Immunodeficiency at the Start of Combination Antiretroviral Therapy in Low-, Middle-, and High-Income Countries

The IeDEA and ART Cohort Collaborations

Objective: To describe the CD4 cell count at the start of combination antiretroviral therapy (cART) in low-income (LIC), lower middle-income (LMIC), upper middle-income (UMIC), and high-income (HIC) countries.

Methods: Patients aged 16 years or older starting cART in a clinic participating in a multicohort collaboration spanning 6 continents (International epidemiological Databases to Evaluate AIDS and ART Cohort Collaboration) were eligible. Multilevel linear regression models were adjusted for age, gender, and calendar year; missing CD4 counts were imputed.

Results: In total, 379,865 patients from 9 LIC, 4 LMIC, 4 UMIC, and 6 HIC were included. In LIC, the median CD4 cell count at cART initiation increased by 83% from 80 to 145 cells/μL between 2002 and 2009. Corresponding increases in LMIC, UMIC, and HIC were from 87 to 155 cells/μL (76% increase), 88 to 135 cells/μL (53%), and 209 to 274 cells/μL (31%). In 2009, compared with LIC, median counts were 13 cells/μL [95% confidence interval (CI): −56 to +30] lower in LMIC, 22 cells/μL (−62 to +18) lower in UMIC, and 112 cells/μL (+75 to +149) higher in HIC. They were 23 cells/μL (95% CI: +18 to +28 cells/μL) higher in women than men. Median counts were 88 cells/μL (95% CI: +35 to +141 cells/μL) higher in countries with an estimated national cART coverage >80%, compared with countries with <40% coverage.

Conclusions: Median CD4 cell counts at the start of cART increased 2000–2009 but remained below 200 cells/μL in LIC and MIC and below 300 cells/μL in HIC. Earlier start of cART will require substantial efforts and resources globally.

Key Words: antiretroviral therapy, CD4 cell count, sub-Saharan Africa, North America, Carribean, Central and South America, Europe, Asia/Pacific

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INTRODUCTION

The prognosis of HIV-positive patients has dramatically improved with the advent, in 1996, of combination antiretroviral therapy (cART).[1,2] Suppressed viral replication allows reconstitution of the immune system: peripheral CD4 cell counts increase rapidly first from redistribution from lymphoid tissues and then gradual by de novo synthesis.[3,4] Since 2002, the Global Fund for Tuberculosis, AIDS, and Malaria; US President's Emergency Plan for AIDS Relief (PEPFAR); and other funders have sharply increased global cART availability. The World Health Organization (WHO) estimated, by 2010, that 6.6 million of the 15 million who needed cART in low- and middle-income countries had access.[5]

When to initiate cART to maximize the benefit of therapy has been debated for years.[6] Benefits of early initiation, at high CD4 cell counts, must be balanced against drug toxicities and the potential for drug resistance. Conversely, starting therapy late, as measured clinically or by CD4 count, is associated with poorer prognosis and increased mortality.[7] A substudy of the Strategies for Management of Antiretroviral Therapy trial showed that delaying cART until the count fell below 250 cells/μL more than tripled the rate of AIDS or death compared with starting above 350 cells/μL.[8] Analyses that combined data from cohort studies also indicated that starting cART above 350 CD4 cells/μL is beneficial, and some, but not all, showed benefit with a threshold of 500 cells/μL.[9–11] The START (NCT00821171) and TEMPRANO (NCT00495651) trials will provide further data on the efficacy of early versus late initiation of cART.

However, many patients enter care late. An analysis of treatment programs in 12 countries in sub-Saharan Africa, South America, and Asia showed that while CD4 cell counts at initiation increased from 2001 to 2005/2006, most patients started well below recommended thresholds.[12] Similarly, an US cohort and a Canada cohort showed that median CD4 cell count at first presentation for HIV care was 317 cells/μL in 2007: more than half of patients initiated therapy below 350 cells/μL.[13] A recent Latin American study reported that the percentage of patients initiating cART late ranged from 56% in Argentina to 91% in Honduras.[14]

Early initiation of cART is recognized as having a broader role in HIV prevention.[15] Already established as a means to prevent mother-to-child transmission (PMTCT),[5] the HIV Prevention Trials Network 052 trial found that cART reduced heterosexual HIV transmission by 96% between discordant couples.[16] Combined with other proven prevention

tools, immediate or early cART might contribute to achieving the goal of an AIDS-free generation.[17]

We examined trends and determinants of the CD4 cell count at cART initiation in patients starting therapy between 2002 and 2010 in low-, middle-, and high-income countries by combining data from 2 HIV cohort consortia, which together span 6 continents.

