Global Trends in CD4 Cell Count at the Start of Antiretroviral Therapy: Collaborative Study of Treatment Programs

The IeDEA and COHERE Cohort Collaborations

**Background.** Early initiation of combination antiretroviral therapy (cART), at higher CD4 cell counts, prevents disease progression and reduces sexual transmission of human immunodeficiency virus (HIV). We describe the temporal trends in CD4 cell counts at the start of cART in adults from low-income, lower-middle-income, upper-middle-income, and high-income countries (LICs, LMICs, UMICs, and HICs, respectively).

**Methods.** We included HIV-infected individuals aged ≥16 years who started cART between 2002 and 2015 in a clinic participating in the International epidemiology Databases to Evaluate AIDS (IeDEA) or the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE). Missing CD4 cell counts at the start of cART were estimated through multiple imputation. Weighted mixed-effect models were used to smooth trends in median CD4 cell counts.

**Results.** A total of 951,855 adults from 16 LICs, 11 LMICs, 9 UMICs, and 19 HICs were included. Overall, the modeled median CD4 cell count at the start of cART increased from 2002 to 2015, from 78/µL (95% confidence interval, 58–104/µL) to 287/µL (250–328/µL) in LICs, from 99/µL (71–140/µL) to 234/µL (192–285/µL) in LMICs, from 71/µL (49–104/µL) to 311/µL (255–379/µL) in UMICs, and from 161/µL (143–181/µL) to 327/µL (286–372/µL) in HICs. In LICs, LMICs, and UMICs, the increase was more pronounced in women; in HICs, the opposite was observed.

**Conclusions.** Median CD4 cell counts at the start of cART increased in all income groups, but generally remained below 350/µL in 2015. Substantial additional efforts and resources are required to achieve earlier diagnosis, linkage to care, and initiation of cART.

**Keywords.** antiretroviral therapy; CD4 cell count; WHO guidelines.

Modeling by the Joint United Nations Programme on HIV/AIDS (UNAIDS) indicates that there is a window of opportunity to end the human immunodeficiency virus (HIV)/AIDS epidemic by reaching the “90-90-90” targets, meaning that 90% of HIV infections are diagnosed, 90% of persons known to be HIV infected are receiving combination antiretroviral therapy (cART), and 90% of individuals receiving cART are virologically suppressed [1, 2]. In response, the World Health Organization (WHO) in its consolidated 2016 guidelines on the use of antiretroviral drugs for treating and preventing HIV infection recommended “lifelong cART to all children, adolescents and adults, including all pregnant and breastfeeding women living with HIV, regardless of CD4 cell count” [3].

Many individuals who live with HIV continue to enter care late. A previous analysis of cART programs and HIV cohort studies from low-income countries (LICs), lower-middle-income countries (LMICs), upper-middle-income countries (UMICs), and high-income countries (HICs) showed that median CD4 cell counts at the start of cART increased from 2000 to 2009 but remained below 200/µL in LICs and middle-income countries (MICs) and below 300/µL in HICs [4]. Similarly, a study published in Morbidity and Mortality Weekly Report [5] found that the percentage of patients starting cART with a CD4 cell count below 200/µL had decreased in 10 LICs and MICs but continued to be substantial in recent years, for example, 37% in Mozambique in 2014, or 34% in Haiti in 2015 [5]. A meta-analysis of African studies showed that the mean estimated CD4 cell count in 2012 was 309/µL at presentation to care and 140/µL at cART initiation [6]. Similarly, a meta-regression analysis of studies in developed countries showed only a small increase in the CD4 cell count at presentation from 1992 to 2011 [7].

For the present study, the International epidemiology Databases to Evaluate AIDS (IeDEA), a large collaboration of cART treatment programs and HIV cohort studies in the Americas, sub-Saharan Africa, and Asia-Pacific joined forces with the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) to examine global trends in CD4 cell counts at cART initiation.
The CD4 cell count at the start of cART was the count nearest to the date of starting cART, within a window of 3 months before and 1 week after initiation of therapy. CD4 cell counts were defined as ≥ 3 antiretroviral drugs, from 2 drug classes. The CD4 cell count at the start of cART was the count nearest to the date of starting cART, within a window of 3 months before and 1 week after initiation of therapy. CD4 cell counts >5000/µL (>3 times above the upper reference range [13]) were considered invalid. Countries were grouped according to the World Bank classification of gross national income per capita in 2015 [14], as LICs ($≤$1025), LMICs ($1026–$4035), UMICs ($4036–$12 475), and HICs ($≥$12476). Severe immunodeficiency was defined as a CD4 cell count <200/µL [15]. Regions were defined according to IeDEA and COHERE conventions [8–11, 16].

