Clinical Infectious Diseases

MAJOR ARTICLE

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

The IeDEA and COHERE Cohort Collaborations[a]

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.

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METHODS

Data Sources

IeDEA is a consortium structured through regional centers to pool clinical and epidemiological data on persons living with HIV and receiving cART. COHERE is a collaboration of European HIV cohorts. Regional cohorts of IeDEA and COHERE have been described in detail elsewhere [8–12]. Institutional review boards approved the pooling of data and their use in collaborative analyses.

Inclusion Criteria and Definitions

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 was 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 (≥$12 476). Severe immunodeficiency was defined as a CD4 cell count <200/μL [15]. Regions were defined according to IeDEA and COHERE conventions [8–11, 16].

Multiple Imputation of Missing CD4 Cell Counts

We imputed square roots of CD4 cell counts using predictive mean matching, adjusting for country and year of cART start and stratifying by sex, country income group, and region. We generated 50 imputed data sets and combined these using Rubin's rule [17].

Weighted Analysis of Temporal Trends

We aggregated data by calendar year (3–14 years, depending on the country), country (55 countries), and sex (2 groups), and we calculated the median CD4 cell count at the start of cART for each of the resulting data cells. We assigned a weight to each data cell that consisted of 2 components, which were multiplied. The first component corresponded to the number of observations, divided by the average number of observations in data cells of the same country income group (and was thus normalized by country income group), and captured the precision of 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.

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
	Female	Male	Female	Male	Female	Male	
Low income							
Benin	2542	1559	33	40	2009	2008	2002–2014
Burkina Faso	7832	3312	35	41	2008	2008	2002–2014
Burundi	3123	1711	35	43	2012	2012	2009–2015
Democratic Republic of the Congo	1425	303	33	41	2011	2011	2005–2014
Guinea	640	323	32	41	2012	2012	2008–2014
Guinea-Bissau	1941	1002	35	40	2010	2010	2007–2014
Haiti	3422	2287	34	40	2013	2013	2003–2015
Malawi	29 965	20 219	31	37	2011	2011	2007–2015
Mali	3222	1800	33	41	2009	2009	2002–2014
Mozambique	6314	2925	29	36	2013	2013	2006–2015
Rwanda	7730	4443	32	38	2008	2008	2004–2015
Senegal	603	407	37	43	2009	2009	2002–2014
United Republic of Tanzania	8798	3999	36	41	2009	2009	2005–2014
Togo	2649	1351	33	40	2009	2009	2005–2009
Uganda	27 644	15 841	32	37	2009	2009	2003–2014
Zimbabwe	15 652	7195	36	40	2012	2012	2004–2015
Overall (IQR)[a]	123 502	68 677	33 (28–40)	38 (32–45)	2011 (2008–2013)	2010 (2008–2012)	2002–2015
Lower middle income							
Cambodia	1136	1003	33	36	2009	2009	2005–2014
Cote d'Ivoire	14 819	7725	35	42	2008	2008	2002–2014
Honduras	436	562	33	38	2006	2007	2002–2015
India	2802	6100	33	36	2009	2008	2002–2014
Kenya	72 329	33 311	33	39	2010	2010	2003–2014
Lesotho	6870	3638	35	40	2011	2011	2005–2015
Nigeria	14 729	7587	32	39	2008	2008	2005–2014
Philippines	16	191	36	30	2010	2009	2008–2010
Ukraine	570	264	29	34	2008	2009	2004–2014
Vietnam	554	918	30	34	2012	2012	2004–2014
Zambia	217 525	133 070	33	37	2011	2011	2003–2015
Overall (IQR)[a]	331 786	194 369	33 (28–40)	38 (32–44)	2010 (2008–2013)	2010 (2007–2013)	2002–2015
Upper middle income							
Argentina	888	2161	35	37	2008	2009	2002–2015
Belarus	235	258	32	34	2009	2008	2006–2013
Brazil	774	1941	38	35	2010	2010	2002–2015
Malaysia	31	129	37	37	2008	2009	2004–2010
Mexico	104	858	35	33	2009	2009	2002–2015
Peru	872	2328	34	33	2010	2011	2004–2015
Russian Federation	159	159	29	32	2008	2008	2003–2012
South Africa	45 359	24 240	33	38	2010	2010	2003–2015
Thailand	451	586	36	37	2008	2008	2003–2010
Overall (IQR)[a]	48 873	32 660	33 (28–40)	37 (32–44)	2010 (2007–2012)	2010 (2007–2012)	2002–2015
High income							
Austria	627	1774	33	38	2008	2010	2002–2014
Belgium	1205	1303	31	39	2007	2010	2002–2014
Canada	295	818	36	39	2008	2009	2003–2013
Chile	160	1415	37	35	2006	2009	2002–2014
Denmark	609	1313	35	42	2007	2008	2002–2013
France	9036	18 094	35	40	2006	2007	2002–2014
Germany	2709	10 686	34	40	2008	2009	2002–2015
Greece	555	2997	36	36	2008	2010	2002–2014
Hong Kong	133	574	36	41	2009	2010	2003–2013
Italy	3631	10 627	37	40	2009	2009	2002–2015
Republic of Korea	18	364	41	37	2011	2010	2002–2015
Netherlands	2806	11 078	33	41	2008	2009	2002–2015
Poland	142	427	31	33	2007	2008	2002–2013
Singapore	117	1643	41	42	2010	2010	2006–2014
Spain	2218	9006	36	37	2008	2009	2002–2014
Sweden	2138	3095	33	41	2009	2009	2002–2015
Switzerland	882	2881	36	40	2008	2009	2002–2014
United Kingdom	5823	13 976	35	38	2007	2008	2002–2013
United States	4187	22 626	42	44	2008	2008	2003–2014
Overall (IQR)[a]	37 291	114 697	35 (29–43)	40 (33–48)	2007 (2005–2010)	2008 (2006–2011)	2002–2015

