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COHORT PROFILE

Cohort Profile: The international epidemiological databases to evaluate AIDS (IeDEA) in sub-Saharan Africa

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How did the study come about?

The HIV/AIDS pandemic is a public health emergency in many low and middle-income countries. Out of the estimated 33.3 million people with HIV at the end of 2009, 22.5 million were in sub-Saharan Africa and the majority of these were women.[1] The introduction in 1996 of combination anti-retroviral therapy (ART) led to a substantial reduction in morbidity and mortality in high-income countries.[2,3] In more recent years, efforts by governmental programmes such as the President's Emergency Program for AIDS Relief (PEPFAR) and The Global Fund as well as non-governmental programmes have resulted in the scale-up of ART in resource-limited settings: at the end of 2009, 5.25 million people were reported to be receiving ART therapy in low- and middle-income countries.[1]

Although still far from achieving universal coverage,[1] the massive concerted scale-up of ART is unprecedented in global health. The long-term outcomes of ART in Africa and other regions are, however, not well defined. Poor retention in care, limited access to second-line ART regimens, co-infections and comorbidities of HIV infection, for example tuberculosis and cancer, and the emergence of drug resistance and toxicities are important challenges to long-term programme effectiveness in resource-limited settings.[7] The World Health Organization (WHO) advocates a public health approach to ART in resource-limited settings, to maximize benefit in a setting of low levels of training for health-care workers, high patient burden and limited availability of drugs. Key characteristics include the standardization of first-line and second-line ART regimens, simplified clinical decision-making and standardized clinical and laboratory monitoring.[4–6]

In 2005, the National Institute of Allergy and Infectious Diseases (NIAID) sought applications for a global consortium structured through regional centres to pool existing clinical and epidemiological data on HIV-infected people, and particularly patients on ART: the International epidemiological Databases to Evaluate AIDS (IeDEA, see Figure 1 for logo).[8] Funding of IeDEA has recently been extended to 2011–2016. The seven regions included in IeDEA are North America, Caribbean/Central and South America, Asia/Pacific and four regions in sub-Saharan Africa. A Coordinating Centre (currently at RTI International, NC, USA) provides logistical and data management and harmonization support to the regional networks. Two of the IeDEA cohorts have previously been described in the journal.[9,10] The objective of the present report is to describe the four African IeDEA

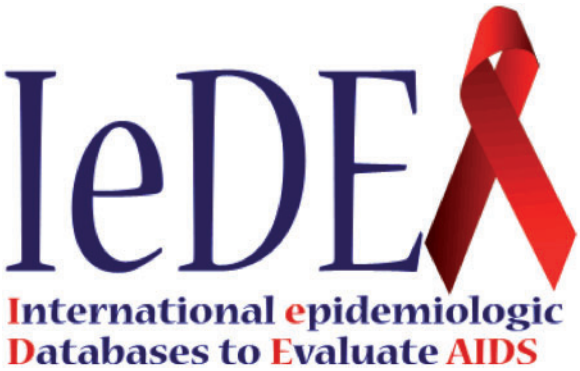

Figure 1 Logo of the IeDEA

regions: West Africa, Central Africa, East Africa and Southern Africa.

What does it cover?

The African networks of IeDEA aim to inform the scale-up of ART in sub-Saharan Africa through clinical and epidemiological research. The specific research questions differ by region, but the objectives are similar and cover all populations, including pregnant women, infants, children, adolescents and adult patients. They can be summarized as follows:

(1) To provide robust evaluation of the delivery of ART in children, adolescents and adults in sub-Saharan Africa, with a focus on long-term programme effectiveness and outcomes.
(2) To describe the long-term and temporal trends in regimen durability and tolerability and to examine monitoring strategies.
(3) To describe important comorbidities and co-infections of HIV infection, including malaria, tuberculosis and cancer.
(4) To examine the pregnancy- and HIV-related outcomes of women initiating ART during pregnancy and of infants exposed to HIV or ART *in utero*.
(5) To develop and apply novel statistical methods to deal with missing data, loss to follow-up, competing risks and time-dependent confounding.
(6) To establish procedures to link the HIV cohort data with other databases, at local or national level, for example routine mortality data or tuberculosis and cancer registries.

Who is in the sample?

