Determinants of Restoration of CD4 and CD8 Cell Counts and their Ratio in HIV-1 Positive

Individuals with Sustained Virological Suppression on Antiretroviral Therapy

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Short title: Immunological Restoration during Virologically Suppressive ART

## Abstract

### Background

An increasing number of HIV-positive individuals now start antiretroviral therapy (ART) with high CD4 cell counts. We investigated whether this makes restoration of CD4 and CD8 cell counts and the CD4:CD8 ratio during virologically suppressive ART to median levels seen in HIV uninfected individuals more likely and whether restoration depends on gender, age and other individual characteristics.

### Methods

We determined median and quartile reference values for CD4 and CD8 cell count and their ratio using cross-sectional data from 2,309 HIV-negative individuals. We used longitudinal measurements of 60,997 HIV-positive individuals from the Antiretroviral Therapy Cohort Collaboration in linear mixed effects models.

### Results

When baseline CD4 cell counts were higher, higher long-term CD4 cell counts and CD4:CD8 ratios were reached. Highest long-term CD4 cell counts were observed in middle-aged individuals. During the first two years median CD8 cell counts converged towards median reference values. However, changes were small thereafter and long-term CD8 cell count levels were higher than median reference values. Median 8-year CD8 cell counts were higher when ART was started with <250 CD4 cells/mm$^3$. Median CD4:CD8 trajectories did not reach median reference values, even when ART was started at 500 cells/mm$^3$.

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**Discussion**

Starting ART with a CD4 cell count of ≥500 cells/mm$^3$ makes reaching median reference CD4 cell counts more likely. However, median CD4:CD8 ratio trajectories remained below the median levels of HIV-negative individuals, because of persisting high CD8 cell counts. To what extent these subnormal immunological responses have impact on specific clinical endpoints requires further investigation.

Keywords: CD4 cell count; CD8 cell count; CD4:CD8 ratio; antiretroviral therapy; HIV; age

**Introduction**

Since 2012, US Guidelines have recommended offering antiretroviral therapy (ART) to all individuals diagnosed with HIV, regardless of their CD4 cell count[1]. As a result, an increasing number of HIV-1- positive individuals start ART at high CD4 cell counts. Furthermore, of those starting ART, a considerable proportion does so at a relatively old age. For example, in the Netherlands in 2015, 37% of those starting ART did so with a CD4 count of ≥500 cells/mm$^3$ and 23% of individuals newly diagnosed with HIV were 50 years or older[2]. Generally, the increase in CD4 cell count during virologically suppressive ART is less in older individuals[3–8][9]. This diminished recovery of CD4 cell count among older individuals has been attributed to lower thymic function[10,11].

Lower CD4 counts with older age are also seen in healthy European HIV-negative populations, although the decrease seems to occur mainly at very advanced age[12–16]. CD4 cell counts have also been reported to differ according to smoking status[17], gender[13], the time of day of sampling[18], season[19] and region of origin[20][21].

Whilst CD4 cell count is considered the key prognostic factor for AIDS morbidity and mortality, some evidence suggests that the CD4:CD8 ratio also independently predicts time to death and to non-AIDS defining endpoints(22–24). In the general population a CD4:CD8 ratio <1.0 is associated with mortality in very elderly people(25). In HIV-positive individuals the ratio is decreased and low ratios are associated with pathological changes in the immune system such as immune activation, exhaustion, senescence and memory abnormalities(26,27,28). The ratio increases rapidly during the first few years on ART and keeps increasing up to 15 years after starting ART, albeit slowly(29) and the ratio does not reach levels higher than 1.0 in two-thirds of individuals despite long-term viral suppression(30)(31).

We studied whether an early start, at high CD4 cell counts followed by long-term virologically suppressive ART, makes restoration to levels of CD4 and CD8 cell counts and the CD4:CD8 ratio seen in HIV-negative individuals more likely. We also investigated the effect of age and other factors on these immunological changes.

**Methods**

**HIV-negative study participants**

To obtain reference values we used 2309 cross-sectional CD4 and CD8 cell counts and CD4:CD8 ratios obtained from HIV-negative individuals recruited from the background population to the Danish HIV-cohort (either healthy staff or blood and stem-cell donors) and HIV-negative individuals from the Dutch AGE$_h$IV cohort (recruited either at the STI clinic of the Amsterdam Public Health Service or the existing Amsterdam Cohort Studies on HIV/AIDS). CD4 and CD8 cell counts and CD4:CD8 ratios were used as dependent variable in 3 linear regression models including age and gender and their interaction as independent

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variables. We used the $25^{th}$, $50^{th}$ and $75^{th}$ prediction percentiles as the lower, median and upper reference values in graphs to put the immunological restoration during virologically suppressive ART in HIV-positive individuals into context. (See Text File, Supplemental Digital Content (SDC) 1,http://links.lww.com/QAI/B244 for further details on the selection and analysis of CD4 and CD8 cell counts and the CD4:CD8 ratio in HIV-negative individuals).

