HHS Public Access

Author manuscript

AIDS. Author manuscript; available in PMC 2015 July 01.

Published in final edited form as:

AIDS. 2015 January 2; 29(1): 67–76. doi:10.1097/QAD.0000000000000520.

Trends in and correlates of CD4+ cell count at antiretroviral therapy initiation after changes in national ART guidelines in Rwanda

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Abstract

Background—Initiation of antiretroviral therapy (ART) in the advanced stages of HIV infection remains a major challenge in sub-Saharan Africa. This study was conducted to better understand barriers and enablers to timely ART initiation in Rwanda where ART coverage is high and national ART eligibility guidelines first expanded in 2007–2008.

Methods—Using data on 6326 patients (≥15 years) at five Rwandan clinics, we assessed trends and correlates of $CD4^+$ cell count at ART initiation and the proportion initiating ART with advanced HIV disease ($CD4^+$ <200 cells/μl or WHO stage IV).

Results—Out of 6326 patients, 4486 enrolling in HIV care initiated ART with median $CD4^+$ cell count of 211 cells/μl [interquartile range: 131–300]. Median $CD4^+$ cell counts at ART initiation increased from 183 cells/μl in 2007 to 293 cells/μl in 2011–2012, and the proportion with advanced HIV disease decreased from 66.2 to 29.4%. Factors associated with a higher odds of advanced HIV disease at ART initiation were male sex [adjusted odds ratios (AOR) = 1.7; 95% confidence interval (CI): 1.3–2.1] and older age ($AOR_{46–55+ \text{ vs. } <25}$ = 2.3; 95% CI: 1.2–4.3). Among those initiating ART more than 1 year after enrollment in care, those who had a gap in

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E.M., K.A., D.R.H. and D.N. designed the study. D.A., D.R.H., and D.N., analyzed the data. E.M., D.A. and D.N. drafted the first manuscript. K.A., D.R.H, J.C.D., B.K., I.I., L.M. and S.N. contributed to the first manuscript preparation. E.M., D.A., K.A., D.R.H., J.C.D., B.K., I.I., L.M., S.N. and D.N. were responsible and contributed and approved the final manuscript writing.

Presentation: This work was presented by E.M. at the 20th Conference on Retroviruses and Opportunistic Infections (CROI, March 2013) (poster #1090), 3–6 March, Atlanta, Georgia USA.

Conflicts of interest

There are no conflicts of interest.

care of 12 or more months prior to ART initiation had higher odds of advanced HIV disease (AOR = 5.2; 95% CI: 1.2–21.1).

Conclusion—Marked improvements in the median $CD4^+$ cell count at ART initiation and proportion initiating ART with advanced HIV disease were observed following the expansion of ART eligibility criteria in Rwanda. However, sex disparities in late treatment initiation persisted through 2011–2012, and appeared to be driven by later diagnosis and/or delayed linkage to care among men.

Keywords

antiretroviral therapy national guidelines; $CD4^+$; determinants; HIV treatment; Rwanda

Introduction

Efforts to expand HIV infection treatment programmes in sub-Saharan Africa (SSA) have demonstrated improvement in access to HAART. The estimated number of HIV-infected individuals in low-income and middle-income countries (LMICs) on antiretroviral therapy (ART) increased five-fold from 1.3 million in 2006 to over 6.6 million in 2013 [1,2], with robust and sustained immune responses for those patients who remain on treatment, especially when starting ART with higher baseline $CD4^+$ cell counts [3]. Overall AIDS-related morbidity and death have declined markedly in countries where access to ART has significantly improved [3–5]. However, the persistent problem of ART initiation in the advanced stages of HIV infection threatens to limit the full potential of HIV scale-up programmes in SSA [6], and is associated with high mortality rates after ART initiation and further HIV transmission [6–8]. The excess mortality is due in large part to ART initiation at low $CD4^+$ cell counts [4]. In resource-limited settings with weak healthcare infrastructure, many operational challenges beside social, economic and clinical determinants are associated with lower $CD4^+$ cell count at enrollment and at ART initiation, all of which mitigate the benefit of HIV treatment programmes [9,10].

With an HIV prevalence of 3.0% [11], Rwanda has been scaling up access to HIV care since 2004, and the mature national programme has achieved more than 93% ART coverage [12] with high rates of retention [13] and medication adherence with viral suppression [14]. We therefore examined the proportion of persons enrolling in HIV care and initiating ART in the advanced stages of HIV infection among patients in Kigali, Rwanda, before and after the first expansion of national ART guidelines from a $CD4^+$ threshold of 200 cells/μl to 350 cells/μl. In order to assess barriers and enablers to timely ART initiation in the context of high ART coverage and high median $CD4^+$ at ART initiation, we examined correlates of advanced HIV infection at ART initiation among persons initiating ART in 2012.

