Drug Saf (2016) 39:959–976
DOI 10.1007/s40264-016-0434-9

ORIGINAL RESEARCH ARTICLE

Targeted Spontaneous Reporting: Assessing Opportunities to Conduct Routine Pharmacovigilance for Antiretroviral Treatment on an International Scale

Beth Rachlis[1] · Rakhi Karwa[2,3] · Celia Chema[3] · Sonak Pastakia[2,3] · Sten Olsson[4] · Kara Wools-Kaloustian[3,5] · Beatrice Jakait[3,6] · Mercy Maina[3,6] · Marcel Yotebieng[7,8] · Nagalingeswaran Kumarasamy[9] · Aimee Freeman[10] · Nathalie de Rekeneire[11] · Stephany N. Duda[12] · Mary-Ann Davies[13] · Paula Braitstein[3,14,15]

Published online: 9 June 2016

Abstract

Introduction Targeted spontaneous reporting (TSR) is a pharmacovigilance method that can enhance reporting of adverse drug reactions related to antiretroviral therapy (ART). Minimal data exist on the needs or capacity of facilities to conduct TSR.

Objectives Using data from the International epidemiologic Databases to Evaluate AIDS (IeDEA) Consortium, the present study had two objectives: (1) to develop a list of facility characteristics that could constitute key assets in the conduct of TSR; (2) to use this list as a starting point to describe the existing capacity of IeDEA-participating facilities to conduct pharmacovigilance through TSR.

Methods We generated our facility characteristics list using an iterative approach, through a review of relevant World Health Organization (WHO) and Uppsala Monitoring Centre documents focused on pharmacovigilance activities related to HIV and ART and consultation with expert stakeholders. IeDEA facility data were drawn from a 2009/2010 IeDEA site assessment that included reported characteristics of adult and pediatric HIV care programs, including outreach, staffing, laboratory capacity, adverse event monitoring, and non-HIV care.

Results A total of 137 facilities were included: East Africa (43); Asia–Pacific (28); West Africa (21); Southern Africa (19); Central Africa (12); Caribbean, Central, and South America (7); and North America (7). Key facility characteristics were grouped as follows: outcome ascertainment and follow-up; laboratory monitoring; documentation—sources and management of data; and human resources.

✉ Paula Braitstein
pbraitstein@gmail.com

1 Ontario HIV Treatment Network, Toronto, ON, Canada

2 College of Pharmacy, Purdue University, West Lafayette, IN, USA

3 Academic Model Providing Access to Healthcare, Eldoret, Kenya

4 Uppsala Monitoring Centre, Uppsala, Sweden

5 School of Medicine, Indiana University, Indianapolis, IN, USA

6 Moi Teaching and Referral Hospital, Eldoret, Kenya

7 College of Public Health, Ohio State University, Columbus, OH, USA

8 Kinshasa School of Public Health, University of Kinshasa, Kinshasa, Democratic Republic of Congo

9 YRGCARE Medical Centre, Chennai Antiviral Research and Treatment Clinical Research Site (CART CRS), Voluntary Health Services, Chennai, India

10 Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA

11 University of Bordeaux, INSERM ISPED U1219, Bordeaux, France

12 Department of Medical Informatics, School of Medicine, Vanderbilt University, Nashville, TN, USA

13 Centre for Infectious Disease Epidemiology and Research, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa

14 Division of Epidemiology, University of Toronto, Dalla Lana School of Public Health, 155 College Street, Toronto, ON M5T 3M7, Canada

15 Department of Medicine, School of Medicine, Moi University College of Health Sciences, Eldoret, Kenya

Facility characteristics ranged by facility and region. The majority of facilities reported that patients were assigned a unique identification number ($n = 114$; 83.2 %) and most sites recorded adverse drug reactions ($n = 101$; 73.7 %), while 82 facilities (59.9 %) reported having an electronic database on site.

Conclusion We found minimal information is available about facility characteristics that may contribute to pharmacovigilance activities. Our findings, therefore, are a first step that can potentially assist implementers and facility staff to identify opportunities and leverage their existing capacities to incorporate TSR into their routine clinical programs.

Key Points

Targeted spontaneous reporting (TSR) is a novel method of pharmacovigilance that integrates elements from cohort event monitoring and spontaneous reporting.

We found there is minimal information about facility characteristics that may contribute to pharmacovigilance activities.

Most facilities explored, including those in low- and middle-income settings, reported characteristics in place that could support TSR activities for conducting routine pharmacovigilance for antiretroviral treatment.

1 Introduction

Antiretroviral therapy (ART) for HIV is one of the largest pharmacological interventions globally and has required massive investments in health systems, including laboratory infrastructure, human capacity development, and the implementation of robust electronic medical record systems [1–3]. Increasing numbers of people living with HIV (PLWH) receive ART—13.5 million people in low- and middle-income countries (LMICs) in 2014 [4]—driving a clear need to enhance global drug safety monitoring [5, 6]. Toxicity from ART is a common reason for patients to switch or stop a medication regimen [7–10]. Adverse drug reactions (ADRs) are characterized by the suspicion of a causal relationship between the drug and the occurrence [11]. Recognizing ADRs in a timely manner is essential to achieving positive clinical outcomes and ensuring the long-term sustainability of ART programs [9]. This is important for PLWH in high-, low-, and middle-income settings. However, while several new antiretroviral agents with excellent safety profiles have been recently released to the market (e.g., integrase inhibitors, tenofovir alafenamide fumarate, etc.), many of these drugs are not readily available in LMICs [12]. As a result, older antiretroviral drugs, which are cheaper but have significant documented side effects, are more commonly prescribed [11, 12]. Furthermore, HIV-infected individuals in LMICs are more likely than individuals in high-income countries to be co-infected with tuberculosis, malaria, and other communicable diseases [7, 8, 13]. These co-morbid conditions and their treatments may mask or amplify ADRs resulting from ART [9]. The drugs used to treat co-morbid conditions can lead to additional ADRs, aggravate those already existing from ART, and create the potential for drug–drug interactions [14–16].

The World Health Organization (WHO) defines pharmacovigilance as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems" [17]. The overarching goal of pharmacovigilance is to ensure safe and appropriate use of medicines [17–20]. Pharmacovigilance activities can involve active or passive forms of surveillance. In "cohort event monitoring" (CEM), a cohort of patients is established and followed at regular intervals to enable the identification of adverse experiences in real time. All adverse events are captured while the patient is receiving the medication, regardless of the cause or severity. This method is expensive because of the requirements for active monitoring of the cohort, including scheduled collection of laboratory and clinical assessments and staffing characteristics. In contrast, "spontaneous reporting" (SR) is a passive method of ADR reporting that relies predominantly on voluntary reporting by provider and patient and is generally less expensive and easier to implement than CEM. Since ADR reporting is voluntary, events are often under-reported and—when reported—the details are often incomplete [20].

While the minimum requirement for SR is clinical suspicion [21], the WHO has recently released 27 core pharmacovigilance indicators needed for establishing and assessing pharmacovigilance systems, including ten structural, nine process, and eight outcome/impact indicators [22]. This long list of indicators demonstrates that the ability to identify and treat ADRs effectively and manage them in a timely manner requires additional resources beyond clinical suspicion. Ideally, if a healthcare provider or a patient suspects that a medication may be even partially responsible for a symptom or ADR, then he/she would report it to a national drug safety monitoring center through national channels as part of SR. However, in LMICs, ADRs are often under-reported because of overburdened healthcare systems, significant resource constraints, limited laboratory capacity to identify and manage

ADRs, and limited knowledge and unfavorable attitudes among healthcare providers towards reporting [9, 10, 20, 23–26]. Furthermore, many countries do not have a national system. Even when ADRs are detected, frequently the best or only response is to switch or substitute medications, although this may not always occur because affordable alternative treatments are lacking, ART is only available in fixed-dose combinations, and drug control/legislation is poor [16, 26].

A novel pharmacovigilance method called "targeted spontaneous reporting" (TSR) builds on SR by adding aspects of CEM. In this method, a sub-group of patients is defined and ADRs are monitored in this cohort as part of routine care [20]. An advantage of TSR is that it can capture measurements over the entire length of the treatment [20]. It can also be adapted to capture all ADRs, only ADRs relevant to the medication of interest, or continual general pharmacovigilance data. General pharmacovigilance monitoring enables researchers to use retrospective observational data as evidence when new medicines are introduced (i.e., without having to design and implement a whole cohort around a target drug as in CEM) and is particularly relevant in ART, where medications are often changing. Similar to SR, TSR depends heavily on reporting by patients and providers [20]. However, as TSR is embedded in routine clinical programs, it may require less time and fewer resources than CEM, and because there is a defined denominator —unlike with SR— incidence rates can be determined. TSR has great potential to enhance reporting of ADRs, and has been used by individual programs in the context of research [7, 27, 28]. However, the feasibility of TSR as a new approach to routine pharmacovigilance [17, 20], especially in but not limited to LMICs, is unknown. Furthermore, to our knowledge, minimal data exist on the needs or capacity of facilities to conduct TSR. Therefore, our goal in the present study was to first explore the characteristics of facilities that can facilitate TSR for monitoring of ART and, second, to describe the capacity at the facility level to report ADRs and perform TSR. In the present study, we used data from the International epidemiologic Databases to Evaluate AIDS (IeDEA) consortium to fulfil two objectives: (1) to develop a list of facility characteristics that could constitute key assets in the conduct of TSR and (2) to use this list as a starting point to describe the existing capacity of IeDEA-participating facilities to conduct pharmacovigilance through TSR.

2 Methods

2.1 Study Setting

The IeDEA consortium (http://www.iedea.org) is a collaborative network of HIV/AIDS treatment programs in seven regions: North America; Caribbean and Latin America; Asia–Pacific; and Central, East, West, and Southern sub-Saharan Africa. The IeDEA network was established to address clinical and operational research questions that required large numbers of individuals and/or programs. The consortium seeks to compare outcomes across a range of settings and delivery models [29]. Each region has an independent data center and governance structure. IeDEA is funded through the US National Institutes of Health (NIH).