We included all individuals aged ≥16 years if they had a recorded cART starting date and sex, were treatment naive, and started therapy between 2002 and 2015. We excluded countries that contributed <100 patients with CD4 cell counts at therapy start and individual patients who started therapy in a year and country for which <10 CD4 cell counts were reported. cART start and individual patients who started therapy in a year and country for which <100 patients with CD4 cell counts at therapy started therapy between 2002 and 2015. We excluded countries recorded cART starting date and sex, were treatment naive, and that contributed <100 patients with CD4 cell counts at therapy started therapy in the aggregated values in each data cell. The second component corresponded to the ratio of the number of patients who were newly enrolled in that cohort and year to the number of patients starting cART in that country and year, as estimated by UNAIDS [18] and was also normalized by country income group.

We used weighted additive mixed models to analyze temporal trends in median CD4 cell counts at the start of cART. The covariates sex and country income group, as well as their interaction, were included as fixed effects, country as a random intercept, and yearly trends smoothed by sex and country income group. Similarly, we analyzed the median CD4 cell count according to region instead of country income group. For this analysis, weights were normalized by region. We also modeled the proportion of patients starting cART with severe immunodeficiency (CD4 cell count <200/µL), using generalized additive mixed models, and we fitted this model to other CD4 cell count thresholds (<50/µL, <100/µL, <350/µL, and <500/µL). We used the data set that included imputed CD4 cell counts. In sensitivity analyses, we fitted models to the data set consisting of complete cases only. We also fitted models including only cohorts that contributed data each year from 2005 to 2014.

We present CD4 cell counts as observed or modeled median CD4 cell counts with interquartile ranges (IQRs) or 95% confidence intervals (CIs). All analyses were done using R software, version 3.2.3 (R Core Team). The appendix gives further technical details (see Supplementary Digital Content).

RESULTS

Descriptive Analyses

We received data from 1 472 098 patients. We excluded a total of 520 243 patients and 22 countries who did not meet the inclusion criteria. Supplementary Figure S1 (see Supplementary Digital Content) shows the inclusion of patients. A total of 951 855 individuals from 55 countries (16 LICs, 11 LMICs, 9 UMICs, and 19 HICs) were included (Table 1 and Figure 1). Five countries contributed 160–499 persons; 6 countries, 500–999; 20 countries, 1000–4999; 5 countries, 5000–9999; 12 countries, 10 000–24 999; and 7 countries, ≥25 000. The number of individuals included in each country ranged from 160 (Malaysia) to 350 595 (Zambia).

The percentage of women was 57% overall and ranged from 5% in South Korea to 82% in the Democratic Republic of the Congo. In LICs, LMICs, and UMICs, the median (IQR) age of individuals starting cART was 35 (29–42) years; in HICs, it was 39 (32–47) years. The median year of cART initiation ranged from 2007 in France and Honduras to 2013 in Haiti and Mozambique. The median CD4 cell count at cART initiation ranged from 106/µL in Senegal, Thailand, and Vietnam to 275/µL in Belgium, and it was 182/µL overall; it was 179/µL (IQR, 85–288/µL) in LICs, 172/µL (85–279/µL) in LMICs, 141/µL (60–227/µL) in UMICs, and 251/µL (128–370/µL) in HICs. The proportion of patients starting cART with severe immunodeficiency (CD4 cell count <200/µL) was 55%, ranging from 31% in Switzerland to 77% in Senegal; this proportion was 56% in LICs, 58% in LMICs, 68% in UMICs, and 38% in HICs. Tables 1 and 2 and Supplementary Table S3 show detailed results by country and sex.