A total of 183 clinics providing ART in 17 countries in sub-Saharan Africa participate in IeDEA's four African regions (Figure 2). Most sites are located in urban areas, operate at the primary care level, are led by nurses or clinical officers rather than physicians and are part of the public health care system of the country (Table 1). About two-thirds of sites have the capacity to measure CD4 cell counts, and a third can do HIV-1 RNA tests. Virtually all sites provide adherence support to patients, screen and provide treatment for tuberculosis. ART provision at most sites started during or after 2004 with the exception of several clinics in West Africa, which introduced ART earlier. Figure 3 shows the cumulative number of treatment sites and adult patients starting ART. There has been a rapid increase in facilities and patients contributing data to IeDEA which is for the most part due to rapid scale-up by a few countries in each region. For example, South Africa and Zambia in Southern Africa and Nigeria in West Africa had the most rapid scale-up in their region. All three contributing countries in East Africa have expanded coverage. Central Africa faces unique challenges in that Rwanda was the only PEPFAR focus country and other countries in the region have extremely weak health systems and government responses to the epidemic. Central Africa has had only modest scale up of treatment and increases in the research database are the result of active data collection and data system strengthening.

Patients are consecutively included as they initiate HIV care at a participating clinic or programmes until the capacity of the site is reached. At most sites, data collection starts when a patient initiates ART; however, some programmes also collect data on patients in the pre-ART period (not yet eligible for ART or eligible but waiting to be treated). Data are stripped of identifiers at the clinic level and all analysis is performed with de-identified data. Given the use of de-identified data, most patients are not individually consented to participate. However, when additional data is collected from patients outside of routine clinical practice, informed consent is sought. All research is overseen by Institutional Review Boards (IRBs) in the countries where data are collected, and additionally by IRBs with oversight over the analytical teams. In West, East and Southern Africa data are obtained from existing clinical databases. In Central Africa, the study team created prospective cohorts as existing health records were not sufficient for epidemiologic research. Table 2 shows the characteristics of the 286 803 adult patients on ART recorded in the African IeDEA databases as of the end of 2010. In all regions, most patients were 30- to 40-years old, female, and started ART with advanced immunedeficiency and advanced clinical stage (WHO stage III or IV). A substantial minority of patients started ART without a recent CD4 cell count, many patients did not have a CD4 count measured around 6 months and only few patients had viral load measurements at baseline or 6 months. In all regions, the most commonly used first-line ART regimen was lamivudine (3TC), stavudine (d4T) and nevirapine (NVP), and the majority of patients were started on one of three