METHODS

Data Sources

The International epidemiological Databases to Evaluate AIDS (IeDEA) is a global consortium structured through regional centers to pool clinical and epidemiological data on HIV-positive individuals, particularly patients on cART. The 7 regions included in IeDEA are North America, Caribbean/Central and South America, Asia/Pacific, East Africa, West Africa, Central Africa, and Southern Africa. Regional cohorts of IeDEA have been described in detail elsewhere.[18–21] The European cohorts of the ART Cohort Collaboration, a network of cohort studies of patients on cART in high-income countries (HIC), were also included.[7] Pooling of data and their use in collaborative analyses were approved by local ethics committees and institutional review boards. For the present study, regional centers sent de-identified data to the University of Bern, Switzerland, for cleaning and analysis.

Inclusion Criteria and Definitions

Patients aged 16 years or older at cART initiation were eligible. cART was defined as a regimen of at least 3 antiretroviral drugs, typically from 2 drug classes. Baseline CD4 cell count was defined as the count nearest to the date of cART start with a window of 6 months before to 1 month after starting. CD4 cell counts above 5000 cells/μL (ie, >3 times above the upper reference range in whites[22]) were considered invalid and set to missing. Countries were grouped according to the World Bank classification of Gross National Income per Capita 2010 as low-income countries (LIC, US $1005 or less per year), lower middle-income countries (LMIC, US$1006 to 3975 per year), upper middle-income countries (UMIC, US$3976 to 12,275 per year), and high-income countries (HIC, US$12,276 or more per year).[23] Data on national cART coverage for 2009 (based on the WHO 2006 treatment guidelines[24]) were obtained from the 2010 progress report on the Global HIV/AIDS response published by WHO[25] for LIC and MIC.

Statistical Analyses

Descriptive analyses were stratified by country, gender, and World Bank country income group. CD4 cell counts at cART start and other baseline characteristics were summarized as medians with interquartile ranges or numbers with percentages. To address the problem of generalizing data from a small sample to an entire country, further analyses were restricted to countries that contributed at least 500 patients with CD4 cell counts from 2 or more sites and had observations after 2007.

Missing CD4 counts were multiply imputed using predictive mean matching and chained equations stratified by gender, age, and country income level. Technical details on the multiple imputation are provided in the Supplemental Digital Content (see http://links.lww.com/QAI/A446). All analyses were performed both for the imputed data and for the complete case dataset. To assess trends and examine individual-level and country-level predictors of median baseline CD4 cell counts, we aggregated the data by sex, age, year, and country. We then fitted 3 types of weighted linear regression models. First, a simple linear regression estimated gender-specific annual changes in median baseline CD4 cell counts by country (model 1). In sensitivity analyses, we weighted individual country data to create a data set that was representative, within each income group, of the number of patients on cART in each country in 2009, as estimated by WHO.[5] The derivation of the weighting factors is shown in Table S1 (see **Supplemental Digital Content**, http://links.lww.com/QAI/A446).

Second, a weighted mixed-effects linear regression was used to estimate the median CD4 cell counts at the start of cART in 2009 and to examine the influence of age, sex, country income level, and, in an analysis restricted to LIC and MIC, of national cART coverage (model 2). Age, calendar year, gender, and country income level were entered as fixed effects and country as random effect. The third model included calendar year, gender, and country income level and was used to model median CD4 cell count trends between 2002 and 2010 (model 3). Finally, the proportions of patients starting cART with CD4 cell counts below 50, 100, and 200 cells/μL were analyzed using generalized linear mixed effects models. Age, calendar year, gender, and country income level were entered as fixed effects and intercept and slope as random effects, by country. Data were analyzed using Stata 12.0 (Stata Corporation, College Station, TX) and R 2.12 (The R Development Core Team, Vienna, Austria).

RESULTS

Descriptive Analyses

Data from 492,915 patients aged 16 years or older who started cART in 48 countries were submitted to the data center (Fig. 1). Among 437,230 ART-naive patients with known age, gender, and start date, 309,564 (63%) had a CD4 cell count at the start of cART. Compared with the 127,666 patients without a CD4 cell count, patients with counts at cART initiation were younger, more likely to be male, and more likely to be from a high-income country. Importantly, those with CD4 cell counts were less likely to have advanced disease (WHO stage III/IV) than patients without CD4 cell counts (see **Table S2, Supplemental Digital Content,** http://links.lww.com/QAI/A446). Only 4.6% (20,217 patients) had an earlier CD4 cell count, 6 months or more before starting ART.