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## Table 1. Characteristics of Persons Living With Human Immunodeficiency Virus Starting Combination Antiretroviral Therapy by World Bank Income Group (2015), Country, and Sex

| Country by Income Status                      | Patients, No. | Age, Median, y | Calendar Year of cART Initiation, Median | Range of Data, Calendar Years |
|-----------------------------------------------|---------------|----------------|------------------------------------------|-------------------------------|
| **Low income**                                |               |                |                                          |                               |
| Benin                                         | 2542          | 33             | 2009                                     | 2008–2014                     |
| Burkina Faso                                  | 7832          | 35             | 2008                                     | 2008–2014                     |
| Burundi                                       | 3123          | 35             | 2012                                     | 2012–2014                     |
| Democratic Republic of the Congo              | 1428          | 33             | 2011                                     | 2011–2014                     |
| Guinea                                        | 640           | 32             | 2012                                     | 2012–2014                     |
| Guinea-Bissau                                 | 1941          | 35             | 2010                                     | 2010–2014                     |
| Haiti                                         | 3422          | 34             | 2013                                     | 2013–2014                     |
| Malawi                                       | 29,965        | 31             | 2011                                     | 2011–2014                     |
| Mali                                          | 3222          | 33             | 2009                                     | 2009–2014                     |
| Mozambique                                    | 6314          | 29             | 2013                                     | 2013–2015                     |
| Rwanda                                        | 7730          | 32             | 2008                                     | 2008–2015                     |
| Senegal                                       | 603           | 37             | 2009                                     | 2009–2014                     |
| United Republic of Tanzania                   | 8798          | 36             | 2009                                     | 2009–2014                     |
| Togo                                          | 2649          | 33             | 2009                                     | 2009–2014                     |
| Uganda                                        | 27,644        | 32             | 2009                                     | 2009–2015                     |
| Zimbabwe                                      | 15,652        | 36             | 2012                                     | 2012–2015                     |
| **Overall (IQR)**                             | 123,502       | 33             | 2011                                     | 2008–2015                     |
| **Lower middle income**                       |               |                |                                          |                               |
| Cambodia                                      | 1136          | 33             | 2009                                     | 2009–2014                     |
| Cote d’Ivoire                                 | 14,819        | 35             | 2008                                     | 2008–2014                     |
| Honduras                                      | 436           | 33             | 2006                                     | 2006–2015                     |
| India                                         | 27,329        | 33             | 2010                                     | 2010–2014                     |
| Kenya                                         | 6870          | 35             | 2011                                     | 2011–2015                     |
| Lesotho                                       | 14,729        | 32             | 2008                                     | 2008–2015                     |
| Philippines                                   | 16            | 36             | 2010                                     | 2010–2014                     |
| Ukraine                                       | 570           | 29             | 2009                                     | 2009–2014                     |
| Vietnam                                       | 554           | 30             | 2012                                     | 2012–2015                     |
| Zambia                                        | 217,525       | 33             | 2011                                     | 2011–2015                     |
| **Overall (IQR)**                             | 331,786       | 33             | 2010                                     | 2008–2015                     |
| **Upper middle income**                       |               |                |                                          |                               |
| Argentina                                     | 888           | 35             | 2008                                     | 2008–2015                     |
| Belarus                                       | 235           | 32             | 2009                                     | 2009–2014                     |
| Brazil                                        | 773           | 35             | 2010                                     | 2010–2014                     |
| Malaysia                                      | 31            | 37             | 2008                                     | 2008–2015                     |
| Mexico                                        | 104           | 35             | 2009                                     | 2009–2014                     |
| Peru                                          | 672           | 34             | 2010                                     | 2010–2014                     |
| Russian Federation                            | 150           | 29             | 2008                                     | 2008–2015                     |
| South Africa                                  | 45,359        | 33             | 2010                                     | 2010–2014                     |
| Thailand                                      | 451           | 36             | 2008                                     | 2008–2015                     |
| **Overall (IQR)**                             | 48,873        | 33             | 2010                                     | 2007–2012                     |
| **High income**                               |               |                |                                          |                               |
| Austria                                       | 627           | 33             | 2008                                     | 2008–2014                     |
| Belgium                                       | 1205          | 31             | 2007                                     | 2007–2014                     |
| Canada                                        | 295           | 36             | 2008                                     | 2008–2014                     |
| Chile                                         | 160           | 37             | 2006                                     | 2006–2014                     |
| Denmark                                       | 609           | 35             | 2007                                     | 2007–2014                     |
| France                                        | 9036          | 35             | 2006                                     | 2006–2014                     |
| Germany                                       | 2709          | 34             | 2008                                     | 2008–2015                     |
| Greece                                        | 555           | 36             | 2008                                     | 2008–2014                     |
| Hong Kong                                     | 133           | 36             | 2009                                     | 2009–2014                     |
| Italy                                         | 3631          | 37             | 2009                                     | 2009–2014                     |
| Republic of Korea                             | 18            | 41             | 2011                                     | 2011–2014                     |
| Netherlands                                   | 2806          | 33             | 2008                                     | 2008–2015                     |
| Poland                                        | 142           | 31             | 2007                                     | 2007–2014                     |
| Singapore                                     | 117           | 41             | 2010                                     | 2010–2014                     |
| Spain                                         | 22,194        | 36             | 2008                                     | 2008–2014                     |
| Sweden                                        | 2138          | 33             | 2009                                     | 2009–2014                     |
| Switzerland                                   | 882           | 36             | 2008                                     | 2008–2014                     |
| United Kingdom                                | 5823          | 35             | 2007                                     | 2007–2014                     |
| United States                                 | 4187          | 42             | 2008                                     | 2008–2014                     |
| **Overall (IQR)**                             | 37,291        | 35             | 2007                                     | 2005–2015                     |

