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Long-term immunologic response to antiretroviral therapy in low-income countries: Collaborative analysis of prospective studies:

The Antiretroviral Therapy in Lower Income Countries (ART-LINC) Collaboration of the International epidemiological Databases to Evaluate AIDS

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Abstract

Background—Few data are available on the long-term immunologic response to ART in resource-limited settings, where antiretroviral therapy (ART) is being scaled up using a public health approach, with a limited repertoire of drugs.

Objectives—To describe immunologic response to ART in a network of cohorts from sub-Saharan Africa, Latin America, and Asia.

Study population/methods—Treatment-naïve patients aged 15 and older from 27 treatment programs were eligible. Multi-level, linear mixed models were used to assess associations between predictor variables and CD4 count trajectories following ART initiation.

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Results—Of 29,175 patients initiating ART, 8,933 patients (31%) were excluded due to insufficient follow-up time and early lost to follow-up or death. The remaining 19,967 patients contributed 39,200 person-years on ART and 71,067 CD4 measurements. The median baseline CD4 count was 114 cells/μL, with 35%<100 cells μL and substantial inter-site variation (range: 61-181 cells/μL). Females had higher median baseline CD4 counts than males (121 vs. 104 cells/μL). The median CD4 count increased from 114 cells/μL at ART initiation to 230 (IQR:144-338) at 6 months, 263 (IQR:175-376) at 1 year, 336 (IQR:224-472) at 2 years, 372 (IQR:242-537) at 3 years, 377 (IQR:221-561) at 4 years, and 395 (IQR:240-592) at 5 years. In multivariable models, baseline CD4 count was the most important determinant of subsequent CD4 count trajectories.

Conclusions—These data demonstrate robust and sustained CD4 response to ART among patients remaining on therapy. Public health and programmatic interventions leading to earlier HIV diagnosis and initiation of ART could substantially improve patient outcomes in resource-limited settings.

Keywords

antiretroviral therapy; CD4 response; CD4 lymphocyte count; low-income countries; baseline CD4 count; ART-LINC; IeDEA

Introduction

CD4 cell count and HIV RNA viral load in response to antiretroviral therapy (ART) are important measures of the efficacy of ART in individual patients and of the effectiveness of ART in populations of patients enrolled in HIV care and treatment programs. However, few data exist on long-term CD4 response to ART among patients receiving care in resource-limited settings, where HIV RNA testing is not generally available or conducted. Several studies in Europe and North America have reported robust improvements in CD4 cell counts following ART initiation in clinical trials and in observational studies.[1-17] In addition, CD4 count at the time of ART initiation is an important determinant of the degree of immunologic and virologic response,[16, 18-21] as well as subsequent risk of morbidity and mortality.[7, 22, 23] Among those patients who are able to remain on ART, robust immunologic responses can be maintained for long periods,[2, 3, 10, 12] and the risk of serious morbidity and mortality may eventually diminish to levels observed in the general population.[24]

Although data from resource-limited settings are less commonly available, some investigators of research and scale-up cohorts in sub-Saharan Africa,[25-31] Barbados,[32] Brazil[33,34] China,[35] Thailand,[36] and Cambodia[37] have reported effects of ART on clinical and immunologic outcomes that were comparable to those observed in resource-rich settings. However the majority of the studies in developing countries have had follow-up times of 1 to 2 years, Thus while it has been shown in developed countries[2, 12, 17], the degree which CD4 responses can be maintained for longer periods of time after ART initiation in developing countries has not been demonstrated. This analysis was conducted to describe the determinants of CD4 response trajectories up to 5 years after initiation of ART in resource-limited settings.

Methods

Study population

The Antiretroviral Therapy in Low-Income Countries (ART-LINC) Collaboration of the International Databases to Evaluate AIDS (IeDEA) (see www.art-linc.org and www.iedea-hiv.org) is a network of HIV/AIDS treatment programs in Africa, Latin America, and Asia, which has been described in detail elsewhere.[38, 39] Briefly, HIV care and treatment programs from low and middle income countries were approached to determine their interest

and capacity to collaborate. Thirty-two treatment programs were approached, 29 agreed to participate, and 27 contributed data to the present analysis.

All patients initiating ART who were ART naïve, aged 15 years or older and had an enrollment date such that they had the potential contribute at least 6 months of follow-up data on ART were eligible for this analysis. Patients with a baseline CD4 count of 500 cells/μL or above or missing data in key variables were excluded. Baseline CD4 count was defined as the CD4 measurement occurring closest to the date of starting ART, within a window of 6 months prior to 1 week after ART initiation. The frequency of CD4 testing varied by site, but was generally about two CD4 tests per year. Data collection was approved by Institutional Review Boards or ethics committees for all cohorts. ART was defined as any combination of at least 3 antiretroviral drugs.

Statistical methods

Patients were classified as being dead, lost to program, or presumed to be alive and on ART based on all available information at the time of the closure of the study database. Lost to follow-up was defined as not returning to clinic for 1 year or longer after the last recorded visit, as described elsewhere for this study population.[40] Time on ART was measured from the ART initiation date to the last known encounter. Data were censored at the closing date of each cohort out to a maximum of 5 years post-ART-initiation. Descriptive analyses were done to examine CD4 count distributions over time on ART, and trends in the mean and median CD4 count over time on ART.