2.2 Generation of the List of Facility-Level Characteristics

We aimed to identify various facility-level characteristics that are relevant for pharmacovigilance, particularly TSR-specific activities. Using an iterative approach, we generated our working list through a review of relevant WHO and Uppsala Monitoring Centre (UMC) documents focused on pharmacovigilance activities related to HIV and ART [11] and consultation with expert stakeholders. This included pharmacists, pharmacovigilance specialists, clinicians, epidemiologists, and policy makers at the Academic Model Providing Access to Healthcare (AMPATH), UMC at the WHO, Kenya Pharmacy and Poisons Board (PPB), and Kenya's National AIDS & STI Control Programme (NASCOP).

2.3 Data Entry and Analysis

In 2009, IeDEA distributed a site assessment survey (164 items) to all participating sites (which included programs and individual facilities) in all regions [30]. The Southern Africa region completed a subset of the survey, gathering data on facility characteristics and opportunistic infection management but not on laboratory capacity and other program characteristics. North American cohorts did not complete sections of the assessment less relevant to their settings (e.g., data on tuberculosis and malaria). Data were collected on adult and pediatric care and pre-ART and ART treatment, as well as program characteristics, such as outreach, laboratory capacity, adverse event monitoring and pharmacovigilance, tuberculosis care, cancer care, and prevention of mother-to-child transmission (PMTCT) services. The assessment tool was available on paper and electronically via the web-based Research Electronic Data Capture (REDCap) system [31], in both English and French. The list of facility-level characteristics was used to describe the capacity for conducting pharmacovigilance. Descriptive statistics and frequency calculations of characteristics are presented by region and by overall category. The sites and coordinating centers for all IeDEA regions had institutional review board approvals in place that

permitted the collection of such operational data through this site-assessment survey.

3 Results

3.1 Generation of Facility List

The majority of the reviewed WHO/UMC literature focused on establishing pharmacovigilance centers/systems nationally or within existing public health programs. Whilst the WHO and UMC handbooks provide detailed descriptions on how to set up national pharmacovigilance centers and SR and CEM within public health programs, minimal data on TSR are provided [11, 32–35]. This could be attributed to TSR being a relatively new approach in the reporting of pharmacovigilance [35]. At a minimum, in addition to meeting the minimum criteria for pharmacovigilance, facilities will require reporting forms, a specialized health cadre such as a physician or pharmacist to evaluate events, and a laboratory to facilitate the identification and monitoring of ADRs. The number of personnel required depends on the patient volumes within the facility. Discussion with key experts determined that facility characteristics that can impact TSR capacity could be grouped into those related to (1) outcome ascertainment and follow-up; (2) laboratory monitoring; (3) data needs; (4) data capacity; and (5) human resources (see Table 1).

3.2 Capacity of Examined International epidemiologic Databases to Evaluate AIDS (IeDEA) Facilities

Of the 142 facilities and programs eligible for this analysis, five facilities were excluded because no data were available (three in Central Africa, one in Asia–Pacific, and one in North America). Therefore, a total of 137 facilities were included: East Africa (43); Asia–Pacific region (28); West Africa (21); Southern Africa (19); Central Africa (12); Caribbean, Central, and South America (7); and North America (7).

Variables related to outcome ascertainment and follow-up are described in Table 2. Approximately 43.1 and 56.2 % of facilities reported that they follow-up pregnant and HIV-exposed/infected children, respectively. Just over half of all included facilities reported the presence of an outreach program for patients who miss visits or become lost to follow-up, although data were missing for 64 (46.7 %) facilities. When data were available, reported outreach methods varied, with just over half of facilities using a combination of telephone calls and home visits ($n = 72$; 52.6 %). Just over one-third (38.7 %) of facilities reported active systems to ascertain vital status, although

Table 1 Rationale for facility characteristics explored

Category	Variables	Rationale
Outcome ascertainment and follow-up	Follow-up of individuals receiving medications, including key populations such as pregnant women and children; presence of an outreach program; ascertainment of deaths; patient fees	Patients lost to follow-up are a source of selection and ascertainment bias in evaluation of ADR. The ability to know and document outcomes among special populations like pregnant women and children is especially important. Service fees can inhibit patient retention in care and routine ordering of laboratory tests and other services that can identify ADRs
Laboratory monitoring	HIV RNA, HIV DNA, CD4 count, hemoglobin, total lymphocytes, ALT/AST, creatinine, and lactate: availability and turnaround time	Laboratory information including baseline and follow-up testing is necessary for detection, identification, and confirmation of ADRs. Lab tests are important for assessment of treatment efficacy
Documentation—sources and management of data	Unique patient identifiers, presence of an electronic database, medical history, history of opportunistic infections (history and follow-up), cancer history, linkage to pharmacy database, ADRs and their outcomes, classification system for ADRs and use of standard definitions, availability of internet	These data are needed to identify ADRs, support TSR activities, and link clinical and pharmacy visits to understand patterns of drug use and their association with ADRs. Critical information includes a unique identifiable patient, their medical history and clinical status at FU to document any changes, standardized, non-free, text on data capture instruments. Longitudinal patient data including medication, clinical and ADR data are needed to appropriately classify ADRs and report the outcomes
Human resources	Availability of physicians, pharmacists, pharmacy assistants and data recorders (to record ADRs)	Core clinic staff are required to identify, capture and report ADRs

ADR adverse drug reaction, *ALT* alanine transaminase, *AST* aspartate transaminase, *TSR* targeted spontaneous reporting

Table 2 Outcome ascertainment and follow-up of included International epidemiologic Databases to Evaluate AIDS (IeDEA) facilities ($n = 137$)

Category and variables	West Africa ($n = 21$)	Southern Africa ($n = 19$)	East Africa ($n = 43$)	Central Africa ($n = 12$[a])	South America ($n = 7$)	Asia ($n = 28$[b])	North America ($n = 7$[c])	Total ($n = 137$)
Follow-up of key populations								
Pregnant women								
Yes	6 (28.6)	0 (0)	37 (86.0)	8 (66.7)	4 (57.1)	4 (14.3)	0 (0)	59 (43.1)
No	6 (28.6)	0 (0)	0 (0)	1 (8.3)	0 (0)	5 (17.9)	0 (0)	12 (8.8)
Missing	9 (42.9)	19 (100)	6 (14.0)	3 (25.0)	3 (42.9)	19 (67.9)	7 (100)	66 (48.2)
Children, HIV-exposed and/or HIV-infected								
Yes	13 (61.9)	0 (0)	38 (88.4)	11 (91.7)	4 (57.1)	12 (42.9)	0 (0)	78 (56.2)
Missing	8 (38.1)	19 (100)	5 (11.6)	1 (8.3)	3 (42.9)	16 (57.1)	7 (100)	59 (43.8)
Presence of an outreach program for patients who miss visits or become LTFU								
Yes	9 (42.9)	0 (0)	39 (90.7)	6 (50.0)	3 (43.9)	11 (39.3)	5 (71.4)	73 (53.3)
Missing	12 (57.1)	19 (100)	4 (9.3)	6 (50.0)	4 (57.1)	17 (60.7)	2 (28.6)	64 (46.7)
Active outreach								
Call only	1 (4.8)	5 (26.3)	1 (2.3)	0 (0)	0 (0)	12 (42.9)	6 (85.7)	25 (18.2)
Call and home visit by clinic staff or outreach workers	11 (52.4)	12 (63.2)	32 (74.4)	9 (0.75)	2 (28.6)	6 (21.4)	0 (0)	72 (52.6)
Home visit only	1 (4.8)	2 (10.5)	8 (18.6)	2 (16.7)	0 (0)	0 (0)	0 (0)	13 (9.5)
Missing	8 (38.1)	0 (0)	2 (4.7)	1 (8.3)	5 (71.4)	10 (35.7)	1 (14.3)	27 (19.7)
Ascertainment of deaths								
Active	7 (33.3)	0 (0)	32 (74.4)	5 (41.7)	3 (42.9)	2 (7.1)	4 (57.1)	53 (38.7)
Missing	14 (66.7)	19 (100)	11 (25.6)	7 (58.3)	4 (57.1)	26 (92.9)	3 (42.9)	84 (61.3)
Methods of death ascertainment (multiple methods provided)								
Family	12 (57.1)	0 (0)	37 (86.1)	9 (75)	7 (100)	15 (53.6)	6 (85.7)	86 (62.8)
Word of mouth	3 (14.3)	0 (0)	32 (74.4)	6 (50)	2 (28.6)	6 (21.4)	4 (57.1)	53 (38.7)
Physician report	5 (23.8)	0 (0)	32 (74.4)	4 (33.3)	5 (71.4)	17 (60.7)	7 (100)	70 (51.7)
Data linkage with patient records	2 (9.5)	11 (57.9)	25 (58.1)	1 (8.3)	4 (57.1)	6 (21.4)	6 (85.7)	55 (40.1)
Phone follow-up	11 (5.2)	0 (0)	27 (62.8)	6 (50)	5 (71.4)	10 (35.7)	4 (57.1)	63 (46.0)
Home follow-up	8 (38.1)	0 (0)	33 (76.7)	9 (75)	1 (14.3)	2 (7.1)	1 (14.3)	54 (39.4)
Other	2 (9.5)	0 (0)	0 (0)	0 (0)	1 (14.3)	0 (0)	0 (0)	3 (2.2)
Missing	7 (33.3)	8 (42.1)	0 (0)	0 (0)	0 (0)	7 (25)	0 (0)	22 (16.1)
Payment structure (user fees)								
General								
Full/partial payment	2 (9.5)	5 (26.3)	2 (4.7)	3 (12.5)	3 (42.9)	10 (35.7)	0 (0)	25 (18.2)
No fees	15 (71.4)	14 (73.7)	41 (95.3)	9 (75)	4 (57.1)	18 (64.3)	7 (100)	108 (78.8)
Missing	4 (19)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (2.9)
Diagnostic exams								
Full/partial payment	5 (23.8)	2 (10.5)	4 (9.3)	4 (33.3)	3 (42.9)	9 (32.1)	0 (0)	27 (19.7)
No fees	11 (52.4)	17 (89.5)	39 (90.7)	8 (66.7)	4 (57.1)	17 (60.7)	7 (100)	103 (75.2)
Missing	5 (23.8)	0 (0)	0 (0)	0 (0)	0 (0)	2 (7.1)	0 (0)	7 (5.1)
Routine follow-up								
Full/partial payment	6 (28.6)	3 (15.8)	0 (0)	2 (16.7)	2 (28.6)	10 (35.7)	0 (0)	23 (16.8)
No fees	11 (52.4)	16 (84.2)	43 (100)	10 (83.3)	5 (71.4)	18 (64.3)	7 (100)	110 (80.3)
Missing	4 (19)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (2.9)
Additional consultation								
Full/partial payment	9 (42.9)	3 (15.8)	3 (7)	4 (33.3)	2 (28.6)	9 (32.1)	0 (0)	30 (21.9)
No fees	8 (38.1)	16 (84.2)	40 (93)	8 (66.7)	5 (71.4)	19 (67.9)	7 (100)	103 (75.1)