The number of included patients from each country varied from 60 from Japan to 147,029 from Zambia (Table 1). There were 12 countries with up to 500 patients, 23 with

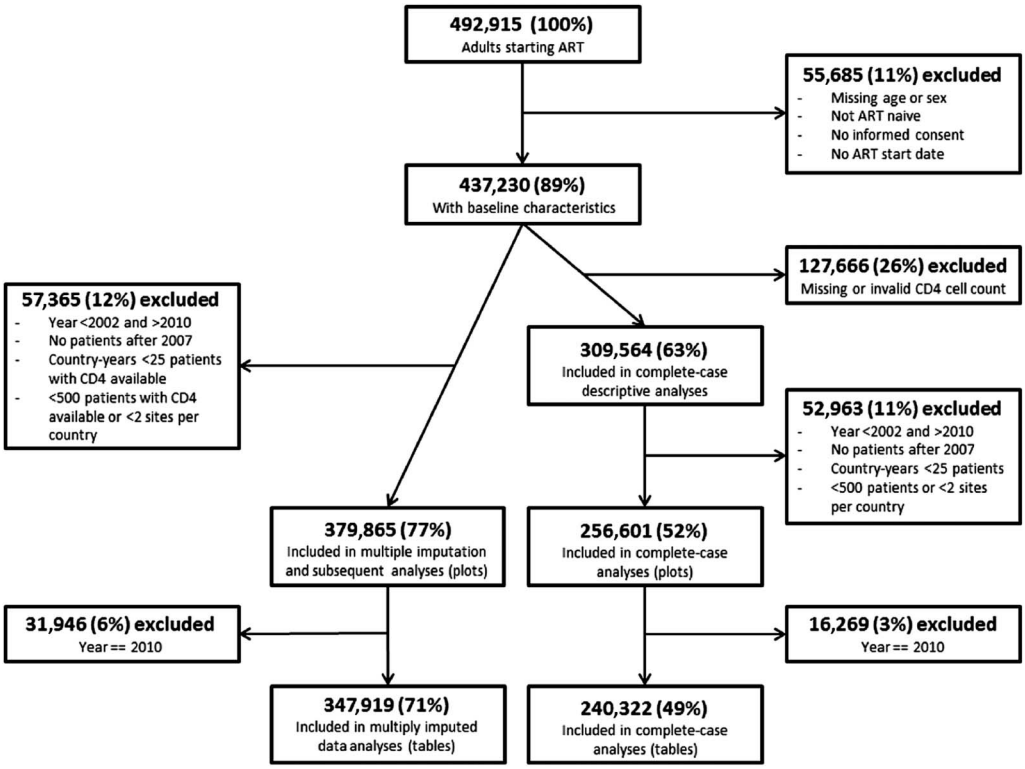

FIGURE 1. Flow chart of patients included and excluded from analyses.

501–5000 patients, 4 with 5001–10,000 patients, 7 with 10,001–50,000, and 2 with more than 50,000 patients (see **Figure S1**, **Supplemental Digital Content**, http://links.lww.com/QAI/A446). The percentage of female patients ranged from 4% in Taiwan to 73% in Burundi, and median age ranged from 30.9 years in Indonesia to 41.5 years in Nigeria (Table 1). The median year of cART initiation ranged from 2000 in Australia and Italy to 2009 in the Philippines. The median CD4 cell count at cART initiation for the entire study period ranged from 56 cells/μL in Indonesia to 290 cells/μL in Australia.

Regression Models

A total of 379,865 patients from 23 countries were included in the regression models, including 86,390 patients from 9 LIC (23%), 176,858 from 4 LMIC (47%), 82,152 from 4 UMIC (22%), and 34,465 from 6 HIC (9%). The Democratic Republic of the Congo, Kenya, Malawi, and Mali were overrepresented when compared with the WHO estimates of the number of patients on cART in the LIC included in our study. In contrast, Tanzania and Zimbabwe were underrepresented. The group of LMIC countries was dominated by Zambia and that of UMIC countries by South Africa. Among HIC, France contributed almost half of all patients, whereas the United States and Italy were underrepresented (see **Table S1, Supplemental Digital Content,** http://links.lww.com/QAI/A446).

