Research Paper

Temporal trends of early mortality and its risk factors in HIV-infected adults initiating antiretroviral therapy in Uganda

Victor Ssempijja[a,b,*], Edith Namulema[c], Racheal Ankunda[c], Thomas C. Quinn[d,e], Frank Cobelens[b,f], Anja van't Hoog[b,f], Steven J. Reynolds[d,e]

[a] Clinical Monitoring Research Program Directorate, Frederick National Laboratory for Cancer Research, Frederick, MD, USA
[b] Department of Global Health, Amsterdam University Medical Centers, Amsterdam, Netherlands
[c] HIV Counseling and Home Care Clinic, Mengo Hospital, Kampala, Uganda
[d] Johns Hopkins School of Medicine, Baltimore, Maryland, USA
[e] Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, USA
[f] Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands

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ABSTRACT

Background: A decline in mortality rates during the first 12 months of antiretroviral therapy (ART) has been mainly linked to increased ART initiation at higher CD4 counts and at less advanced World Health Organization (WHO) clinical stages of HIV infection; however, the role of improved patient care has not been well studied. We estimated improvements in early mortality due to improved patient care.
Methods: We conducted a retrospective cohort study of HIV-infected individuals ages 18 and older who initiated ART at the Mengo HIV Counseling and Home Care Clinic between 2006 and 2016. We conducted a mediation analysis using generalized structural equation models with inverse odds ratio weighting to estimate the natural direct and indirect effects of ART initiation time on early mortality.
Findings: Among 6,847 patients, most were female (69%), with a median age of 32 (interquartile range [IQR] = 28–38), versus a median age of 38 (IQR = 32–45) for males. The median CD4 count at ART initiation increased from 142 cells/ul (95% confidence interval [CI] = 135–150) in 2006–2010 to 302 cells/ul (95% CI = 283–323) in 2015–2016 ($p < 0.001$). The number of patients at WHO clinical stages I/II increased from 52% in 2006–2010 to 78% in 2015–2016 ($p < 0.001$). Annual early mortality decreased from 8.8 deaths/100 person years (PYS) in 2006 to 2.5 deaths/100 pys in 2016 ($p < 0.001$). Mediation by CD4 counts and WHO clinical stages accounted for 54% of the total effect of ART initiation timing on early mortality. In comparison, 46% remained as the direct effect, reflecting the contribution of improved patient care.
Interpretation: Improved patient care practices should be promoted as a strategy for reducing early mortality after ART initiation, above and beyond the effects from ART initiation at higher CD4 counts and less advanced WHO clinical stage alone.
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1. Introduction

Rapid scale-up of antiretroviral therapy (ART) has led to its expansion to over 25.4 million HIV-infected individuals globally, including 15 million in sub-Saharan countries [1]. Mortality among HIV-infected individuals has been reduced dramatically over the past decade due to expanded access to ART, with many HIV-infected individuals enjoying full life expectancies [2]. Despite this progress, an estimated 300,000 people in sub-Saharan Africa died from HIV-related diseases in 2019 [1].

For those on ART, mortality rates are highest in the first 12 months after initiation and gradually decline with increased time on ART [3–5]. Early mortality, i.e., death within 12 months of ART initiation, is significantly higher (6.4%) in low- and middle-income settings (e.g., Africa, Asia, and South America) compared to high-income settings (1.8%; e.g., North America and Europe), and increases with lower CD4 count and advanced World Health Organization (WHO) clinical stage (III/IV) at ART initiation [4,6–8]. HIV-infected

Research in context

Evidence before this study

We searched PubMed for HIV cohort studies that included mortality after starting antiretroviral therapy, and HIV care and treatment in sub-Saharan Africa published from database inception up to December 1, 2019. Key search terms included "HIV or AIDS," "cohort," "HIV patient care," "ART," "antiretroviral therapy," "mortality," "HIV patient management," "HIV patient care," "treatment adherence support," "HIV-related death ascertainment," and "Africa." No language limitation was used. This search identified studies reporting on mortality occurring after ART initiation, and on care and management of HIV-infected individuals; however, we did not find any studies quantifying the role of patient care quality in averting mortality after ART initiation.

Added value of this study

To our knowledge, this is the first study to quantify the contribution of improved patient care in reducing mortality after ART initiation.

Implications of all the available evidence

The available evidence indicates the need to emphasize improved patient care as an additional tool to further reduce mortality after ART initiation.

individuals with low CD4 counts and/or at advanced WHO clinical stages are likely to have developed opportunistic infections, such as tuberculosis, cryptococcal meningitis, or severe bacterial infections; are susceptible to drug intolerance and developing immune reconstitution inflammatory syndrome; and are at risk of drug interactions from using different drugs to treat multiple infections [3,9−11].

Over time, improvements to ART programs have occurred due to guideline changes that have allowed for earlier ART initiation after HIV infection; improved linkage to HIV care services after diagnosis, facilitating timely ART initiation; improved ART regimens; improved health care delivery; and faster identification of HIV-positive individuals after infection. However, a large number of HIV-infected individuals still present with advanced immunosuppression at HIV diagnosis [12,13]. Actively identifying ART-naïve individuals with advanced immunosuppression and ART-experienced individuals that disengage from care is encouraged [14,15] to maximize the survival benefits of earlier ART initiation [16-19].

In sub-Saharan Africa, studies have reported declining trends of early mortality in ART programs and attributed such declines to ART initiation at higher CD4 counts and less advanced WHO clinical stages [20,21]. However, these studies have not described the extent to which such declines are attributable to improved patient care, which includes improvements in clinical practice, ART regimens, and patient support systems, as well as active tracing of non-adhering individuals.