Table 2 continued

Category and variables	West Africa ($n = 21$)	Southern Africa ($n = 19$)	East Africa ($n = 43$)	Central Africa ($n = 12$[a])	South America ($n = 7$)	Asia ($n = 28$[b])	North America ($n = 7$[c])	Total ($n = 137$)
Missing	4 (19)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (2.9)
Laboratory								
Full/partial payment	8 (38.1)	2 (10.5)	4 (9.3)	6 (50)	3 (42.9)	10 (35.7)	0 (0)	33 (24.1)
No fees	9 (42.9)	17 (89.5)	39 (90.7)	6 (50)	4 (57.1)	18 (64.3)	7 (100)	100 (73.0)
Missing	4 (19)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (2.9)
First/second-line ARVs								
Full/partial payment	1 (4.8)	2 (10.5)	0 (0)	0 (0)	1 (14.3)	9 (32.1)	0 (0)	13 (9.5)
No fees	16 (76.2)	17 (89.5)	43 (100)	12 (100)	6 (85.7)	19 (67.9)	7 (100)	120 (87.6)
Missing	4 (19)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (2.9)
Prophylaxis/treatment for opportunistic infections								
Full/partial payment	9 (42.9)	3 (15.8)	0 (0)	6 (50)	3 (42.9)	12 (42.9)	0 (0)	33 (24.1)
No fees	8 (38.1)	16 (84.2)	43 (100)	6 (50)	4 (57.1)	16 (57.1)	7 (100)	100 (73.0)
Missing	4 (19)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (2.9)
Travel to the clinic								
Full/partial payment	12 (57.1)	15 (78.9)	39 (90.7)	12 (100)	5 (71.4)	22 (78.6)	3 (42.9)	108 (78.8)
No fees	5 (23.8)	4 (21.1)	4 (9.3)	0 (0)	2 (28.5)	6 (21.4)	4 (57.1)	25 (18.2)
Missing	4 (19)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (2.9)

The data are presented as *n* (%). No data were available for "routine clinical monitoring and follow-up" or "standard operating procedures in place (clinical, laboratory, pharmacovigilance reporting)"

ARVs antiretrovirals, *LTFU* lost to follow-up

[a] Central Africa has 15 facilities but no data were available for three facilities

[b] Asia–Pacific Region has 29 facilities but no data were available for one facility

[c] North America has eight facilities but no data were available for one facility

the methods reported were heterogeneous. The most frequently reported methods for ascertainment were family contacts ($n = 86$; 62.8 %) and physician reports ($n = 70$; 51.7 %). Payment/user fees varied widely across facilities, although, in most sites, patients did not have to pay out of pocket for general services, consultations, follow-up, laboratory tests, or treatment for opportunistic infections. However, at 108 (78.8 %) facilities, patients had to pay—in full or in part—for transport to the clinic. No data were available from Southern Africa on the follow-up of pregnant women and children, the use of an electronic database, the presence of an outreach program or active ascertainment of deaths, although the Republic of South Africa has an active national vital statistics registry that is used for ascertainment of mortality in that country. No data were available from North America on the follow-up of pregnant women or of children, as the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) cohort includes adult populations only.

Laboratory monitoring is described in Table 3. No data were available from Southern African facilities. In general, laboratory monitoring varied across facilities and by test, although almost three-quarters of facilities reported performing hemoglobin testing on site ($n = 99$; 72.3 %). On-site availability of laboratory monitoring existed for the following: HIV RNA polymerase chain reaction (PCR), $n = 44$ (32.1 %); HIV DNA PCR, $n = 25$ (18.2 %); $CD4^+$ cell count, $n = 72$ (52.6 %); total lymphocyte count, $n = 72$ (52.6 %); alanine transaminase/aspartate transaminase (ALT/AST), $n = 70$ (51.1 %); cholesterol, $n = 57$ (41.6 %); creatinine, $n = 71$ (51.8 %); and lactate, $n = 46$ (33.6 %). The reported turnaround time varied across facilities and by type of laboratory test, ranging from 1 day to up to 100 days. Turnaround time was shortest for Lactate (<1–30 days) and longest for CD4 count (1–100 days). In general, turnaround time was shortest for sites in Central Africa, Asia–Pacific, and North America.

Table 4 shows results for "documentation—sources and management of data" for pharmacovigilance. The majority of facilities reported that patients were assigned a unique identification number ($n = 114$; 83.2 %) for tracking purposes. Respondents from 92 facilities also noted that patients' history of opportunistic infections was captured at the first visit, either in the patient chart/record ($n = 60$; 43.8 %) or in an electronic database ($n = 32$; 23.4 %). Opportunistic infections were recorded at diagnosis in 111

Table 3 Laboratory monitoring of included International epidemiologic Databases to Evaluate AIDS (IeDEA) facilities

Category and variables	West Africa ($n = 21$)	Southern Africa ($n = 19$)	East Africa ($n = 43$)	Central Africa ($n = 12$[a])	South America ($n = 7$)	Asia ($n = 28$[b])	North America ($n = 7$[c])	Total ($n = 137$)
HIV RNA PCR								
On site	5 (23.8)	0 (0)	5 (11.6)	7 (58.3)	4 (57.1)	18 (64.3)	5 (71.4)	44 (32.1)
Off site	7 (31.8)	0 (0)	23 (53.5)	0 (0)	2 (28.6)	5 (17.9)	2 (28.6)	39 (28.5)
Test not available	1 (4.8)	0 (0)	10 (23.3)	5 (41.7)	0 (0)	1 (3.6)	0 (0)	17 (12.4)
Missing	8 (38.1)	19 (100)	5 (11.6)	0 (0)	1 (14.3)	4 (14.3)	0 (0)	37 (27.0)
Turnaround time (range)	1–60	Unknown/ missing	7–60	14–30	7–60	1–60	1–10	1–60
HIV DNA PCR								
On site	3 (14.3)	0 (0)	7 (16.3)	3 (25)	2 (28.6)	9 (32.1)	1 (14.3)	25 (18.2)
Off site	8 (38.1)	0 (0)	33 (76.7)	0 (0)	2 (28.6)	8 (28.6)	1 (14.3)	52 (37.9)
Test not available	2 (9.5)	0 (0)	3 (7)	7 (58.3)	0 (0)	3 (10.7)	0 (0)	15 (10.9)
Missing	8 (38.1)	19 (100)	0 (0)	2 (16.7)	3 (42.9)	8 (28.6)	5 (71.4)	45 (32.8)
Turnaround time (range)	8–30	Unknown/ missing	7–30	30	14–60	3–60	4–10	3–60
$CD4^+$ count								
On site	11 (52.4)	0 (0)	17 (39.5)	9 (75)	6 (85.7)	24 (85.7)	5 (71.4)	72 (52.6)
Off site	3 (14.3)	0 (0)	26 (60.5)	3 (25)	1 (14.2)	4 (14.3)	2 (28.6)	39 (28.5)
Test not available	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Missing	7 (33.3)	19 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	26 (19.0)
Turnaround time (range)	1–100	Unknown/ missing	1–30	1–7	1–15	1–14	1–5	1–100
Hemoglobin								
On site	12 (57.1)	0 (0)	38 (88.4)	12 (100)	7 (100)	25 (89.3)	5 (71.4)	99 (72.3)
Off site	2 (9.5)	0 (0)	4 (9.3)	0 (0)	0 (0)	3 (10.7)	2 (28.6)	11 (8.0)
Test not available	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Missing	7 (33.3)	19 (100)	1 (2.3)	0 (0)	0 (0)	0 (0)	0 (0)	27 (19.7)
Turnaround time (range)	1–100	Unknown/ missing	1–30	<1–3	1–15	<1–3	<1–2	<1–100
Total lymphocyte count								
On site	11 (52.4)	0 (0)	16 (37.2)	10 (83.3)	7 (100)	24 (85.7)	4 (57.1)	72 (52.6)
Off site	3 (14.3)	0 (0)	26 (60.5)	1 (8.3)	0 (0)	3 (10.7)	3 (42.9)	36 (26.3)
Test not available	0 (0)	0 (0)	0 (0)	1 (8.3)	0 (0)	0 (0)	0 (0)	0 (0)
Missing	7 (33.3)	19 (100)	1 (2.3)	0 (0)	0 (0)	1 (3.6)	0 (0)	28 (20.4)
Turnaround time (range)	1–100	Unknown/ missing	1–30	1–3	1–15	<1–14	<1–2	<1–100
ALT/AST								
On site	11 (52.4)	0 (0)	16 (37.2)	7 (58.3)	7 (100)	24 (85.7)	5 (71.4)	70 (51.1)
Off site	3 (14.3)	0 (0)	26 (60.5)	2 (16.7)	0 (0)	3 (10.7)	2 (28.6)	36 (26.3)
Test not available	0 (0)	0 (0)	0 (0)	3 (25.0)	0 (0)	0 (0)	0 (0)	0 (0)
Missing	7 (33.3)	19 (100)	1 (2.3)	0 (0)	0 (0)	1 (3.6)	0 (0)	28 (20.4)
Turnaround time (range)	1–100	Unknown/ missing	1–30	1–3	1–15	<1–2	1–2	<1–100