The annual increase in median CD4 cell counts at the start of cART initiation from 2002 to 2009, estimated through linear regression (model 1), varied within and across World Bank country groups and tended to be greater among women than men (Table 2). Among LIC, the annual change in median CD4 cell counts ranged from −14 cells/μL [95% confidence interval (CI): −37 to +9 cells/μL] among women in the Democratic Republic of the Congo to +32 cells/μL (95% CI: +22 to +42 cells/μL) among Rwandan women. For LMIC, the corresponding range was from −2 cells/μL (95% CI: −14 to +9 cells/μL) among Nigerian men to +13 cells/μL (95% CI: +8 to +19 cells/μL) among women in Côte d'Ivoire. In UMIC, the range was from −1 cells/μL (−17 to +15 cells/μL) in Botswana men to +15 cells/μL (95% CI: 0 to +29 cells/μL) among Brazilian men. Finally, in HIC, the range was from −3 cells/μL (95% CI: −12 to +7 cells/μL) in Australian men to +16 cells/μL (95% CI: +12 to +20 cells/μL) in Canadian men. Crude (unweighted) and weighted pooled estimates of annual increases in CD4 cell count at cART initiation by country group were generally similar (Table 2). Also, results were similar in the complete case analysis (see **Table S3**, **Supplemental Digital Content**, http://links.lww.com/QAI/A446).

Table 3 shows estimated median CD4 cell counts at the start of cART in 2009 by age, gender, and country income level, as estimated from the mixed effects linear regression (model 2). Median CD4 cell counts were higher in women compared with men (difference +23 cells/μL, 95% CI: +18 to +28 cells/μL) and lower for patients aged 30 to 40 years or younger (difference −16 cells/μL, 95% CI: −21 to −10 cells/μL) and 40 to 50 years or younger (difference −17 cells/μL, 95% CI: −24 to −10 cells/μL) compared with those younger than 30 years. Median counts were similar in LIC, LMIC, and UMIC but were higher in HIC (difference compared with low-

TABLE 1. Characteristics of Patients Starting cART by Country and World Bank Income Groups

	No. Patients		Median Age in Years (IQR)		Median Calendar Year of Starting cART (IQR)		Median CD4 Cell Count at Start of cART in Cells/μL (IQR)	
Country	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**
Low-income								
Benin	413	298	33.8	40.1	2005	2005	119	90
Burkina Faso	822	348	35.7	41.3	2007	2006	182	137.5
Burundi	332	139	36.4	43.0	2009	2009	209.5	157
Cambodia	107	110	33.8	36.6	2005	2005	103	70.5
DR Congo	1828	800	38.5	43.3	2008	2008	145	139.5
Gambia	140	77	37.4	45.0	2006	2006	160	130
Haiti	780	668	38.0	40.0	2004	2004	115.5	92.5
Kenya	19,454	10,571	35.2	39.6	2007	2006	135	109
Malawi	4337	3365	33.3	37.2	2008	2008	150	122
Mali	1020	650	32.7	40.2	2006	2006	134	101
Mozambique	284	177	32.1	37.5	2008	2008	242	204
Rwanda	1500	521	33.8	38.0	2006	2007	218	183
Tanzania	2168	1050	36.5	41.4	2007	2007	107	106
Uganda	4229	2552	34.2	38.3	2007	2007	130	114
Zimbabwe	3112	1388	37.1	39.7	2009	2009	133	96
Overall	40,526	22,714	35.1 (29–41)	39.4 (33–46)	2007 (2006–2008)	2007 (2006–2008)	139 (65–213)	113 (40–186)
Lower middle-income								
Cameroon	1821	829	33.9	39.3	2009	2009	158	139
Côte d'Ivoire	8531	4857	34.5	41.1	2006	2005	156	125
Honduras	101	159	35.0	38.0	2005	2005	120	98
India	91	364	31.9	34.1	2004	2003	177	129.5
Indonesia	92	227	29.1	31.4	2008	2008	89.5	45
Nigeria	4728	2678	41.2	41.3	2006	2006	162	127
Philippines	27	234	39.3	30.5	2008	2009	186	180
Senegal	183	126	35.4	42.0	2004	2004.5	122	97.5
Zambia	50,096	32,054	33.5	37.3	2008	2008	150	129
Overall	65,670	41,528	34.5 (28–41)	38.4 (33–44)	2007 (2006–2008)	2007 (2006–2008)	152 (76–228)	128 (55–201)
Upper middle-income								
Argentina	208	479	34.0	36.0	2004	2004	181	148
Botswana	549	367	34.3	38.4	2003	2003	140	116
Brazil	371	740	37.0	36.1	2007	2007	208	186
Chile	56	383	34.1	36.6	2003	2003	138	112
China	124	409	38.9	39.6	2005	2007	169.5	91
Malaysia	111	380	34.1	36.2	2007	2008	159	113
Mexico	49	349	35.0	35.0	2004	2004	131	84
Peru	208	495	32.0	35.0	2005	2005	85.5	74
South Africa	32,920	21,673	33.6	39.0	2007	2007	124	111
Thailand	731	907	35.7	36.3	2007	2008	95	89
Overall	35,327	26,182	33.7 (28–39)	38.5 (32–45)	2007 (2006–2008)	2006 (2004–2008)	124 (60–188)	111 (42–180)
High-income								
Australia	74	1261	33.7	39.1	2001	1999	280	290
Canada	850	3651	36.0	41.0	2002	2002	210	220
France	10,023	20,739	34.3	38.8	2003	2001	237	233
Germany	269	955	33.9	38.5	2004	2002	177	173
Italy	915	2312	35.4	37.6	2000	2000	265	244
Japan	4	56	46.1	38.1	2006	2007	236	253.5
The Netherlands	1617	5125	32.4	39.4	2003	2002	210	189
Singapore	19	83	33.9	41.4	2004	2003	134	57
South Korea	10	182	41.2	38.0	2003.5	2006	123	222.5
Spain	2596	8406	34.0	36.8	2002	2003	224	201

