and clinical progression after HAART.

**Methods**

**Patients**

The EuroSIDA study is a prospective, European study of patients with HIV in 63 centres across Europe (including Israel - see appendix). From 2 May 1994 centres provided data on consecutive patients seen in the outpatient clinic until a predefined number of patients was enrolled from each centre. This original cohort of 3118 patients was defined as the EuroSIDA I cohort. Enrolment of a second cohort of 1367 patients began in December 1995 (Eurosida II cohort) and 2844 patients were recruited from April 1997, defined as the EuroSIDA III cohort. A further cohort of 1227 patients was enrolled from March 1999 and forms the EuroSIDA IV cohort. Information from up to thirteen follow-up visits is available from cohort I, up to ten visits for cohort II, seven visits for Cohort III and three 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 of below 500/mm$^3$, 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 enrolment. Information was collected from patient case notes onto a standardised data collection form at baseline and every six 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 have also been recorded, using the 1993 clinical definition of AIDS from the Centers for Disease Control. [21] Recurrence of diseases are collected for some diagnoses, but this data has not been included in the present analysis. Cause of death is collected wherever possible for patients who have
died. Members of the co-ordinating office visit all centres to ensure correct patient selection and that accurate data was provided by checking the information provided against case-notes for a proportion of patients.

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

**Inclusion criteria**

Patients were (1) previously naïve to PI and NNRTI and starting a HAART regime including at least two nucleoside reverse transcriptase inhibitors and at least one PI or NNRTI, (2) had at least one viral load measurement (the most recent of which was >500 copies/ml) and one CD4 measurement in the six months preceding the start of HAART, 3) had at least one CD4 count and viral load during follow up. The small number of eligible individuals in the Eastern geographic region (74) were excluded.

**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 (two consecutive measurements above 500 copies/ml, the date of the first being taken as the date of virological failure), 3) the time to failure (either the time of virological rebound or at 32 weeks – if not <500 copies/ml by this time), 4) the time to achieving a 100 cell rise in CD4 count and 5) the time to progression to new AIDS or 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 $\chi^2$ 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 comparing females to 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 virological rebound (described above), those not achieving the endpoint being censored at the last viral load or CD4 measurement (for virological and immunological outcomes respectively) or at the last recorded clinic visit (for clinical outcomes). Hazard ratios for the outcomes, comparing female to male rates, were derived using the Cox proportional hazards model in univariate and multivariate analyses after testing the proportional hazards assumption using the $\chi^2$ 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. naïve v non-naïve, 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, haemoglobin level and geographical region. The analysis was based on intention to treat i.e. treatment changes or stoppages were not accounted for in the analysis.

Duration of pre-HAART nucleoside exposure was treated as cumulative months on treatment and both haemoglobin levels and weight were categorised as ‘low’ or ‘normal’ according to gender-based reference ranges. HAART regimen was categorised as one of eight possibilities: ritonavir, indinavir, nelfinavir or saquinavir (hard or soft gel) with at least two nucleoside agents; boosted PI (with ritonavir) or double PI regimes with at least two nucleosides; either efavirenz or neviripine with at least two nucleosides. Changes in HAART regime during follow up were assessed and categorised according to the first change in regime 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 Caucasian but significantly more of the females were non-Caucasian (128 [25.1%] v 215 [10.6%], P<0.001). Males were significantly older than females (median age 39 v 35 years, P<0.0001). CD4 counts were lower in males than females at the time of starting of HAART (211 v 240/mm³, P=0.03), viral loads higher (4.6 v 4.4 log copies/ml, P<0.0001) and a history of previous AIDS more likely (26% v 18%, P<0.001). Males had higher Haemoglobin levels (14.0 v 12.5 g/dl, P<0.0001) and were heavier (72 v 59 kg, P<0.001). Males were more likely to be naïve to antiretrovirals when starting HAART (34% v 29%, P=0.03), 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<0.001.

First HAART regimes 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 regime throughout the period of follow up (Table 1). Overall, in those who did alter their therapy, females first changed their original regime at an earlier stage of follow up (median 10.0 months versus 13.0 months [males], P<0.0001). Amongst those whose original HAART was protease inhibitor based and who changed their regime during the follow up time (n=1795), similar proportions of males and females as the cohort as a whole first added (30.8% of males and 30.0% of females), stopped (29.1% of males and 30.8% of females) or swapped (40.4% and 39.3% respectively), P=0.83 with females similarly altering their regime at an earlier stage than males (11 versus 13 months, P<0.001). In those whose HAART regime was initially NNRTI based (202 patients, 80% taking Neviripine),
however, males were less likely than females to stop all or part of their regime (35.3% vs 59.2%), more likely to add to their regime (20.4% vs 12.2%), and more likely to swap (43.8% vs 28.6%), P=0.01. Median number of months until a change was 3.2 in females and 7.9 in males, P<0.0001.