Table 3 continued

Category and variables	West Africa ($n = 21$)	Southern Africa ($n = 19$)	East Africa ($n = 43$)	Central Africa ($n = 12$[a])	South America ($n = 7$)	Asia ($n = 28$[b])	North America ($n = 7$[c])	Total ($n = 137$)
Cholesterol								
On site	9 (42.9)	0 (0)	6 (14)	5 (41.7)	7 (100)	25 (89.3)	5 (71.4)	57 (41.6)
Off site	5 (23.8)	0 (0)	32 (74.4)	4 (33.3)	0 (0)	3 (10.7)	2 (28.6)	46 (33.6)
Test not available	0 (0)	0 (0)	3 (7)	2 (16.7)	0 (0)	0 (0)	0 (0)	5 (3.6)
Missing	7 (33.3)	19 (100)	2 (4.7)	1 (8.3)	0 (0)	0 (0)	0 (0)	29 (21.2)
Turnaround time (range)	1–100	Unknown/ missing	<1–30	1–3	1–15	<1–7	<1–7	<1–100
Creatinine								
On site	11 (52.4)	0 (0)	15 (34.9)	8 (66.7)	7 (100)	25 (89.3)	5 (71.4)	71 (51.8)
Off site	3 (14.3)	0 (0)	27 (62.8)	1 (8.3)	0 (0)	3 (10.7)	2 (28.6)	36 (26.3)
Test not available	0 (0)	0 (0)	0 (0)	2 (16.7)	0 (0)	0 (0)	0 (0)	2 (1.5)
Missing	7 (33.3)	19 (100)	1 (2.3)	1 (8.3)	0 (0)	0 (0)	0 (0)	28 (20.4)
Turnaround time (range)	1–100	Unknown/ missing	1–30	1–3	1–15	<1–3	<1–1	<1–100
Lactate								
On site	7 (33.3)	0 (0)	6 (14)	2 (16.7)	5 (71.4)	21 (75)	5 (71.4)	46 (33.6)
Off site	2 (9.5)	0 (0)	31 (72.1)	2 (16.7)	1 (14.3)	7 (25)	2 (28.6)	45 (32.8)
Test not available	3 (14.3)	0 (0)	3 (7)	6 (50)	0 (0)	0 (0)	0 (0)	12 (8.8)
Missing	9 (42.9)	19 (100)	3 (7)	2 (16.7)	1 (14.3)	0 (0)	0 (0)	34 (24.8)
Turnaround time (range)	<1–21	Unknown/ missing	1–30	1–3	1–2	<1–3	<1–2	<1–30

The data are presented as *n* (%). No data were available for the following laboratory tests: serum albumin, INR, alkaline phosphate, triglycerides, high-density lipoprotein, low-density lipoprotein, glucose, platelet count, total white blood count, urine albumin, urine glucose

ALT/AST alanine transaminase/aspartate transaminase, *INR* international normalized ratio, *PCR* polymerase chain reaction

[a] Central Africa has 15 facilities but no data were available for three facilities

[b] Asia–Pacific region has 29 facilities but no data were available for one facility

[c] North America has eight facilities but no data were available for one facility

(81 %) facilities, but only captured at each visit until resolved in 85 (62 %) facilities. Respondents reported that malignancies were routinely recorded at 105 facilities, either on paper ($n = 53$; 38.7 %) or in an electronic database ($n = 52$; 37.9 %). As part of pharmacovigilance reporting, adverse events are routinely monitored and recorded in only 66 (48.1 %) facilities, with variable monitoring at an additional 55 (40.1 %) facilities. The facilities reported applying various ADR classification methods, including WHO guidance. This involves a fixed algorithm for decision making [36] ($n = 42$; 30.7 %) and global introspection through group discussion where clinical expertise and experience are used to classify identified ADRs ($n = 25$; 18.2 %). Approximately 67 facilities recorded the outcome of the ADR either on paper only ($n = 16$; 11.7 %), on paper and in an electronic database ($n = 25$; 18.2 %), or in the electronic database only ($n = 26$; 18.9 %). No outcome was recorded at 39 (28.5 %) facilities. Almost all sites recorded ADRs ($n = 101$), as free text ($n = 45$; 32.8 %), using a code ($n = 30$; 21.9 %), or as a reason for treatment interruption ($n = 26$; 18.95 %). No data were available for Southern Africa regarding relevant medical history, ADR classification, or the recording of ADR outcomes. A total of 82 facilities (59.9 %) reported having an electronic database on site (100 % of facilities in North America), and an additional 32 facilities (23.4 %) used patient forms that were then transferred to a central data center. The ability to link patient records to a pharmacy database was reported in only 47 facilities (34.3 %), with an additional 28 facilities (20.4 %) reporting that linkage was possible with additional effort. No pharmacy database existed at 20 (14.6 %) facilities. Approximately half of included facilities used some standard definition for ADRs, although data on the

Table 4 Documentation—sources and management of data in included International epidemiologic Databases to Evaluate AIDS (IeDEA) facilities

Category and variables	West Africa ($n = 21$)	Southern Africa ($n = 19$)	East Africa ($n = 43$)	Central Africa ($n = 12$[a])	South America ($n = 7$)	Asia ($n = 28$[b])	North America ($n = 7$[c])	Total ($n = 137$)
Patients given a unique ID								
Yes	12 (57.1)	14 (73.7)	39 (90.7)	11 (91.7)	7 (100)	24 (85.7)	7 (100)	114 (83.2)
No	2 (9.5)	5 (26.3)	4 (9.3)	1 (8.3)	0 (0)	0 (0)	0 (0)	12 (8.8)
Missing	7 (33.3)	0 (0)	0 (0)	0 (0)	0 (0)	4 (14.3)	0 (0)	11 (8.0)
Use of an electronic database								
Yes, on site	18 (85.7)	0 (0)	18 (41.9)	10 (83.3)	5 (71.4)	24 (85.7)	7 (100)	82 (59.9)
No, patient forms transferred to data center	1 (4.8)	0 (0)	25 (58.1)	2 (16.7)	1 (14.3)	3 (10.7)	0 (0)	32 (23.4)
Other	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.6)	0 (0)	1 (0.7)
Missing	2 (9.5)	19 (100)	0 (0)	0 (0)	1 (14.3)	0 (0)	0 (0)	22 (16.1)
Relevant medical history captured								
History of opportunistic infections at first visit								
Yes, in charts or records	13 (61.9)	0 (0)	16 (37.2)	6 (50.0)	5 (71.4)	19 (67.9)	1 (14.3)	60 (43.8)
Yes, in electronic database	1 (4.8)	0 (0)	10 (23.3)	5 (41.7)	2 (28.6)	8 (28.6)	6 (85.7)	32 (23.4)
No	0 (0)	0 (0)	0 (0)	1 (8.3)	0 (0)	1 (3.6)	0 (0)	2 (1.5)
NA	0 (0)	0 (0)	17 (39.5)	0 (0)	0 (0)	0 (0)	0 (0)	17 (12.4)
Missing	7 (33.3)	19 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	26 (18.9)
Monitoring of opportunistic infections								
At initial diagnosis	6 (28.6)	0 (0)	4 (9.3)	7 (58.3)	2 (28.6)	6 (21.4)	1 (14.3)	26 (18.9)
At each visit until resolved	8 (38.1)	0 (0)	39 (90.7)	5 (41.7)	5 (71.4)	22 (78.6)	6 (85.7)	85 (62.0)
Not routinely documented	1 (4.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)
Missing	6 (28.6)	19 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	25 (18.2)
Monitoring of malignancies								
Yes, on paper	10 (47.6)	0 (0)	17 (39.5)	8 (66.7)	3 (42.9)	15 (53.6)	0 (0)	53 (38.7)
Yes, in electronic database	3 (14.3)	0 (0)	24 (55.8)	4 (33.3)	4 (57.1)	10 (35.7)	7 (100)	52 (37.9)
Not routinely captured	2 (9.5)	0 (0)	1 (2.3)	0 (0)	0 (0)	3 (10.7)	0 (0)	6 (4.4)
Missing	6 (28.6)	19 (100)	1 (2.3)	0 (0)	0 (0)	0 (0)	0 (0)	26 (18.9)
Linkage to pharmacy data								
Yes	12 (57.1)	7 (36.8)	8 (18.6)	3 (25)	3 (43.9)	9 (32.1)	5 (71.4)	47 (34.3)
No	0 (0)	0 (0)	8 (18.6)	3 (25)	0 (0)	9 (32.1)	2 (28.6)	22 (16.1)
Perhaps with work	5 (2.4)	0 (0)	11 (25.6)	0 (0)	4 (57.1)	8 (28.6)	0 (0)	28 (20.4)
Don't know	0 (0)	7 (36.8)	1 (2.3)	0 (0)	0 (0)	0 (0)	0 (0)	8 (5.8)
There is no pharmacy database	1 (4.8)	5 (26.3)	10 (23.3)	3 (25)	0 (0)	1 (3.6)	0 (0)	20 (14.6)
NA	3 (14.2)	0 (0)	5 (11.6)	3 (25)	0 (0)	1 (3.6)	0 (0)	12 (8.8)
ADRs routinely monitored								
Yes, almost universally	10 (47.6)	10 (52.6)	14 (32.6)	8 (66.7)	3 (42.9)	18 (64.3)	3 (42.9)	66 (48.1)
Yes, but with variable consistency	7 (33.3)	0 (0)	27 (62.8)	3 (25)	4 (57.1)	10 (35.7)	4 (57.1)	55 (40.1)
Usually not	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	0 (0)	6 (31.6)	1 (2.3)	0 (0)	0 (0)	0 (0)	0 (0)	7 (5.1)