(*continued on next page*)

TABLE 1. (*Continued*) Characteristics of Patients Starting cART by Country and World Bank Income Groups

	No. Patients		Median Age in Years (IQR)		Median Calendar Year of Starting cART (IQR)		Median CD4 Cell Count at Start of cART in Cells/μL (IQR)	
Country	Women	Men	Women	Men	Women	Men	Women	Men
Switzerland	1414	3124	33.9	38.4	2001	2001	201	205
Taiwan	8	186	32.2	32.9	2001.5	2003	132	225
UK	369	1016	34.3	36.9	2003	2002	158	206
USA	3362	8991	39.0	40.0	2003	2003	241.5	215
Overall	21,530	56,087	34.9 (28–41)	38.9 (33–45)	2002 (2000–2004)	2002 (1999–2005)	230 (110–350)	217 (89–345)

Results from complete case descriptive analyses based on 309,564 patients.
IQR, interquartile ranges.

income countries +112 cells/μL, 95% CI: +75 to +149 cells/μL). In the analysis restricted to LIC and MIC, those with cART coverage of 80% or greater (Botswana, Brazil, Cambodia, Rwanda, and Zambia) had substantially higher CD4 cell counts at cART initiation (difference +88 cells/μL; 95% CI: +35 to +141 cells/μL) than countries with a coverage below 40% (Côte d'Ivoire, Democratic Republic of the Congo, Indonesia, Nigeria, and Malaysia). Results were again similar in the complete case analysis (see **Table S4, Supplemental Digital Content,** http://links.lww.com/QAI/A446).

Figure 2 shows trajectories of median CD4 cell counts at cART initiation and the percentage of patients starting cART below 200 cells/μL and below 100 cells/μL, by country income group and gender, estimated by model 3. In LIC, median CD4 cell count at the start of cART increased by 91% in women from 2002 to 2009 (from 82 to 157 cells/μL) and by 62% (from 79 to 127 cells/μL) in men. Corresponding increases for LMIC were from 83 to 166 cells/μL in women (a 102% increase) and from 97 to 138 cells/μL in men (a 42% increase). The increases in UMIC were from 86 to 141 cells/μL in women (a 63% increase) and from 91 to 125 cells/μL in men (a 36% increase). Finally, in HIC, median CD4 cell counts at cART initiation increased by 26% (from 211 to 266 cells/μL) in women and by 34% (from 208 to 280 cells/μL) in men.

In LIC, the percentage of patients starting cART below 200 cells/μL declined from 85% in 2002 to 81% in 2009 in women and from 88% to 70% in men. Corresponding figures for LMIC were from 78% to 59% in women and from 79% to 67% in men and for UMIC from 86% to 65% in women and from 78% to 71% in men. In HIC, the decline was from 46% to 31% in women and from 49% to 35% in men. For threshold below 100 cells/μL, the declines were from 50% to 28% in women and from 57% to 36% in men in LIC, from 47% to 27% in women and from 51% to 36% in men in LMIC, from 54% to 31% in women and from 49% to 40% in men in UMIC, and from 22% to 15% in women and from 27% to 17% in men in HIC. Trends were similar in the complete case analysis (see **Figure S2**, **Supplemental Digital Content**, http://links.lww.com/QAI/A446).