**HIV-positive study participants**

We used data from the Antiretroviral Therapy Cohort Collaboration (ART-CC; http://www.art-cohort-collaboration.org), an international collaboration of 21 cohort studies from Europe and North America that was established in 2000 to examine the prognosis of HIV-1-positive, treatment-naive individuals initiating ART, a combination of at least 3 antiretroviral drugs (32). Participation of cohorts has been approved by their ethics committees or institutional review boards according to local regulations (see Text File, SDC 2 for a list of participating cohorts). We only included individuals who were 18 years of age or older and had a CD4 cell count and viral load measured at the start of ART. All included individuals had a decrease in HIV RNA viral load to below 400 copies/ml within 9 months from start of ART. In sensitivity analyses we changed the time limit to six months and cut-off to 50 copies/ml.

**Outcome**

We modeled longitudinal CD4 and CD8 cell counts and CD4:CD8 ratios after the start of ART. We excluded follow-up after an ART interruption longer than two weeks and after the first of two consecutive plasma viral load measurements ≥400 copies/ml. In sensitivity analyses we only included measurements until an ART interruption longer than one week or

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until the first plasma viral load measurement ≥400 copies/ml. Models including CD8 cell counts or CD4:CD8 ratios only included participants from the 14 cohorts which had collected data on these variables.

**Statistical methods**

Trends in CD4 and CD8 cell counts and their ratio were modeled via linear mixed effects models (lme4 package(33) in R version 3.0.3(34)). CD4 cell counts were found to best comply with normality assumptions when square root transformed, CD8 cell counts when log transformed and the CD4:CD8 ratio when fifth root transformed. The trends over time since start of ART were modeled using restricted cubic splines with knots at 0, 0.1, 0.25, 0.5, 3 and 7.5 years. We used a random intercept and two random slopes (one slope between 0 and 6 months and one slope from 6 months onwards, with an unstructured covariance matrix) per individual as well as a random intercept for cohort.

All models included gender, region of birth (Europe/North America, Caribbean/South America, Sub Saharan Africa, and other regions), transmission risk group (men who have sex with men (MSM), injecting drug use (IDU), heterosexual, other and unknown), age, CD4 cell count and HIV RNA at the start of ART (measurement closest to the start of ART in the period 90 days before to 6 days after starting ART). CD4 cell count trends were also allowed to vary according to period of starting ART (2001-2003, 2004-2006, 2007-2009 and 2010-2012).

Because data on smoking status, CD8 cell count and hepatitis C virus (HCV) and cytomegalovirus (CMV) co-infection were not collected in all cohorts, we only used data from cohorts with at least 85% complete data on smoking status, CD8 cell count and HCV co-infection. For CMV co-infection we used data from the five cohorts with available data on CMV. Therefore, these variables were not evaluated together in one model but in separate

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models. For more detailed information on interaction terms and continuous covariables modeling, see Text File, SDC 3.

To help interpretation the fitted values were backtransformed to their original scale, where they can be considered as median values. They are graphically displayed for selected values of age and CD4 and CD8 cell count at the start of ART.

## Results

### HIV-negative population

Median CD4 and CD8 cell count in HIV negative participants decreased with older age while the median CD4:CD8 ratio was higher with older age (see Figures A-C, SDC 4),http://links.lww.com/QAI/B244. For a 37-year old male the median CD4 cell count was 830 cells/mm$^3$ and 1005 CD4 cells/mm$^3$ for a female. These values for the CD8 cell count and the CD4:CD8 ratio were 499 cells/mm$^3$ and 1.69 for males and for females 519 CD8 cells/mm$^3$ and 1.98, respectively. Modeling age using splines (see Figures SDC 5-7),http://links.lww.com/QAI/B244 gave a better data fit than modeling age linearly, but as the resulting trajectories were not consistently increasing or decreasing with higher age, we chose to model age linearly.