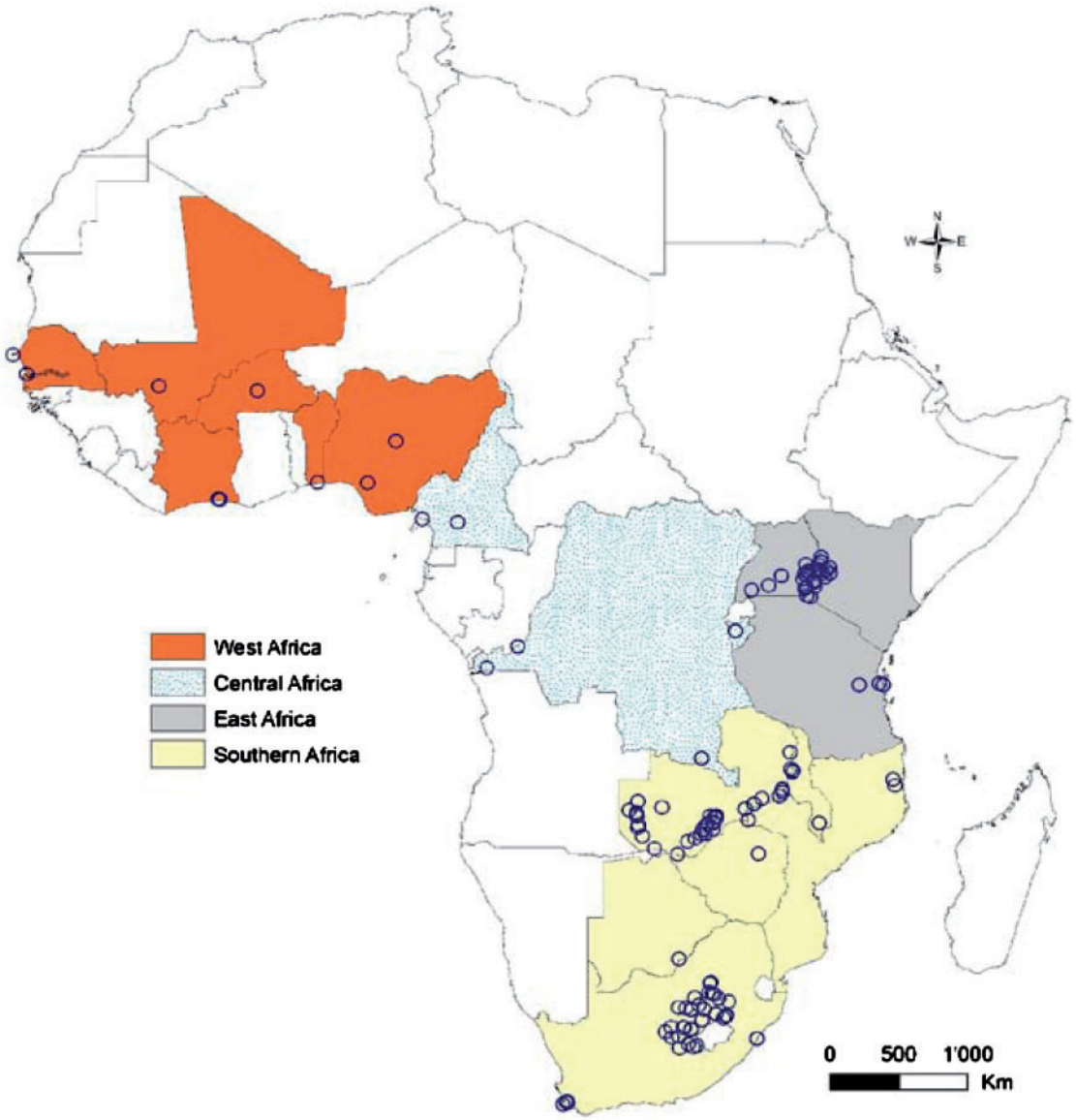

Figure 2 Map of 183 ART facilities participating in the four African regions of the International epidemiological Databases to Evaluate AIDS

regimens (Table 3). The African IeDEA regions also include smaller cohorts of paediatric patients, which will be described in a separate report.

How often are patients followed up and what is measured?

As IeDEA is based on routine clinical records, the patient follow-up reflects the standards of care in the participating clinics. For most patients, visits are initially bi-monthly or monthly, and then drop to every 2–3 months as therapy is stabilized (Table 1). Clinics have various methods for tracing patients who miss visits including mobile phone calls/SMS or home visits. Some sites also involve volunteers from community-based organizations to track patients. Patient tracing is clinic specific, and the methods and capacity for tracing patients is heterogeneous within the regions.

Most data are collected in the context of routine care at baseline and each follow-up visit, including socio-demographic data, contact details to facilitate the tracing of patients, the date of starting ART, type of treatment initiated, and, where available, CD4 counts and HIV-1 plasma RNA levels at baseline and during follow-up. The switching to second-line ART regimens is recorded in all sites, and the reasons for switching in some sites. Resistance testing is not routinely available in any of the programmes, but is

Table 1 Characteristics of 183 facilities providing ART in the African regions of the IeDEA