Table 4 continued

Category and variables	West Africa ($n = 21$)	Southern Africa ($n = 19$)	East Africa ($n = 43$)	Central Africa ($n = 12$[a])	South America ($n = 7$)	Asia ($n = 28$[b])	North America ($n = 7$[c])	Total ($n = 137$)
NA	0 (0)	0 (0)	0 (0)	1 (8.3)	0 (0)	0 (0)	0 (0)	1 (0.7)
Missing	4 (19)	3 (15.8)	1 (2.3)	0 (0)	0 (0)	0 (0)	0 (0)	8 (5.8)
ADR outcome recorded								
No	3 (14.3)	0 (0)	20 (46.5)	3 (25)	1 (14.3)	10 (35.7)	2 (28.6)	39 (28.5)
Yes, on paper only	3 (14.3)	0 (0)	8 (18.6)	2 (16.7)	2 (28.6)	1 (3.6)	0 (0)	16 (11.7)
Yes, on paper and in database	4 (19)	0 (0)	4 (9.3)	2 (16.7)	0 (0)	15 (53.6)	0 (0)	25 (18.2)
Yes, in database only	9 (42.9)	0 (0)	6 (14)	4 (33.3)	4 (57.1)	0 (0)	3 (42.9)	26 (18.9)
No database available	0 (0)	0 (0)	1 (2.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Missing	3 (14.3)	19 (100)	4 (9.3)	1 (8.3)	0 (0)	2 (7.1)	2 (28.6)	31 (22.6)
Format of recorded ADRs								
Yes, free text	12 (63.2)	0 (0)	5 (11.6)	7 (58.3)	3 (42.9)	15 (53.6)	3 (42.9)	45 (32.8)
Yes, coded	1 (4.8)	0 (0)	12 (27.9)	2 (16.7)	4 (57.1)	8 (28.6)	3 (42.9)	30 (21.9)
Yes, only as reason for treatment interruption	1 (4.8)	0 (0)	19 (44.2)	3 (25)	0 (0)	2 (7.1)	1 (14.3)	26 (18.9)
No	4 (19)	0 (0)	0 (0)	0 (0)	0 (0)	3 (10.7)	0 (0)	7 (5.1)
Missing	3 (14.3)	19 (100)	7 (16.3)	0 (0)	0 (0)	0 (0)	0 (0)	29 (21.1)
ADR classification								
DAIDS toxicity grading scheme	0 (0)	0 (0)	1 (2.3)	0 (0)	1 (14.3)	8 (28.6)	0 (0)	10 (7.3)
ACTG/HPTN Appendix 60	0 (0)	0 (0)	0 (0)	0 (0)	1 (14.3)	0 (0)	2 (28.6)	3 (2.2)
IMPAACT Appendix 40	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
WHO	12 (57.1)	0 (0)	18 (41.9)	6 (50)	1 (14.3)	5 (17.9)	0 (0)	42 (30.7)
ANRS	3 (14.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (2.2)
TAHOD specification	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	8 (28.6)	0 (0)	8 (5.8)
Clinical experience	2 (9.5)	0 (0)	6 (14)	6 (50)	3 (42.9)	5 (17.9)	3 (42.9)	25 (18.2)
Other	0 (0)	0 (0)	18 (41.9)	0 (0)	1 (14.3)	2 (7.1)	1 (14.3)	22 (16.1)
Missing	4 (19)	19 (100)	0 (0)	0 (0)	0 (0)	0 (0)	1 (14.3)	24 (17.5)
Use of standard ADR definitions[d]								
Immune reconstitution syndrome								
Yes	10 (47.6)	0 (0)	15 (34.9)	11 (91.7)	4 (57.1)	21 (0.75)	3 (42.9)	64 (46.7)
No	4 (19)	0 (0)	23 (53.5)	0 (0)	3 (42.9)	7 (0.25)	4 (57.1)	41 (29.9)
Other	1 (4.8)	0 (0)	1 (2.3)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.5)
Missing	6 (28.6)	19 (100)	4 (9.3)	1 (8.3)	0 (0)	0 (0)	0 (0)	30 (21.9)
Rash								
Yes	12 (57.1)	0 (0)	16 (37.2)	10 (83.3)	4 (57.1)	21 (0.75)	3 (42.9)	66 (48.1)
No	3 (14.3)	0 (0)	23 (53.5)	2 (16.7)	3 (42.9)	7 (0.25)	4 (57.1)	42 (30.7)
Other	1 (4.8)	0 (0)	1 (2.3)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.5)
Missing	5 (2.4)	19 (100)	3 (7)	0 (0)	0 (0)	0 (0)	0 (0)	27 (19.7)
Peripheral neuropathy								
Yes	11 (52.3)	0 (0)	14 (32.6)	10 (83.3)	4 (57.1)	18 (64.3)	3 (42.9)	60 (43.8)
No	4 (19)	0 (0)	24 (55.8)	2 (16.7)	3 (42.9)	10 (35.7)	4 (57.1)	47 (34.3)
Other	1 (4.8)	0 (0)	1 (2.3)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.5)
Missing	5 (2.4)	19 (100)	3 (7)	0 (0)	0 (0)	0 (0)	0 (0)	27 (19.7)
Hepatotoxicity								
Yes	13 (61.9)	0 (0)	18 (41.9)	10 (83.3)	4 (57.1)	24 (85.7)	4 (57.1)	73 (53.3)

Table 4 continued

Category and variables	West Africa ($n = 21$)	Southern Africa ($n = 19$)	East Africa ($n = 43$)	Central Africa ($n = 12$[a])	South America ($n = 7$)	Asia ($n = 28$[b])	North America ($n = 7$[c])	Total ($n = 137$)
No	2 (9.5)	0 (0)	22 (51.2)	2 (16.7)	3 (42.9)	4 (14.3)	3 (42.9)	36 (26.3)
Other	1 (4.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)
Missing	5 (23.8)	19 (100)	3 (7)	0 (0)	0 (0)	0 (0)	0 (0)	27 (19.7)
Internet availability								
On site	11 (52.4)	0 (0)	10 (23.3)	5 (41.7)	2 (28.6)	9 (32.1)	7 (100)	44 (32.1)
Within the larger facility	2 (9.5)	0 (0)	7 (16.3)	1 (8.3)	2 (28.6)	3 (10.7)	0 (0)	15 (10.9)
Within 5 km	1 (4.8)	0 (0)	15 34.9)	3 (25)	0 (0)	0 (0)	0 (0)	19 (13.9)
Missing	7 (33.3)	19 (100)	11 (25.6)	3 (25)	3 (42.9)	16 (57.1)	0 (0)	59 (43.1)

The data are presented as *n* (%)

ACTG/HPTN AIDS Clinical Trials Group/HIV Prevention Trials Network, *ADR* adverse drug reaction, *ANRS* Agence Nationale de Recherche sur le Sida, *DAIDS* Division of AIDS at National Institutes of Allergies and Infectious Diseases, *ID* identifier, *IMPAACT* International Maternal Pediatric Adolescent AIDS Clinical Trials Group, *NA* not available, *OI* opportunistic infection, *TAHOD* Treat Asia and Australian HIV Observational Databases, *WHO* World Health Organization

[a] Central Africa has 15 facilities but no data were available for three facilities

[b] Asia–Pacific region has 29 facilities but no data were available for one facility

[c] North America has eight facilities but no data were available for one facility

[d] This question is being used as a proxy for whether facilities have access to a standardized concept dictionary to identify codes and determine event terms

use of standardized definitions were missing for 27 (approximately 20 %) facilities. In total, 44 (32.1 %) facilities reported having internet access on site, 15 (10.9 %) could access internet within the larger facility, and 19 (13.9 %) had internet available within 5 km of the facility. No data on internet capacity were reported for 59 (43.1 %) sites.

Table 5 describes the human resources characteristics reported by participating IeDEA facilities. The type and number of staff were provided for each day of the week. The number of full-time pharmacists and pharmacy assistants available on site ranged from 0 (e.g., if the facility was closed) to 32. The number of physicians available to assess events ranged from 0 to 30. Fewer

Table 5 Human resources available at included International epidemiologic Databases to Evaluate AIDS (IeDEA) facilities

Category and variables	West Africa ($n = 21$)	Southern Africa ($n = 19$)	East Africa ($n = 43$)	Central Africa ($n = 12$[a])	South America ($n = 7$)	Asia ($n = 28$[b])	North America ($n = 7$[c])	Total ($n = 137$)
Full time pharmacist	0–6	0–32	0–3	0–2	0–11	0–4	0–5	0–32
Missing	2 (9.5)	0 (0)	3 (7)	3 (25)	0 (0)	0 (0)	0 (0)	8 (5.8)
Pharmacy assistants	0–5	0–32	0–10	0–7	0–4	0–3	0–3	0–32
Missing	2 (9.5)	0 (0)	2 (4.7)	4 (33.3)	1 (14.3)	0 (0)	0 (0)	9 (6.6)
Physician to asses events	0–20	0–30	0–4	0–6	0–51	0–23	0–30	0–30
Missing	2 (9.5)	0 (0)	3 (7)	0 (0)	0 (0)	1 (3.6)	0 (0)	6 (4.4)
Data capturer	0–8	0–32	0–26	0–5	0–18	0–4	0–5	0–32
Missing	2 (9.5)	0 (0)	1 (2.3)	0 (0)	0 (0)	1 (3.6)	0 (0)	4 (2.9)

Data are presented as number per day and n (%)

[a] Central Africa has 15 facilities but no data were available for three facilities

[b] Asia–Pacific region has 29 facilities but no data were available for one facility

[c] North America has eight facilities but no data were available for one facility

physicians were available at facilities in Central Africa and the Caribbean and Central and South America. The number of individuals who were available to capture/record data ranged from 0 to 32, with Southern Africa (up to 32) and East Africa (up to 26) having the most individuals available. In general, fewer staff were available on Saturdays and Sundays (data not shown).