### HIV-positive population

The majority of 60,997 included HIV-positive individuals were men (75%) and born in Europe/North America (73%), as shown in Table 1. Forty percent were in the MSM transmission risk group. Median age was 39 years (IQR 32-46). Median CD4 cell count was

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246 cells/mm$^3$ (IQR 130-350). The median CD8 cell count in the subset of 37,305 individuals included in the analysis of CD8 cell count and CD4:CD8 ratio was 830 cells/mm$^3$ and the median CD4:CD8 ratio was 0.21 (Table 2). Median CD8 cell count and CD4:CD8 ratio were both lower when ART was started at lower CD4 cell count.

**CD4 cell count trajectories**

We used 599,445 CD4 cell count measurements. The number of individuals with measurements after two, four, six, and eight years of virologically suppressive ART was 29,791 (49%), 16,679 (27%), 8,836 (14%), and 4,209 (7%), respectively. The median observed CD4 cell count at eight years for those starting with a CD4 count of 0-49 (n=728), 50-99 (n=480), 100-199 (n=1,025), 200-349 (n=1,359), 350-499 (n=377), and ≥500 cells/mm$^3$ (n=240) was 485, 507, 570, 667, 793, and 923 cells/mm$^3$, respectively.

Higher CD4 cell count at the start of ART was associated with higher median 8-year counts (Figure 1). Only when ART was started with a CD4 count of 500 cells/mm$^3$ the median 8-year CD4 cell count in men reached the median reference value. CD4 cell count was non-linearly associated with age. Middle-aged men showed higher median CD4 cell counts at eight years compared to older and younger men when ART was started with a CC4 count of 350 or 500 cells/mm$^3$. Women showed a similar, but stronger pattern. Among those starting at a CD4 count of 500 cells/mm$^3$ 45-year-old reference males (911 cells/mm$^3$, 95% CI 889-933) and 51-year old females (971 cells/mm$^3$, 95% CI 932-1011) reached highest median 8-year CD4 cell counts. Trajectories of women aged 20 years at the start of ART were initially higher than those of older women during the first 2 years of ART but flattened whilst trajectories of

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women aged 37, 54 or 70 years at baseline kept increasing (see Figure, SDC

8),http://links.lww.com/QAI/B244. Similar results were obtained when analyses were

restricted to those who reached <50 HIV copies/ml within six months from starting ART.

CD4 cell count trajectories were also similar according to start year of ART (results not

shown).

CD4 cell counts at eight years were lower with increasing baseline CD8 cell counts until 400

cells/mm$^3$, but the relation flattened off beyond 400 cells/mm$^3$ (see Figure, SDC

9,http://links.lww.com/QAI/B244 in analysis additionally adjusted for baseline CD8 cell

count in subset of 37,305 individuals with CD8 cell counts available).

### CD8 cell count trajectories

We used 374,985 CD8 cell count measurements from 37,305 individuals. The number of

individuals with CD8 cell counts during virologically suppressive ART after two, four, six,

and eight years was 18,316 (49%), 10,310 (28%), 5,480 (15%), and 2,525 (7%), respectively.

The median CD8 cell count at eight years was 765 cells/mm$^3$ (IQR 558-1040). For those

starting with 0-49 (410 individuals remaining in follow-up), 50-99 (n=281), 100-199 (n=655),

200-349 (n=794), 350-499 (n=242), and ≥500 CD4 cells/mm$^3$ (n=143) the median 8-year

CD8 cell count was 800 (IQR 575-1,100), 770 (566-1075), 774 (570-1,006), 740 (540-1,030),

751 (558-1,050), and 810 (557-1,072) cells/mm$^3$, respectively.

Median CD8 cell counts at eight years after the start of ART showed a similar downward

trend with higher age as the trend observed in HIV-negatives. This downward trend was not

observed in men and women younger than 40 years, median 8-year CD8 cell counts were

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similar across all ages below 40 years of age. Higher CD8 cell counts at the start were associated with higher CD8 cell counts at 8 years. Median 8-year CD8 counts were similar to median reference values when ART was started with a CD8 cell count of 300 cells/mm$^3$ and a CD4 cell count of 200, 350 or 500 cells/mm$^3$. Similar median CD8 cell counts at 8 years were reached for those starting with a CD4 count of 200, 350 or 500 cells/mm$^3$. However, median 8-year CD8 cell counts were higher when ART was started with a CD4 count of 50 cells/mm$^3$. The association between lower baseline CD4 cell counts and higher CD8 cell counts at 8 years starts from CD4 cell counts below approximately 250 cells/mm$^3$ (Figure, SDC 10),http://links.lww.com/QAI/B244.