Abbreviations: IQR, interquartile range.
[a]IQRs provided for median values.

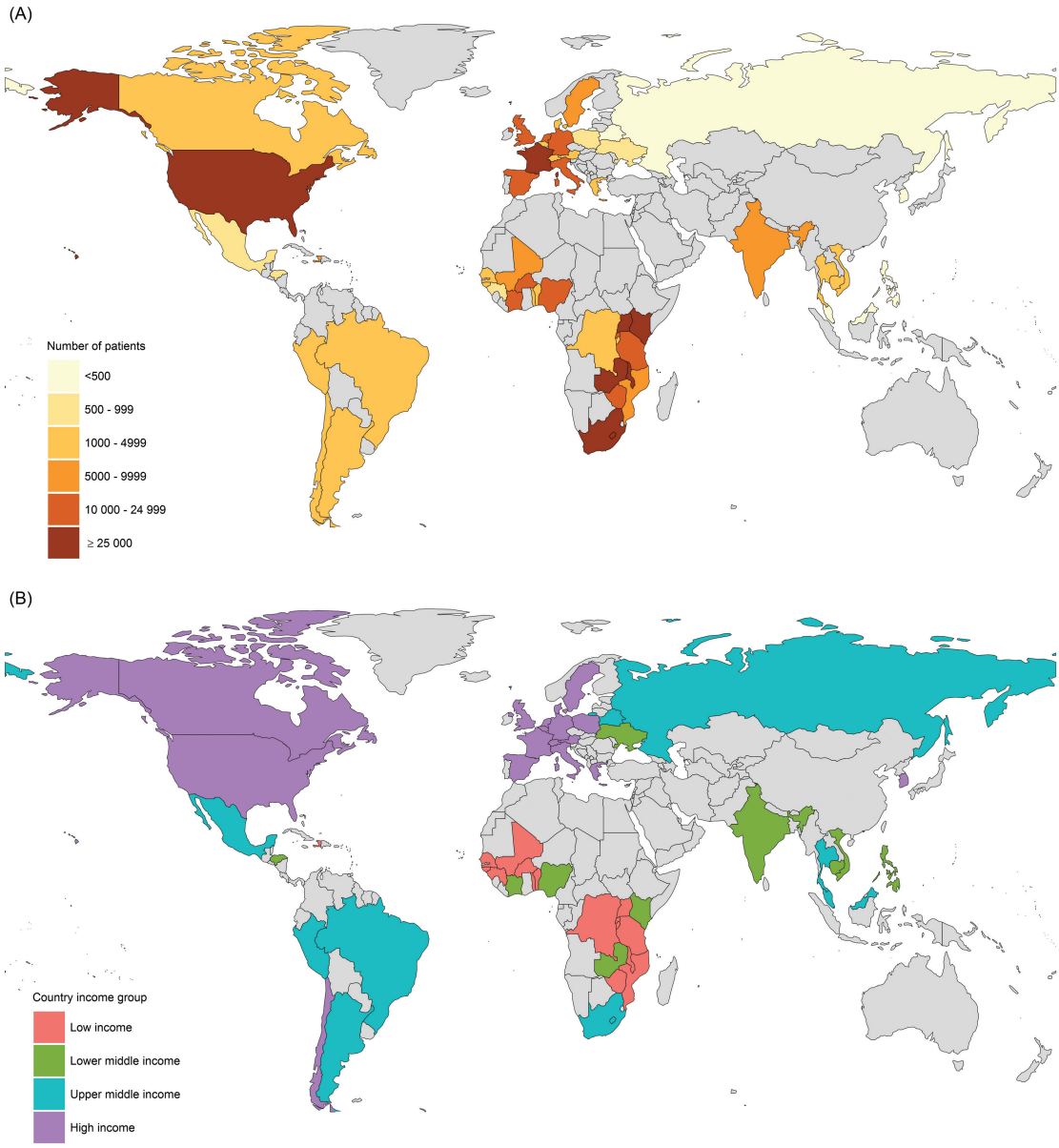

Figure 1. Map of countries contributing patients to the collaborative analysis by number of patients (*A*) and country income group (*B*).

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

Table 2. Median CD4 Cell Count and Proportion of Persons Living With Human Immunodeficiency Virus Starting Combination Antiretroviral Therapy With Severe Immunodeficiency in 2002–2015 by World Bank Income Group (2015), Country, and Patient Sex

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	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	41	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)[a]	44	43	192 (97–303)	156 (68–258)	193 (98–304)	156 (68–255)	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)[a]	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

Table 2. Continued.

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	Female Patients	Male Patients
Mexico	22	12	131	160	132	160	67	59	66	59
Peru	24	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)[a]	28	26	151 (70–232)	123 (48–218)	156 (72–242)	125 (49–220)	66	71	64	70
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	36
Overall (IQR)[a]	24	22	241 (128–360)	254 (128–372)	240 (128–360)	253 (130–370)	40	37	40	37

Abbreviations: IQR, interquartile range.

[a]IQRs provided for median values.