4 Discussion

Our goal in the present study was to explore facility characteristics that may enhance TSR for monitoring of ART and then use this list to begin to describe capacity at the facility level to report ADRs and perform TSR. To our knowledge, this is the first attempt to describe the current capacity of HIV care and treatment facilities to perform TSR for the purposes of routine pharmacovigilance activities. We found that there is minimal information about facility characteristics that may contribute to pharmacovigilance activities. This descriptive analysis can be viewed as a starting point given that we used our own expertise and experience with TSR, the literature, and the facility characteristics that are measured through IeDEA to begin the process of defining necessary facility-level characteristics.

The list of elements needed to enhance TSR can be updated and made more comprehensive over time. Our purpose in the present study was to leverage the facility-level data available from the 137 facilities participating in the IeDEA consortium to better understand the existing capacity for TSR in these facilities. Our primary finding was that many facilities have characteristics that can help in conducting TSR. With a few minor enhancements, particularly related to data collection specific to identifying and capturing ADRs, TSR could become a standard and routine component of facility activities in many of these programs. Importantly, while we focused on HIV in this manuscript, TSR is a method that can enhance reporting of adverse events involving other diseases, particularly those treated within discrete health settings such as a tuberculosis clinic.

Facility capacity for pharmacovigilance varied by the different elements explored. We found that, when data were available, approximately 50 % of facilities were already following key populations, including pregnant women and children, and also had an outreach program to ascertain outcomes for patients who missed visits. Following up key populations and having the capacity to ascertain their outcomes is important for developing and monitoring the safety profiles of antiretrovirals. The presence of an outreach program is critical for following up individuals who miss visits and capturing their outcomes. Importantly, side effects are a common reason for patients to stop taking their medications, and patients who experience severe ADRs may be more likely to drop out of care or die [37–41].

Laboratory monitoring varied across facilities and by test. Importantly, good laboratory capacity and turnaround times have previously been positively associated with retention in care [42, 43]. The availability and accessibility of laboratory monitoring is critical for identifying ADRs and supporting patient care. Fee-for-service laboratory tests and long turnaround times can negatively affect retention [44] and prevent clinicians from making timely identification of ADRs.

To conduct TSR, and pharmacovigilance more generally, several essential data elements are needed, although it is worth noting that different resources are needed for different drugs. While beyond the scope of this manuscript, a score that determines the number of facilities that are already ready to conduct TSR could be explored in a later analysis. In this study, the more essential elements were generally documented more often. Unique patient identifiers, one of the minimum requirements for pharmacovigilance, were reportedly used in the majority of sites. A relevant medical history is needed to understand any co-morbid conditions that can mask ART-associated ADRs or cause drug interactions with ART [7, 11, 13, 14]. It is worth noting that a full relevant medical history was captured universally only in North America. ADRs were routinely monitored in 88 % of sites and recorded in more than half of the sites; the outcome of the ADR was recorded in just under half of the sites, where information was recorded.

Although we did not directly address staff training in the identification and documenting of ADRs, this is an important part of TSR that requires consideration. The ability of facilities to identify and record ADRs largely depends on not only the capacity of the facilities but also on the availability of health staff. However, it is important to note that staffing likely reflects patient volume, which greatly differs between regions as well as between facilities within the same region. The findings showed that all regions had a full-time pharmacist, pharmacy assistants, physicians, and data capturers at least 1 day during the week. Most programs had trained staff at the facility every day except on weekends. High patient loads, little or no budget for pharmacovigilance activities, and a lack of incentives to report adverse events [26] may further hamper reporting in such settings. While education is essential, it is important to also consider the process and ease of reporting. If nothing in the system encourages or promotes pharmacovigilance, then the rate of reporting is likely to be low, especially when the prioritisation of other tasks is taken into consideration. A designated point person(s) for

pharmacovigilance within a facility is recommended to facilitate pharmacovigilance activities [11]. We found that the majority of facilities reported having some electronic database capacity, although linkage to pharmacy databases was less common. Given that globally/universally standardized definitions can be used to compare ADRs across facilities, programs, and settings, further harmonization between facilities and regions is needed [45].

Future studies should explore the willingness of facilities to increase their capacity for performing TSR and begin to identify and focus on organizational needs, including staffing, cost, and funding mechanisms that may help to support these activities. Note that, while several countries included in the present analysis do participate in the WHO Programme for International Drug Monitoring [46] and have national reporting systems, information on which programs report through these systems was not captured in the assessment and should be explored further in future analysis.

This study has numerous strengths, including its international scope as it included HIV care and treatment facilities from numerous regions around the world. Second, our comprehensive list of facility-level characteristics can be used to leverage the existing capacity of facilities to conduct TSR activities. The existing capacity does range, but we identified numerous opportunities for enhancements. Finally, the iterative process, in-depth literature review, and consultation with expert stakeholders helped identify all essential facility characteristics influencing pharmacovigilance. Limitations include reporting bias, particularly given that the assessment relied on self-reported data of facility services from HIV clinical providers at the individual sites. The responses were not validated, so clinic staff may have over-reported or under-reported certain characteristics. Indeed, there may be some variability between facilities and regions. For example, Southern Africa and NA-ACCORD only filled in subsets relevant to their programs due to logistical restrictions. We only assessed the availability of characteristics and did not assess actual access, use, or quality of services. These data are based on the 2009/2010 assessment, and facility capacity may have increased or decreased since then. For example, other than baseline CD4 and follow-up viral loads for those receiving ART, laboratory monitoring in some programs has been curtailed or become fee-for-service to patients as a result of both reduced donor spending on healthcare and national funding restrictions. Therefore, a patient needing a liver function test may now have to pay for it. This undermines the programs' capacity to conduct TSR because many patients may not be able to afford the test. Finally, our findings may not generalize to other HIV facilities not affiliated with IeDEA.

5 Conclusion

In the present study, we found that many facilities, including those in LMICs, appear to have resources in place to support TSR, including personnel to capture and record ADRs. While an identifiable patient, an event, a suspected drug, and an individual to capture the information [38, 39] are critical for conducting pharmacovigilance activities, we have highlighted additional factors, including the use of electronic monitoring systems, that can greatly enhance routine TSR. In addition to identifying the existing capacity of such programs, it is important to identify what program enhancements may be needed to improve pharmacovigilance activities. Both steps are critical to provide an avenue for conducting routine due diligence around drug safety for the millions of people receiving these life-saving medications over the long term. Therefore, our findings are a first step in assisting implementers and facility staff in identifying opportunities and leveraging their existing capacity to incorporate TSR into their routine clinical programs. Investment in the development of pharmacy databases and their linkage to electronic medical records may be key in facilitating routine ADR monitoring and reporting. While facilities should consider adopting these to increase their capacity for identifying and reporting ADRs, the feasibility and willingness of staff to adopt TSR requires consideration and further investigation. While the focus of this analysis was on IeDEA facilities providing HIV care, TSR can potentially enhance reporting of adverse events, including ADRs, in other non-HIV related programs and should be explored further.

Acknowledgments The contents of this journal article are the sole responsibility of AMPATH and do not necessarily reflect the views of the US Agency for International Development (USAID) or the US Government.

The authors would like to thank the following programs, site investigators, and data managers who contributed data to this study and made this analysis possible.

The IeDEA East Africa region

Tanzania: Rita Lyamuya (principal investigator [PI]), Mayanga Francis Mbaula Morogoro (data manager), Emanuel Lugina, Rebecca Mtiko—Ocean Road Cancer Institute (ORCI); Kapella Ngonyani, Jerome Lwali—Tumbi Regional Hospital; Geoffery Somi—National AIDS Control Program (NACP); Mark Urassa, Denna Mkwashapi, Richard Machemba—National Institute for Medical Research (NIMR)/Kisesa.

Uganda: John Ssali (PI), Matthew Ssemakadde (data manager)—Masaka Regional Referral Hospital; Mwebesa Bwana, Michael Kanyesigye—Mbarara University of Science and Technology (MUST) ISS Clinic; Andrew D. Kambugu, Barbara Castelnuovo, Richard Orama—Infectious Diseases Institute, Makerere; Fred Nalugoda, Francis Wasswa—Rakai Health Sciences Program.

Kenya: AMPATH PIs: Samuel Ayaya, Lameck Diero; **AMPATH site contact persons, data managers/assistants:** Emma Mboya, Clinical Officer Incharge—Chulaimbo Clinic; Paula Braitstein, Regional Director—IeDEA East Africa; Edwin Sang, Senior Data Manager—AMPATH, IeDEA East Africa; Janet Chebet, Clinical

Officer Incharge—Mt Elgon Clinic; Francis Chelobei, Clinical Officer Incharge—Kabarnet Clinic; Maiyo Josphat, Clinical Officer Incharge—Iten Clinic; Patrick Ariya, Clinical Officer Incharge—Teso Clinic; Jentrix Namaemba, Clinical Officer Incharge—Webuye Clinic; Consolata Munyisi, Clinical Officer Incharge—Khunyangu Clinic; Rachel Ototo, Clinical Officer Incharge—Turbo Clinic; Kaibei Caroline, Clinical Officer Incharge—Amukura Clinic; Oscar Busaka, Clinical Officer Incharge, Lynn Mildred Bett, Data Assistant—Busia Clinic; Lilian Simatwa, Clinical Officer Incharge—Uasin Gishu District Hospital (UGDH) Clinic; Some Hosea, Clinical Officer Incharge, Wamboi Nancy, data assistant—Burnt Forest Clinic; Lilian Boit, Clinical Officer Incharge, James Biyegon, data assistant—Mosoriot Clinic; Chege Peter, Clinical Officer Incharge—Kitale Clinic; Moses Paron, Clinical Officer Incharge—Kapenguria Clinic; Susan Nandi, Clinical Officer Incharge—Port Victoria; Kivairo Ngadi Wycliffe, Clinical Officer Incharge—Naitiri.