Methods

Study population and data source

The study population included HIV-infected adult patients (≥15 years) enrolling in care, and initiating ART at five urban HIV care clinics [Women's Equity in Access to Care and Treatment, Carrefour, Bethsaida, Kicukiro and Makasa] in Kigali from January 2003 to June

2012 participating in the International epidemiologic Databases to Evaluate AIDS (IeDEA) consortium (http://www.iedea.org). We used electronic patient-level data collected as part of routine service delivery from clinics that are part of the national HIV care and treatment programme in Rwanda. Patient information at enrollment and/or ART initiation was collected routinely by nurses and trained data clerks using standard national patient medical records and then entered into an electronic database. Data were de-identified prior to being shared with researchers for analysis.

Outcome definition

We defined advanced HIV disease at enrollment into care or ART initiation as either having a $CD4^+$ cell count of less than 200 cells/μl or a WHO stage IV condition at the time of enrollment or ART initiation, respectively. The $CD4^+$ cell count at ART initiation included $CD4^+$ results measured up to 90 days before or 30 days after the date of ART initiation, with priority given to $CD4^+$ cell counts prior to ART initiation and otherwise closest to the ART initiation date. A small proportion of patients (<5%) who did not have WHO staging information and $CD4^+$ cell counts at enrollment into care or ART initiation were included in analyses and categorized as missing/unknown.

HIV-infected patients who enrolled into care, and were not eligible for treatment were offered various services that included monitoring of their $CD4^+$ cell counts on a 6-month basis and prophylaxis for opportunistic infections and prevention of mother-to-child transmission (PMTCT) according to guidelines in place at the time. Patients received HIV voluntary counseling and testing (VCT) or provider-initiated voluntary counseling and testing (PVCT) and were enrolled into care. Enrollment into care often occurred at the same testing site as all five study clinics routinely offer HIV prevention, diagnostic and treatment services including $CD4^+$ cell count determination. Patients who enrolled into care from 2003 to 2006 were considered ART eligible under the 2004 national ART guidelines in Rwanda [12] (WHO stage IV diagnosis irrespective of $CD4^+$ cell count, or a WHO clinical stage of III with a $CD4^+$ cell count of <350 cells/μl, or WHO stage I or II with a $CD4^+$ cell count of <200 cells/μl). Patients enrolled into care from 2007 to 2011 were considered ART eligible under the 2007 national guidelines (WHO stage IV or a $CD4^+$ cell count of less than 350 cells/μl irrespective of WHO stage). Patients enrolling into care in 2012 were considered ART eligible under the 2012 national ART guidelines ($CD4^+$ cell count of<500 cells/μl irrespective of WHO stage). Women who were pregnant and not already on ART were referred to PMTCT services. Also, those with active tuberculosis disease, WHO stage III and IV and, beginning in 2012, those in a serodiscordant relationships were initiated on ART regardless of their $CD4^+$ cell count.

Statistical analysis

We examined trends in the median $CD4^+$ cell count and percentage of patients enrolling in care and initiating ART with $CD4^+$ cell count more than 200, more than 350 and more than 500 cells/μl during 2003–2012, before and after the first expansion of ART eligibility criteria in the national guidelines. Relative risk (RR) ratios for the proportion of patients with advanced disease at enrollment into care and ART initiation were calculated, comparing the risk before 2007 with that in 2011–2012 within patient characteristics. For

patients initiating ART in 2011–2012, we examined factors associated with advanced HIV disease ($CD4^+$ <200 cells/μl or WHO stage IV). Adjusted odds ratios (AOR) and 95% confidence intervals (CIs) were generated using generalized estimating equations to account for clustering of patients within sites. Statistical analyses were carried out using SAS version 9.2 (SAS Institute, Cary, North Carolina, USA).

Ethical review

Ethical approvals for this study were obtained from the Rwandan National Ethics Committee and the Institutional Review Board of Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, New York, USA.

Results

Characteristics of patients at enrollment into care and at antiretroviral therapy initiation

Sociodemographic characteristics of the 6326 patients at least 15 years enrolled into care from 2003 to 2012 are presented in Table 1. Median age was 35 years [interquartile range (IQR): 29–42] and 62% were women, of whom 3.4% were pregnant. Twenty percent of patients were married and 64% were enrolled through a voluntary testing and counseling center. About 71% (n = 4486) of patients initiated ART during the study follow-up to 2012, with 2.0% of women (n = 87) pregnant at ART initiation.

The proportion of patients with advanced HIV disease enrolling into care and initiating ART was 23.8 and 45.7%, respectively (Table 2). Median $CD4^+$ cell count for all patients at enrollment was 349 cells/μl (IQR: 194–543) and for those who initiated ART was 211 cells/μl (IQR: 131–300) at the point of ART initiation. For those with data available at enrollment (n = 5280), the proportion of patients with WHO stage III or IV at enrollment into care was 21% compared with 27% at ART initiation (Table 2). Approximately 48% of all patients were immediately eligible for ART at enrollment based on the Rwanda national guidelines in effect at the time of their enrollment.