DISCUSSION

This global analysis of CD4 cell counts at cART initiation between 2002 and 2010 was conducted in 2 HIV cohort collaborations, which together span 6 continents.[7,18–21] We found that median CD4 cell counts at cART initiation were substantially higher in HIC, with only small differences between LIC and MIC. Median CD4 cell counts at the start of cART increased over the study period in most countries. These increases were greater in LIC and MIC than in HIC, and greater in women than in men. Among LIC and MIC, median CD4 cell counts at the start of cART were substantially higher in the few countries with national cART coverage of 80% or above.

In LIC and MIC, the median CD4 cell count remained well below 200 cells/μL between 2002 and 2009, despite the 2001 WHO recommendation to start when the CD4 gets near or falls below 200 cells/μL or, in persons with advanced clinical disease (WHO stage IV), irrespective of the CD4 cell count.[26] Following a 2006 recommendation to consider treatment at CD4 cell counts below 350 cells/μL for patients in WHO stage III, WHO indicated in 2009 that cART should be initiated at 350 cells/μL irrespective of clinical symptoms.[27] National guidelines in resource-limited settings generally echoed WHO guidelines,[28] whereas HIC have more rapidly increased the CD4 cell count threshold for initiation. Of note, North American guidelines recently converged in their recommendation that cART should be offered to all HIV-positive individuals, irrespective of the CD4 cell count.[29,30]

A substantial rise in HIV testing in many countries, supported by Global Fund for Tuberculosis, AIDS and Malaria, PEPFAR, national or state/provincial level governments, and other donors, may have contributed to increasing CD4 cell counts at the start of cART. A monitoring and evaluation analysis of PEPFAR-supported HIV care clinics in 8 sub-Saharan African countries found that CD4 cell counts at cART initiation increased with HIV testing coverage in the region.[31] In sub-Saharan Africa, PEPFAR supported over 140 million testing and counseling sessions between 2004 and 2011, with the number of sessions increasing from 1.9 million in 2004 to over 40 million in 2011.[32] Two Demographic and Health Surveys from 7 PEPFAR countries conducted between 2003 and 2010 showed a dramatic increase in population level coverage of HIV testing and counseling.[32] In Kenya, for example, the percentage of men reporting testing in the last 12 months increased from 7.5% to 22.7%. The corresponding increase was even greater in women, from 6.7% to 29.3%. Similarly, in Lesotho, testing increased from 6.3% to 42.0% in women and from 4.8% to 24.0% in men. Provider-

TABLE 2. Annual Change Between 2002 and 2009 in Median CD4 Cell Count at the Start of cART in LIC, LMIC, UMIC, and HIC, by Gender

Country	Women CD4 Cells/μL (95% CI)	Men CD4 Cells/μL (95% CI)
Low-income		
Benin	+8 (−15 to +31)	+4 (−11 to +19)
DR Congo	−14 (−37 to +9)	+6 (−11 to +22)
Kenya	+15 (+13 to +18)	+11 (+8 to +14)
Malawi	+9 (+2 to +15)	+12 (+4 to +21)
Mali	+12 (−2 to +27)	+4 (−1 to +10)
Rwanda	+32 (+22 to +42)	+31 (+12 to +51)
Tanzania	+7 (−1 to +14)	+2 (−4 to +8)
Uganda	+23 (+11 to +35)	+16 (+1 to +31)
Zimbabwe	+8 (+1 to +15)	+5 (−1 to +11)
Pooled		
Crude	+12 (+6 to +17)	+11 (+7 to +15)
Weighted*	+11 (+4 to +17)	+9 (+4 to +14)
Lower middle-income		
Cameroon	+10 (−4 to +24)	+13 (−4 to +31)
Côte d'Ivoire	+13 (+8 to +19)	+10 (0 to +20)
Nigeria	+4 (−13 to +21)	−2 (−14 to +9)
Zambia	+11 (+9 to +13)	+8 (+4 to +11)
Pooled		
Crude	+9 (+6 to +12)	+7 (+4 to +10)
Weighted*	+6 (+1 to +11)	+5 (+1 to +9)
Upper middle-income		
Botswana	+9 (−4 to +23)	−1 (−17 to +15)
Brazil	+8 (−8 to +24)	+15 (0 to +29)
South Africa	+9 (+8 to +11)	+4 (+1 to +7)
Thailand	+10 (+2 to +17)	+6 (−6 to +18)
Pooled		
Crude	+9 (+6 to +11)	+4 (+1 to +7)
Weighted*	+7 (+1 to +13)	+6 (−1 to +13)
High-income		
Australia	+10 (−18 to +38)	−3 (−12 to +7)
Canada	+7 (−1 to +15)	+16 (+12 to +20)
France	+11 (+8 to +13)	+9 (+3 to +15)
Italy	+4 (−3 to +11)	+6 (−3 to +14)
Spain	+3 (−1 to +7)	+6 (+2 to +10)
USA	+9 (+2 to +16)	+13 (+6 to +20)
Pooled		
Crude	+9 (+6 to +11)	+9 (+6 to +12)
Weighted*	+7 (+4 to +11)	+9 (+6 to +13)

Results from linear regression (model 1) based on 347,919 patients, with missing values imputed using multiple imputation.