Abbreviations: IQR, interquartile range.

*QRIs provided for median values.*
Multiple Imputation of Missing CD4 Cell Counts
The CD4 cell count measurement at the start of cART was missing in 311,647 patients, in 44% of individuals in LICs, 33% in LMICs, 27% in UMICs, and 22% in HICs (Table 2). Compared with them, the 640,208 individuals who had a CD4 cell count reported at the start of cART were more likely to be female and less likely to be from a LIC (Supplementary Table S1). Five countries from Southern Africa provided information about the WHO stage of patients at cART initiation. The WHO stage distributions were similar overall in patients with and those without reported CD4 cell counts (Supplementary Table S2).

Medians of imputed CD4 cell counts from the main analysis and the complete cases (sensitivity analysis) were similar (Table 2 and Supplementary Table S3). Differences in CD4 cell counts ranged from −10/µL in Ukraine to +10.5/µL in Burundi. Similarly, the proportion of patients starting cART with counts <200/µL were similar for imputed and complete data. The differences ranged from −4.7% in Togo to +3.4% in Ukraine.

Temporal Trends in CD4 Cell Counts
The estimated median CD4 cell count at the start of cART from 2002 to 2015 varied across income groups (Figure 2). The modeled median CD4 cell count at cART initiation increased in LICs by 268%, from 78/µL (95% CI, 58–104/µL) to 287/µL (250–328/µL); in LMICs by 136%, from 99/µL (71–140/µL) to 234/µL.
| Country by Income Status | Proportion of Patients Missing CD4 cell Count Measurements, % | CD4 Cell Count at cART Initiation, Median, Cells/µL | Proportion Starting cART With CD4 Cell Count <200/µL, % |
|-------------------------|-------------------------------------------------|---------------------------------|---------------------------------|
|                         | Complete Case Analysis | Imputed Data | Complete Case Analysis | Imputed Data |
|                         | Female Patients | Male Patients | Female Patients | Male Patients | Female Patients | Male Patients | Female Patients | Male Patients |
| Low income              |                     |                     |                     |                     |                     |                     |                     |                     |
| Benin                   | 35                  | 35                  | 153                  | 97                  | 155                  | 100                  | 63                  | 77                  | 62                  | 76                  |
| Burkina Faso            | 37                  | 37                  | 212                  | 159                 | 211                  | 163                  | 47                  | 58                  | 47                  | 57                  |
| Burundi                 | 64                  | 63                  | 252                  | 233                 | 263                  | 242                  | 34                  | 41                  | 33                  | 40                  |
| Democratic Republic of the Congo | 16       | 20                  | 237                  | 198                 | 241                  | 200                  | 41                  | 51                  | 61                  | 50                  |
| Guinea                  | 38                  | 42                  | 196                  | 167                 | 195                  | 167                  | 51                  | 58                  | 51                  | 59                  |
| Guinea-Bissau           | 21                  | 18                  | 164                  | 153                 | 162                  | 153                  | 60                  | 64                  | 61                  | 64                  |
| Haiti                   | 31                  | 31                  | 267                  | 213                 | 269                  | 211                  | 35                  | 48                  | 35                  | 48                  |
| Malawi                  | 71                  | 64                  | 187                  | 154                 | 196                  | 157                  | 54                  | 63                  | 51                  | 62                  |
| Mali                    | 23                  | 22                  | 165                  | 119                 | 165                  | 119                  | 56                  | 70                  | 57                  | 70                  |
| Mozambique              | 38                  | 23                  | 270                  | 214                 | 275                  | 214                  | 35                  | 47                  | 34                  | 47                  |
| Rwanda                  | 21                  | 22                  | 246                  | 198                 | 246                  | 198                  | 39                  | 50                  | 39                  | 51                  |
| Senegal                 | 44                  | 42                  | 109                  | 101                 | 112                  | 106                  | 75                  | 80                  | 74                  | 79                  |
| United Republic of Tanzania | 34        | 33                  | 126                  | 113                 | 130                  | 115                  | 72                  | 75                  | 71                  | 74                  |
| Togo                    | 95                  | 94                  | 154                  | 150                 | 144                  | 156                  | 71                  | 72                  | 69                  | 63                  |
| Uganda                  | 37                  | 34                  | 176                  | 146                 | 172                  | 138                  | 57                  | 65                  | 58                  | 67                  |
| Zimbabwe                | 31                  | 29                  | 197                  | 149                 | 208                  | 154                  | 51                  | 65                  | 48                  | 63                  |
| Overall (IQR)           | 44                  | 43                  | 192 (97–303)         | 156 (88–258)        | 193 (100–304)        | 156 (88–255)        | 52                  | 62                  | 52                  | 62                  |
| Lower middle income     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |
| Cambodia                | 6                   | 6                   | 178                  | 115                 | 179                  | 115                  | 57                  | 68                  | 56                  | 68                  |