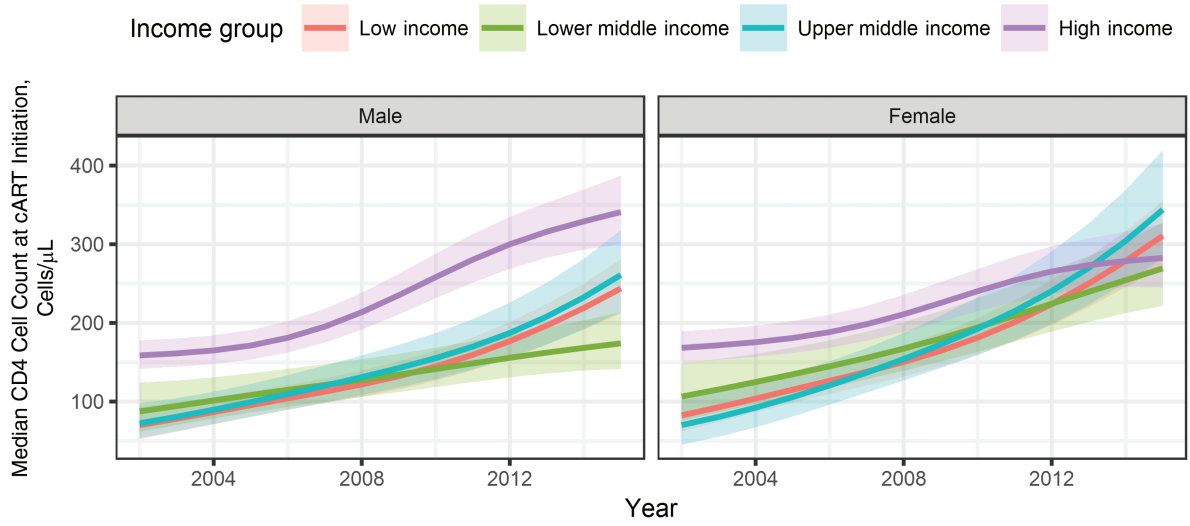

Figure 2. Median CD4 cell count in adults at the start of combination antiretroviral therapy (cART) by sex and country income group. Results from additive mixed-effects model based on 951 855 adults after imputation of missing data. 95% confidence intervals are shown as shaded areas.

(192–285/μL); in UMICs by 338%, from 71/μL (49–104/μL) to 311/μL (255–379/μL); and in HICs by 103%, from 161/μL (143–181/μL) to 327/μL (286–372/μL). 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 S2*A* and S2*B*, 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 S3*A* and S3*B*, 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 S4*A* and S4*B*, 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