Trends in $CD4^+$ cell count among patients at enrollment into care and at antiretroviral therapy initiation

From 2003 to 2012, there was a near doubling in median $CD4^+$ cell count at enrollment in care for all patients from 185 (IQR: 109–378) in 2003 to 340 cells/μl (IQR: 184–480) in 2012 (Fig. 1a). Women had higher median $CD4^+$ cell counts at enrollment than men for the entire time period of 2003–2012. Overall, the median $CD4^+$ cell count at enrollment into care for men and women were 317 cells/μl (IQR: 168–508) and 372 cells/μl (IQR: 217–571) respectively, $P < 0.001$. Men on average initiated ART at a lower $CD4^+$ cell count than women; 198 cells/μl, (IQR 120–290) vs. 223 cells/μl (IQR: 140–305) for men and women, respectively, $P < 0.001$ (data not shown). The median $CD4^+$ cell count at ART initiation increased steadily during 2003–2012. During the first Rwandan national guidelines expansion in 2007–2008, which increased the $CD4^+$ cell count for treatment initiation to less than 350 cells/μl, the median $CD4^+$ cell count for patients in our study increased from 183 to 246 cells/μl within 1 year of national guideline expansion, and ultimately reached 293 cells/μl in 2011 (Fig. 1b).

The proportion of patients who initiated ART at $CD4^+$ cell count of more than 200, more than 350 and more than 500 cells/μl over time is shown in Fig. 1c. Whereas there was a large increase in the proportion of patients initiating ART with $CD4^+$ cell count of greater than 200 cells/μl from 38.2 to 67.3% after the 2007 national guideline expansion, the proportion of patients in 2012 with $CD4^+$ cell count of greater than 350 cells/μl at ART initiation was 19.7%. Patients initiating ART at a $CD4^+$ cell count of greater than 500 cells/μl rose from 5.3% in 2011 to 9.8% in 2012 during the year where national guidelines expanded to include treatment for all patients with a $CD4^+$ cell count of less than 500 cells/μl. The median $CD4^+$ cell counts of patients enrolling in HIV care who ultimately initiated ART appeared to increase more in women than men, with an overall median $CD4^+$ cell count of 377 cells/μl by 2012, with women at 430 cells/μl vs. men 322 cells/μl $P < 0.001$ (data not shown).

Advanced HIV disease at antiretroviral therapy initiation before and after Rwanda national guideline expansion

Data on the proportion of patients of enrolling in care and initiating ART with advanced HIV disease before 2007 vs. 2011–2012 and RR for different sociodemographic and clinical categories are summarized in Table 3. Overall, there was a decrease in the proportion of patients enrolling into care with advanced HIV disease from 28.2% for those who enrolled before 2007 to 22.6% in 2011–2012. An even more dramatic decrease was found in the proportion of patients initiating ART with advanced HIV disease before 2007 and in 2011–2012 at 66.2 to 29.4%, respectively (Table 3). The decrease in the risk during 2007 to 2011–2012 was also observed in most subgroups. A decreased risk was found in both men and women [$RR_{men} = 0.56$ (95% confidence interval or CI: 0.48–0.65), $RR_{women} = 0.35$ (95% CI: 0.30–0.42)], those who were younger [$RR_{15–25} = 0.30$ (95% CI: 0.20–0.45)] and older [$RR_{46–55} = 0.64$ (95% CI: 0.50–0.84)], those married [$RR_{married} = 0.52$ (95% CI: 0.41–0.67)] or single [$RR_{single} = 0.51$ (95% CI: 0.39–0.68)], entering enrollment through the voluntary counseling and testing center: VCT [$RR_{VCT} = 0.44$ (95% CI: 0.37–0.50)], or those with clinical WHO stage I at enrollment [$RR_{WHO\ stage\ I} = 0.39$ (95% CI: 0.33– 0.47)] among other factors.

Factors associated with initiating antiretroviral therapy with advanced HIV disease in 2011– 2012

The multivariable model of factors associated with higher odds of initiating ART with advanced HIV disease is presented in Table 4. Male sex ($AOR_{men\ vs.\ women} = 1.66$, 95% CI: 1.34–2.05) and older age: ($AOR_{36–45\ vs.\ <25} = 1.68$, 95% CI: 1.11–2.56, and $AOR_{46–55\ vs.\ <25} = 2.26$, 95% CI: 1.20–4.30) were associated with higher odds of having advanced HIV disease at ART initiation after adjusting for covariates. Among those initiating ART more than 1 year after enrollment in care, those who had a gap in care of 12 or more months prior to ART initiation had higher odds of advanced HIV disease (AOR = 5.23, 95% CI: 1.23–21.13). Living with a partner and unknown eligibility for ART at enrollment were associated with lower odds of having advanced HIV disease at ART initiation $AOR_{living\ with\ a\ partner\ vs.\ married} = 0.75$, 95% CI: 0.58–0.98 and $AOR_{unknown\ eligibility\ vs.\ eligible\ for\ ART} = 0.16$, 95% CI: 0.04–0.63, respectively.