| Cote d'Ivoire           | 36                  | 40                  | 176                  | 144                 | 172                  | 142                  | 57                  | 64                  | 58                  | 65                  |
| Honduras                | 22                  | 19                  | 120                  | 110                 | 123                  | 110                  | 77                  | 74                  | 77                  | 74                  |
| India                   | 11                  | 9                   | 166                  | 122                 | 167                  | 122                  | 64                  | 74                  | 63                  | 74                  |
| Kenya                   | 36                  | 32                  | 177                  | 120                 | 182                  | 124                  | 57                  | 73                  | 55                  | 71                  |
| Lesotho                 | 20                  | 19                  | 226                  | 169                 | 234                  | 173                  | 44                  | 57                  | 42                  | 56                  |
| Nigeria                 | 27                  | 26                  | 203                  | 152                 | 205                  | 154                  | 49                  | 62                  | 49                  | 61                  |
| Philippines             | 12                  | 3                   | 204                  | 192                 | 209                  | 192                  | 50                  | 52                  | 48                  | 52                  |
| Ukraine                 | 34                  | 58                  | 246                  | 200                 | 240                  | 199                  | 34                  | 49                  | 36                  | 51                  |
| Vietnam                 | 13                  | 9                   | 170                  | 70                  | 168                  | 71                  | 59                  | 77                  | 60                  | 78                  |
| Zambia                  | 35                  | 31                  | 188                  | 158                 | 195                  | 161                  | 54                  | 62                  | 51                  | 61                  |
| Overall (IQR)           | 34                  | 30                  | 186 (97–297)         | 149 (70–248)        | 191 (100–307)        | 152 (71–255)        | 54                  | 64                  | 52                  | 63                  |
| Upper middle income     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |
| Argentina               | 35                  | 33                  | 209                  | 196                 | 208                  | 193                  | 48                  | 51                  | 48                  | 51                  |
| Belarus                 | 28                  | 26                  | 196                  | 171                 | 196                  | 185                  | 52                  | 57                  | 53                  | 55                  |
| Brazil                  | 17                  | 16                  | 239                  | 227                 | 236                  | 226                  | 41                  | 45                  | 42                  | 45                  |
| Malaysia                | 13                  | 19                  | 175                  | 151                 | 175                  | 151                  | 59                  | 64                  | 58                  | 64                  |
| Country by Income Status | Proportion of Patients Missing CD4 cell Count Measurements, % | CD4 Cell Count at cART Initiation, Median, Cell/µL | Proportion Starting cART With CD4 Cell Count <200/µL, % |
|--------------------------|------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
|                          | Female Patients | Male Patients | Female Patients | Male Patients | Female Patients | Male Patients | Female Patients | Male Patients | Female Patients | Male Patients | Female Patients | Male Patients |
| Mexico                   | 22 | 12 | 131 | 160 | 132 | 160 | 67 | 59 | 66 | 59 |
| Peru                     | 26 | 18 | 145 | 113 | 151 | 113 | 60 | 68 | 60 | 68 |
| Russian Federation       | 50 | 43 | 209 | 196 | 211 | 196 | 44 | 52 | 43 | 51 |
| South Africa             | 28 | 27 | 149 | 114 | 154 | 116 | 67 | 76 | 65 | 75 |
| Thailand                 | 10 | 11 | 123 | 97  | 125 | 99  | 75 | 75 | 73 | 75 |
| Overall (IQR)            | 28 | 26 | 151 | (70–232) | 123 | (48–218) | 156 | (72–242) | 125 | (49–220) |
| High income              |                          |                          |                          |                          |                          |                          |
| Austria                  | 15 | 17 | 237 | 266 | 236 | 264 | 40 | 35 | 40 | 35 |
| Belgium                  | 36 | 32 | 266 | 280 | 265 | 280 | 34 | 30 | 35 | 29 |
| Canada                   | 18 | 17 | 224 | 238 | 227 | 243 | 43 | 38 | 42 | 37 |
| Chile                    | 29 | 29 | 201 | 191 | 191 | 181 | 48 | 52 | 53 | 54 |
| Denmark                  | 29 | 30 | 231 | 234 | 232 | 238 | 39 | 40 | 38 | 39 |
| France                   | 18 | 17 | 249 | 266 | 250 | 266 | 36 | 35 | 36 | 35 |
| Germany                  | 29 | 26 | 223 | 237 | 220 | 235 | 43 | 41 | 44 | 42 |
| Greece                   | 20 | 22 | 192 | 249 | 192 | 249 | 52 | 38 | 51 | 38 |
| Hong Kong                | 1  | 2  | 112 | 111 | 109 | 111 | 70 | 66 | 70 | 66 |
| Italy                    | 27 | 27 | 252 | 258 | 254 | 257 | 39 | 39 | 38 | 39 |
| Republic of Korea        | 6  | 4  | 207 | 221 | 207 | 221 | 47 | 44 | 47 | 44 |
| Netherlands              | 28 | 25 | 230 | 260 | 230 | 260 | 42 | 35 | 42 | 35 |
| Poland                   | 55 | 51 | 203 | 238 | 217 | 228 | 50 | 39 | 48 | 41 |
| Singapore                | 9  | 9  | 138 | 128 | 134 | 133 | 62 | 62 | 62 | 61 |
| Spain                    | 19 | 18 | 229 | 260 | 229 | 260 | 43 | 36 | 43 | 36 |
| Sweden                   | 29 | 27 | 230 | 240 | 225 | 240 | 43 | 38 | 43 | 39 |
| Switzerland              | 16 | 13 | 259 | 270 | 259 | 270 | 34 | 30 | 34 | 30 |
| United Kingdom           | 34 | 34 | 220 | 245 | 220 | 244 | 44 | 37 | 44 | 37 |
| United States            | 14 | 14 | 274 | 272 | 276 | 273 | 36 | 37 | 36 | 37 |
| Overall (IQR)            | 24 | 22 | 241 | (128–360) | 254 | (128–372) | 240 | (128–360) | 253 | (130–370) |