Virological 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, Figure 1]. Median time to reaching <500 copies/ml was 4.0 months in males and 5.0 months in females in the total 1877 person-years of follow up and by one 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, comparing females to males). Factors independently associated with an increased hazard of becoming undetectable were higher baseline CD4 count and later HAART start date whilst 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 non significant 9% lesser probability of achieving <500 copies/ml, HR 0.91 (95%CI 0.81-1.03, P=0.17).

Virological rebound
Ninety-six percent of those achieving undetectable viral load had further follow up and of these, 708 patients (33%) experienced virological rebound (31% of the males and 40% of the females, [Table 2, Figure 1]). Within six months, 17% of males and 21% females had rebounded and after two 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). 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 adjusted HR was 1.17 (95%CI 0.95-1.44, P=0.15), showing a non significant 17% increased probability of virological failure in women.

**Virological failure**

Fifty-three percent of males and 60% of females experienced virological failure during the 4097 patient-years of follow up, the majority of both male and female failures being at the arbitrary 32 week cut-off point (due to failure to achieve < 500 by this time) [Table 2, Figure 1]). Univariate analysis suggested that females failed at a faster rate than males, crude HR 1.16 (95%CI 1.03-1.32, P=0.02). In multivariate analysis factors associated with reduced probability of failure were being treatment naïve, later HAART start date and older age. Previous history of AIDS and higher baseline RNA were associated with increased probability of the outcome. After adjustment the hazard ratio was slightly altered, becoming non- significant with women having a 15% greater hazard of failure than males, HR 1.15 (95%CI 0.98-1.33, P=0.10).

**Immunological response**

Median time to improvement in CD4 count by at least 100x10^6 cells/l was nine months after starting treatment for both males and females (Table 2, Figure 2). Overall, females appeared to achieve this at the same rate as males, crude HR 0.96 (95%CI 0.86-1.07, P=0.47) and adjusted 0.99 (95%CI 0.88-1.14, P=0.99). Factors independently associated with increased hazard of achieving a 100 cell/mm^3 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 six months preceeding a new AIDS diagnosis or death, females (n=34) had higher CD4 counts than males (n=145), but not significantly so (103
v 100/mm³ P=0.09) and at death females (n=7) had lower counts than males (n=41) (18 v 68, P=0.13).

Clinical Progression

During a total of 6874 person-years of follow up 229 (11%) males and 52 (10%) females experienced progression (Table 2, Figure 2). One year after starting HAART 6% of the males and 4% of the females had either developed a new AIDS defining illness [ADI] or died. Of the 229 males who progressed 72% had a new AIDS diagnosis and 31% died, 7% of those who died having a new ADI on the same date. Amongst the 52 progressing women 72% had a new ADI and 35% died, 17% of those dying also having a new AIDS defining illness diagnosed on the same date. Univariate analysis suggested a similar rate of progression in males and females, crude HR 0.94 (95%CI 0.70-1.28) though adjustment reversed the hazard ratio leading to the suggestion of a slightly increased hazard for females to progress compared to males, HR 1.11 (95%CI 0.78-1.58). Previous AIDS, higher baseline RNA and greater age were associated with increased probability of progression and higher CD4 count with lesser probability of failure. Repeating the analysis excluding Kaposi’s sarcoma (20 cases) and replacing these cases with a subsequent diagnosis if one existed did not alter the adjusted hazard ratio.

Assessment of clinical outcome within different virological response subgroups was made. In the group achieving and sustaining suppression to <500 copies, adjusted Hazard Ratios for progression (comparing female to male) revealed results not dramatically dissimilar to those of the original analysis, 1.15 (0.68-1.97). In the group rebounding after achieving <500 copies the adjusted hazard ratio was 1.71 (0.86-3.40 whilst in the group never achieving <500 copies the gender difference was less, 1.09 (0.46-2.56).
Discussion

In the EuroSIDA study commencement of HAART resulted in virological suppression to undetectable levels in the majority of patients. Females suppressed at a slightly lower rate than males, median time to achievement of <500 copies being similar to that found in previous studies, [22,23] though we did not find a significant difference between responses in the two genders. Confidence intervals for adjusted hazard ratios for both virological rebound and virological failure, however, show that we cannot exclude a fairly substantial disadvantage for women (results similar to those found in other studies examining durability of virological 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 have suggested that for equivalent viral loads women may progress at a faster rate than males. [9] Our results show similar rates of virological suppression and rebound to those previously reported in other observational studies [22,24] but less favourable results than in clinical trials [27,28,29] and appear to show a possible virological disadvantage for females that may ultimately translate into a clinical disadvantage. This is despite the fact that women were less likely to have had an AIDS diagnosis when starting HAART and had slightly higher CD4 counts than males.