Discussion

Our analyses showed substantial improvements in the median $CD4^+$ cell counts at ART initiation in our sample of five clinics from Rwanda, where the ART coverage has risen to over 93% [12] and national ART eligibility guidelines have been expanded, often in advance of other countries in the region. The five HIV clinics included in our study comprised of two private clinics and three government-owned clinics where IeDEA programmes initially started. They are among the HIV clinics in the country with a large volume of patients, and are located in both urban and periurban settings. The median $CD4^+$ cell count at ART initiation in our study of HIV-infected Rwandan patients is higher than reported in other studies in the region [10,15,16]. A global analysis of data from 48 countries, including those in North America, Europe, and SSA, found that in 2009 the United States had the highest mean $CD4^+$ cell count at ART initiation (307 cells/μl) followed, remarkably, by Rwanda (287 cells/μl) [17,18]. Given this and other HIV programmatic scale-up successes in Rwanda [13,14,19], there are likely important lessons to be learned by comparing Rwanda's experience with those of other countries in SSA.

Surprisingly, although this was an analysis of specific HIV sites in an urban setting, our reported median $CD4^+$ cell count at ART initiation reached up to 293 cells/μl in 2011, and is considerably higher than the recent estimates of median $CD4^+$ of 155 cells/μl in 2009 from clinical sites in various LMICs [18]. Therefore, our observation of higher median $CD4^+$ cell count at ART initiation is different from the consistently reported low median $CD4^+$ cell count at ART initiation in other SSA settings [3,4,7–10]. One recent study of trends in $CD4^+$ cell count at ART initiation in four SSA studies, including Rwanda, found an increase in median $CD4^+$ of 125–185 cells/μl during 2006–2011, or only about 10 cells/per year [20]. We believe the larger increases in median $CD4^+$ cell count at ART initiation in Rwanda demonstrates rapid achievement of very high ART programme coverage, achievable in part because of lower HIV prevalence than that of other East and Southern African countries. Systematically identifying specific reasons for this progress that may be replicable in other settings is an important research priority for the region.

We observed an overall improvement in the timeliness of ART initiation, with risk of initiating ART with $CD4^+$ cell count less than 200 cells/μl falling from 58.7% in 2007 to less than 32.0% in 2008–2012. More timely ART initiation has several benefits associated with improved individual patient survival, lower burden on the healthcare system, and decreased likelihood of onward HIV transmission [15,21]. The observed increase in the proportion of people initiating ART with $CD4^+$ cell count more than 200 cells/μl was restricted to those with $200<CD4^+<350$ cells/μl is further evidence that the guideline change drove the increase. The reason for the increase followed by the decline in the median $CD4^+$ cell count at enrollment into HIV care beginning in 2010 is less clear, but likely because of factors outside the HIV care system such as improvements in testing coverage and linkage. For example, increases testing coverage could have the effect of identifying a large bolus of prevalent positives in the short term. Over the long term, those undiagnosed people living with HIV (PLWH) who are more marginalized and thus less likely to be tested before development of symptoms could be driving declines in the median $CD4^+$ cell count at enrollment (possibly representing a return to baseline/steady state).

In this study, several factors were independently associated with greater likelihood of late ART initiation in 2011/12, including male sex and older age. Other studies from SSA have also reported that men start ART at lower median $CD4^+$ cell count, and the rate of change in $CD4^+$ cell count over time is significantly lower in men than women [22–25]. Our study found that the disparity persists even in Rwanda where the ART coverage is high, and that the sex difference is largely explained by men being more likely to be ART eligible (i.e. sicker) at enrollment than women, likely because of later diagnosis and/or delayed linkage to HIV care [7]. This in turn suggests that guideline changes and a strong HIV care system alone will not eliminate sex disparities in late treatment initiation, and more research is needed on how to address this important sex disparity in the timeliness of ART initiation, which appears to be worsening with time [20].

In addition to earlier ART initiation, we observed an increase in median $CD4^+$ cell count at enrollment in care from 185 to 340 cells/μl. This finding is likely a result of improved timeliness in diagnosing and linking HIV-positive patients to care, and not a direct result of expanding treatment guidelines, which tend to affect the timeliness with which treatment is initiated among those already enrolled in HIV care. The finding of increasing median $CD4^+$ cell count at enrollment into HIV care may be explained in part by several synergistic factors associated with improved primary healthcare access in Rwanda. This includes a strong healthcare system and infrastructure which is being rapidly developed, with community-based health insurance [19,26,27,28], improved workforce skills promotion of performance-based financing and strong leadership commitment [19,29,30].