Median CD8 cell count trajectories show a rapid decline in CD8 cell count during the first year when ART was started with a CD8 count of 800 or 1200 cells/mm$^3$ and a more gradual decline after 1 year. CD8 cell counts remained higher than the median reference range during the first eight years (see Figure, SDC 11),http://links.lww.com/QAI/B244.

**CD4:CD8 ratio trajectories**

Median CD4:CD8 ratio at eight years was 0.81 (IQR 0.57-1.11). The median 8-year ratio for those starting with 0-49, 50-99, 100-199, 200-349, 350-499, and ≥500 CD4 cell/mm$^3$ was 0.63 (IQR 0.45-0.85), 0.66 (0.47-0.87), 0.76 (0.54-1.01), 0.89 (0.64-1.19), 1.05 (0.75-1.38), and 1.09 (0.88-1.50) cells/mm$^3$ respectively.

Figure 3 shows that higher median CD4:CD8 ratios were reached when CD4 cell counts at the start of ART were higher and CD8 cell counts were lower (i.e. the ratio at the start was higher). Among the combinations shown, median reference values were only reached in men aged <60 years (at 8 years) who had started ART with the combination of a CD4 count of 500

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cells/mm$^3$ and CD8 count of 300 cells/mm$^3$. Men and women with a CD4 count of 350 or 500

cells/mm$^3$ at the start reached median CD4:CD8 ratios ≥1.0 at 8 years, irrespective of the CD8

cell count at the start, except in men older than 60 years of age at 8 years.


Median CD4:CD8 ratio trajectories continued to increase during the first 8 years of ART (see

Figure, SDC 12),http://links.lww.com/QAI/B244. Ratio trajectories were higher in women

compared to men.


**Association of other variables with trajectories**

The association between region of origin, transmission risk group, HIV RNA, smoking status

and HCV and CMV co-infection at the start of ART and CD4 and CD8 cell count and ratio

trajectories and levels reached at 8 years is discussed in text and shown in figures (see

Figures, SDC 13-15,http://links.lww.com/QAI/B244 and Table, SDC

16),http://links.lww.com/QAI/B244. In short, CD4 and CD8 cell count after eight years of

virologically suppressive ART were higher in smokers compared to non-smokers. Median

trajectories of CD4 cell count and the CD4:CD8 ratio were lower in individuals infected by

IDU compared to non-IDU. CMV-negative individuals showed a stronger decrease in CD8

cell count in the first year after starting ART compared to CMV-positive individuals and as

CD4 cell count trajectories were fairly similar CD4:CD8 ratio trajectories in CMV-positive

individuals were lower compared to those in CMV-negative individuals.

**Discussion**

As ART is now both recommended and often started at high CD4 cell counts, we investigated whether median trajectories of CD4 and CD8 cell count and the CD4:CD8 ratio reach median reference values when ART is started with high (e.g. 500 cells/mm$^3$) and lower CD4 cell counts (such as 350, 200 and 50 cells/mm$^3$). During 8 years of virologically suppressive ART median reference CD4 cell counts (about 800 cells/mm$^3$) were reached only by men starting at high CD4 cell counts ≥500 cells/mm$^3$. Despite virologically suppressive ART CD8 cell count trajectories converged after two years to a stable level above the median reference value. Median reference CD8 cell counts were only reached when ART was started at low CD8 cell count (such as 300 cells/mm$^3$). As a result of persisting high CD8 cell counts median reference CD4:CD8 ratios were not reached, even when ART was started at high CD4 cell counts.

Measurements after interruption of ART of more than 2 weeks and after a confirmed HIV RNA >400 copies/ml were not included in the analysis. Our results are therefore not generalizable to all individuals who start ART but rather provide an estimate of the maximum capacity of the immune system to restore CD4 and CD8 cell counts and their ratio during long-term virologically suppressive ART. Our selection of individuals therefore will also include some immunological non-responders, individual with non-perfect adherence, women during pregnancy and individuals with certain co-morbidities or co-medication which may impact CD4 and CD8 cell count trajectories. Furthermore, generalizability may be slightly impaired if those that interrupt ART or with virological failure have different CD4 or CD8 cell count trajectories before interruption or failure.

Median reference CD4 cell counts were only reached within 8 years in more than 50% of men when ART was started with high CD4 cell counts (such as 500 cells/mm$^3$). By definition, approximately 50% of individuals will have had a pre-HIV-infection CD4 cell count below the population median, and some even below 500 cells/mm$^3$. Hence those who start ART with a CD4 count more than 500 cells/mm$^3$ are already a selected subgroup that probably had pre-HIV CD4 counts above the population median. Likewise, those who had lower than average CD4 counts before they acquired HIV are more likely to start ART with low CD4 counts. Ideally, one would like to compare CD4 cell counts during virologically suppressive ART with an individuals' pre-HIV-infection CD4 cell count level but we did not have data on pre-HIV infection CD4 cell counts for the individuals in our study. The level of the first post-seroconversion CD4 cell count has been shown to be predictive for the CD4 cell count recovery after the start of ART(35). However, also the timing of seroconversion, and post-seroconversion CD4 cell count were mostly unknown in our data.