Abbreviations: IQR, interquartile range.

*IQRs provided for median values.*
Immunodeficiency at cART Initiation

In LICs, LMICs, and UMICs the increase was more pronounced in women (+277% in LICs, +153% in LMICs, and +391% in UMICs) than in men (+248% in LICs, +99% in LMICs, and +261% in UMICs); in HICs the opposite was the case (+68% in women and +115% in men). Results of the complete case analysis and analysis restricted to cohorts contributing data from 2005–2014 were similar (Supplementary Figure S2A and S2B, Supplementary Digital Content).

Figure 3 shows modeled temporal trends in the proportion of patients starting cART with severe immunodeficiency (CD4 cell count <200/µL) and below other thresholds. In LICs, the estimated proportion of adults starting with severe immunodeficiency declined from 95% (95% CI, 90%–97%) in 2002 to 31% (26%–36%) in 2015. Corresponding declines were from 75% (95% CI, 65%–83%) to 40% (33%–47%) in LMICs, from 79% (71%–86%) to 26% (20%–33%) in UMICs, and from 59% (54%–64%) to 29% (24%–34%) in HICs. For the lowest 3 CD4 thresholds (<50/µL, <100/µL, and <200/µL) the proportions of patients starting cART below the threshold declined over the study-period. However, trends plateaued toward the end of the study period, for example, for individuals from HICs or LMICs who started therapy with CD4 cell counts below 100/µL or 200/µL. The proportions for the 2 highest CD4 thresholds (<350/µL and <500/µL) were constant over the first few years and then started to decrease. Results of the complete case analysis and analysis restricted to cohorts contributing data from 2005–2014 were similar (see Figure S3A and S3B, Supplementary Digital Content).