Linear mixed regression models for repeated measures were used to evaluate the association between independent variables and CD4 response over time on ART. We constructed a multi-level model (CD4 measurements within patients nested within cohorts) with random intercepts for each patient and cohort. CD4 count response values were square-root transformed to achieve a normal distribution. Baseline CD4 count was included in the models as a categorical variable (0-24, 25-49, 50-99, 100-149, 150-199, 200-299, 300+ cell/μL). To allow flexible modeling of the CD4 response with time on ART we tested a series of fractional polynomial (FP) functions up to the third order.[41, 42] The FP function was allowed to vary between baseline CD4 categories by including interaction terms. We further allowed for random variation in the slope of the FP function between individuals. The model with the highest gain in fit, a second order FP with time transformed to the power -0.5 and the natural logarithm of time (FP[2, (-0.5, ln)], was used in final modeling.

The following variables were considered or their influence on CD4 trajectory: gender, age at ART initiation; clinical stage of disease, year of ART initiation and initial ART regimen. For age we used three categories: 15-29, 30-39, and 40-65 years. Clinical stage was categorized as less advanced (CDC stage A/B, WHO stage I/II), more advanced (CDC stage C, WHO stage III/IV), or not assessed/unknown. Year of HAART initiation was entered as before 2001, 2001, 2002, 2003, 2004, 2005, 2006 and 2007. Type of ART regimen was classified as protease inhibitor (PI) based (2 nucleoside reverse transcriptase inhibitors (NRTIs) + 1 PI, including ritonavir boosted PI), non nucleoside reverse transcriptase inhibitor (NNRTI) based (2 NRTIs + 1 NNRTI), and other or unknown regimens.

Some patients had missing information on baseline CD4 cell count and baseline clinical stage. In order to account for missing data, we used multiple imputation by chained equations to impute the data conditional on the first CD4 cell count after start of HAART, the time form start of HAART until the first CD4 response, as well as the other predictor variables.[43, 44] Details are given in the appendix. Modelling of the CD4 response over time as described above was on five imputed datasets; results were combined using Rubin's rules. Model results were similar in raw and imputed data sets. Analyses were done using SAS version 9.1 (SAS Institute,

Inc, Cary, NC) and Stata version 10.0 (Stata Corporation, College Station, TX). Results are presented as medians and interquartile ranges (IQR).

Results

Of 35,010 treatment-naïve patients aged 15 and over who initiated ART in 1995 or later at one of the ART-LINC collaborating centers, 5,835 patients (17%) were ineligible because the maximum follow-up time they could contribute was less than 6 months, and 264 patients (0.8%) were ineligible because the baseline CD4 count was ≥500 cells/μL. Of the 28,911 eligible patients, 8,933 (26%) were excluded because they had either no recorded CD4 count (n=2,291) or had a baseline CD4 count, but no follow-up counts (n=6,642). An additional 11 patients were excluded due to missing information on their sex. The 19,967 patients included in analyses contributed a total of 71,067 CD4 count measurements (median per patient 3, range 1-27) up to 5 years post-ART initiation. 15,778 patients (79.0%) had a baseline and >1 follow-up CD4 count, 2,670 (13.4%) had >1 follow-up count but no baseline measurement, and 1,519 (7.6%) had 1 follow-up CD4 count but no baseline measurement. The overall time on ART for patients included in this analysis was 39,200 person-years.

Patients excluded from analyses due to missing CD4 counts (n=8,933) were more likely to be male (43% vs. 40%, p<0.001) and of either a less advanced (50% vs. 57%, p<0.001) or unknown stage of disease (17% v 9%, p<0.001) when compared to those included in the analysis. Of the 8,933 excluded, 4,370 (49%) were presumed to be alive and attending clinic; 1,352 (15%) were known to have died (86% within six months following ART initiation); and 3,111 (35%) were considered lost to follow up as of the closing date of the database.

Characteristics of study population

Characteristics of the 19,967 patients in the cohort are described in Table 1. There were 16,170 patients from 22 centers in Africa (81%), 1,398 patients from 3 centers in Latin America (7%), 2,399 patients from 2 centers in India and Southeast Asia (12%). The majority of patients (60%) was female, and the median age at ART initiation was 35 years. Among those with a baseline weight recorded (80% of patients), the median was 55 kg for females (IQR 48-63 kg) and 58 for males (IQR 52-65 kg). Among patients with a baseline CD4 count (79% of patients), the median was 114 cells/μL;121 cells/μL for females (IQR: 56-186) and 104 for males (IQR 45-179). The range of the median CD4 count at ART initiation varied widely by cohort (from 61 to 181 cells/μL) with higher counts in females compared to males in all but 2 sites (Figure 1). Among those with less advanced clinical stage and a baseline CD4 count (n=5,460), 4,221 (77%) had a count below 200 cells/μL. A majority of patients initiated ART in an advanced clinical stage of HIV disease and most patients started on regimens with 2 NRTIs and 1 NNRTI (92%), with 6% starting with 2 NRTIs and a PI (Table 1).

During follow-up, 568 patients died (3%) and 1,790 were lost to follow-up (9%); 820 patients (4%) from eight sites were followed up beyond 4 years after starting ART.

CD4 count trajectories after ART initiation

The median time on ART was 1.6 years (IQR: 1.1-2.7 years). The median number of CD4 counts over the follow-up period was 1.8 per person-year on ART (range across centers: 0.4-3.5). The median CD4 was 114 cells/μL among all patients at baseline and increased to 395 cells/μL among those remaining on ART for 5 years. Figure 2 shows the crude median CD4 over time on ART stratified by sex, age, clinical stage, initiation regimen, baseline CD4, and status of patient at closure of the database. Increases were steeper in females than males, with differences widening with time on ART. Increases were also more pronounced in younger patients compared to older patients. Smaller differences were observed between patients

initiating ART in more advanced and less advanced clinical stages, and patients starting ART with different regimens. The baseline CD4 count was the most important factor: patients initiating ART with higher CD4 counts tended to maintain higher levels up to 5 years. CD4 counts increased in all patients except in patients who died. Of note, those who were lost to follow up had CD4 trajectories similar to those who were known to be alive (Figure 2).