The highest CD4 cell counts after eight years of virologically suppressive ART were observed for women aged 51-52 years. Whereas in women we observed a peak CD4 cell count response during middle age at all levels of CD4 cell count at the start, in men a similar peak was only observed when ART was started at CD4 counts of 500 cells/mm$^3$ but not at lower CD4 cell counts. A similar non-linear age-CD4 response pattern was found in a recent study(36). As we did not observe such a trend in the HIV-negative population, it is not clear whether an underlying biological process contributes to our findings. Adherence to ART has been shown to be less in younger individuals(37) and differences in compliance may exist even when all HIV RNA measurements are below the limit of detection. Poorer adherence may explain the smaller increases in CD4 cell count after 2-8 years after the start of ART when ART was started at 20 years of age compared to middle aged men and women. We aimed to select more adherent individuals in the sensitivity analysis with a stricter definition

of virologically suppressive ART but results were similar to the main analysis. The peak in CD4 response in women coincides with the mean age of natural menopause but studies have found no evidence for a difference in CD4 cell count response after ART initiation between pre- and post-menopausal women with a virological response(38,39).

A recent study found that CD8 cell count trajectories, adjusted for baseline CD4 cell count but not for baseline CD8 cell count, were very similar when for those starting with a CD4 count of 200 cells/mm$^3$ or higher but long term CD8 cell count trajectories were higher when started with counts <200 cells/mm$^3$(29). We show that reaching higher long term CD8 cell counts is, associated with lower baseline CD4 cell count but also with younger age and higher baseline CD8 cell count. CD8 cell counts at eight years were lower with older age, similar, albeit at a higher value, compared to the trend in HIV-negative individuals. The association between higher baseline CD4 cell counts and lower CD8 cell count trajectories is counterbalanced by the association between higher baseline CD8 cell counts. Higher baseline CD8 cell counts usually accompany higher baseline CD4 cell counts, and are associated with higher CD8 cell count trajectories. Together this results in long-term CD8 cell counts which are similar when ART is started with a CD4 count of 200 cells/mm$^3$ or higher. Lack of normalization of CD8 cell counts in HIV-positive individuals was also observed in a recent study by the Danish HIV Cohort(40). Elevated CD8 cell count levels are suggestive of ongoing residual immune activation and residual HIV viraemia, co-infections (such as cytomegalovirus(41)), microbial translocation, loss of immunoregulatory responses and hypercoagulability are all thought to contribute(42,43).

When ART was started at CD4 counts above 200 cells/mm$^3$ in men and 250 cells/mm$^3$ in women median CD4 cell count trajectories reached ≥500 cells/mm$^3$ within 8 years of virologically suppressive ART. When ART was started at a CD4 count of 350 or 500 cells/mm$^3$, median ratios >1 were reached within 8 years. These cutoffs are frequently used to identify individuals at increased risk of morbidity and/or mortality. However, there continues to be an association of a lower risk of AIDS and death with a higher CD4 cell count, even above 500 cells/mm$^3$ (44,45). For the CD4:CD8 ratio and CD8 cell count these associations are less clear cut. Several studies have suggested that the CD4:CD8 ratio, independent of CD4 cell count, predicts time to death and non-AIDS defining morbidity(22–24,46). In addition, both low CD8 cell count in the first year after starting ART and increased CD8 cell counts >1500 cells/mm$^3$ at 10 years after the start of ART have been associated with mortality(40). In contrast, a recent ART-CC study found only a small effect of CD8 cell counts and no significant effect of the CD4:CD8 ratio on all-cause mortality(47). It may be that associations between either CD8 cell count or CD4:CD8 ratio and clinical outcome are only limited to specific causes of morbidity or death.