Drivers of timely ART initiation include timely HIV diagnosis following infection, followed by timely linkage to care and ART initiation [7]. There are several measurable proximal factors that could explain why Rwanda appears to have superior outcomes with regard to the timeliness of enrollment into HIV care and ART initiation. In countrywide Demographic Health Survey surveys, 92.0% of adult HIV-infected Rwandans report having previously been tested for HIV, compared with only 74.9% of Ethiopians and 74.3% of Tanzanians [31]. Perhaps as a result of greater testing coverage, HIV-infected Rwandans appear to exhibit less stigma against PLWH infection (94.9% would buy vegetables from a HIV-infected vendor, compared with 71.5% of Ethiopians and 77.6% of Tanzanians), have better prevention knowledge (95.9% endorse condoms as a risk reduction method vs. 78.2% in Ethiopia and 82.1% in Tanzania) and greater understanding of PMTCT (98.5% know transmission can occur during delivery vs. 83.9% in Ethiopia and 79.2% in Tanzania) [31]. Overall, 62% of HIV-infected Rwandans have comprehensive HIV knowledge, compared with only 31.2% of Ethiopians and 53.1% of Tanzanians, with a particularly stark contrast among women (65.1 vs. 25.1 and 48.1%, respectively) [31].

It is likely that other more upstream factors are responsible for these HIV-specific outcomes. In addition to the increasing proportion of Rwandans with national community-based health insurance, Rwanda's healthcare system and infrastructure has been improving over time [19]. Despite being one of the poorest countries in the world, with approximately 63% of its population living on less than $1.25 USD per day [32], the country has harmonized donor support for its HIV programme, retaining ownership of all developmental programmes to ensure that support funds are sustainable in the medium to long term [19,26]. The

availability of trained community health workers or animateurs de santé to deliver preventive, diagnostic and therapeutic services at each village level or Umudugudu, further help link patients to healthcare facilities in a timely manner [12,26].

Our study has some limitations. First, our sample was limited to patients enrolled in HIV care programmes in urban settings. Urban patients may have greater opportunity and capacity than rural patients to access HIV services, with fewer barriers to access, for instance, shorter distance to clinic, higher education and better socioeconomic demographic characteristics. Our analysis also included only sites that have electronic data systems, which may not be representative of HIV programmes without such systems. Additionally, the five urban sites included in our study are not representative of all HIV care sites in Kigali or Rwanda. Finally, the observational nature of our study limits our ability to assess and quantify any underlying causal effect of the risk factors and correlates examined.

The strengths of our study include use of routinely collected patient data from several urban private and government-owned HIV sites. This allows for analysis of routine clinical data rather than data collected for research purposes only. Secondly, our analyses include broad data for the sites over 10 years from 2003 to 2012, a period when the Rwandan national guidelines eligibility criteria for ART initiation changed in 2007–2008 from $CD4^+$ cell counts of less than 200 cells/μl +/− WHO stage IV or WHO stage III with 200–350 cells/μl to $CD4^+$ cell counts less than 350 cells/μl irrespective of WHO stage.

In conclusion, we observed a marked increase in the median $CD4^+$ cell count at ART initiation, and a dramatic increase in the proportion of patients initiating ART with $CD4^+$ more than 200 cells/μl following the expansion of ART eligibility criteria in 2007–2008. Although the increase in the median $CD4^+$ cell count at ART initiation was observed in both women and men, men were significantly more likely than women to initiate ART at lower $CD4^+$ cell counts, and to initiate ART with $CD4^+$ cell counts less than 200 cells/μl or WHO IV. Despite high levels of ART coverage in Rwanda, a substantial proportion of persons continue to initiate ART well below the $CD4^+$ thresholds specified in national guidelines, even with near universal coverage. Additional research is therefore needed on the determinants of late diagnosis, enrollment into care, and treatment initiation, even in the context of very high ART coverage. It is also important to better understand the mechanisms by which men initiate ART later than women, and to diagnose and link them to HIV care earlier through VCT and PMTCT with partner testing. As Rwanda is among the few countries in SSA with rapid HIV scale up programmes that has achieved high treatment coverage, further studies are needed to examine whether programme quality can be maintained, and to understand how best to replicate the successes of Rwanda in other settings.

Acknowledgements

The authors acknowledge the efforts of the entire IeDEA community and clinic staff at various HIV sites tasked with collecting the data used for this analysis.