Regression models

In multivariable regression models, CD4 counts and age at baseline continued to predict trajectories, whereas the effect of sex virtually disappeared. Tables 2a and 2b give predicted mean CD4 counts over time by age and baseline CD4 count for males and females. Only patients initiating ART at 200 cells/μL and higher would be expected attain a CD4 count near or above 500 cells/μL after 5 years of therapy. Figure 3 shows the predicted trajectory in median CD4 counts by baseline CD4 and the observed median CD4 count at each time point. Starting ART at CD4 counts below 100 cells/μL was associated with substantially worse predicted CD4 trajectories when compared with those of patients who started at higher CD4 counts. The model fit was good when comparing predicted with observed data.

Discussion

This study combined data from 27 centers from resource-limited settings in Africa, Latin America, and Asia to assess CD4 trajectories after ART initiation at sites engaged in the scale-up of HIV care and treatment. The data demonstrate robust CD4 responses to ART that are sustained over several years. Our results are thus encouraging regarding the long-term effectiveness of ART in resource-limited settings, but they naturally are only applicable to those who are able to remain on ART for extended periods.

The availability of information on CD4 count in and of itself was likely a critical factor in getting many patients on to ART earlier than they otherwise would have in these programs. Were the programs to rely solely on clinical staging criteria, 77% of patients with less advanced clinical stage had CD4 counts<200 cells/μL, suggesting that they would have started therapy even later or not in time, limiting the full potential to benefit from therapy. Thus, extending access to CD4 testing in programs that don't currently have it would likely improve treatment outcomes substantially.

Apart from the amount of time on ART, the single most important factor determining CD4 trajectories and the maximum CD4 count reached was the baseline CD4 count. Patients with higher CD4 counts at ART initiation achieved a higher CD4 count in the following months and years. While this has been shown by other investigators in both resource-rich[12, 20, 45] and resource-limited settings,[28, 46] the importance of this observation cannot be overstated. The baseline CD4 count, second only to subsequent medication adherence (which we could not measure), is the most important predictor of clinical progression and survival after ART initiation.[7, 22, 23, 30, 47-49] Patients with lower baseline CD4 count remain at risk for opportunistic infections for a substantially longer period than patients starting ART at higher CD4 counts, increasing their risk for serious morbidity and death. In this analysis 35% of patients had a baseline CD4 count below 100 cells/μL, and 29% had a count between 100 and 199 cells/μL. Fortunately, a recent analysis of the ART-LINC database indicated that median CD4 counts at the start of ART, while still low in most of the cohorts, have increased in recent years.[50] However, our models predictions suggest that, after several years of therapy, only those few patients initiating ART at 200 cells/μL or higher could be expected to achieve CD4 counts near or above 500 cells/ μL or higher (Tables 2a and 2b), the level at which their risk of mortality may diminish to that observed in the general population in some settings.[24]

While most patients quickly achieved CD4 counts above the important clinical milestone of 200 cells/μL, we also note that there remains increased risk of morbidity and mortality at CD4 counts of 200 cells/μL, especially in developing countries.[24] In our study of survival in these cohorts, we showed that the risk of mortality continues to diminish with increasing CD4 count, even among patients with CD4 counts above 200 cells/μL.[39] For example, relative to those patients with baseline CD4 counts below 25 cells/μL, we found an RR of 0.67 in patients with baseline CD4 count between 100-200 cells/μL, 0.44 in patients with baseline CD4 between 200 and 349 cells/μL, and 0.26 in patients with baseline CD4 counts above 350 cells/μL. Additionally, in one study of South African patients on ART for 3 or more years, the risk of incident TB was still 5-10 times higher than in the general population.[51] Finally, the SMART study recently reported a higher incidence of OIs in those patients who interrupted therapy, almost all of whom had CD4 counts>200 cells/μL.[52]

Our findings on long-term CD4 response appear to be consistent with those of other long-term investigations in Switzerland[12], the US[2], and the Netherlands[17], which examined immunologic response up to 4, 6, and 7 years after ART initiation, respectively. However, these studies were restricted to continuously treated, virologically suppressed patients, making a comparison with our patients difficult. Other factors may further confound this comparison, such as lower in CD4 counts in the general populations in developing versus developed countries, which could be due to other differences such as the prevalence of TB or helminth co-infections. Nonetheless, an important next step, therefore, is to conduct more direct comparisons of CD4 response between developed and developing countries within strata of baseline CD4 while controlling for other differences between the patient populations.

An intriguing finding in our investigation and others is the differences in trajectories by sex in crude analyses. We have previously reported sex differences in the CD4 count at ART initiation.[53] In the present study, females had higher baseline CD4 counts in 25 of the 27 cohorts included in the analysis. Similar to other investigators who have reported sex differences in CD4 response after ART initiation in Spain[54], we found that differences in CD4 trajectories after starting ART were largely explained by different CD4 counts at baseline.

Given that baseline CD4 count is such an important determinant of CD4 trajectories after ART initiation, it is important to gain a better understanding of the determinants of baseline CD4 count among patients initiating ART in resource-limited settings. These determinants operate at multiple levels, starting with knowledge of being at risk for HIV infection, access to and uptake of HIV testing and counseling, intensity of active screening for HIV in the health care setting, entry points in to care, availability of CD4 testing, and, among programs providing pre-ART care, frequency and intensity of clinical monitoring and CD4 testing. Some of these factors are more easily modifiable than others. A recent investigation in the Netherlands suggested that entry into care with low CD4 counts explained a substantial portion of the variation in mortality rates across HIV care and treatment centers.[55] Clearly, further studies are needed to help inform efforts aimed at getting patients on to ART at higher CD4 counts.