Supplementary Figure S4 shows the modeled temporal trends in median CD4 cell count at the start of cART by sex and region. Regions showed different trends, with the largest increases in median CD4 cell count at the start of cART from 2003 to 2014 seen in Southern Africa (from 93/µL [95% CI, 60–146/µL] to 259/µL [224–300/µL]) and North America (from 172/µL [131–227/µL] to 435/µL [317–597/µL]) and the smallest increases seen in West Africa (from 118/µL [88–158/µL] to 186/µL [160–217/µL]) and East Europe (from 160/µL [101–254/µL] to 261/µL [199–342/µL]). Results from complete case analysis and analysis restricted to cohorts contributing data from 2005–2014 were similar (see Supplementary Figure S4A and S4B, Supplementary Digital Content).

DISCUSSION

This global analysis of the CD4 cell count at cART initiation included almost 1 million individuals living with HIV in North America, Latin America and the Caribbean, Asia-Pacific, sub-Saharan Africa, and Europe. The median CD4 cell count substantially increased in all 4 groups of countries defined by per capita income, with steeper increases in LICs and UMICs than in LMICs or HICs. In 2015, these counts were highest in HICs, followed by UMICs, LICs, and LMICs. There were also important differences between regions. For example, the estimated median CD4 cell count in individuals starting cART in North America rose to 435/µL in 2014; at the other end of the spectrum, it was 186/µL in individuals starting cART in West Africa in the same year. Median CD4 cell counts were higher and increases steeper in women than in men, except in HICs, where in recent years women started cART with lower counts than men. The proportion starting therapy with severe immunodeficiency decreased substantially, but trends seemed to have plateaued in recent years, especially in HICs.

The decreases in the proportion of patients starting therapy below the different CD4 thresholds mirror the WHO guidelines to some extent. For example, the proportion starting with
a CD4 cell count below 350/µL was close to 100% in LICs, LMICs, and UMICs until about 2010, and started declining after that point, possibly owing to the implementation of the 2009 guideline [19]. In HICs the decline had already started before the guideline expansion, in 2008. This reflects the fact that national guidelines in resource-limited settings generally echoed WHO guidelines [20], whereas HICs have more rapidly increased the CD4 cell count threshold for initiation of cART. For example, in 2012 North American guidelines converged in their recommendation that cART should be offered to all HIV-infected individuals, irrespective of CD4 cell count [21, 22]. The WHO followed suit in 2016, recommending “lifelong cART for all children, adolescents and adults, including all pregnant and breastfeeding women living with HIV, regardless of CD4 cell count” [3]. The impact of these recommendations will be the subject of future collaborative analyses.

Figure 3. Proportion of patients starting combination antiretroviral therapy (cART) with CD4 cell counts below 50/µL, 100/µL, 200/µL, 350/µL, and 500/µL (rows) by sex (columns) and country income group (colors). Results from generalized additive mixed effects models based on 951,886 adults after imputation of missing data. 95% confidence intervals are shown as shaded areas.
It is likely that the substantial rise in HIV testing in many countries, supported by governments, the US President's Emergency Plan for AIDS Relief (PEPFAR), the Global Fund, and other donors contributed to increasing CD4 cell counts at the start of cART [23], but this may not have been the case in all settings [24, 25]. The steeper increase in CD4 cell count among women compared with men in LICs and MICs may be explained by increased testing coverage after scale-up of programs to prevent mother-to-child transmission. UNAIDS estimates that 90% of pregnant women living with HIV in Eastern and Southern Africa, 48% in Central and West Africa and 41% in Asia and the Pacific received antiretroviral drugs [26], up from <5% in 2002 [27]. However, among the 22 UNAIDS priority countries [28], several still had coverage rates below 50% in 2015 for programs to prevent mother-to-child transmission, including India, Chad and Nigeria [26].