	West Africa	Central Africa	East Africa	Southern Africa	All regions (%)
No. of facilities	15	10	32	126	183 (100)
Location					
Urban	15	8	18	69	110 (60.1)
Semiurban	0	2	10	20	32 (17.5)
Rural	0	0	4	37	41 (22.4)
Level of care					
Primary	8	6	10	102	131 (71.6)
Secondary	0	3	15	15	33 (18.0)
Tertiary	7	1	7	4	19 (10.4)
Type of facility					
Public	12	4	28	108	152 (83.1)
Private not for profit	3	6	4	12	25 (13.7)
Private for profit	0	0	0	6	6 (3.3)
Patient contributions to costs of care	1	0	1	71	74 (40.4)
Availability of laboratory tests					
CD4 cell count	15	10	12	71	108 (59.0)
Total lymphocyte count	15	7	12	42	76 (41.5)
HIV-1 RNA	0	10	4	50	64 (35.0)
TST (tuberculin skin test)	15	0	2	64	81 (44.3)
Sputum smear	15	4	31	50	100 (54.6)
Culture for *Mycobacterium tuberculosis*	15	2	23	0	40 (21.9)
Chest X-ray	5	3	32	15	55 (30.1)
Other interventions and services					
Nutritional support	0	10	32	69	111 (60.7)
Voluntary testing and counselling	15	10	32	62	119 (65.0)
Adherence support	15	10	32	123	180 (98.4)
Screening for Tb	0	9	32	126	167 (91.3)
Treatment for Tb	0	4	29	121	154 (84.2)
Visits after starting ART					
Weekly	0	0	7	0	7 (3.8)
Two weekly	0	0	23	69	92 (50.3)
Monthly	15	10	2	58	85 (46.5)
Visits when stable on ART					
Monthly	15	1	13	49	78 (42.6)
Every 2 months	0	0	10	9	19 (10.4)
Every 3 months	0	9	9	69	87 (47.5)
Tracing of patients not returning					
Phone calls	8	10	26	125	157 (92.4)
Home visits	2	10	29	88	129 (70.5)
Community-based organizations	0	10	0	42	52 (28.4)
Other	0	0	4	6	10 (5.5)
No routine tracing	0	0	0	27	27 (14.8)

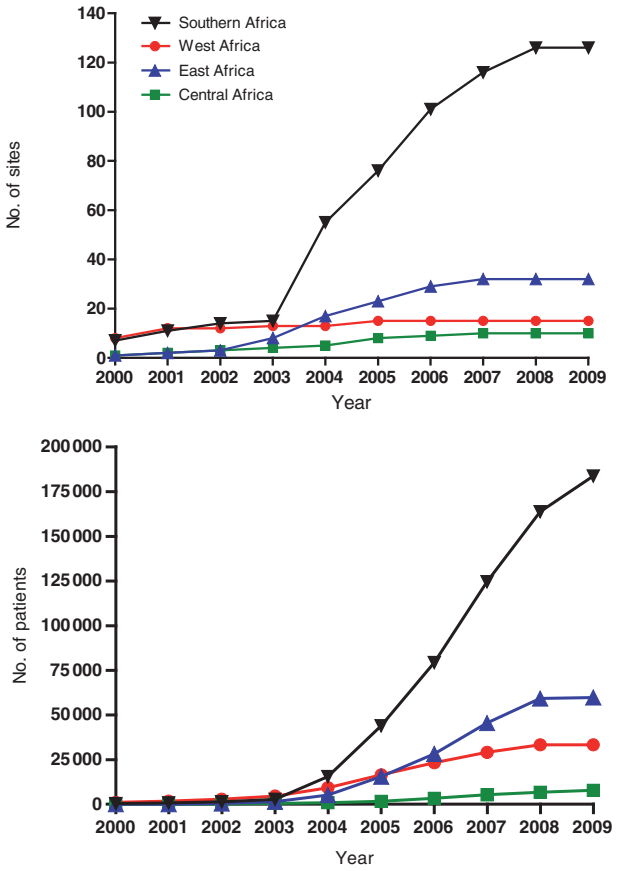

Figure 3 Cumulative number of treatment sites (a) and cumulative number of patients starting antiretroviral therapy (b) in the four African regions of the IeDEA

done at some sites in a research context. Important comorbidities and co-infections, including malaria, tuberculosis and cancer, are recorded in most sites.

A survey of sites is conducted regularly to collect data on (i) level of care (primary, secondary, tertiary), points of entry to programme, typical travel time of patients to clinic, costs to patients; (ii) availability of laboratory tests and radiology, availability of other services (family planning, nutritional support), level of staffing; (iii) eligibility and preparation of patients for ART, waiting times, first-line and second-line ART regimens, and monitoring of ART; (iv) follow-up and assessment of adherence, transfers, tracing of patients lost to follow-up, ascertainment of deaths; (v) and the diagnosis and management of HIV-associated complications, including tuberculosis, cryptococcus, cytomegalovirus and malaria.