Most national care and treatment programs have adapted the WHO criteria for ART eligibility. Updated in 2006, they recommend initiating ART in i) patients in WHO stage 4; ii) all patients with CD4 counts below 200 cells/μL (irrespective of WHO stage), and iii) in patients with WHO stage 2/3 and CD4 counts below 350 cells/μL.[56] In our analysis, only 6% of patients were eligible based on having less advanced disease with CD4 counts between 200 and 350 cells/μL. In other words, 94% of patients who initiated ART at ART-LINC sites were in the advanced clinical and immunologic stages by the time they initiated treatment. Our analysis clearly suggests that there is substantial room for improvement in earlier initiation of ART across a diversity of geographic settings.

Our study has several strengths. Twenty-seven sites on three continents were represented in the analysis, and the overall finding (substantial improvements in CD4 counts after ART initiation) was consistent across the diversity of geographical settings and contexts. Our results should thus be applicable to a wide range of lower-income settings. In addition, this investigation benefited from a large amount of follow-up time (up to 5 years for some patients). While the numbers of patients remaining in follow-up decreased substantially with time since start of ART, there were still 820 patients from 8 clinics who were actively followed up in the fifth year. These findings are thus encouraging for patients, providers, and program implementers involved in the scale-up of HIV care and treatment service delivery in some of the most affected areas of the world.

Our study also has limitations. We had to exclude a substantial number of patients due to lack of follow-up CD4 counts. These patients differed systematically from those who were included in the analysis: they were more likely to die or be lost before a follow-up CD4 count could be measured. Our analysis will thus probably overestimate the true impact of ART on CD4 counts in all patients initiating ART, particularly in the first 6 months after ART initiation. This is illustrated by the CD4 trajectories of patients known to have died or lost to follow up (Figure 2). However, since excluded patients had no follow-up CD4 count measurements, we had no way of taking this into account in our analysis. Of note, the median baseline CD4 count among patients excluded from analyses because follow-up CD4 counts were measured was 82 cells/μL for patients who died and 117 cells/μL for patients lost to follow up. This is very comparable to the median counts in patients included in analyses that died or were lost to follow up (79 and 121 cells/μL, respectively). Nevertheless, we emphasize the point that our findings apply only to those patients who survived and remained in care with follow-up CD4 counts.

The range of calendar years during which participating sites contributed data varied. While there was substantial overlap between sites, data were not contributed uniformly over the entire time period. While we controlled for site and calendar year of ART initiation in our statistical model, it is possible that this may have influenced results. Finally, the sites participating in the ART-LINC collaboration of IeDEA represent a convenience sample, which are unlikely to be representative of all treatment programs in the country. While there are no data that we can use to assess this directly, the ART-LINC sites are almost exclusively in urban settings, and more likely to represent secondary and tertiary care facilities or centers of excellence than other sites not participating in the collaboration. Similar studies using data from other scale-up sites in primary health centers and rural settings are therefore needed.

In conclusion, our study demonstrates robust CD4 response to ART among patients in multiple treatment programs in resource-limited settings. The response appears to be sustained among those remaining in programs for up to 5 years. Our results thus support the notion that a programmatic, public health approach to ART in resource-limited settings using a limited repertoire of drugs can result in sustained immunologic and virologic outcomes that are comparable to industrialized countries.[57] However, given that the most important determinant of long-term CD4 response was the baseline CD4 count at ART initiation, our data also suggest that many patients in developing countries must be started much earlier in order to achieve an optimal on treatment CD4 count over the long term. In light of evidence suggesting that treated HIV positive persons who achieve a CD4 cell count of 500 cells/μL or higher can expect normal life expectancy[24], we feel that it is very important for programs and clinicians to aim for CD4 counts closer to 500 cells/μL at 3-5 years by enrolling and initiating patients on ART earlier, so that lower risks of morbidity and mortality may be attained. Thus, our study has important implications for development of guidelines and for future trials regarding when to start antiretroviral therapy.

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Roles of authors

D Nash, M Brinkhof, and M Egger designed the analysis and wrote the paper. M Brinkhof, M Katyal, and D Nash conducted the statistical analysis, and M Brinkhof conducted the statistical modeling and multiple imputation. M May and R Hughes contributed to the statistical modeling approach. Olivia Keiser, Francois Dabis, Robin Wood, Eduardo Sprinz, Mauro Schechter, and Matthias Egger contributed ideas for analysis and to the writing and editing of the manuscript.