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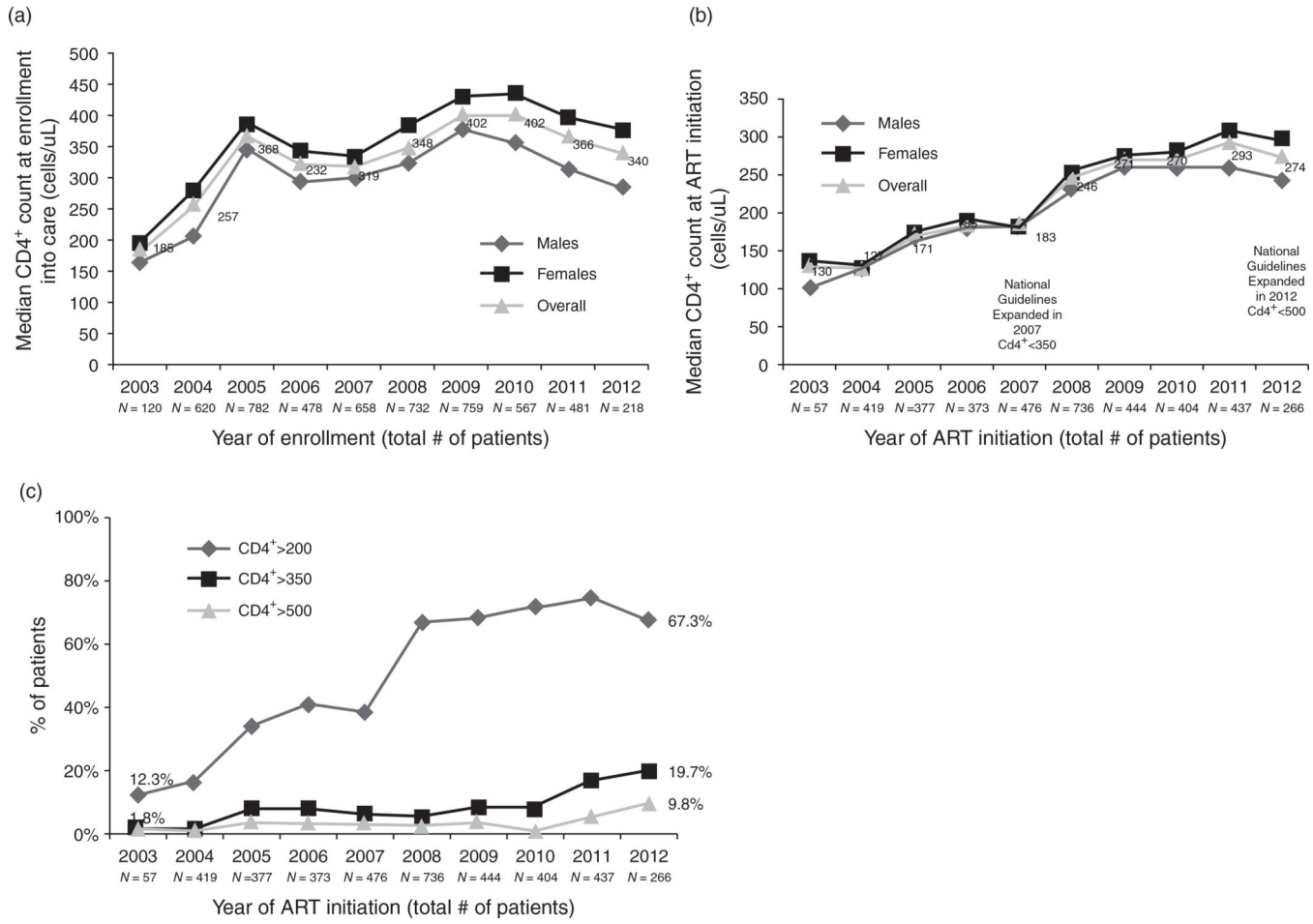

Fig. 1.

Median CD4$^+$ cell count by sex among (a) all patients at enrollment and (b) antiretroviral therapy (ART) patients at ART initiation between 2003 and 2012. (c) The proportion of patients with a CD4$^+$ cell count at more than 200, 350, and 500 cells/μl between 2003 and 2012.

Table 1

Sociodemographic characteristics of patients at enrollment into care and antiretroviral therapy initiation from five sites in Rwanda, 2003–2012.

	All patients at enrollment into care		ART patients at enrollment into care	
	N	%	*N*	%
Total, *N* (%)	6326	100	4486	100
Sex				
Men	2384	37.7	1794	40.0
Women (not pregnant)	3732	59.0	2605	58.0
Women (pregnant)	210	3.3	87	1.9
Age (years)				
Median (IQR)	35 (29–42)		36 (30–43)	
15–25	975	15.4	512	11.4
26–35	2471	39.1	1666	37.1
36–45	2008	31.7	1602	35.7
46–55	718	11.4	584	13.0
≥56	154	2.4	122	2.7
Marital status				
Married	1266	20.0	919	20.5
Living with partner	732	11.6	495	11.0
Single	947	15.0	597	13.3
Divorced	125	2.0	78	1.8
Widowed	810	12.8	573	12.8
Missing	2446	38.7	1824	41.0
Enrollment point of entry				
VCT	4015	63.5	2892	64.5
PMTCT	1245	19.7	814	18.2
TB clinic	15	0.2	11	0.3
Inpatient	64	1.0	46	1.0
Outpatient	281	4.4	197	4.4
Other	706	11.2	526	11.7
Site				
WE-ACTx	1501	23.7	1075	24.0
Bethsaida	611	9.7	377	8.4
Masaka	1037	16.4	654	14.6
Kicukiro	2517	39.8	1908	42.5
Carrefour	660	10.4	472	10.5
Type of site				
Private	2161	34.2	1547	34.5
Public	4165	65.8	2939	65.5
Year of enrollment				

	All patients at enrollment into care		ART patients at enrollment into care	
	N	%	*N*	%
2003	177	2.8	151	3.4
2004	833	13.2	711	15.9
2005	937	14.8	683	15.2
2006	543	8.6	379	8.5
2007	722	11.4	521	11.6
2008	843	13.3	577	12.9
2009	879	13.9	601	13.4
2010	605	9.6	386	8.6
2011	544	8.6	350	7.8
2012	243	3.8	127	2.8

ART, antiretroviral treatment; IQR, interquartile range; PMTCT, prevention of mother-to-child transmission; TB, tuberculosis; VCT, voluntary counseling and testing; WE-ACTx, Women's Equity in Access to Care and Treatment.