We estimated the mediated effect of ART initiation time on early mortality through CD4 counts and WHO clinical stage at ART initiation, and the direct effect due to improvements in patient care. We also described the temporal trends of early mortality in a low-income setting using a retrospective cohort study of HIV-infected patients at the Mengo HIV Counseling and Home Care Clinic ART treatment program (MHCHC).

2. Methods

2.1. Study setting and population

The MHCHC is a moderately well-resourced non-academic clinic in an urban setting providing comprehensive HIV services at Mengo Hospital in Kampala City, Uganda. It began providing HIV care services in 1988 and started offering ART in 2005 with support from the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) [22] and other donors. The clinic's main HIV-infected patient population consists of urban dwellers in Kampala City.

Study participants included HIV-infected patients aged 18 and older who were initiated on ART based on their CD4 counts and/or WHO clinical stage between 2006 and 2016 at the MHCHC. However, in supplementary analysis we also included HIV-infected patients aged 18 and older who initiated ART in 2017 and 2018 during the ART initiation guidelines of universal test and treat (UTT) only in the estimation of early mortality rate trends. CD4 counts and WHO clinical stage data at the time of ART initiation was not available during UTT. Patients who had transferred to the MHCHC after ART initiation were excluded because their baseline characteristics at ART initiation could not be established.

2.2. Temporal trends in ART initiation guidelines

The MHCHC followed Ugandan national policy guidelines on the criteria for initiating ART in HIV-infected patients [23−26]. Table 1 shows the year when respective ART initiation criteria were implemented. The first ART policy period is defined as 2006−2010, the second is defined as 2011−2012, the third is defined as 2013−2014, and the fourth is defined as 2015−2016. In 2017 and thereafter, ART for all HIV-positive individuals (UTT) was implemented to provide unrestricted treatment for all HIV-infected individuals regardless of WHO clinical stage or CD4 count. Once patients were initiated on ART, they were scheduled for one- to three-month drug refills and clinical review. Treatment effectiveness was assessed at six months post-ART and then annually using CD4 testing from 2006 to 2014 and using viral load testing from 2015 and thereafter.

2.3. Data collection and management

Participant data was recorded on structured clinic forms separately for each clinic visit and later captured in electronic databases. Electronic data entry started in 2006, one year after the start of ART services at MHCHC, and was performed in Epi Info^{TM} [27] until 2012, when data entry was transferred to OpenMRS^{TM} [28]. The structured clinic forms varied by ART service centers throughout the country until 2010, when nationally standardized HIV clinic visit forms were rolled out. To standardize the patient records across time, MHCHC retrospectively transferred clinical record information for HIV-infected patients receiving care onto the national standard forms and then captured the data in OpenMRS^{TM}. Information for patients no longer receiving HIV care through the MHCHC program only remained in the Epi Info^{TM} platform. Therefore, to generate a dataset for this analysis, we utilized both data systems to create a complete dataset of all HIV-infected patients who were ever initiated on ART.

Death event documentation and ascertainment at the MHCHC was based on passive death reports about deceased patients, and it improved over the course of the study with more passive data collection options. At the beginning of the study period, death-events were reported voluntarily from by either next of kin to the deceased HIV patients by other HIV-infected patients who had contact with the deceased patient or his/her family. Subsequently, death-event reporting improved with increased mobile phone access, which enabled successful remote contact with next of kin to provide death information. In 2013, formal peer-support programs with family members, health workers, and fellow HIV-infected patients were introduced. A one-off funding in 2016 supported field reach-out programs of health care counselor teams that actively visited the homes of HIV-infected patients lost to follow-up to establish treatment discontinuation outcomes that allowed for more accurate death-event reporting. In 2017, death reporting returned to routine passive reporting using
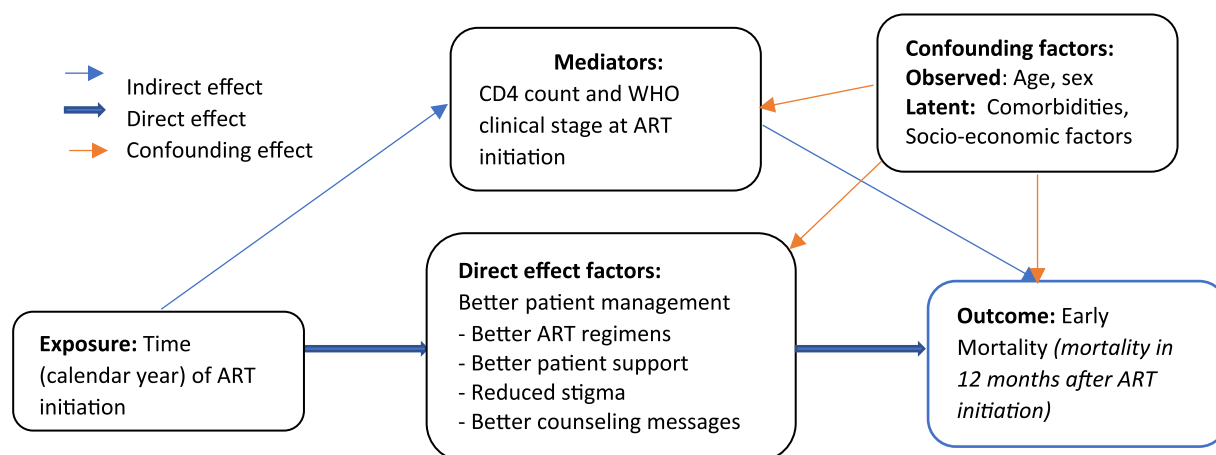
Fig. 1. Theoretical conceptual framework. We hypothesized that the association between ART initiation year (exposure) and early mortality (outcome) was partly mediated through changes in CD4 counts and WHO clinical stages at ART initiation (mediators), which occurred because of ART initiation guideline changes (Table 1) and partly through improvements in HIV patient management..

cell phone contacts, next of kin, or other HIV-infected patients coming to the clinic. Missing data in the primary exposure variables of CD4 count and WHO clinical stages at ART initiation for patients initiating ART from 2006 to 2016 was imputed as the CD4 count or WHO clinical stage values closest to the ART initiation date. Patients who had undocumented end-of-study outcomes were assumed as lost to follow-up.