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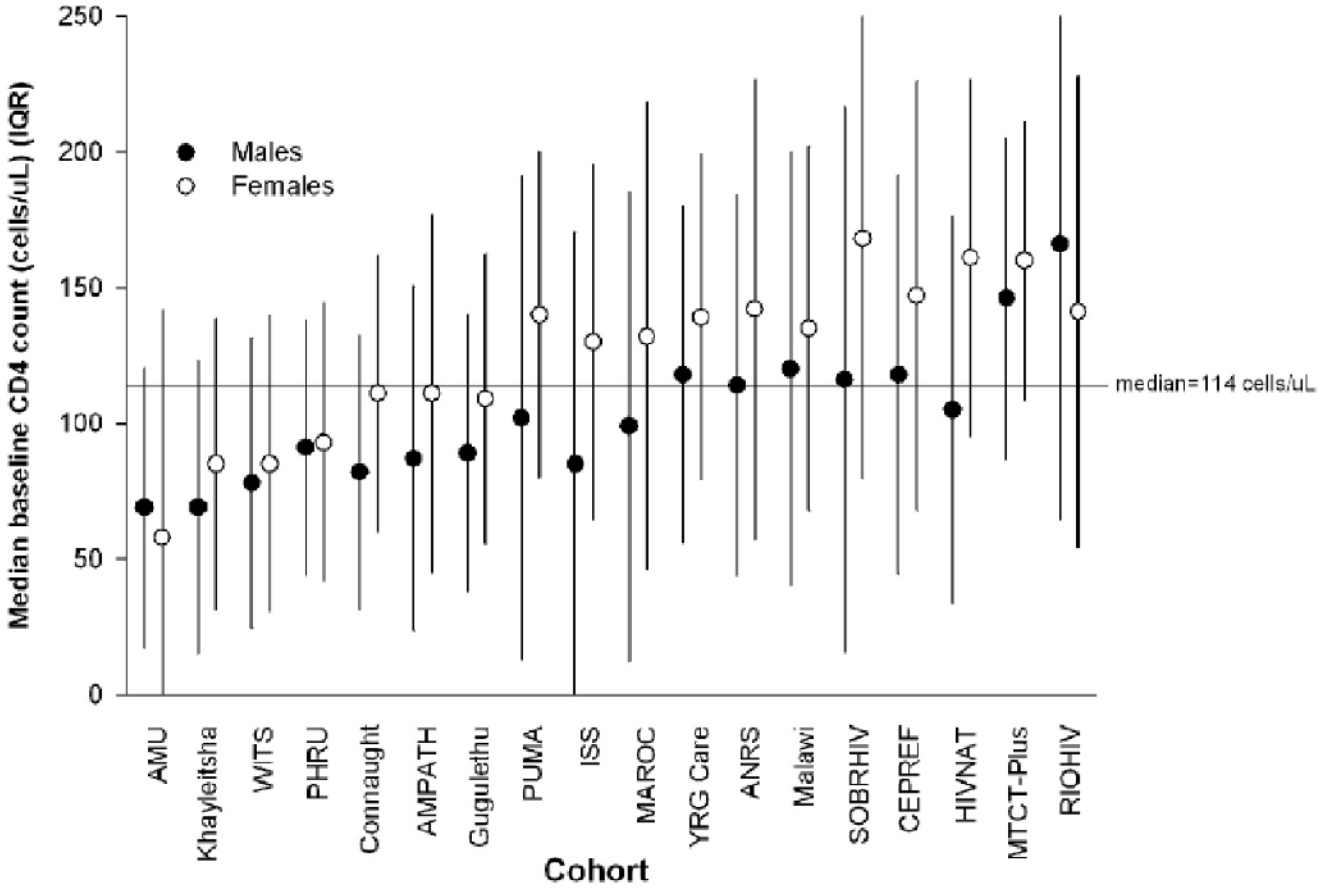

Figure 1.
Median CD4 count at ART initiation by sex and cohort.