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Table 2

Clinical and immunological characteristics at enrollment into care and antiretroviral therapy initiation of patients at five Rwandan sites between 2003 and 2012.

	All patients at enrollment into care		ART patients at enrollment into care		ART patients at ART initiation	
	N	%	*N*	%	*N*	%
Total	6326	100	4486	100	4486	100
Advanced HIV disease[a]						
Data available	6024	95.2	4243	94.5	4383	97.7
Yes	1434	23.8	1315	31.0	2003	45.7
No	4590	76.2	2928	69.0	2380	54.3
$CD4^+$ cell count (cells/μl)						
Data available	5415	85.6	3826	85.2	3989	88.9
Median (IQR)	349 (194–543)		280 (158–426)		211 (131–300)	
Clinical WHO stage						
Data available	5280	83.5	3662	81.6	3939	87.8
Stage I	2877	54.5	1784	48.7	1803	45.8
Stage II	1292	24.5	961	26.2	1067	27.1
Stage III	994	18.8	817	22.3	942	23.9
Stage IV	117	2.2	100	2.7	127	3.2
ART eligibility at enrollment[b]						
Data available	5600	88.5	3877	86.4	–	–
Not eligible for ART	2914	52.0	1592	41.1	–	–
Eligible for ART	2686	48.0	2285	58.9	–	–
Year of enrollment/ART initiation						
2003	177	2.8	151	3.4	71	1.6
2004	833	13.1	711	15.9	517	11.5
2005	937	14.8	683	15.2	456	10.2
2006	543	8.6	379	8.5	440	9.8
2007	722	11.4	521	11.6	540	12.0
2008	843	13.3	577	12.9	792	17.7

	All patients at enrollment into care		ART patients at enrollment into care		ART patients at ART initiation	
	N	%	*N*	%	*N*	%
2009	879	13.9	601	13.4	480	10.7
2010	605	9.6	386	8.6	438	9.8
2011	544	8.6	350	7.8	467	10.4
2012	243	3.8	127	2.8	285	6.4
Documented TB						
Yes	122	1.9	97	2.2	0	0
No/unknown	6204	98.1	4389	97.8	4486	100

ART, antiretroviral treatment; IQR, interquartile range; PMTCT, prevention of mother-to-child transmission; TB, tuberculosis; VCT, voluntary counseling and testing.

[a] Advanced HIV disease at enrollment or ART initiation is defined as having a $CD4^+$ cell count <200 cells/μl or WHO stage IV.

[b] Eligibility based on Rwanda HIV national guidelines.

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Table 3

Unadjusted comparison of proportions and relative risk ratios for years before 2007 vs. 2011–2012 for patients initiating antiretroviral therapy with advanced HIV disease[a] by sociodemographic and clinical characteristics.

	Before 2007 (Reference)		2011–2012		RR (95% CI) for 2011–12 vs. 2007 association within row strata[a]
	N	% Advanced HIV disease	*N*	% Advanced HIV disease	Before 2007 vs. 2011–2012
Total	1414	66.2	752	29.4	0.44 (0.40, 0.50)
Sex					
Men	545	71.0	301	39.9	0.56 (0.48, 0.65)
Women	869	63.2	451	22.4	0.35 (0.30, 0.42)
Age					
15–25	77	63.6	121	19.0	0.30 (0.20, 0.45)
26–35	506	65.0	290	25.1	0.39 (0.31, 0.48)
36–45	584	68.5	228	35.5	0.52 (0.43, 0.62)
46–55	202	64.4	94	41.5	0.64 (0.50, 0.84)
≥56	45	62.2	19	26.3	0.42 (0.19, 0.93)
Marital status					
Married	220	58.2	177	30.5	0.52 (0.41, 0.67)
Living with partner	64	48.44	107	19.6	0.41 (0.26, 0.64)
Single	67	65.7	158	33.5	0.51 (0.39, 0.68)
Divorced/widowed	177	58.8	89	38.2	0.65 (0.49, 0.87)
Missing	886	71.0	221	26.7	0.38 (0.30, 0.47)
Enrollment point of entry					
VCT	933	71.1	469	30.9	0.44 (0.37, 0.50)
PMTCT	308	60.7	141	16.3	0.27 (0.18, 0.39)
Outpatient	28	46.4	60	51.7	1.11 (0.70, 1.78)
Other/Unknown	145	50.3	82	26.8	0.53 (0.36, 0.79)
Type of site					
Private	214	48.6	221	29.4	0.60 (0.47, 0.77)
Public	1200	69.3	531	29.4	0.42 (0.37, 0.49)
$CD4^+$ cell count at enrollment into care (cells/μl)					