2.4. Theoretical conceptual framework

In Fig. 1, we hypothesized that the impact of ART initiation year on early mortality occurred directly due to improvements in HIV patient care in the ART treatment program or indirectly through changes in CD4 counts and WHO clinical stage at ART initiation, as a result of changes in ART treatment guidelines that allowed for ART initiation in patients with higher CD4 counts (Table 1). Age and sex were observed as potential confounders. ART treatment guidelines allowed for earlier ART initiation in pregnant females. Therefore, we hypothesized that sex is a confounding factor related to CD4 counts and WHO clinical stages at ART initiation. We also hypothesized that age is a confounding factor because older patients may be more compliant with treatment and counseling guidelines and have been infected longer with more advanced HIV disease. Conceptually, comorbidities and socio-economic status were also potential confounders but were treated as latent variables in the analysis because of missing data. Comorbidities like tuberculosis, cryptococcal meningitis, or severe bacterial infections are also potential confounders because they can affect treatment outcomes in patients. Socio-economic status is a potential confounder to treatment outcomes as it impacts nutrition and a patient's ability to afford the out of pocket costs associated with free ART treatment through PEPFAR.

2.5. Data analysis

The primary outcome for this study was early mortality, which was defined as death from any cause within the first 12 months of starting ART. The primary exposures were year of ART initiation, and CD4 count and WHO clinical stage at ART initiation. Potential confounders included age at ART initiation, gender, and ART regimen type. CD4 count was recorded as cells/ul.

The study observation period was measured from the start of ART to death, loss to follow-up, transfer out, or the 12-month clinical visit after starting ART, whichever came first. Patients were defined as lost to follow-up if they missed their scheduled ART refill appointments for more than 90 days and defined as transferred out if they

discontinued care at MHCHC but had evidence of transferring to another ART center. Patients who died were listed in the death registry maintained at the MHCHC.

We described the temporal trends of ART initiation, CD4 count (categorized as: 0−100, 101−250, 251−350, 351-500 and ≥501 cells/ul), and WHO clinical stage (categorized as: I/II or III/IV) at ART initiation with time-line graphs, and tested for univariate significant trends using chi-square tests of trend.

We computed early mortality rates as the number of death events per 100 person years (pys) of survival time from ART initiation to death or censoring, and the corresponding 95% confidence interval (CI) using quadratic approximation to the Poisson log likelihood for the log-rate parameter. To estimate the effect of population composition trends on estimated early mortality rates, we calculated standardized mortality rates for the second, third, and fourth ART initiation policy periods through direct standardization using the first ART initiation period as the standard population for sex and age.

We used the chi-square test of the annual mortality regression to measure temporal trends of mortality rates. We used the Cox proportional hazards model to compute unadjusted hazard ratios (uHRs) and adjusted hazard ratios (adjHRs) with 95% CIs of mortality rate ratios. Confounders in the adjusted analysis included patient age at ART initiation, categorized as 18−24, 25−34, 35−44, and 45+ years (patients aged 45 years or older were grouped together to allow for adequate power to estimate mortality rates in adjusted analyses.); gender; and type of ART regimen, classified as efavirenz-, nevirapine-, or lopinavir/atazanavir-based regimens.

To assess the direct effects of ART initiation time and its indirect (mediated) effects through CD4 count (categorized as: 0−100, 101−250, or ≥251 cells/ul) and WHO clinical stage (categorized as: I/II or III/IV) at ART initiation on early mortality, we used generalized structural equations to model the joint probability distributions of the Weibull distribution accelerated failure time for early mortality and logistic distributions of the multinomial logistic regression models for the categorical mediating factors, CD4 count, and WHO clinical stage at ART initiation.

We used the inverse odds ratio weighting (IORW) method to estimate natural direct and indirect effects to determine the mediated effect of ART initiation time on early mortality. IORW summarizes information on the odds ratio for the relationship between exposure and multiple mediators using the odds ratio's invariance property, by regressing exposure on mediators and covariates [29,30]. Analyses were performed using STATA software version 14·2 (STATA Inc, Texas, USA).

Table 1
Onset of criteria for ART initiation.

ART initiation criteria	Year of ART initiation											
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017 and after
CD4 count ≤250 cells/ul or WHO clinical stage III or IV	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓
CD4 count ≤350 cells/ul						▓	▓	▓	▓	▓	▓	▓
TB/HIV co-infection						▓	▓	▓	▓	▓	▓	▓
Discordant sexual relationship								▓	▓	▓	▓	▓
Short-term ART in pregnant women from third trimester to end of breast feeding								▓	▓	▓	▓	▓
CD4 count ≤500 cells/ul								▓	▓	▓	▓	▓
High-HIV risk populations (sex workers, drug users, etc.)										▓	▓	▓
ART for life in pregnant women										▓	▓	▓
Universal test and treat (UTT)												▓

The color shade marks the onset of the respective ART initiation policies: first ART initiation policy period (2006–2010); second ART initiation policy period (2011–2012); third ART initiation policy period (2013–2014); fourth ART initiation policy period (2015–2016).