A limitation of our study was that analyses including data on CD8 cell counts, smoking and HCV and CMV co-infection was performed in different subsets of individuals which limits the interpretation of the results because we did not adjust for all covariates at the same time. Furthermore, there were few HIV-negatives older than 65 years of age. Therefore, comparisons to median HIV-negative values beyond 65 years is mostly based on extrapolation. Another limitation is that both HIV-negative cohorts were from a Western European population whilst CD4 cell counts are generally reported to be lower in Sub-Saharan African populations(48). In our study, CD4 and CD8 cell count and CD4:CD8 ratio trajectories in HIV-positive individuals from Sub-Saharan Africa were all somewhat lower

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compared to those from Western Europe or North America. Whether these differences translate into differential risk for morbidity or mortality is difficult to investigate because of other socioeconomic and psychosocial differences.

## Conclusion

Starting ART with a CD4 cell count of ≥500 cells/mm$^3$ makes reaching a CD4 cell count comparable to those seen in HIV-negative individuals more likely. However, even when ART is started with high CD4 cell count, median CD4:CD8 ratio trajectories remained below the reference levels of HIV-negative individuals, because of persisting high CD8 cell counts. To what extent these subnormal immunological responses have an impact on specific clinical endpoints requires further investigation.

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**Figure 1.** Median CD4 cell count at eight years of virologically suppressive ART (95% CI's in colour) in men and women by age at 8 years after the start of ART. Trends are shown for specific baseline CD4 cell counts of 100, 200, 350, and 500 cells/mm$^3$. Curves are for an average reference heterosexual individual born in Western Europe/North America starting ART between 2004 and 2006 with a plasma viral load of 4.81 $\log_{10}$ copies/ml and a random intercept and slopes equal to zero. Dashed lines show the lower and normal reference CD4 cell count by age as estimated in HIV-negative men and women.

**Figure 2**. Median CD8 cell count after eight years of virologically suppressive ART by age, gender, and CD4 and CD8 cell count at the start of ART, for an average reference heterosexual individual born in Western-Europe or North-America and starting ART with 4.81 $\log_{10}$ copies/ml and random intercept and slopes equal to zero. Dashed lines show the upper, normal and lower reference CD8 cell count values.

**Figure 3**. Median CD4:CD8 ratio at eight years after the start of ART (95% confidence intervals in color) according to age at eight years after the start of ART , gender, and CD4 and CD8 cell count at the start of ART. Median ratios shown are those for an average reference individual in the heterosexual transmission risk group, born in Europe/North America, 37 years of age at the start of ART, and a plasma viral load of 4.81 $\log_{10}$ copies/ml at the start of ART and random intercept and slopes equal to zero. Dashed lines show the normal and lower reference CD4:CD8 ratio in HIV-negative men and women.

**Table 1. Demographical and clinical characteristics at the start of ART.**

| | N | % |
|---|---|---|
| **Total** | 60,997 | 100.0 |
| | | |
| **Gender** | | |
| Men | 46,076 | 75.5 |
| Women | 14,921 | 24.5 |
| **Transmission risk group** | | |
| MSM* | 24,591 | 40.3 |
| Injecting drug use | 4,685 | 7.7 |
| Heterosexual contact | 23,335 | 38.3 |
| Other/Unknown | 8,386 | 13.7 |
| **Age at start of ART (years), median, IQR** | | 39, 32-46 |
| 16-29 | 10,796 | 17.7 |
| 30-39 | 21,796 | 35.7 |
| 40-49 | 17,798 | 29.2 |
| ≥50 | 10,607 | 17.4 |
| **Region of birth** | | |
| Europe/North America | 44,717 | 73.3 |
| Caribbean / South America | 3,569 | 5.9 |
| Sub Saharan Africa | 7,729 | 12.7 |
| Other/Unknown | 4,982 | 8.2 |
| **Year of start ART (median, IQR)** | | 2007, 2004-2009 |
| 2001-2003 | 12,765 | 20.9 |
| 2004-2006 | 14,827 | 24.3 |
| 2007-2009 | 19,231 | 31.5 |
| 2010-2012 | 14,174 | 23.2 |
| **CD4 cell count at start of ART (cells/mm$^3$), median, IQR** | | 246, 130-350 |
| 0-49 | 7,301 | 12.0 |
| 50-99 | 4,838 | 7.9 |
| 100-199 | 11,263 | 18.5 |
| 200-349 | 22,206 | 36.4 |
| 350-499 | 9,575 | 15.7 |
| ≥500 | 5,814 | 9.5 |
| **HIV RNA at start of ART (copies/ml), median, IQR** | | 64,500, 14,300-182,800 |
| <10000 | 12,963 | 21.2 |
| 10000-100000 | 23,701 | 38.9 |
| ≥100000 | 24,333 | 39.9 |
| **Smoking status at the start of ART, missing in 1683/16650** (10.1%)** | | |
| Non-smoker | 8,515 | 56.9 |
| Current smoker | 6,452 | 43.1 |
| **Hepatitis C status at the start of ART, missing in 2093/21176** (9.9%)** | | |
| HCV-negative | 17,072 | 89.5 |

| | | |
|---|---|---|
| HCV-positive | 2,011 | 10.5 |
| **CMV status at the start of ART, missing in 1922/8418** (22.8%)** | | |
| CMV-negative | 740 | 11.4 |
| CMV-positive | 6,496 | 88.6 |