	Before 2007 (Reference)		2011–2012		RR (95% CI) for 2011–12 vs. 2007 association within row strata[a]
	N	% Advanced HIV disease	*N*	% Advanced HIV disease	Before 2007 vs. 2011–2012
$CD4^+$ <150	428	100	110	100	–
150≤$CD4^+$<200	176	100	48	100	–
200≤$CD4^+$<350	297	33.7	153	8.5	0.25 (0.15, 0.43)
350≤$CD4^+$<500	121	33.1	167	7.2	0.22 (0.12, 0.40)
$CD4^+$≥500	115	33.9	214	9.8	0.29 (0.18, 0.47)
Missing	277	55.2	60	28.3	0.51 (0.34, 0.78)
Clinical WHO stage at enrollment into care					
Stage I	326	61.0	490	23.8	0.39 (0.33, 0.47)
Stage II	306	59.5	138	39.9	0.67 (0.54, 0.84)
Stage III	417	63.1	48	52.1	0.83 (0.62, 1.09)
Stage IV	45	100	16	100	–
Missing	320	77.2	60	13.3	0.17 (0.10, 0.33)
Documented TB treatment at enrollment/ART initiation					
Yes	N/A	N/A	N/A	N/A	N/A
No/unknown	1414	66.2	752	29.4	0.44 (0.40, 0.50)

ART, antiretroviral treatment; CI, confidence interval; IQR, interquartile range; PMTCT, prevention of mother-to-child transmission; RR, relative ratio; TB, tuberculosis; VCT, voluntary counseling and testing.

[a]RR is for having Advanced HIV disease at ART initiation (defined as having a $CD4^+$ cell count <200 cells/μl or WHO stage IV) for 2011–2012 vs. before 2007.

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Table 4

Adjusted odds ratio of advanced HIV disease at antiretroviral therapy initiation in 2011–2012[a].

	N	% advanced HIV disease[b]	Crude OR	95% CI	Adjusted OR	95% CI
Total	752	29.4				
Sex						
Men	301	39.9	2.30	**1.90, 2.78**	**1.66**	**1.34, 2.05**
Women	451	22.4	Referent		Referent	
Age (years) at ART initiation						
15–25	121	19.0	Referent		Referent	
26–35	290	25.2	1.40	**1.14, 1.71**	1.17	0.84, 1.63
36–45	228	35.5	**2.34**	**1.84, 2.98**	**1.68**	**1.11, 2.56**
46–55	94	41.5	**2.95**	**1.92, 4.54**	**2.26**	**1.20, 4.30**
≥56	19	26.3	1.60	0.32, 8.06	1.27	0.22, 7.47
Type of site						
Public	531	29.4	Referent		Referent	
Private	221	29.4	1.00	0.52,1.94	1.08	0.88, 1.32
Point of entry						
VCT	469	30.9	Referent		Referent	
PMTCT	141	16.3	0.43	0.24, 0.78	0.78	0.49, 1.24
Outpatient	60	51.7	**2.33**	**1.20, 4.53**	1.62	0.57, 4.61
Other/unknown	82	26.8	0.87	0.29, 2.58	0.85	0.43, 1.68
Marital status						
Married	177	30.5	Referent		Referent	
Living with partner	107	19.6	**0.60**	**0.42, 0.85**	**0.75**	**0.58, 0.98**
Single	158	33.5	1.15	0.80, 1.68	1.23	0.91, 1.66
Divorced/widowed	89	38.2	1.44	0.96, 2.16	1.32	0.83, 2.01
Missing	221	26.7	0.80	0.62, 1.05	1.09	0.69, 1.72
ART eligibility at enrollment[c]						
Not eligible for ART	374	9.4	**0.10**	**0.07, 0.15**	**0.15**	**0.11, 0.21**
Eligible for ART	365	50.4	Referent		Referent	
Unknown	13	15.4	0.19	0.02, 1.43	**0.16**	**0.04, 0.63**

	N	% advanced HIV disease[b]	Crude OR	95% CI	Adjusted OR	95% CI
≥12 month gap in pre-ART care[d]						
No	207	5.8	Referent		Referent	
Yes	89	31.5	**7.24**	**2.49, 21.01**	**5.23**	**1.23, 21.13**
Initiated ART during 1st year after enrollment	456	39.7	**10.44**	**4.32, 25.22**	**3.59**	**1.91, 6.75**

ART, antiretroviral treatment; CI, confidence interval; OR, odds ratio; PMTCT, prevention of mother-to-child transmission; VCT, voluntary counseling and testing.

[a] Adjusted for site-cluster effect and for all covariates listed.

[b] Advanced HIV disease at enrollment or ART initiation is defined as having a $CD4^+$ cell count <200 cells/μl or WHO stage IV.

[c] Eligibility based on Rwanda HIV national guidelines.

[d] Defined as not having had a clinic visit for more than 12 months prior to ART initiation.

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