It should be noted that the standard of care regarding viral load is to achieve ‘undetectable’ levels, generally in current clinical practise 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 virological cut-off point were used, our findings would alter. The virological 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 interesting to examine the effect on the results of the definition of ‘failure’ used (in this analysis viral load not <500 copies/ml at 32 weeks or rebound after achieving <500 copies/ml). Using this definition meant that the majority of failures in our study occurred at our arbitrary cut-off point of 32 weeks and the experience of males and females was similar up until this point. In clinical practice patients may well not be classified as failures (and have their antiretroviral therapy changed) at this time point if there is; 1) evidence of an improvement in immunological function and 2) viral load, although not optimally suppressed, is responding favourably. Notably, when the virological response subgroups were examined, the majority of patients achieved a 100 cell increase in CD4 count regardless of their virological response. This has also been found in other studies. [23]

It is known that in women have higher CD4 counts than men the HIV-negative population and early in HIV infection, women have higher CD4 counts than men (approximately 100 cells higher in females than males in the HIV-negative population and in HIV-positive individuals for up to five years after infection). [11,32,33,34,35,36] 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, females having slightly higher CD4 counts at new AIDS diagnosis and at death thought the number of events is small. The ‘normal range’ for CD4 count may indeed, however, continue to be gender specific throughout the course of HIV infection. Parallels with haemoglobin [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 favourable 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.

Recently updated BHIVA guidelines [30] and current USA guidelines suggest commencement of HAART at CD4 counts of between 200 and 350x10^6/ml [31]. In this study only 22% of males and 23% of females had CD4 counts of >350x10^6/ml at baseline (when starting HAART), 48% of the males and 41% of the females having counts of <200x10^6/ml.

Though our results may suggest a possible disadvantage for females in terms of virological response we do not have conclusive evidence of a clinical disadvantage, the ultimate test of the benefit of HAART. Two possibilities for gender bias arise when assessing the clinical outcome disease progression. Cervical cancer (added as an AIDS defining illness in 1993) [21] can be diagnosed only in women whilst Kaposi's sarcoma [KS] has been found to occur relatively early in the disease and most commonly in homosexual males. [38,39] There were no new cases of cervical cancer in the cohort during the study and when substitution of Kaposi's sarcoma 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. Whilst 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.