Linkages to routine data sources have been conducted in the Republic of South Africa. For example, cohort data were linked with the database of the South African National Health Laboratory Services (NHLS) to obtain additional CD4 cell counts, which were not recorded in the HIV database.[11] Similarly, cohorts were linked to the routine mortality data to improve ascertainment of deaths.[11–13] Linkages with cancer registries are under way.

What is attrition like?

Retention in care is an important issue for the African sites participating in IeDEA, and for treatment programmes in resource-limited settings in general.[14,15,16] In a recent IeDEA study of 11 treatment programmes in 10 countries (Botswana, Côte d'Ivoire, Kenya, Malawi, Rwanda, Senegal, South Africa, Uganda, Zambia, Zimbabwe) loss to follow-up at 1 year ranged from 2.8% to 28.7%. In this study, a patient was considered lost to follow-up if the last visit was >9 months before the closure date for that site, with the closure date defined as the most recent visit date recorded in the database.[17] A study from the Central African region found that rates of lost to follow-up, defined as not attending the clinic for six months or longer, were 35% in the Democratic Republic of Congo, 38% in Burundi and 27% in Cameroon.[18] Using the same definition, an analysis of IeDEA West Africa found that among patients with at least one follow-up visit 20% of patients were lost to follow-up at 1 year.[19] The most appropriate definition of loss to follow-up was examined in the Ministry of Health-Centre for Infectious Disease Research in Zambia (MoH-CIDRZ) programme, the largest cohort in the Southern African region.[20] The definition that minimized misclassification was 'at least 2 months late for the last scheduled clinic appointment'.[20] Efforts to standardize definitions within and across IeDEA regions are now under way.[21]

The successful treatment of individual patients and the monitoring and evaluation of ART programmes both depend on regular and complete patient follow-up. Programmes with high rates of loss to follow-up and poor ascertainment of deaths in patients lost will underestimate mortality of all patients starting ART. A meta-analysis of studies tracing patients lost to follow-up found that these patients experience high mortality[22] compared with patients remaining in care.[23] Standard survival analyses, which censors lost patients, will underestimate overall clinic mortality as censored mortality is estimated from the mortality of patients remaining in care. Analyses of the determinants of survival may also be biased, as empirically demonstrated in an analysis from East Africa.[24]

IeDEA investigators developed approaches for more accurate and less biased measurements of mortality and determinants of survival. East Africa used methods based on the concept of 'double sampling'[25,26] to adjust mortality estimates based not on those in care, but instead on a subset of patients lost to follow-up whose status was ascertained through extensive tracing efforts.[27] In another analysis, the same region used patient tracing data to construct weighted Kaplan–Meier curves, which assign the proper

Table 2 Baseline characteristics of patients starting antiretroviral therapy at sites participating in the African regions of the IeDEA

	West Africa	Central Africa	East Africa	Southern Africa
Total No. of patients	33 368	8902	60 137	184 386
No. of female	21 057 (63.1)	6252 (70.2)	40 531 (67.4)	116 349 (63.1)
Gender unknown	145 (0.43)	3 (0.03)	303 (0.50)	4 (0.00)
Age (years)	40.6 (34.1–42.8)	38 (32–46)	35.8 (30.2–42.6)	29 (24–36)
Unknown	355 (1.1)	7 (0.08)	3680 (6.1)	564 (0.31)
Weight (kg)	57 (49–65)	60 (52–70)	55.4 (49.0–62.5)	55 (48–62)
Not measured	3367 (10.1)	27 (0.30)	2937 (4.9)	15 107 (8.2)
Height (cm)	165 (159–170)	164 (159–170)	164.5 (159.5–170.5)	164.0 (158–170)
Not measured	12 340 (37.0)	43 (0.48)	21 964 (36.5)	71 141 (38.6)
Advanced clinical stage (WHO stage III/IV)	12 713 (38.1)	5990 (67.3)	32 237 (53.6)	102 178 (55.4)
WHO stage unknown	6271 (18.8)	29 (0.33)	4973 (8.3)	22 702 (12.3)
Active Tuberculosis	2042 (6.1)	1892 (21.3)	14 326 (23.8)	11 771 (6.4)
Unknown	7517 (22.5)	0	0	128 190 (69.5)
Haemoglobin (g/dl)	10.2 (9.0–11.6)	11.5 (9.9–13.2)	11.1 (9.5–12.7)	11 (9.4–12.3)
Not measured	10 506 (31.5)	4197 (47.2)	34 770 (57.8)	72 340 (39.2)
CD4 count (cells/μl)[a]				
At baseline	145 (62–237)	211 (110–335)	130 (54–211)	126 (62–192)
Not measured	8245 (24.7)	3070 (34.50)	19 590 (32.6)	39 694 (21.5)
At 6 month	274 (173–402)	318 (213–481)	254 (162–380)	253 (169–362)
Not measured	18 555 (55.6)	8428 (94.7)	38 570 (64.1)	103 791 (56.3)
HIV–1 RNA (log copies/ml)[a]				
At baseline	5.11 (4.07–5.63)	1.97 (1.70–2.40)	5.12 (3.94–5.54)	11.14 (9.74–12.39)
Not measured	32 175 (96.4)	8513 (95.6)	59 819 (99.5)	155 906 (84.6)
At 6 month	2.48 (2.00–2.48)	2.0 (2.00–2.00)	2.60 (2.60–2.60)	4.79 (3.53–5.56)
Not measured	32 114 (96.2)	8880 (99.7)	59 689 (99.3)	155 135 (84.1)