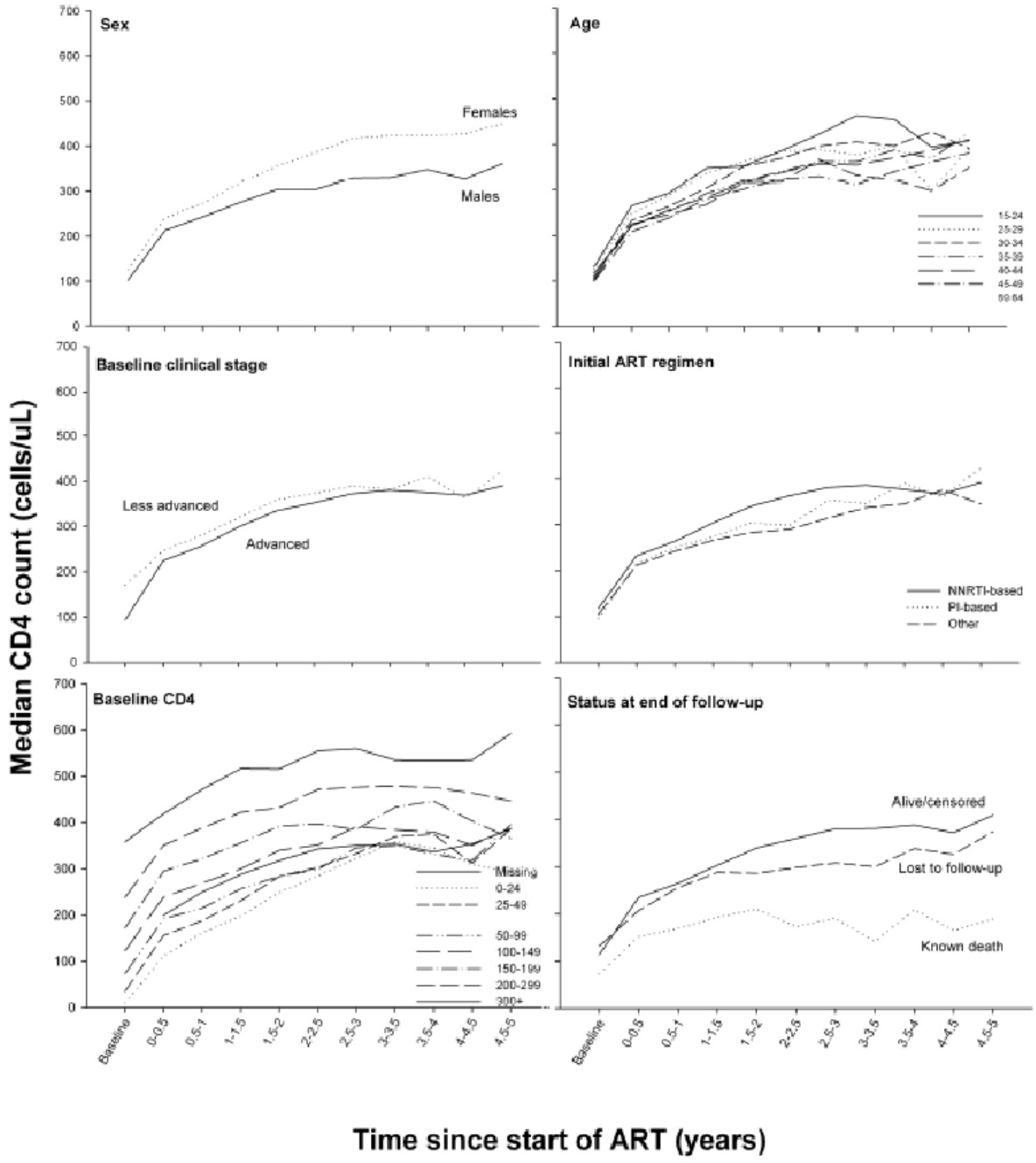

Figure 2.
Median CD4 count over time on ART by sex, age at ART initiation, clinical stage, ART regimen, CD4 count at ART initiation, and status at the end of the follow-up period.

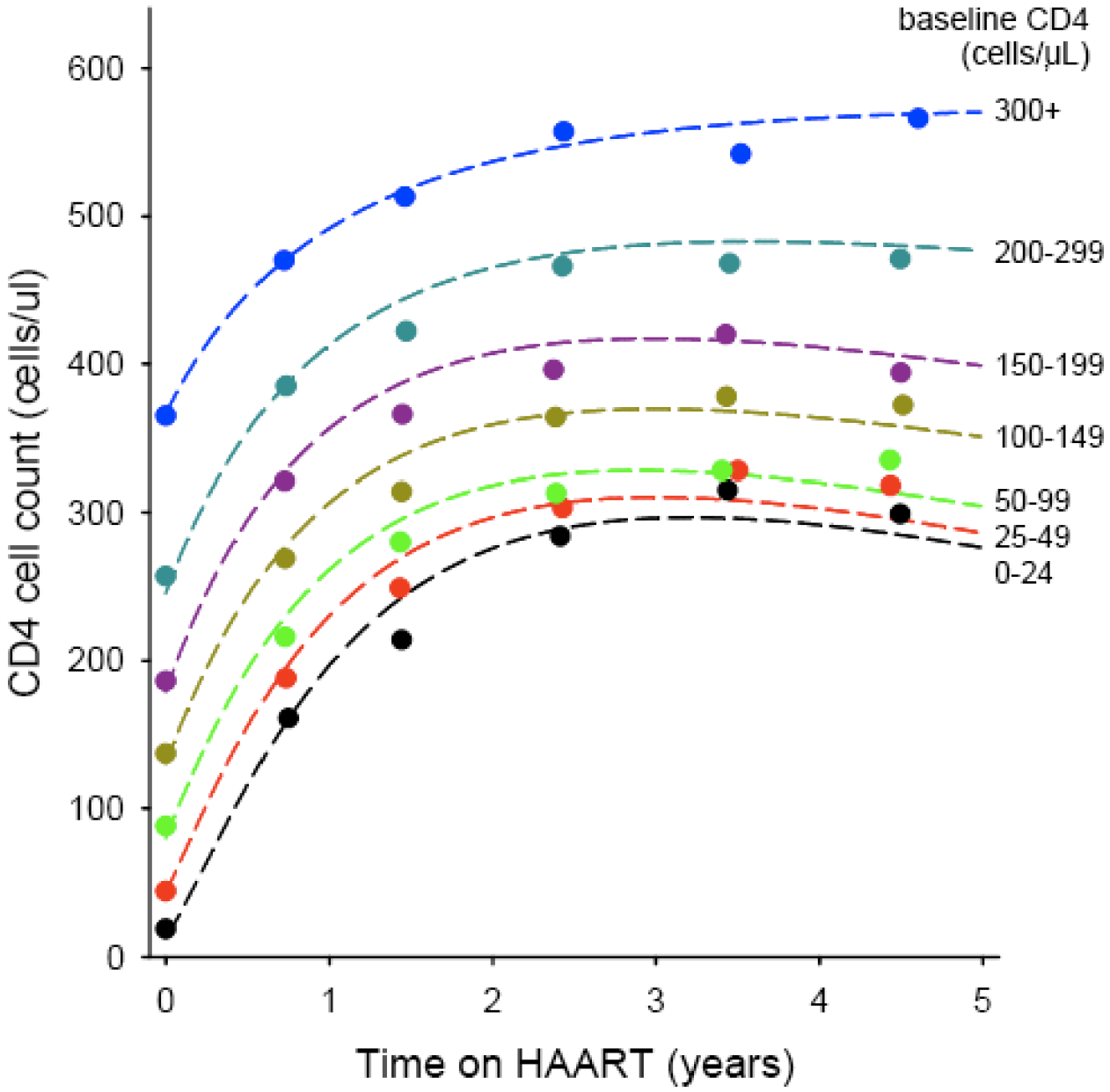

Figure 3.

Median CD4 count with time of HAART, stratified by baseline CD4 cell count. The lines give the predicted response for baseline CD4 categories from the mixed-effects model. Fractional polynomials for each baseline CD4 category were modelled with an overall intercept (constant) representing the most common patient group: age 30-39, female and year 2004. The symbols give the overall observed median CD4 cell count in each baseline CD4 category by successive time periods on HAART.