*Weighted by the number of patients on cART in the respective country, as estimated by WHO.[5]

TABLE 3. Individual-Level and Country-Level Predictors of the Median CD4 Cell Count at the Start of cART in 2009

Variable	Median CD4 Cell Count (Cells/μL)
Sex	
Male	164 (intercept, 140 to 189)
Female	23 (18 to 28)
Income group	
Low	164 (intercept, 140 to 189)
Lower middle	−13 (−56 to 30)
Upper middle	−22 (−62 to 18)
High	112 (75 to 149)
Age group (yrs)	
<30	164 (intercept, 140 to 189)
30 to <40	−16 (−21 to −10)
40 to <50	−17 (−24 to −10)
≥50	−3 (−12 to 6)
National cART coverage (%)*	
<40	144 (intercept, 103 to 185)
40 to <60	10 (−38 to 57)
60 to <80	−6 (−58 to 46)
≥80	88 (35 to 141)

Results from mixed effects linear regression (model 2) based on 55,007 patients starting cART in 2009, missing values imputed using multiple imputation. Intercepts and coefficients (95% confidence intervals) are shown. All models include calendar year, age, gender, and income group. The intercept of 164 cells/μL corresponds to men in low-income countries.

*Separate analysis based on 52,482 patients starting cART in 2009 in low-income and middle-income countries (model 2). The intercept of 144 cells/μL corresponds to men in low-income countries. Estimates of national cART coverage in 2009, based on WHO 2006 guidelines were as follows[25]: Benin 72%, Democratic Republic of the Congo 26%, Kenya 65%, Malawi 63%, Mali 65%, Rwanda >95%, Tanzania 44%, Uganda 53%, Zimbabwe 49%, Cameroon 41%, Côte d'Ivoire 39%, Nigeria 31%, Zambia 85%, Botswana >95%, Brazil 80%, South Africa 56%, and Thailand 76%.

initiated testing and counseling may not, however, be sufficient to prevent late HIV diagnosis. Uganda adopted provider-initiated HIV testing in the health care setting in 2005, but in a recent randomized controlled trial, half of HIV-positive patients screened had CD4 cell counts below or equal to 250 cells/μL.[33]

The steeper increase of HIV testing coverage among women compared with men may be explained by scale-up of programs to PMTCT. More frequent testing leads to earlier diagnosis and then earlier initiation of cART in eligible women. The scale-up of PMTCT could thus also account for the greater increases of CD4 cell counts at the start of cART in women than men observed in the present study. A review of national program data for 2004 to 2005 showed that the scale-up of PMTCT had gained momentum in many countries and that provider-initiated (opt-out) HIV testing had become nearly universal in some regions (eg, in East and Southern Africa) but not in others (eg, in West Africa).[34] A systematic review and meta-analysis of 44 studies of pregnant women who attended PMTCT programs in sub-Saharan Africa showed that uptake at antenatal care services was 94% for opt-out testing compared with 58% for opt-in testing.[35] Coverage with any type of antiretroviral prophylaxis was 70%, and 62% of pregnant women eligible for cART received treatment.[35] Similarly, a meta-analysis of 6 studies that reported on numbers of adults followed up between HIV diagnosis and start of cART showed that of every 100 patients with a positive HIV test, 72 had a CD4 cell count measured, 40 were eligible for cART, and 25 started cART. Of note, men were more likely to be lost to program and less likely to start cART than women.[36]

Our study has several limitations. We could only examine information up to 2010 because more recent data were not yet available from many sites participating in the IeDEA and ART cohort collaborations. CD4 cell counts at the