2.6. Ethics

The retrospective use of de-identified, routinely collected clinical data was approved by the Mengo Hospital Research Ethics Committee (MHREC) and the Uganda National Council for Science and Technology. Individual written informed consents were obtained for patient care.

2.7. Role of funding source

3. Results

We identified 6847 HIV-infected individuals who initiated ART between 2006 and 2016. The patients' age range was 18−78 years, with a median age of 34 (interquartile range [IQR] = 29−41). Only 4.4% of patients were aged 55 years or older (Supplementary Table s1). Most of the individuals (69%) were female, with a median age of 32 (IQR = 28−38), while the median age in males was 38 (IQR = 32−45). There were consistently more women than men across all ART policy periods (Table 2). Eligibility screening criteria outcomes are shown in Supplementary Figure s1.

Also, we identified 1790 HIV-infected individuals who initiated ART between 2017 and 2018 and contributed to the estimation of temporal trends of early mortality in 2017 and 2018 (Supplementary Fig. s1).

3.1. Temporal trends in population composition at ART initiation

Thirty-four percent of all patients initiated ART during the first ART policy period, while 24%, 23%, and 19% initiated in the second, third, and fourth ART policy periods, respectively. Over time, patients initiated ART when they had higher CD4 counts and/or were at less advanced WHO clinical stages (Supplementary Fig. s2a, s2b). The percentage of patients initiating ART with CD4 counts ≤100 cells/ul decreased from 37% in the first ART policy period to 23% in the second ART policy period and remained stable in the third and fourth ART policy periods. The percentage of patients initiating ART with CD4 counts of 101−250 cells/ul decreased from 41% in the first ART policy period to 25% in the second ART policy period and reduced further to 21% by the fourth ART policy period (Table 2; Supplementary Fig. s1). The median CD4 count at ART initiation increased from 142 cells/ul (IQR = 58−238) in the first ART policy period to 302 cells/ul (IQR = 113−476) in the fourth ART policy period ($p < 0.001$). Likewise, the number of patients at WHO clinical stages I/II increased from 52% in the first ART policy period to 78% in the fourth ART policy period ($p < 0.001$; Table 2). Females had consistently higher CD4 counts, while there were no differences by age (Fig. 2a, 2b). However, most patients (56%) initiated ART with a CD4 count of 0−250 cells/ul, and patients initiating ART with a CD4 count >250 cells/ul were more likely to be younger and at WHO clinical stages I /II (Supplementary Table s1).

The composition of WHO clinical stages at ART initiation also changed over time. The number of patients initiating ART at WHO clinical stages III and IV decreased from 48% in the first ART policy period to 22% in the fourth ART policy period ($p < 0.001$; Table 2). Similarly, women were consistently more likely to initiate ART at WHO clinical stages I and II, while there were no differences by age (Fig. 2c, 2d).

3.2. Temporal trends in early mortality rates

Annual crude early mortality rates decreased by 72% from 8.8 deaths/100 pys in 2006 to 0.8 deaths/100 pys in 2015, increased to 2.5 deaths/100 pys in 2016, then decreased to 1.0 deaths/100 pys in 2017 and 0.2 deaths/100 pys in 2018 ($p < 0.001$; Fig. 3,supplementary Fig. 3, Supplementary Table s2). Summarized by ART initiation policy periods, the crude early mortality rates were 4.3 deaths/100 pys in the first ART policy period; 2.4 deaths/100 pys in the second ART policy period; 1.6 deaths/100 pys in the third ART policy

Table 2
Baseline characteristics of HIV-infected individuals on ART.

	Year of ART initiation				
	2006−2010	2011−2012	2013−2014	2015−2016	p-value
Baseline characteristics					
Population	2353(34%)	1640(24%)	1549(23%)	1305(19%)	
Baseline characteristics					
Gender					
Female	1547(66%)	1154(70%)	1129(73%)	921(71%)	<0·001
Male	806(34%)	486(30%)	420(27%)	384(29%)	
Age in years					
18−24	188(8%)	176(11%)	93(6%)	100(8%)	<0·001
25−34	1001(43%)	751(46%)	704(45%)	578(44%)	
35−44	785(33%)	484(30%)	475(31%)	369(28%)	
45−78	379(16%)	229(14%)	277(18%)	258(20%)	
CD4 at ART initiation (cells/ul)					
Median (IQR)	142·0(58−239)	262·0(114−385)	312·0(116−464)	302·0(113−476)	<0·001
</=100	871(37%)	372(23%)	350(23%)	300(23%)	<0·001
101−250	953(41%)	404(25%)	289(19%)	269(21%)	
251−350	278(12%)	369(23%)	250(16%)	165(13%)	
351−500	164(7%)	275(17%)	351(23%)	293(22%)	
501+	87(4%)	220(13%)	309(20%)	278(21%)	
WHO clinical stage					
I	546(23%)	727(44%)	810(52%)	725(56%)	<0·001
II	694(29%)	350(21%)	320(21%)	284(22%)	
III	817(35%)	449(27%)	315(20%)	214(16%)	
IV	296(13%)	114(7%)	104(7%)	82(6%)	
ART regimen at initiation					
EFV-based regimen	810(35%)	922(57%)	1316(85%)	1155(89%)	<0·001
NVP-based regimen	1429(62%)	679(42%)	130(8%)	73(6%)	
LPVr/ATVr/other regimen	80(3%)	26(2%)	101(7%)	77(6%)	
12-month follow-up outcome					
Active	2065(88%)	1453(89%)	1358(88%)	1092(84%)	<0·001
Dead	116(5%)	46(3%)	28(2%)	24(2%)	
Transferred	84(4%)	58(4%)	70(5%)	58(4%)	
Lost to follow-up	88(4%)	83(5%)	93(6%)	131(10%)	