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Table 1

Baseline characteristics of patients included in analyses

	All patients (n=19,967		Men (n=7943)		Women (n=12024)		p[1]
Age (years)							
Median (range)	35	(15-65)	37	(16-65)	33	(15-65)	<0.001
15-24	1189	(6%)	202	(3%)	987	(8%)	
25-29	3468	(17%)	868	(11%)	2600	(22%)	
30-34	5050	(25%)	1835	(23%)	3215	(27%)	
35-39	4263	(21%)	1977	(25%)	2286	(19%)	<0.001
40-44	2826	(14%)	1396	(18%)	1430	(12%)	
45-49	1679	(8%)	844	(11%)	835	(7%)	
50-=<65	1492	(7%)	821	(10%)	671	(6%)	
Weight (kg)							
Median (range)	56	(50-64)	58	(52-65)	55	(48-63)	<0.001
Missing	3947	(20%)	2009	(25%)	1938	(16%)	
19-49	4002	(20%)	1028	(13%)	2974	(25%)	
50-54	3005	(15%)	1095	(14%)	1910	(16%)	<0.001
55-62	4439	(22%)	1904	(24%)	2535	(21%)	
63-180	4574	(23%)	1907	(24%)	2667	(22%)	
CD4 count (cells/uL)[2]							
Median (IQR)	114	(51-84)	104	(45-179)	121	(56-186)	<0.001
Missing	4189	(21%)	1842	(23%)	2347	(20%)	
0-24	2165	(11%)	929	(12%)	1236	(10%)	
25-49	1671	(8%)	734	(9%)	937	(8%)	
50-99	3129	(16%)	1273	(16%)	1856	(15%)	<0.001
100-149	2918	(15%)	1070	(13%)	1848	(15%)	
150-199	2782	(14%)	950	(12%)	1832	(15%)	
200-299	2238	(11%)	832	(10%)	1406	(12%)	
300+	875	(4%)	313	(4%)	562	(5%)	
Stage of HIV disease[3]							
Advanced	11427	(57%)	4671	(59%)	6756	(56%)	
Less advanced	6709	(34%)	2509	(32%)	4200	(35%)	<0.001

	All patients (n=19,967		Men (n=7943)		Women (n=12024)		p[1]
Unknown	1831	(9%)	763	(10%)	1068	(9%)	
Year of ART initiation							
<2001	866	(4%)	550	(7%)	316	(3%)	
2001	581	(3%)	314	(4%)	267	(2%)	
2002	1249	(6%)	669	(8%)	580	(5%)	
2003	2412	(12%)	1111	(14%)	1301	(11%)	<0.001
2004	7254	(36%)	2509	(32%)	4745	(39%)	
2005	5117	(26%)	1853	(23%)	3264	(27%)	
2006/7	2488	(12%)	937	(12%)	1551	(13%)	
Initial HAART regimen[4]							
2NRTIs+1NNRTI	18322	(92%)	7081	(89%)	11241	(93%)	
2NRTIs+1PI	1134	(6%)	659	(8%)	475	(4%)	<0.001
Other/unknown	511	(3%)	203	(3%)	308	(3%)	
Location							
Africa (22 sites)	16170	(81%)	5275	(66%)	10895	(91%)	
Asia (2 sites)	2399	(12%)	1755	(22%)	644	(5%)	<0.001
Latin America (3 sites)	1398	(7%)	913	(11%)	485	(4%)	

[1] Comparing males and females (Chi-square test for categorical variables and t-test for continuous variables)

[2] Baseline CD4 defined as the CD4 count closest to and within -6 months to + 1 week of the date of ART initiation

[3] Less advanced (CDC stage A/B, WHO stage I/II); advanced (CDC stage C, WHO stage III/IV)

[4] NRTI=Nucleoside reverse transcriptase inhibitor; NNRTI=non-Nucleoside reverse transcriptase inhibitor; PI=Protease Inhibitor

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Table 2

Table 2a: Predicted CD4 response with time on treatment in women, by baseline CD4 category and age at start of ART.

Age group	Baseline CD4 (cells/μL)	Mean CD4 count (cells/μL) with 95% confidence interval					
		At start of HAART	At 1 year	At 2 years	At 3 years	At 4 years	At 5 years
15-29	<25	15 (14 - 17)	202 (196 - 208)	282 (272 - 292)	302 (289 - 316)	298 (280 - 316)	282 (261 - 303)
	25-49	45 (43 - 48)	236 (229 - 243)	303 (291 - 315)	317 (298 - 336)	309 (284 - 334)	292 (262 - 323)
	50-99	84 (81 - 87)	267 (261 - 274)	325 (315 - 334)	335 (322 - 348)	326 (310 - 343)	310 (291 - 330)
	100-149	135 (131 - 139)	313 (306 - 320)	366 (355 - 377)	376 (361 - 392)	370 (350 - 391)	357 (333 - 382)
	150-199	185 (180 - 189)	364 (356 - 371)	415 (404 - 426)	424 (409 - 440)	418 (399 - 438)	406 (383 - 429)
	200-299	252 (247 - 257)	420 (412 - 429)	473 (460 - 486)	489 (470 - 508)	490 (466 - 515)	484 (454 - 515)
	300+	373 (366 - 381)	500 (487 - 513)	545 (525 - 566)	565 (538 - 594)	575 (539 - 612)	579 (535 - 624)
30-39	<25	14 (13 - 15)	197 (191 - 203)	276 (266 - 286)	296 (283 - 310)	291 (274 - 309)	276 (256 - 297)
	25-49	43 (41 - 45)	230 (223 - 238)	297 (285 - 309)	310 (292 - 329)	302 (278 - 328)	286 (256 - 317)
	50-99	81 (78 - 83)	262 (255 - 268)	318 (309 - 328)	328 (315 - 341)	320 (304 - 336)	304 (285 - 323)
	100-149	131 (127 - 134)	307 (300 - 313)	359 (348 - 370)	369 (354 - 385)	363 (343 - 384)	351 (326 - 375)
	150-199	180 (176 - 184)	357 (349 - 364)	407 (396 - 418)	417 (402 - 432)	411 (392 - 430)	399 (376 - 422)
	200-299	246 (241 - 251)	413 (404 - 422)	465 (453 - 478)	481 (463 - 499)	482 (458 - 507)	476 (447 - 507)
	300+	367 (359 - 374)	492 (479 - 505)	537 (517 - 557)	557 (529 - 585)	566 (531 - 603)	570 (527 - 615)
40-65	<25	13 (12 - 15)	195 (189 - 201)	274 (264 - 283)	294 (280 - 308)	289 (272 - 307)	274 (253 - 295)
	25-49	42 (40 - 44)	228 (221 - 236)	294 (282 - 306)	308 (290 - 326)	300 (276 - 325)	284 (254 - 314)
	50-99	79 (77 - 82)	259 (253 - 266)	316 (306 - 325)	325 (313 - 339)	317 (301 - 334)	302 (283 - 321)
	100-149	129 (126 - 133)	304 (297 - 311)	356 (345 - 368)	367 (351 - 383)	361 (341 - 381)	348 (324 - 373)
	150-199	178 (174 - 182)	354 (347 - 361)	404 (394 - 415)	414 (399 - 429)	408 (389 - 428)	396 (373 - 419)
	200-299	244 (239 - 249)	410 (402 - 419)	462 (449 - 475)	478 (459 - 497)	479 (455 - 504)	473 (443 - 504)
	300+	364 (356 - 372)	489 (476 - 502)	534 (514 - 554)	554 (526 - 582)	563 (528 - 599)	567 (524 - 611)