No. of patients or median (interquartile range) are shown.
[a]Baseline was defined as the measurement closest to the start of therapy within a window of 3 months before and 1 week after starting therapy. At 6 month was defined as the measurement closed to 6 months within a window of 3–9 months.

weight to deaths discovered through patient outreach.[28] A study based on data from three regions filled the missing survival times of patients lost to follow-up by multiple imputation, using estimates of mortality from studies that traced patients lost to follow-up.[29] The Southern Africa region extended these methods to create a simple nomogram and web calculator (see www.iedea-sa.org) which can be used by programme managers to correct mortality estimates for loss to follow-up.[17]

Key findings and publications

Here, we provide an indicative summary of some of the major research themes. A complete list of publications and presentations from the different IeDEA regions can be found at www.iedea-hiv.org. Mortality and retention in care in children and adults are central to evaluating ART programmes in resource-limited settings, and have been the focus of several analyses. Analyses have considered the first year of ART,[15,17,30–33] or the first few years,[34–36] and documented high early mortality and loss to follow-up (LTFU), and very high mortality in patients waiting to be treated.[11] Significant for programme evaluation, IeDEA Southern Africa found that estimates of adult mortality in South Africa substantially increased after data from the Free State Province,[11] the Khayelitsha programme,[12] or the Themba Lethu Clinic cohort[13] were linked with the South African death registry and deaths among patients LTFU included. Analyses of the South African IeDEA data contributed to evaluating the National Antiretroviral

Table 3 The three most common antiretroviral first-line regimens used in facilities enrolled in the four African regions of the IeDEA, 2000–10

Anti-retroviral regimen	West Africa		Central Africa		East Africa		Southern Africa	
	Rank	No. on regimen (%)	Rank	No. on regimen (%)	Rank	No. on regimen (%)	Rank	No. on regimen (%)
3TC-d4T-NVP	1	10 098 (30.3)	1	4374 (49.2)	1	36 418 (60.6)	1	66 369 (36.0)
AZT-3TC-NVP	2	5033 (15.1)	2	1745 (19.6)	2	7486 (12.4)		
AZT-3TC-EFV	3	4992 (15.0)	3	696 (7.8)	3	4730 (7.9)	3	29 098 (15.8)
3TC-d4T-EFV							2	45 421 (24.6)
Other	–	13 255 (39.6)	–	2087 (23.4)	–	11503 (19.1)	–	43 498 (23.6)

3TC, lamivudine; d4T, stavudine; NVP, nevirapine; AZT, zidovudine; EFV, efavirenz.