EFV=Efavirenz; NVP=Nevirapine; LPVr=Lopinavir/Ritonavir; ATVr=Atazanavir/Retonavir; pys= person years; WHO=World Health Organization; 95% CI=95% confidence interval.
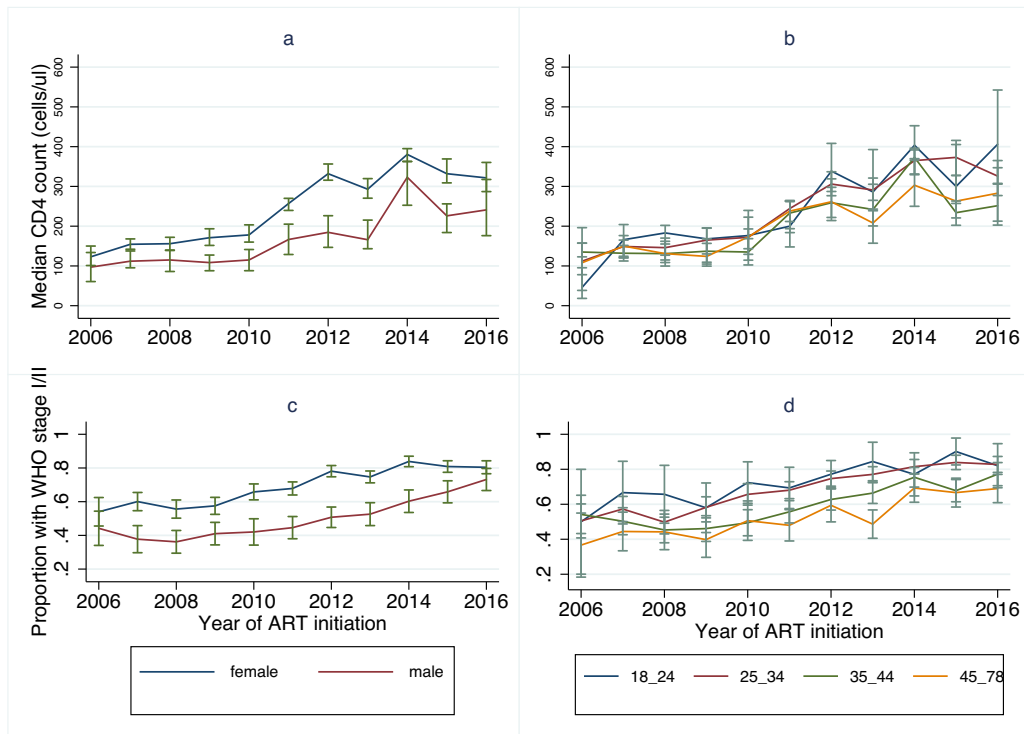

Fig. 2. Trends of median CD4 count (95% CI) at ART initiation by gender (a) and age (b), and proportion of patients with WHO clinical stage I/II at ART initiation by gender (c) and age (d).
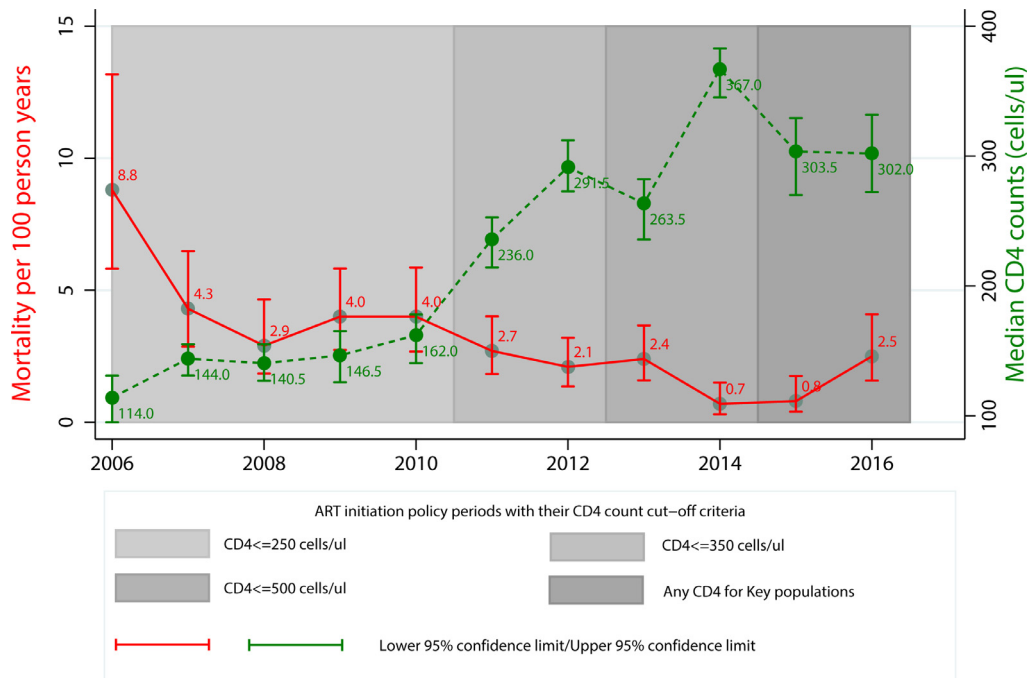
Fig. 3. Overall trends of median CD4 counts at ART initiation and trends of early mortality rates (2006−2016).

period; and 1·6 deaths/100 pys in the fourth ART policy period (Table 3). The corresponding standardized mortality rates standardized on the first ART initiation policy period for age and sex were similar to the crude mortality rates in the second, third, and fourth ART policy periods at 2·6 deaths/100 pys (95% CI = 1·8−3·3), 1·7 deaths/ 100 pys (95% CI = 1·1−2·4), and 1·6 deaths/100 pys (95% CI = 0·9−2·3), respectively; therefore, the declines in early mortality were not due to changes in age and sex population composition.