Differences in adherence to treatment are likely to also play a role and this cohort currently has no data on this. Changes in the HAART regimen were also not adjusted for, the analysis being based on intention to treat. Notably no data was collected on socio-economic status - shown in some studies to be associated with survival [15,40] - or education level. Observational studies are an increasingly important 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 (also said in the discussion). 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 only be reached with a still larger cohort and still more follow up data. To date however, whilst we have no significant evidence of a gender difference and our findings could all be the result of chance, there is a suggestion that viral load responses could be poorer overall in women. The issue of gender and HIV therefore requires continued monitoring and cannot yet be laid to rest.
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Table 1: Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Male (n=2037)</th>
<th>Female(n= 511)</th>
<th>P value</th>
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<tr>
<td>Age</td>
<td>38.8 (34.0-46.2)</td>
<td>35.0 (31.1-40.7)</td>
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<tr>
<td>Caucasian race</td>
<td>1821 (89.4)</td>
<td>383 (75.0)</td>
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<tr>
<td>Homosexual</td>
<td>1233 (60.6)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
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<td>IDU</td>
<td>380 (18.7)</td>
<td>153 (29.9)</td>
<td></td>
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<tr>
<td>Heterosexual</td>
<td>297 (14.6)</td>
<td>304 (59.5)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>126 (6.2)</td>
<td>54 (10.6)</td>
<td></td>
</tr>
<tr>
<td>History of AIDS</td>
<td>530 (26.02)</td>
<td>90 (17.6)</td>
<td>&lt;0.001</td>
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<tr>
<td>CD4</td>
<td>211 (98-336)</td>
<td>240 (125-339)</td>
<td>0.03</td>
</tr>
<tr>
<td>Log RNA</td>
<td>4.6 (4.0-5.2)</td>
<td>4.4 (3.7-5.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NRTIs pre-HAART: 0</td>
<td>696 (34.2)</td>
<td>148 (29.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1</td>
<td>82 (4.0)</td>
<td>37 (7.2)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>656 (32.2)</td>
<td>146 (28.6)</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>602 (29.5)</td>
<td>180 (35.2)</td>
<td></td>
</tr>
<tr>
<td>NRTI-months pre-HAART</td>
<td>46.0 (22.0-81.1)</td>
<td>55.0 (28.0-85.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Indinavir-based HAART</td>
<td>845 (41.5)</td>
<td>212 (41.5)</td>
<td>0.07</td>
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<tr>
<td>Ritonavir-based HAART</td>
<td>316 (15.5)</td>
<td>58 (11.4)</td>
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</tr>
<tr>
<td>Boosted/dual PI HAART</td>
<td>594 (29.1)</td>
<td>168 (32.9)</td>
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<tr>
<td>Efavirenz-based HAART</td>
<td>78 (3.9)</td>
<td>13 (2.5)</td>
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<td>Neviripine-based</td>
<td>203 (10.0)</td>
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<td>New nucleosides: 0</td>
<td>572 (28.1)</td>
<td>163 (31.9)</td>
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<tr>
<td>1</td>
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<td>127 (24.9)</td>
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<tr>
<td>3</td>
<td>14 (0.7)</td>
<td>2 (0.4)</td>
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<tr>
<td>No change during f'up</td>
<td>452 (22.2)</td>
<td>98 (19.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Add agent during f'up</td>
<td>473 (22.2)</td>
<td>115 (22.5)</td>
<td></td>
</tr>
<tr>
<td>Stop agent during f'up</td>
<td>471 (23.1)</td>
<td>141 (27.6)</td>
<td></td>
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<tr>
<td>Swap agent</td>
<td>640 (31.4)</td>
<td>157 (30.7)</td>
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</tr>
<tr>
<td>Outcome</td>
<td>All</td>
<td>Males</td>
<td>Females</td>
</tr>
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<td>--------------------------------------</td>
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<td>-----------</td>
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</tr>
<tr>
<td><strong>HIV RNA &lt;500 copies/ml</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%) achieving success</td>
<td>2259 (89)</td>
<td>1810 (89)</td>
<td>449 (88)</td>
</tr>
<tr>
<td>median months to success</td>
<td>4.01</td>
<td>4.01</td>
<td>4.96</td>
</tr>
<tr>
<td>crude HR (95%CI, P)</td>
<td>0.93 (0.84-1.03, P=0.19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>adjusted HR (95%CI, P)</td>
<td>0.91 (0.81-1.03, P=0.17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rebound after &lt;500 copies/ml</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%) rebounding</td>
<td>708 (33)</td>
<td>538 (31)</td>
<td>170 (40)</td>
</tr>
<tr>
<td>% rebounded at 6 months</td>
<td>18</td>
<td>17</td>
<td>21</td>
</tr>
<tr>
<td>crude HR (95%CI, P)</td>
<td>1.40 (1.18-1.67, P&lt;0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>adjusted HR (95%CI, P)</td>
<td>1.17 (0.95-1.44, P=0.15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Virological Failure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%) failing</td>
<td>1527 (60)</td>
<td>1192 (59)</td>
<td>335 (66)</td>
</tr>
<tr>
<td>median months to failure</td>
<td>6.97</td>
<td>7.06</td>
<td>5.52</td>
</tr>
<tr>
<td>crude HR (95%CI, P)</td>
<td>1.16 (1.03-1.32, P=0.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>adjusted HR (95%CI, P)</td>
<td>1.15 (0.98-1.33, P=0.10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>100 cell rise in CD4 count</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%) achieving success</td>
<td>2113</td>
<td>1702</td>
<td>411</td>
</tr>
<tr>
<td>median months to success</td>
<td>9.01</td>
<td>9.07</td>
<td>9.00</td>
</tr>
<tr>
<td>crude HR (95%CI, P)</td>
<td>0.96 (0.86-1.70, P=0.47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>adjusted HR (95%CI, P)</td>
<td>1.02(0.88-1.14, P=0.99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Progression</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%) progressing</td>
<td>281 (11)</td>
<td>229 (11)</td>
<td>52 (10)</td>
</tr>
<tr>
<td>% progressing at 12 months</td>
<td>6</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>crude HR (95%CI, P)</td>
<td>0.94 (0.70-1.28, P=0.71)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>adjusted HR (95%CI, P)</td>
<td>1.11 (0.77-1.58, P=0.59)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All multivariate models include adjustment for CD4 and RNA at the time of starting HAART, previous AIDS diagnosis, treatment history (i.e. naïve v non-naïve, 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, haemoglobin level and geographical region.
Figure 1: Virological outcomes.

i) Achievement of <500 copies

Kaplan-Meier survival estimates, by gender

ii) Rebound after <500 copies

Kaplan-Meier survival estimates, by gender

iii) Failure

Kaplan-Meier survival estimates, by gender
Figure 2: Immunological and clinical outcomes

i) **Achievement of 100 cell/mm³ rise in CD4 count**

Kaplan-Meier survival estimates, by gender

- **Proportion achieving 100 cell increase**
- **Months since starting HAART**

ii) **Clinical progression (to new AIDS or death)**

Kaplan-Meier survival estimates, by gender

- **Proportion progressing**
- **Months since starting HAART**