Treatment Programme, both for adults[32,33] and children.[35]

Using data for adult patients who started ART in four scale-up programmes in Côte d'Ivoire, South Africa, and Malawi from 2004 to 2007, IeDEA investigators developed two prognostic models to estimate the probability of death in patients starting ART in sub-Saharan Africa.[23] One model with CD4 cell count, clinical stage, bodyweight, age and sex (CD4 count model); and one that replaced CD4 cell count with total lymphocyte count and severity of anaemia (total lymphocyte and haemoglobin model), because CD4 cell count is not routinely available. Probability of death at 1 year ranged from 0.9% to 52.5% with the CD4 model, and from 0.9% to 59.6% with the total lymphocyte and haemoglobin model. Both models accurately predicted early mortality in patients starting ART in sub-Saharan Africa compared with observed data. A web calculator is available at www.iedea-sa.org.

The durability of first-line ART regimens and switching to second-line ART has been another focus. A recent analysis of the United States Agency for International Development–Academic Model Providing Access to Healthcare (USAID-AMPATH) partnership, a large treatment programme in western Kenya, found that ART discontinuation was more common among patients with advanced disease and those receiving a zidovudine-containing regimen.[37] A further analysis of data from all four African IeDEA regions found that many patients did not switch to a second-line regimen, despite developing treatment failure.[38] Unsurprisingly, these patients experienced high mortality.[38]

IeDEA has also supported public health programmes through analyses for UNAIDS or WHO. African IeDEA data were used to parameterize the Spectrum projection package, used to estimate the impact of HIV in low and middle-income countries.[39] Similarly, IeDEA data were used to evaluate different sampling strategies to assess programmatic indicators of the quality of care.[40] A study comparing mortality of HIV-infected patients starting ART in sub-Saharan Africa with background mortality in Côte d'Ivoire, Malawi, South Africa and Zimbabwe used estimates of HIV-unrelated mortality rates from WHO's Global Burden of Disease project.[36] Finally, IeDEA West Africa documented important differences in treatment response in patients infected with HIV-1 and HIV-2, with implications for future treatment guidelines.[1]

What are the main strengths and weaknesses?

The IeDEA networks in Africa provide a unique platform for operational and clinical research that is highly relevant to the scale-up of ART in sub-Saharan Africa. The large number of participating sites and large number of patients followed in high burden countries are important strengths allowing for determination of outcomes at the individual and programme level. The data reflect routine care across the range of care settings: urban and rural clinics, large and very large programmes run by national health systems, smaller clinics run by non-governmental organizations, and private clinics. The data undergo considerable data cleaning, and the regional teams work closely with clinic staff to understand and correct data quality problems. The AMPATH programme in East Africa provides next day access to study data and individual patient temporal trend graphs, for instance weight and CD4 count, to improve clinical management. These graphs are put in patient charts after data entry so that they are readily available and interpretable. By making data relevant to clinic personnel, the consortium strengthens the relevance of data and increases clinical commitment to collection. The service delivery models, clinical protocols, monitoring schedules and efforts in place to trace patients lost to follow-up vary widely between sites. This diversity of data gives IeDEA substantial ability to generalize findings across different care delivery settings.

The data collected within IeDEA are observational and causal inferences are challenging. Furthermore, participation in IeDEA indicates that the facility has

a certain level of capacity in data management and patient follow-up. The participating programmes are more likely than non-participating facilities to be equipped with electronic medical record systems and to have access to CD4 cell counts and second-line therapy, which may reflect a higher clinical capacity generally. Understanding the contextual variables which differentiate IeDEA sites from other care facilities is therefore important. Other weaknesses relate to the quality of the data, with missing data in key variables, varying definitions and data collection protocols, and a high rate of loss to follow-up. In the years to come, the African regions of IeDEA will address these challenges by an iterative process of quality improvement where those variables found to be the most important are harmonized first and their quality emphasized in data improvement efforts. IeDEA will also perform dedicated multicentre studies to address specific questions, and continue to develop advanced statistical methods that can account for missing data, loss to follow-up and competing risks, and time-dependent confounding.

Where can I find out more?

The participating sites sign an agreement to allow their data to be used in IeDEA, however, data ownership remains at the clinic level and all analyses have to be approved by the regional Steering Groups and, if analyses involve several regions, by the Executive Committee of IeDEA. The IeDEA Executive Committee is charged with facilitating data access for all worthy research projects. We welcome collaborations with other cohort studies or cohort collaborations, and other interested parties, for example mathematical modelers or colleagues working in international organizations. Readers who wish to find out more should visit the IeDEA website (www.iedea-hiv.org) where they will find contact details and links to the websites of the different regions.

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