Early mortality trend patterns varied by CD4 count and WHO clinical stage at ART initiation. Among participants with CD4 counts of 0−100 cells/ul at ART initiation, mortality significantly decreased, from 7·8 deaths/100 pys in the first ART policy period to 3·3 deaths/ 100 pys in the fourth ART policy period (p-value = 0.006). Early mortality rates were consistently low for patients with CD4 counts >100 cells/ul (Fig. 4a; Supplementary Table s3). When stratified by WHO clinical stage, early mortality rates were low and remained

Table 3
Mediation analysis of the association between ART initiation time and early mortality occurring in HIV-infected patients within 12 months of ART initiation.

Characteristics	Deaths/pys	Mortality/100 pys (95% CI)	Univariable analysis		Multivariable mediation analysis	
			uHRs (95% CI)	p-value	adjHRs (95% CI)	p-value
Exposure variable (X)			Total effects		Direct effects	
Year of ART initiation (X)						
2006−2010	116/2718	4·3(3·6−5·1)	Ref			
2011−2012	46/1930	2·4(1·8−3·2)	0·56(0·4−0·8)	<0·001	0·83(0·6−1·2)	0·311
2013−2014	28/1801	1·6(1·1−2·3)	0·36(0·2−0·5)	<0·001	0·58(0·4−0·9)	0·012
2015−2016	24/1507	1·6(1·1−2·4)	0·37(0·2−0·6)	<0·001	0·62(0·4−1·0)	0·036
Mediator variables (M)					Indirect Effects	
CD4 at ART initiation (cells/ul) (M)						
</=100	128/2129	6·0(5·1−7·2)	Ref			
101−250	58/2224	2·6(2·0−3·4)	0·44(0·3−0·6)	<0·001	0·53(0·4−0·7)	<0·001
251−350	10/1264	0·8(0·4−1·5)	0·13(0·1−0·3)	<0·001	0·20(0·1−0·4)	<0·001
351−500	11/1288	0·9(0·5−1·5)	0·14(0·1−0·3)	<0·001	0·26(0·1−0·5)	<0·001
501+	7/1051	0·7(0·3−1·4)	0·11(0·1−0·2)	<0·001	0·21(0·1−0·5)	<0·001
WHO clinical stage (M)						
I	34/3278	1·0(0·7−1·5)	Ref			
II	30/1960	1·5(1·1−2·2)	1·48(0·9−2·4)	0·117	0·99(0·6−1·6)	0·955
III	93/2065	4·5(3·7−5·5)	4·33(2·9−6·4)	<0·001	2·38(1·6−3·6)	<0·001
IV	57/652	8·7(6·7−11·3)	8·33(5·4−12·7)	<0·001	3·96(2·4−6·5)	<0·001
Confounder variables						
Gender						
Female	124/5517	2·2(1·9−2·7)	Ref		Ref	
Male	90/2439	3·7(3−4·5)	1·64(1·3−2·2)	<0·001	1·03(0·8−1·4)	0·854
Age in years						
18−24	16/620	2·6(1·6−4·2)	Ref		Ref	
25−34	81/3517	2·3(1·9−2·9)	0·90(0·5−1·5)	0·706	0·86(0·5−1·5)	0·586
35−44	67/2486	2·7(2·1−3·4)	1·06(0·6−1·8)	0·833	0·82(0·5−1·4)	0·496
45−78	50/1333	3·7(2·8−4·9)	1·47(0·8−2·6)	0·179	1·16(0·6−2·1)	0·620

Pys=person years; uHRs=unadjusted hazard ratios; adjHRs=adjusted hazard ratios; WHO=World Health Organization; Mediation Outcomes model=(mediator [M], exposure [X]) -> early mortality [Y].
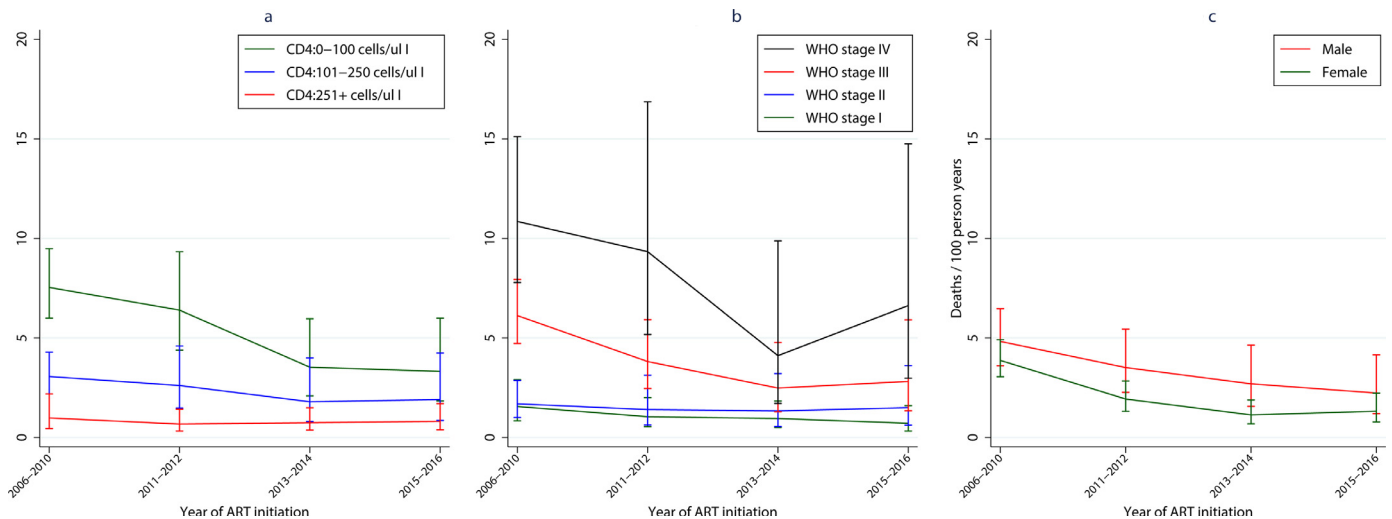
Fig. 4. Overall trends of early mortality during the different ART initiation policy periods by CD4 count (a), WHO clinical stage (b), and gender (c) at ART initiation time.