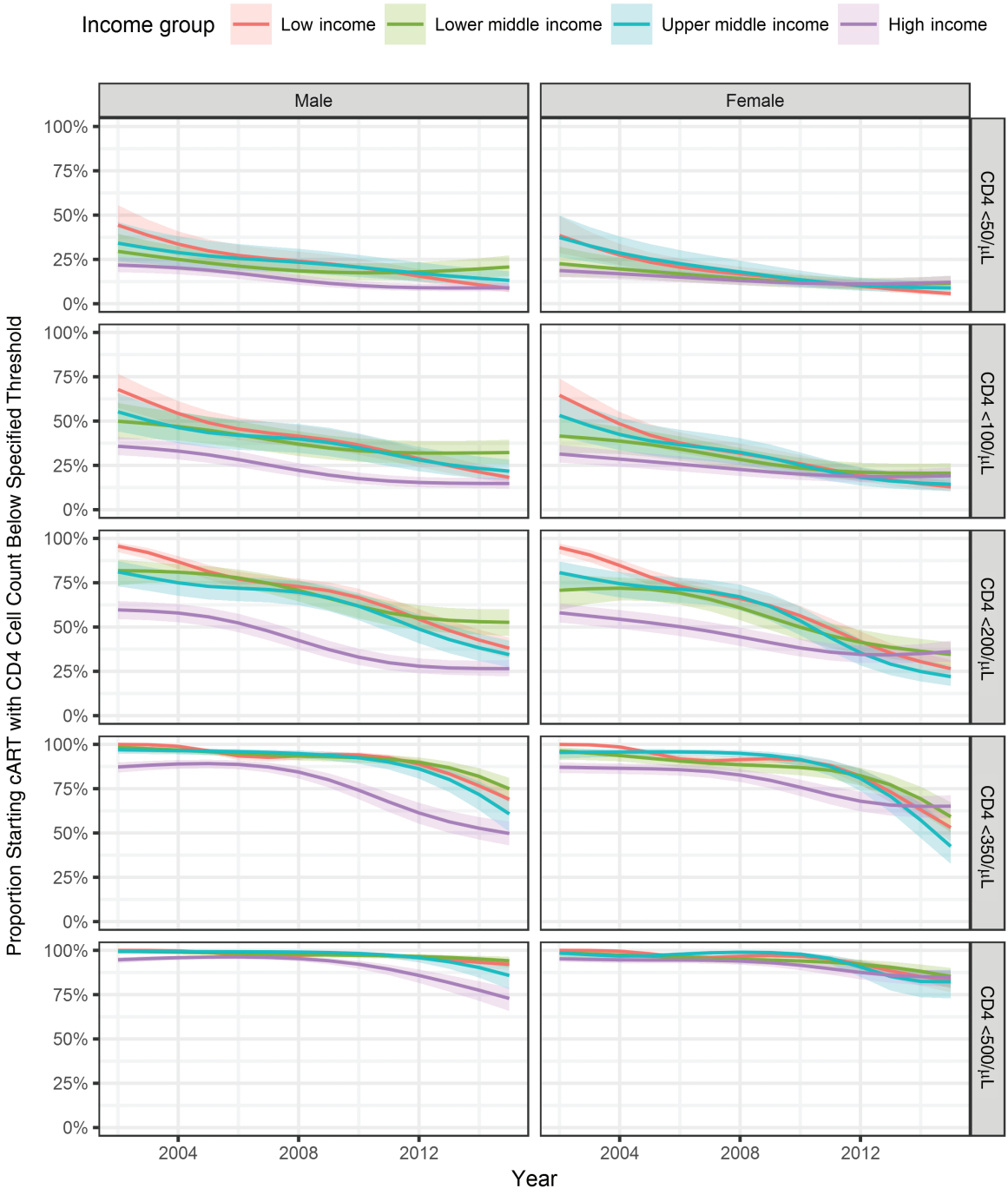

Figure 3. Proportion of patients starting combination antiretroviral therapy (cART) with CD4 cell counts below 50/μL, 100/μL, 200/μL, 350/μL, and 500/μL (rows) by sex (columns) and country income group (colors). Results from generalized additive mixed effects models based on 951 855 adults after imputation of missing data. 95% confidence intervals are shown as shaded areas.

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.