Table 2b: Predicted CD4 response with time on treatment in men, by baseline CD4 category and age at start of ART.

		Mean CD4 count (cells/μL) with 95% confidence interval

Table 2a: Predicted CD4 response with time on treatment in women, by baseline CD4 category and age at start of ART.

Age group	Baseline CD4 (cells/μL)	Mean CD4 count (cells/μL) with 95% confidence interval					
		At start of HAART	At 1 year	At 2 years	At 3 years	At 4 years	At 5 years
Age group	Baseline CD4 (cells/μL)	At start of HAART	At 1 year	At 2 years	At 3 years	At 4 years	At 5 years
15-29	<25	14 (12 - 15)	196 (190 - 202)	274 (265 - 284)	295 (281 - 308)	290 (273 - 308)	274 (254 - 296)
	25-49	42 (40 - 45)	229 (222 - 236)	295 (283 - 308)	309 (290 - 328)	301 (276 - 326)	284 (255 - 315)
	50-99	80 (77 - 83)	260 (253 - 267)	316 (307 - 326)	326 (313 - 339)	318 (302 - 334)	302 (284 - 322)
	100-149	130 (126 - 133)	305 (298 - 312)	357 (346 - 369)	368 (352 - 384)	362 (341 - 382)	349 (325 - 374)
	150-199	178 (174 - 183)	355 (347 - 363)	405 (394 - 417)	415 (400 - 431)	409 (390 - 429)	397 (374 - 420)
	200-299	245 (239 - 250)	411 (402 - 420)	463 (450 - 476)	479 (461 - 497)	480 (456 - 505)	474 (445 - 505)
	300+	365 (357 - 373)	490 (477 - 503)	535 (515 - 555)	555 (527 - 583)	564 (528 - 601)	568 (525 - 613)
30-39	<25	12 (11 - 13)	191 (185 - 197)	268 (259 - 278)	288 (275 - 302)	284 (267 - 301)	269 (249 - 289)
	25-49	40 (38 - 42)	224 (216 - 231)	289 (277 - 301)	302 (284 - 321)	295 (270 - 320)	278 (249 - 309)
	50-99	77 (74 - 79)	254 (248 - 261)	310 (301 - 319)	320 (307 - 332)	312 (296 - 327)	296 (278 - 315)
	100-149	126 (122 - 129)	299 (292 - 306)	351 (340 - 362)	361 (345 - 377)	355 (335 - 375)	342 (318 - 367)
	150-199	174 (170 - 178)	348 (341 - 356)	398 (387 - 409)	408 (393 - 423)	402 (383 - 421)	389 (367 - 413)
	200-299	239 (234 - 244)	404 (395 - 413)	455 (443 - 468)	471 (453 - 489)	472 (448 - 496)	467 (437 - 497)
	300+	358 (350 - 365)	482 (469 - 495)	526 (507 - 546)	546 (519 - 574)	555 (520 - 592)	559 (516 - 604)
40-65	<25	12 (11 - 13)	189 (183 - 195)	266 (257 - 276)	286 (273 - 300)	281 (264 - 299)	266 (246 - 287)
	25-49	39 (37 - 41)	221 (214 - 229)	287 (275 - 299)	300 (282 - 318)	292 (268 - 317)	276 (247 - 306)
	50-99	75 (73 - 78)	252 (246 - 259)	308 (298 - 317)	317 (305 - 330)	309 (293 - 325)	294 (275 - 313)
	100-149	124 (121 - 128)	296 (289 - 303)	348 (337 - 359)	358 (343 - 374)	352 (332 - 373)	339 (316 - 364)
	150-199	172 (168 - 176)	346 (338 - 353)	395 (385 - 406)	405 (390 - 420)	399 (380 - 418)	387 (364 - 410)
	200-299	237 (232 - 242)	401 (392 - 410)	452 (440 - 465)	468 (450 - 486)	469 (445 - 494)	464 (434 - 494)
	300+	355 (348 - 363)	479 (466 - 492)	523 (504 - 543)	543 (516 - 571)	552 (517 - 588)	556 (514 - 600)