Table 4
Decomposing the direct and indirect (mediated) effects of ART initiation time on early mortality.

Effect of ART initiation time on early mortality	Mediator(s)					
	CD4 count and WHO clinical stage			CD4 count only		
	Observed coefficient (95%CI)	% of total effect	HRs (95%CI)	Observed coefficient (95%CI)	% of total effect	HRs (95%CI)
Indirect effect	−0·43(−0·6, −0·3)	53·8(15·5, 92·1)	0·65(0·5, 0·8)	−0·33(−0·5, −0·2)	40·7(12·7, 68·8)	0·72(0·6, 0·8)
Direct effect	−0·37(−0·8, 0·0)	46·2(7·9, 84·5)	0·69(0·4, 1·0)	−0·48(−0·8, −0·1)	59·3(31·2, 87·3)	0·62(0·4, 0·9)
Total effect	−0·80(−1·2, −0·4)	–	0·45(0·3, 0·6)	−0·80(−1·2, −0·4)		0·45(0·3, 0·6)

HRs=hazard ratios; CI=confidence interval; CD4 count and WHO clinical stage were measured at time of ART initiation.

unchanged among participants at WHO clinical stages I and II, but significantly decreased in patients initiating ART at WHO clinical stage III, from 6·1 deaths/100 pys in the first ART policy period to 2·8 deaths/100 pys in the fourth ART policy period ($p = 0.016$). Early mortality rates non-significantly decreased in patients starting ART at WHO clinical stage IV, from 10·9 deaths/100 pys in the first ART policy period to 6·6 deaths/100 pys in the fourth ART policy period ($p = 0.193$; Fig. 4b; Supplementary Table s3). Mortality rates also varied at different WHO clinical stages for the same CD4 count category (Supplementary Table s4).

Mortality rates decreased for both men and women but were consistently higher in males. Among males, mortality decreased from 5 deaths/100 pys in the first ART policy period to 2·2 deaths/100 pys in the fourth ART policy period ($p = 0.045$). Among females, mortality rates decreased from 3·8 deaths/100 pys in the first ART policy period to 0·8 deaths/100 pys in the fourth ART policy period ($p < 0.001$; Fig. 4c).

3.3. Assessment of the mediated effect of ART initiation time on early mortality

We found significant indirect effects and direct effects of ART initiation time on reduced early mortality. The total effects hazard of ART initiation time on early mortality decreased by 44% (uHRs = 0·56, 95% CI = 0·4−0·8) in the second policy period compared to the first policy period, and decreased thereafter by 63% (uHRs = 0·37, 95% CI = 0·2−0·8) in the fourth ART policy period. This reduction was partially due to direct effects, for which the hazard of early mortality due to ART initiation time when compared to the first ART policy period did not significantly decrease in the second policy period ($p = 0.311$), but decreased by 42% (adjHRs = 0·58, 95% CI = 0·4−0·9) in the third

ART policy period and by 38% (adjHRs = 0·62, 95% CI = 0·4−1·0) in the fourth ART policy period (Table 3). Overall, 53·8% (95% CI = 15·5−92·1) of the total effect of ART initiation time on early mortality was indirect, i.e. mediated through changes in CD4 counts and WHO clinical stages at ART initiation, while the direct effect attributed to improved patient care was 46·2% (95% CI = 7·9−84·5). CD4 count alone accounted for mediating 40·7% (95% CI = 12·7−68·8) of the total effects (Table 4).

4. Discussion

In this observational study conducted in a routine HIV clinical practice, mortality rates for HIV-infected adults during the first 12 months of ART initiation decreased from 8·8 deaths/100 pys to 2·5 deaths/100 pys over the 10-year observation period (2006−2016). During this period, changes in ART initiation policy guidelines progressively allowed ART initiation in healthier HIV-infected individuals with higher CD4 counts and at less advanced WHO clinical stages. We found that about half of the decline in early mortality was mediated through higher CD4 counts and less advanced WHO clinical stages at ART initiation, while the other half occurred directly, most likely reflecting better clinical management practices over time. We observed variations in the temporal trends of early mortality given the same CD4 counts and/or WHO clinical stages of the individual at ART initiation. We found a significant decline in early mortality in sicker patients with CD4 counts of 0−100 cells/ul or those at WHO clinical stage III or IV with a high risk of early mortality. We found no significant changes in early mortality for patients initiating ART with higher CD4 counts or at less advanced WHO clinical stages with a low risk of mortality. Therefore, better patient care seems to have mainly benefitted the sicker patients at ART initiation.