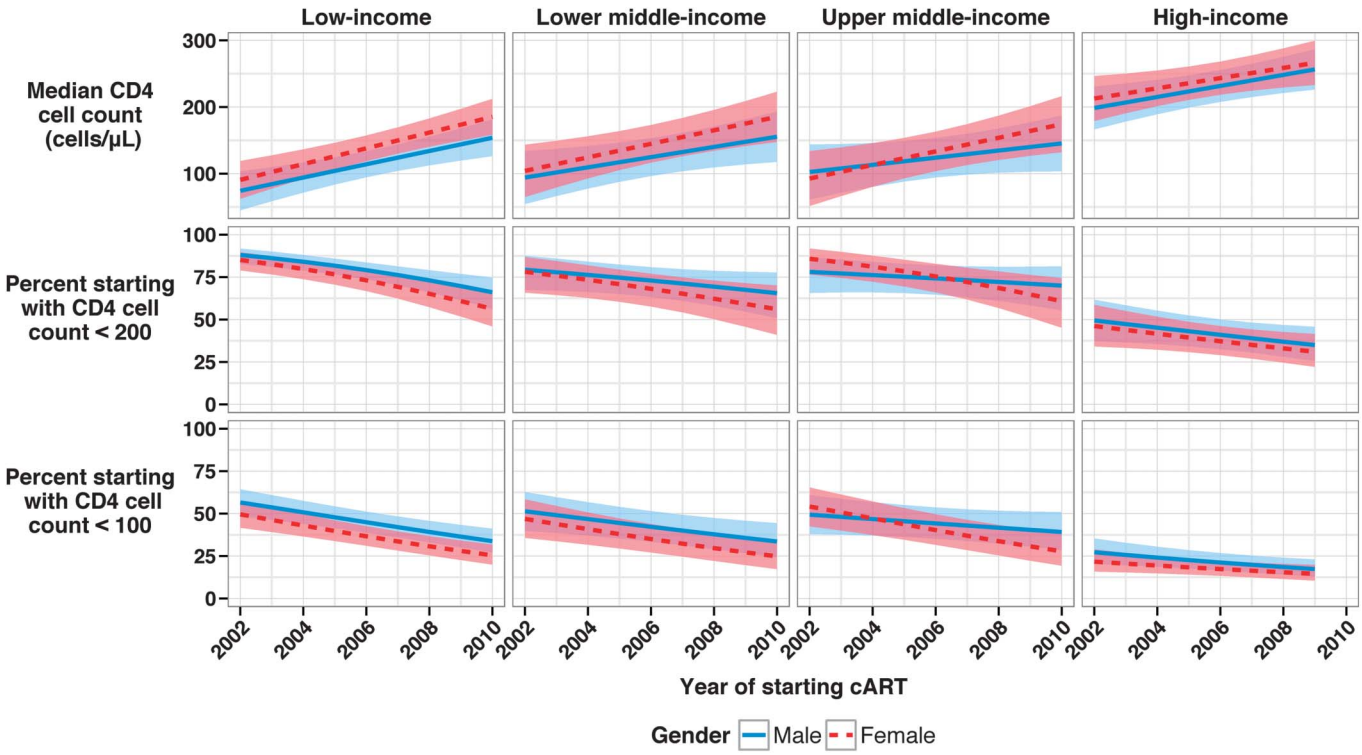

FIGURE 2. Trends of median CD4 cell counts at the start of cART (upper panel) and in proportions of men and women starting cART below 200 cells/μL (middle panel) or below 100 cells/μL (lower panel) in low-, middle-, and high-income countries, 2002–2010. The shaded areas represent the 95% CI for each year. Results from mixed effects linear regression (model 3) are based on 379,865 patients; missing values imputed using multiple imputation.

start of cART were missing in approximately 1 quarter of patients, who were more likely to be from LIC and MIC and in a more advanced stage of disease than patients with measured CD4 cell counts. It is thus likely that our estimates of median CD4 cell counts at cART initiation are biased upward for these countries. Data from some countries were limited to a small number of patients from a single clinic. We decided to include these in descriptive analyses, but because the data are probably not representative of all patients on cART in those countries, we excluded them from analyses of time trends and predictors of CD4 cell count at the start of cART. In sensitivity analyses, we weighted individual country data, with the aim of creating a data set that was representative, within each income group, of the number of patients on cART in each country, as estimated by WHO.[5] Some of the data included in these sensitivity analyses may, however, not be representative of all patients on cART in the country. In particular, the clinics from LIC and MIC 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. Nevertheless, our 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, our results illustrate the enormous challenges that lie ahead. Despite the massive scale up of cART in LIC, from 300,000 patients on cART in 2002 to 6.6 million by the end of 2010, the increases in median CD4 cell count at the start of cART during this period have been modest. In 2009, most patients in LIC and MIC and many patients in HIC started cART with CD4 cell counts below 200 cells/μL, which means that they were already at high risk of complications and had spent years at high risk of HIV transmission. Substantial efforts and resources are needed to achieve earlier implementation of cART globally. Finally, continued monitoring of the CD4 cell count at which HIV-positive patients start cART in LIC, middle-income countries, and HIC is needed to evaluate the results of these efforts.

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