FACES (KEMRI)—PI: Elizabeth Bukusi, Walter Mukhwana, Julius Koech, Edwin Wasing'a, Evelyne Owengah—Lumumba Health Centre; David Oyuko Ndiege—Macalder District Hospital; John Owiti—Mbita District Hospital; Jayne Kulzer, Erick N. Juma—Kisumu District Hospital.

The IeDEA Central Africa region (2006–2011)

Wilfred Akam, Esperance Urayeneza, Rose Uwingabiye, Kumbu Modeste, Wibina Patou, Ebondo Coucou, Kumbu Kassamina, Marie-Agnès Mpukela, Kambale Mafutaming, Nadine Munyungu, Jean Kabwe, Marcel Mbaya, Sylvie Lufindusu, Ashu Balimba, Bokeng Susan, Brigitte Mfangam Molu, Bongason Blessing, Théodore Niyongabo, Emmanuel Nindagiye, Cyrille Dusengamungu, Marcel Manariyo.

The IeDEA West Africa Collaboration Study Group, Participating Sites (members of the *Steering Committee, §Executive Committee)

Cotonou, Benin

Adults: Djimon Marcel Zannou*, Carin Ahouada, Jocelyn Akakpo, Christelle Ahomadegbé, Jules Bashi, Alice Gougounon-Houéto, Angèle Azon-Kouanou, Fabien Houngbé, Jean Sehonou—Centre National Hospitalier Universitaire (CNHU) Hubert Maga.

Pediatrics: Sikiratou Koumakpaï*§, Florence Alihonou, Marcelline d'Almeida, Irvine Hodonou, Ghislaine Hounhoui, Gracien Sagbo, Leïla Tossa-Bagnan, Herman Adjide (CNHU Hubert Maga).

Burkina Faso

Adults: Joseph Drabo*, René Bognounou, Arnaud Dienderé, Eliezer Traore, Lassane Zoungrana, Béatrice Zerbo—CHU Yalgado, Ouagadougou; Adrien Bruno Sawadogo*§, Jacques Zoungrana, Arsène Héma, Ibrahim Soré, Guillaume Bado, Achille Tapsoba—CHU Souro Sanou, Bobo Dioulasso.

Pediatrics: Diarra Yé*, Fla Kouéta, Sylvie Ouedraogo, Rasmata Ouédraogo, William Hiembo, Mady Gansonré—CH Charles de Gaulle, Ouagadougou.

Côte d'Ivoire, Abidjan

Adults: Eugène Messou*, Joachim Charles Gnokoro, Mamadou Koné, Guillaume Martial Kouakou—ACONDA-CePReF; Clarisse Amani Bosse*, Kouakou Brou, Achi Isidore Assi—ACONDA-MTCT-Plus; Henri Chenal*, Denise Hawerlander, Franck Soppi—CIRBA; Albert Minga*, Yao Abo, Jean-Michel Yoboue—CMSDS/CNTS; Aristophane Koffi Tanon*§, Mensah Deborah Noelly Amego, Viviane Andavi, Zelica Diallo, Frédéric Ello—SMIT, CHU de Treichville; Serge Olivier Koule*, Koffi Charles Anzan, Calixte Guehi—USAC, CHU de Treichville.

Pediatrics: Marie-Sylvie N'Gbeche*, Edmond Addi Aka, Koffi Ladji Issouf, Jean-Claude Kouakou—ACONDA-CePReF; Touré Pety*, Divine Avit-Edi—ACONDA-MTCT-Plus; Kouadio Kouakou*, Magloire Moh, Valérie Andoblé Yao—CIRBA; Madeleine Amorissani Folquet*, Marie-Evelyne Dainguy, Cyrille Kouakou, Véronique Tanoh Méa-Assande, Gladys Oka-Berete, Nathalie Zobo, Patrick Acquah, Marie-Berthe Kokora—CHU Cocody; Tanoh François Eboua*, Marguerite Timité-Konan, Lucrèce Diecket Ahoussou, Julie Kebé Assouan, Mabéa Flora Sami, Clémence Kouadio—CHU Yopougon.

Ghana, Accra

Pediatrics: Lorna Renner*§, Bamenla Goka, Jennifer Welbeck, Adziri Sackey, Seth Ntiri Owiafe—Korle Bu TH.

Guinea-Bissau

Adults: Christian Wejse*§, Zacarias José Da Silva*, Joao Paulo—Bandim Health Project. The Bissau HIV cohort study group: Amabelia Rodrigues—Bandim Health Project; David da Silva—National HIV program Bissau; Candida Medina—Hospital National Simao Mendes, Bissau; Ines Oliviera-Souto—Bandim Health Project; Lars Østergaard, Alex Laursen—Department of Infectious Diseases, Aarhus University Hospital; Morten Sodemann—Department of Infectious Diseases, Odense University Hospital; Peter Aaby—Bandim Health Project; Anders Fomsgaard—Department of Virology, Statens Serum Institut, Copenhagen; Christian Erikstrup—Department of Clinical Immunology; Jesper Eugen-Olsen—Department of Infectious Diseases, Hvidovre Hospital, Copenhagen.

Guinea

Adults: David Leuenberger*, Jean Hebelamou§—Centre Medical Macenta.

Mali, Bamako

Adults: Moussa Y Maïga*§, Fatoumata Fofana Diakité, Abdoulaye Kalle, Drissa Katile—CH Gabriel Toure; Hamar Alassane Traore*, Daouda Minta*, Tidiani Cissé, Mamadou Dembelé, Mohammed Doumbia, Mahamadou Fomba, Assétou Soukho Kaya, Abdoulaye M Traoré, Hamady Traoré, Amadou Abathina Toure—CH Point G.

Pediatrics: Fatoumata Dicko*, Mariam Sylla, Alima Berthé, Hadizatou Coulibaly Traoré, Anta Koïta, Niaboula Koné, Clémentine N'Diaye, Safiatou Touré Coulibaly, Mamadou Traoré, Naïchata Traoré—CH Gabriel Toure.

Nigeria

Adults: Man Charurat*—UMB/IHV; Vivian Kwaghe*§, Samuel Ajayi, Georgina Alim, Stephen Dapiap, Otu—UATH, Abuja; Okwara Benson*, Clément Adebamowo*, Jesse James, Obaseki, Philip Osakede—UBTH, Benin City.

Senegal, Dakar

Adults: Moussa Seydi*§, Papa Salif Sow, Bernard Diop, Noël Magloire Manga, Judicael Malick Tine§, Coumba Cissé Bassabi—SMIT, CHU Fann.

Pediatrics: Haby Signate Sy*, Abou Ba, Aida Diagne, Hélène Dior, Malick Faye, Ramatoulaye Diagne Gueye, Aminata Diack Mbaye—CH Albert Royer.

Togo, Lomé

Adults: Akessiwe Patassi*§, Awèrou Kotosso, Benjamin Goilibe Kariyare, Gafarou Gbadamassi, Agbo Komi, Kankoé Edem Mensah-Zukong, Pinuwe Pakpame—CHU Tokoin/Sylvanus Olympio.

Pediatrics: Elom Takassi*§, Yawo Atakouma, Améyo Djeha, Ayoko Ephoévi-gah, Sherifa El-Hadj Djibril—CHU Tokoin/Sylvanus Olympio.

Executive Committee: François Dabis (PI), Bordeaux, France; Emmanuel Bissagnene (co-PI), Abidjan, Côte d'Ivoire; Elise Arrivé, Bordeaux, France; Patrick Coffie, Abidjan, Côte d'Ivoire; Nathalie de Rekeneire, Bordeaux, France; Didier Ekouevi, Abidjan, Côte d'Ivoire; Antoine Jaquet, Bordeaux, France; Valériane Leroy, Bordeaux, France; Annie J. Sasco, Bordeaux, France.

Operational and Statistical Team: Jean-Claude Azani, Abidjan, Côte d'Ivoire; Eric Balestre, Bordeaux, France; Richard Castaing, Bordeaux, France; Caroline Coulibaly, Abidjan, Côte d'Ivoire; Sophie Karcher, Bordeaux, France; Jérôme Le Carrou, Bordeaux, France; Karen Malateste, Bordeaux, France.

Administrative Team: Abdoulaye Cissé, Abidjan, Côte d'Ivoire; Alexandra Doring§, Bordeaux, France; Adrienne Kouakou, Abidjan, Côte d'Ivoire; Guy Gneppa, Abidjan, Côte d'Ivoire; Elodie Rabourdin, Bordeaux, France; Jean Rivenc, Pessac, France.

Consultants/working groups: Xavier Anglaret, Bordeaux, France; Boubacar Ba, Bamako, Mali; Renaud Becquet, Bordeaux, France; Juan Burgos Soto, Bordeaux, France; Jean Bosco Essanin, Abidjan; Andrea Ciaranello, Boston, USA; Sébastien Datté, Abidjan, Côte d'Ivoire; Sophie Desmonde, Bordeaux, France; Jean-Serge Elvis Diby, Abidjan, Côte d'Ivoire; Geoffrey S. Gottlieb*, Seattle, USA; Apollinaire Gninlgninrin Horo, Abidjan, Côte d'Ivoire; Julie Jesson, Bordeaux, France; Serge N'zoré Kangah, Abidjan, Côte d'Ivoire; David Meless, Abidjan, Côte d'Ivoire; Aida Mounkaila-Harouna, Bordeaux, France; Camille Ndondoki, Bordeaux, France; Caroline Shiboski, San Francisco, USA; Boris Tchounga, Abidjan, Côte d'Ivoire; Rodolphe Thiébaut, Bordeaux, France; Gilles Wandeler, Dakar, Senegal.