We observed significant gender differences in our study. Males consistently initiated ART with lower CD4 counts and had higher mortality rates than females. However, it was reassuring that a significant decline in early mortality was observed in both genders. Similar findings have been reported in other settings [18,31,32]. Even though HIV-infected males have been known as late presenters for HIV care, the treatment guidelines also inevitably allowed for earlier initiation of ART in females compared to males. In 2013−2014, when the CD4 count threshold for ART initiation was increased to 500 cells/ul, an exception was made for lifetime ART initiation for all pregnant women irrespective of CD4 count, while ART initiation was still restricted for men.

Substantial proportions of patients continued to initiate ART with CD4 counts lower than ART initiation policy guideline cut-offs. From the start of the second ART policy period in 2011 and after that, at least 23% of patients initiated ART with CD4 counts ≤100 cells/ul, and at least 19% of patients initiated ART with CD4 counts in the range of 101−250 cells/ul. Such late initiation remains a challenge for further reductions in early mortality rates, treatment success, and HIV prevention strategies. While innovative methods of initiating all HIV-infected individuals on ART are encouraged, patients initiating late should be closely followed for their increased risk of mortality soon after starting ART [33]. It is worth noting that the increase in CD4 counts at ART initiation observed in this study was higher than increases reported in similar low-income countries [34], which could point to successful identification at MHCHC of ART-naïve patients before advanced HIV.

The significant direct effect of ART initiation time on early mortality observed in our study can be considered evidence of better patient care practices beyond initiating ART in HIV-infected individuals with higher CD4 counts or at less advanced WHO clinical stages. These direct effects could be due to an array of factors, including improved clinical management of sicker patients resulting from better treatment of co-infections like tuberculosis; improved patient support systems; improved nutrition; and improved ART regimens. In this study, we were not able to apportion the direct effect to each of these factors, but we believe that improved clinical management of sicker patients likely contributes to the direct effects observed.

We noticed an increase in patients initiating ART when their CD4 counts were less than 250 cells/ul in 2015−2016, which was followed by an increase in mortality in 2016. This seemingly unexpected occurrence could have been the result of the active community campaigns that were implemented at the MHCHC to identify HIV-infected individuals not linked to HIV care services, determine the status of those lost to follow-up, and complete verbal autopsies for those who died. As a result, more deaths may have been verified compared to previous periods in which these individuals would have been misclassified as lost to follow-up.

The setting of our study is a moderately well-resourced non-academic clinic in an urban setting. Therefore, we think these findings are generalizable to other settings in Uganda and beyond where quality improvement strategies in HIV care is achievable with proper resources and training, which will ultimately reduce patient mortality.

Our study had some limitations, including the potential for misclassifying mortality outcomes. The study lacked specific cause of death information because deaths were reported by next of kin and not confirmed with autopsy information. A reasonable proportion of patients lost to follow-up may have died, which could have caused an underestimation of mortality; therefore, the estimated mortality outcomes in this study may be conservative estimates. Death ascertainment also improved over time, resulting in improved sensitivity of death reporting, which would have biased the observed decline in mortality towards the null due to mistakenly reporting surviving patients as deceased. While comorbidities were effectively managed in patients, incomplete records were available on severity and treatment outcomes. We believe that comorbidity management is reflected in the quality of patient care; therefore, the estimation of the impact of comorbidities on early mortality is not missed. Similarly, socio-economic status information was unavailable in the study. However, we believe that its impact is reflected in the quality of patient care by providing customized counseling messages to patients based on their socio-economic status to enable them to achieve similar treatment outcomes despite differences in socio-economic status. We could not adjust for adherence because the adherence recording was incomplete 65% of the time in the early years of the ART program. Where adherence information was available, patients were graded with good adherence on a scale of good/fair or poor 97% of the time. So, we found the adherence data to be incomplete or non-discriminative. However, it was reassuring that adherence rates were high overall. Also, HIV stigma may have had a direct impact on early mortality rates by causing poor adherence in the earlier years of ART. We were limited to extend the analysis beyond 2016 when the Universal Test and Treat policy for HIV-infected individuals was implemented because of missing CD4 counts. As a result, we failed to quantify the proportion of patients initiating ART with CD4 counts of ≤100 cells/ul from 2017 and thereafter. These patients need to be prioritized for early mortality prevention and monitoring programs.

In conclusion, early mortality was reduced by 72% from 2006 to 2016. Improved patient care contributed significantly to these declines in addition to changes in ART initiation policy that allowed for ART initiation in HIV-infected patients with higher CD4 counts and at less advanced WHO clinical stages. The baseline immune status of patients initiated on ART has improved. A substantial number of HIV-infected patients still initiate ART when their CD4 counts are ≤100 cells/ul or when they are at WHO clinical stage IV of the disease, even in 2016. Although mortality in this group was reduced by half over the study period, early mortality rates remain high for such patients. Strategies to implement timely ART initiation before advanced immune suppression occurs and continued close monitoring of patients who initiate late should be prioritized to reduce early mortality and improve survival.

Declaration of Competing Interest

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Authors' Contributions

VS developed the research concept, performed data management, data analysis, data interpretation and writing. EN and RA supported

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Data Sharing Statement

De-identified data that underlie the results reported in this article can be requested through the corresponding author for approved research concepts.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2020.100600.

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