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

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References

1. Joint United Nations Programme on HIV/AIDS (UNAIDS). "15 by 15"—A global target achieved. **2015**. Available at: http://www.unaids.org/en/resources/documents/2015/15_by_15_a_global_target_achieved. Accessed 1 May 2016.
2. Joint United Nations Programme on HIV/AIDS (UNAIDS). 90-90-90: An ambitious treatment target to help end the AIDS epidemic. **2014**. Available at: http://www.unaids.org/sites/default/files/media_asset/90-90-90_en_0.pdf. Accessed 5 April 2015.
3. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2nd ed. 2016. Geneva, Switzerland: World Health Organization, **2016**.
4. Avila D, Althoff KN, Mugglin C, et al. Immunodeficiency at the start of combination antiretroviral therapy in low-, middle-, and high-income countries. J Acquir Immune Defic Syndr **2014**; 65:e8–16.
5. Auld AF, Shiraishi RW, Oboho I, et al. Trends in prevalence of advanced HIV disease at antiretroviral therapy enrollment: 10 countries, 2004–2015. Morb Mortal Wkly Rep **2017**; 66:558–63.
6. Siedner MJ, Ng CK, Bassett IV, Katz IT, Bangsberg DR, Tsai AC. Trends in CD4 count at presentation to care and treatment initiation in Sub-Saharan Africa, 2002–2013: a meta-analysis. Clin Infect Dis **2014**; 60:1120–7.
7. Lesko CR, Cole SR, Zinski A, Poole C, Mugavero MJ. A systematic review and meta-regression of temporal trends in adult $CD4^+$ cell count at presentation to HIV care, 1992–2011. Clin Infect Dis **2013**; 57:1027–37.
8. Egger M, Ekouevi DK, Williams C, et al. Cohort profile: the International Epidemiological Databases to Evaluate AIDS (IeDEA) in sub-Saharan Africa. Int J Epidemiol **2012**; 41:1256–64.
9. McGowan CC, Cahn P, Gotuzzo E, et al. Cohort profile: Caribbean, Central and South America Network for HIV research (CCASAnet) collaboration within the International Epidemiologic Databases to Evaluate AIDS (IeDEA) programme. Int J Epidemiol **2007**; 36:969–76.
10. Gange SJ, Kitahata MM, Saag MS, et al. Cohort profile: the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD). Int J Epidemiol **2007**; 36:294–301.
11. Zhou J, Kumarasamy N, Ditangco R, et al. The TREAT Asia HIV observational database. J Acquir Immune Defic Syndr **2005**; 38:174–9.
12. Chêne G, Phillips A, Costagliola D, et al. Cohort profile: Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord. Int J Epidemiol **2017**; 46:797.
13. Bofill M, Janossy G, Lee CA, et al. Laboratory control values for CD4 and CD8 T lymphocytes. Implications for HIV-1 diagnosis. Clin Exp Immunol **1992**; 88:243–52.
14. The World Bank. How we classify countries. Available at: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups. Accessed November 2017.