Analyses were based on raw data from many HIV-infected individuals starting cART, which is an important strength of this study. Such individual patient data meta-analyses have been described as the “yardsticks” against which the quality of other reviews should be judged [29]. Our results are consistent with an earlier analysis of IeDEA and European data, based on individual patient data from 379,865 patients in 23 countries, which showed that CD4 cell counts in LICs and MICs increased from about 90/μL in 2002 to about 150/μL in 2009 [4]. Our results are also in line with analyses of individual patient data from a smaller number of countries [5, 30, 31].

The weighting of estimates was another strength, with more weight given to the more precise estimates of median CD4 cell count, and by the number of patients starting cART in a given country and year [18], so that countries with many patients starting cART were adequately represented in our analysis. Our study also had several limitations. We included data up to 2015, but not all countries contributed data spanning the entire period from 2002 to 2015. It is reassuring that results were very similar when we restricted analyses to the cohorts that contributed data for each year from 2005 to 2014.

Another limitation was that many individuals had missing CD4 cell counts at cART initiation, which we addressed by multiple imputation. Results including the imputed values were very similar to those of complete case analyses. If some of the CD4 cell counts were missing owing to poorer health, this would violate the assumption of values missing at random and lead to overestimation of the median count. For example, some patients with missing CD4 cell counts may have started therapy immediately because of an opportunistic infection and might thus be more likely to have a lower count, especially in LICs. Data on opportunistic infections and clinical stage was incomplete, and we could not use this information in our imputation models. However, for the 5 Southern African countries, which provided information on clinical stage, the WHO stage distribution overall was similar in patients with reported and those with missing CD4 cell counts. These data indicate that, at least in Southern Africa, only a small portion of missing counts are due to poorer health.

Data from some countries were limited to a small number of patients from a single clinic. We excluded these data sets because the data were probably unrepresentative of all patients receiving cART in those countries. Some data included in modeling of time trends may also not be representative of all patients receiving cART in the country. In particular, the clinics from LICs and MICs participating in IeDEA are mainly urban and capture data in electronic databases, indicating a higher level of resources. They may more closely reflect best practice in urban settings than in the country as a whole [8]. Nevertheless, our collaborative study is a unique source of information on trends and determinants of the CD4 cell count in adult patients starting cART across the globe.

In conclusion, median CD4 cell counts at the start of cART have increased in all country income groups over the last few years, and the proportion of individuals starting cART with severe immunodeficiency has decreased. However, the median CD4 cell count at cART start generally remained below 350/μL in 2015 and the decline in severe immunodeficiency appears to have plateaued in some countries. Clearly, substantial additional efforts and resources will be needed to achieve early diagnosis, rapid linkage to care, and prompt initiation of cART globally.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Writing committee. The writing committee included the following: Nanina Anderegg (Department of Social and Preventive Medicine, University of Bern, Switzerland), Klea Panayidou (Institute of Social and Preventive Medicine, University of Bern, Switzerland), Yao Abo (Programme PAC-CI, Centre Hospitalier Universitaire de Treichville, Abidjan, Côte d’Ivoire), Belen Alejos (National Center of Epidemiology, Instituto de Salud Carlos III, Madrid, Spain), Keri N. Althoff (Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland), Kathryn Anastos (Departments of Medicine and Epidemiology & Population Health, Albert Einstein College of Medicine, Bronx NY), Andrea Antinori (HIV/AIDS Department, National Institute for Infectious Diseases L. Spallanzani, IRCCS, Rome, Italy), Eric Balestre (Centre INSERM U1219, Bordeaux Population Health, Université de Bordeaux, France), Renaud Becquet (INSERM, Centre de Recherche INSERM U1219 and Institut de Santé Publique Épidémiologie Développement, Université Bordeaux, France), Antonella Castagna (Department of Infectious Diseases, San Raffaele Scientific Institute, University Vita-Salute San Raffaele, Milan, Italy), Barbara Castelnuovo (Infectious Diseases Institute, Makerere University, Mulago Hospital, Kampala, Uganda), Geneviève Chêne (INSERM, ISPED, Centre INSERM U1219-Bordeaux Population Health, Bordeaux, France), Lara Coelho (Instituuto de Pesquisa Clinica Evandro Chagas, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil), Imrita Jeannie Collins (Medical Research Council [MRC] Clinical Trials Unit, Institute of Clinical Trials & Methodology, University College London, United Kingdom), Dominique Costagliola (Sorbonne Universités, UPMC Université Paris 06, INSERM, Institut Pierre Louis d’Épidémiologie et de Sante Publique, Paris, France), Brenda Crabtree-Ramírez (Department of Infectious Diseases, Instituto...
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