*MSM: Men who have sex with men, HCV: Hepatitis C virus, CMV: Cytomegalovirus

** Total number of participants in the subset of cohorts used in the analysis

**Table 2. Median (IQR) CD8 cell count and CD4:CD8 ratio at the start of ART for different CD4 categories.**

| CD4 cell count at the start of ART (cells/mm³) | N | CD8 cell count, median, IQR (cells/mm³) | CD4:CD8 ratio, median, IQR |
|---|---|---|---|
| 0-49 | 3,914 | 392, 233-610 | 0.05, 0.03-0.09 |
| 50-99 | 2,704 | 600, 402-890 | 0.11, 0.08-0.17 |
| 100-199 | 6,860 | 757, 525-1070 | 0.20, 0.14-0.28 |
| 200-349 | 13,654 | 900, 650-1250 | 0.27, 0.19-0.37 |
| 350-499 | 6,206 | 995, 717-1394 | 0.37, 0.26-0.52 |
| ≥500 | 3,967 | 1040, 753-1472 | 0.58, 0.41- 0.79 |
| Any CD4 cell count | 37,305 | 830, 560-1195 | 0.21, 0.11-0.34 |

CD8 cell count at the start of cART (cells/mm$^3$)
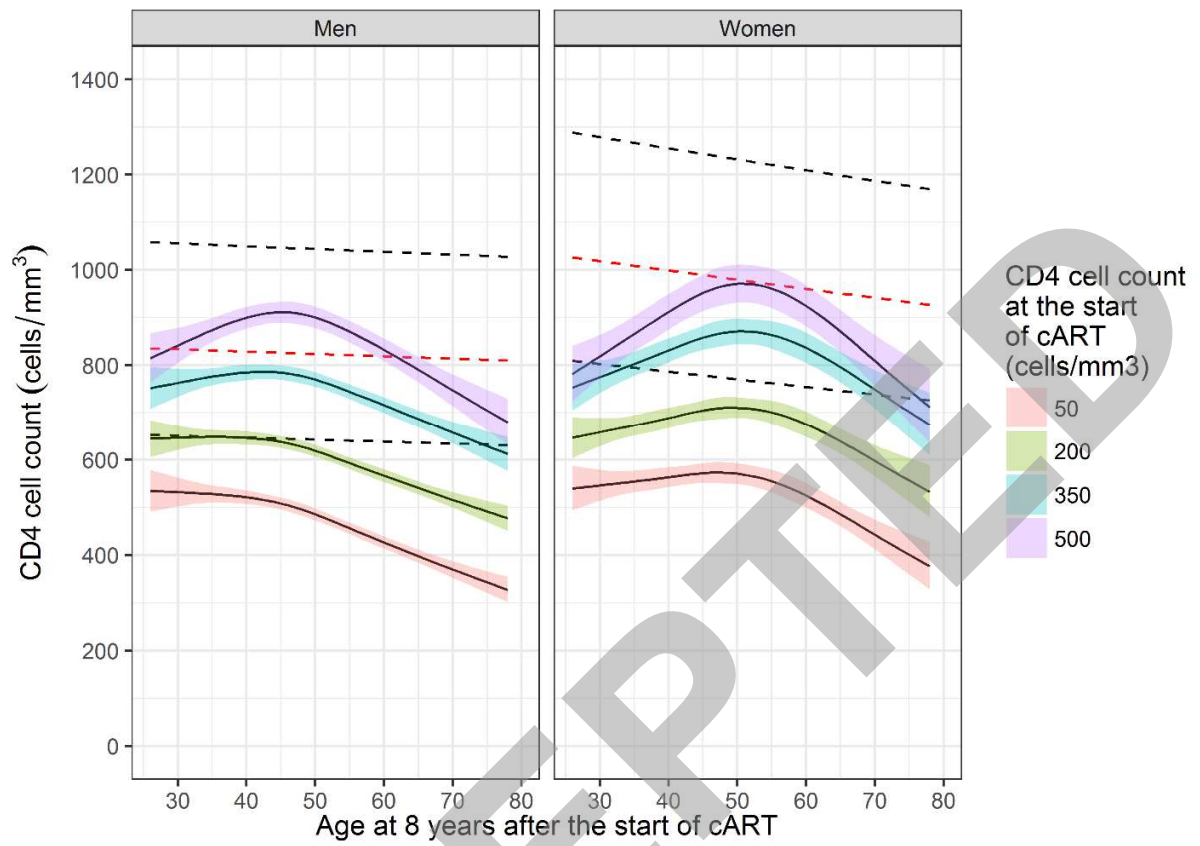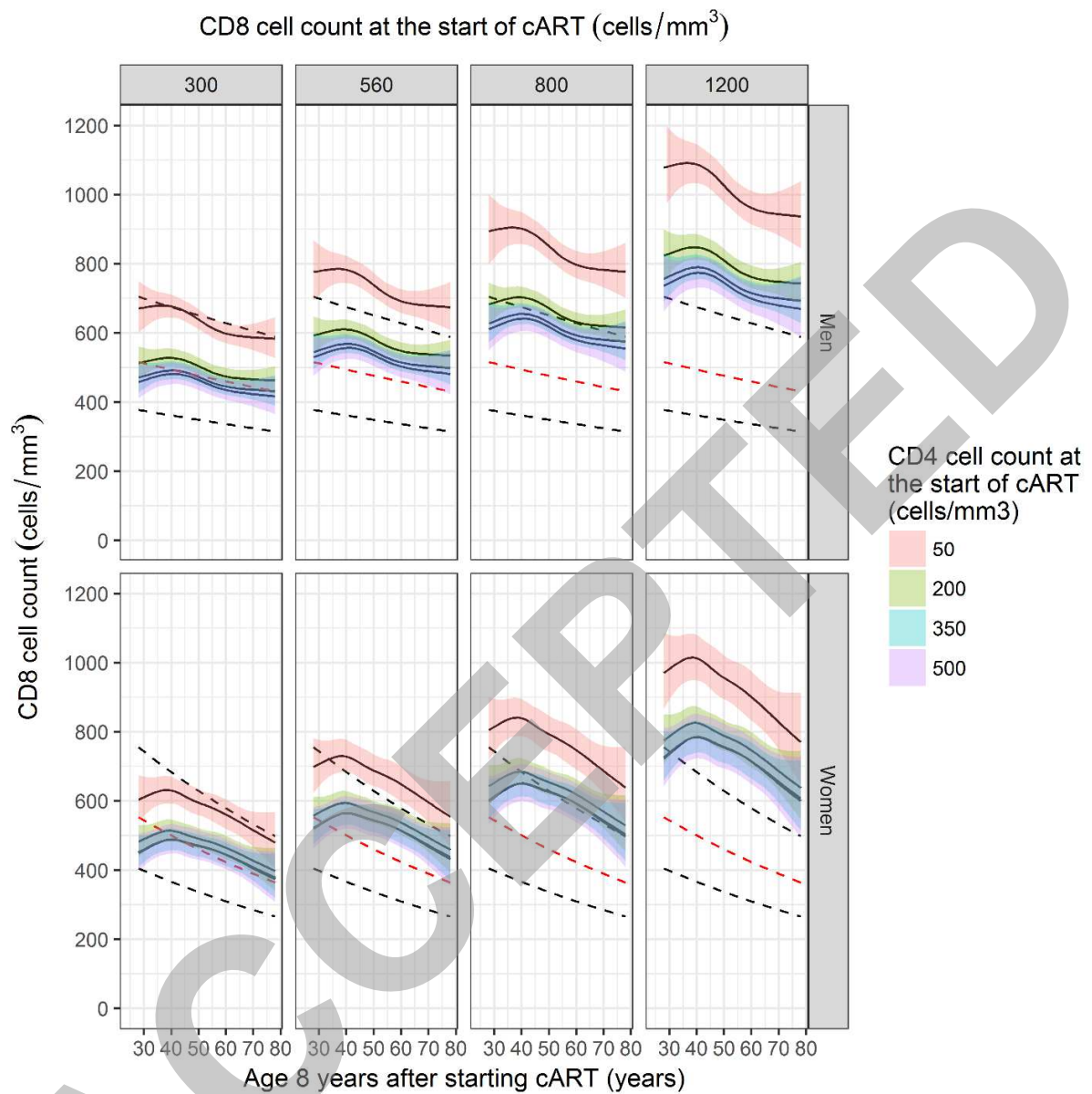
CD8 cell count at start cART (cells/mm$^3$)