15. World Health Organization. Scaling up antiretroviral therapy in resource-limited settings: treatment guidelines for a public health approach. 2003 Revision. Geneva, Switzerland: World Health Organization, **2004**.
16. Mocroft A, Lundgren JD, Sabin ML, et al. Risk factors and outcomes for late presentation for HIV-positive persons in Europe: results from the Collaboration of Observational HIV Epidemiological Research Europe Study (COHERE). PLoS Med **2013**; 10:e1001510.
17. Rubin DB. Multiple imputation for nonresponse in surveys. New York, NY: John Wiley, **1987**.
18. AIDSinfo online database. Available at: www.aidsinfo.unaids.org. Accessed November 2017.
19. World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach. 2010 revision. Geneva, Switzerland: World Health Organization, **2010**:1–359.
20. Beck EJ, Vitoria M, Mandalia S, Crowley S, Gilks CF, Souteyrand Y. National adult antiretroviral therapy guidelines in resource-limited countries: concordance with 2003 WHO guidelines? AIDS **2006**; 20:1497–502.
21. Panel on Antiretroviral Guidelines for Adult and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. 29 January 2008. Washington, DC: Department of Health and Human Services, **2008**.
22. Thompson MA, Aberg JA, Hoy JF, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society-USA panel. JAMA **2012**; 308:387–402.
23. Marum E, Taegtmeyer M, Parekh B, et al. "What took you so long?" the impact of PEPFAR on the expansion of HIV testing and counseling services in Africa. J Acquir Immune Defic Syndr **2012**; 60(suppl 3):S63–9.
24. Liggett A, Medina N, Samayoa B, et al. Is expanded HIV testing associated with earlier HIV diagnosis? results from an HIV clinic in Guatemala City. J Int Assoc Provid AIDS Care **2016**; 15:201–4.
25. Wanyenze RK, Kamya MR, Fatch R, et al. Missed opportunities for HIV testing and late-stage diagnosis among HIV-infected patients in Uganda. PLoS One **2011**; 6:e21794.
26. Joint United Nations Programme on HIV/AIDS (UNAIDS). AIDS data. Geneva, Switzerland: UNAIDS, **2016**.
27. Prendergast AJ, Essajee S, Penazzato M. HIV and the millennium development goals. Arch Dis Child **2015**; 100(suppl 1):S48–52.
28. Joint United Nations Programme on HIV/AIDS (UNAIDS). Global plan towards the elimination of new HIV infections, 2011–2015. Geneva, Switzerland: UNAIDS, **2015**.
29. Chalmers I. The Cochrane collaboration: preparing, maintaining, and disseminating systematic reviews of the effects of health care. Ann N Y Acad Sci **1993**; 703:156–63; discussion 163–5.
30. Mutimura E, Addison D, Anastos K, et al. Trends in and correlates of $CD4^+$ cell count at antiretroviral therapy initiation after changes in national ART guidelines in Rwanda. AIDS **2015**; 29:67–76.
31. Lahuerta M, Wu Y, Hoffman S, et al. Advanced HIV disease at entry into HIV care and initiation of antiretroviral therapy during 2006–2011: findings from four Sub-Saharan African Countries. Clin Infect Dis **2014**; 58:432–41.