Coordinating Centre: ISPED, Univ Bordeaux, Bordeaux, France. **Regional Office:** PAC-CI, Abidjan, Côte d'Ivoire. **Methodologic Support:** MEREVA, Bordeaux, France. **Website:** http://www.mereva.net/iedea.

The IeDEA Southern Africa Region

We thank all the staff at participating IeDEA-SA sites for completing the site assessment and contributing to the IeDEA-SA collaboration. Thanks to the IeDEA-SA Data Centre teams at the Universities of Cape Town (Mary-Ann Davies [PI], Andrew Boulle, Morna Cornell, Leigh Johnson, Nicky Maxwell, Michael Schomaker, Jolly-Ann Maulit) and Bern (Matthias Egger [PI], Marie Ballif, Julia Bohlius, Cam Ha Dao Ostinelli, Lukas Fenner, Kelly Goodwin, Olivia Keiser, Justine Locher, Gilles Wandeler).

IeDEA-SA Steering Group: Frank Tanser—Africa Centre for Health and Population Studies, University of Kwazulu-Natal, Somkhele, South Africa; Christopher Hoffmann—Aurum Institute for Health Research, Johannesburg, South Africa; Michael Vinikoor—Centre for Infectious Disease Research in Zambia, Lusaka, Zambia; Denise Naniche—Centro de Investigação em Saúde de Manhiça, Manhiça, Mozambique; Robin Wood—Desmond Tutu HIV Centre (Gugulethu and Masiphumelele clinics), Cape Town, South Africa; Kathryn Stinson—Khayelitsha ART Programme and Médecins Sans Frontières, Cape Town, South Africa; Geoffrey Fatti—Kheth'Impilo Programme, South Africa; Sam Phiri—Lighthouse Trust Clinic, Lilongwe, Malawi; Janet Giddy—McCord Hospital, Durban, South Africa; Cleophas Chimbetete—Newlands Clinic, Harare, Zimbabwe; Kennedy Malista—Queen Elizabeth Hospital, Blantyre, Malawi; Brian Eley—Red Cross War Memorial Children's Hospital and Department of Paediatrics and Child Health, University of Cape Town, Cape Town, South Africa; Olatunbosun Faturiyele—SolidarMed SMART Programme, Lesotho; Michael Hobbins—SolidarMed SMART Programme, Pemba Region, Mozambique; Kamelia Kamenova—SolidarMed SMART Programme, Masvingo, Zimbabwe; Matthew Fox—Themba Lethu Clinic, Johannesburg, South Africa; Hans Prozesky—Tygerberg Academic Hospital, Stellenbosch, South Africa; Karl Technau—Empilweni Clinic, Rahima Moosa Mother and Child Hospital, Johannesburg, South Africa; Shobna Sawry—Harriet Shezi Children's Clinic, Chris Hani Baragwanath Hospital, Soweto, South Africa.

The IeDEA Asia–Pacific Region

The TREAT Asia HIV Observational Database (TAHOD): PS Ly*, V Khol—National Center for HIV/AIDS, Dermatology & STDs, Phnom Penh, Cambodia; FJ Zhang*, HX Zhao, N Han—Beijing Ditan Hospital, Capital Medical University, Beijing, China; MP Lee*†, PCK Li, W Lam, YT Chan—Queen Elizabeth Hospital, Hong Kong, China; S Pujari*, K Joshi, S Gaikwad, A Chitalikar—Institute of Infectious Diseases, Pune, India; TP Merati*, DN Wirawan, F Yuliana—Faculty of Medicine Udayana University & Sanglah Hospital, Bali, Indonesia; E Yunihastuti*, D Imran, A Widhani—Working Group on AIDS Faculty of Medicine, University of Indonesia/Cipto Mangunkusumo Hospital, Jakarta, Indonesia; S Oka*, J Tanuma, T Nishijima—National Center for Global Health and Medicine, Tokyo, Japan; A Kamarulzaman*, SF Syed Omar, S Ponnampalavanar, I Azwa—University Malaya Medical Centre, Kuala Lumpur, Malaysia; BLH Sim*, YM Gani, R David—Hospital Sungai Buloh, Sungai Buloh, Malaysia; R Ditangco*, E Uy, R Bantique—Research Institute for Tropical Medicine, Manila, Philippines; WW Wong*‡, WW Ku, PC Wu—Taipei Veterans General Hospital, Taipei, Taiwan; R Chaiwarith*, T Sirisanthana, W Kotarathititum, J Praparattanapan—Research Institute for Health Sciences, Chiang Mai, Thailand; P Phanuphak*, K Ruxrungtham, A Avihingsanon, C Phadungphon—HIV-NAT/Thai Red Cross AIDS Research Centre, Bangkok, Thailand; S Kiertiburanakul*, S Sungkanuparph, L Chumla, N Sanmeema—Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; OT Ng*, PL Lim, LS Lee, R Martinez-Vega—Tan Tock Seng Hospital, Singapore; JY Choi*, Na S, JM Kim—Division of Infectious Diseases, Department of Internal Medicine, Yonsei University College of Medicine, Sl, South Korea; AH Sohn*, N Durier*, B Petersen—TREAT Asia, amfAR—The Foundation for AIDS Research, Bangkok, Thailand; DA Cooper, MG Law*, A Jiamsakul*, DC Boettiger—The Kirby Institute, UNSW Australia, Sydney, Australia (*TAHOD Steering Committee member; †Steering Committee Chair; ‡ co-Chair).

Australian HIV Observational Database (AHOD): J Hoy*, K Watson*, M Bryant, S Price—The Alfred Hospital, Melbourne, South Australia; M O'Sullivan, S White—Gold Coast Sexual Health Clinic, Miami, Queensland, Australia; DJ Templeton*†, CC O'Connor, S Phan—RPA Sexual Health Clinic, Camperdown, New South Wales, Australia; D Cooper, A Carr, F Lee, K Hesse, K Sinn, R Norris—St Vincent's Hospital, Darlinghurst, New South Wales, Australia (*AHOD Steering Committee member; †Steering Committee Chair).

TREAT Asia Pediatric HIV Observational Database (TApHOD): PS Ly*, V Khol—National Center for HIV/AIDS, Dermatology & STDs, Phnom Penh, Cambodia; N Kurniati*, D Muktiarti—Cipto Mangunkusumo General Hospital, Jakarta, Indonesia; SM Fong*†, M Thien, M Lim, F Daut—Hospital Likas, Kota Kinabalu, Malaysia; NK Nik Yusoff*, P Mohamad—Hospital Raja Perempuan Zainab II, Kelantan, Malaysia; KA Razali*, TJ Mohamed, NF Abdul Rahman, NADR Mohammed—Pediatric Institute, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia; T Sudjaritruk*, V Sirisanthana, L Aurpibul, P Oberdorfer—Department of Pediatrics, Faculty of Medicine, Chiang Mai University and Research Institute for Health Sciences, Chiang Mai, Thailand; R Hansudewechakul*, S Denjanta, W Srisuk, A Kongphonoi—Chiangrai Prachanukroh Hospital, Chiang Rai, Thailand; P Lumbiganon*‡, P Kosalaraksa, P Tharnprisan, T Udomphanit—Division of Infectious Diseases, Department of Pediatrics, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand; K Chokephaibulkit*, K Lapphra, W Phongsamart, S Sricharoenchai—Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (*TApHOD Steering Committee member; †Steering Committee Chair; ‡Co-Chair).

IeDEA Caribbean, Central, and South America (CCASAnet): Catherine C McGowan, Daniel R Masys, Brenda Minor, Firas Wehbe, Pedro Cahn, Alejandro Krolewiecki, Carina Cesar, Mauro Schechter, Jose Claudio Faulhaber, Marcelo Wolff, Claudia Cortes, Jean W Pape, Adias Marcelin, Denis Padgett, Juan Sierra-Madero, Yanink Caro Vega, Eduardo Gotuzzo.

North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD): We wish to thank all of our NA-ACCORD collaborators that assisted with the site survey data collection. **NA-ACCORD Collaborating Cohorts and Representatives**: **AIDS Link to the IntraVenous Experience:** Gregory D Kirk. **Adult AIDS Clinical Trials Group Longitudinal Linked Randomized Trials:** Constance A Benson and Ronald J. Bosch. **Fenway Health HIV Cohort:** Stephen Boswell, Kenneth H Mayer, and Chris Grasso. **HAART Observational Medical Evaluation and Research:** Robert S Hogg, P Richard Harrigan, Julio SG Montaner, Angela Cescon, and Hasina Samji.

HIV Outpatient Study: John T Brooks and Kate Buchacz. **HIV Research Network:** Kelly A Gebo and Richard D Moore. **Johns Hopkins HIV Clinical Cohort:** Richard D Moore. **John T. Carey Special Immunology Unit Patient Care and Research Database, Case Western Reserve University:** Benigno Rodriguez. **Kaiser Permanente Mid-Atlantic States:** Michael A Horberg. **Kaiser Permanente Northern California:** Michael J Silverberg. **Longitudinal Study of Ocular Complications of AIDS:** Jennifer E Thorne. **Multicenter Hemophilia Cohort Study–II:** James J Goedert.
Multicenter AIDS Cohort Study: Lisa P Jacobsonc and Gypsyamber D'Souza.
Montreal Chest Institute Immunodeficiency Service Cohort: Marina B Klein.
Ontario HIV Treatment Network Cohort Study: Sean B Rourke, Ann N Burchell, and Anita R. Rachlis. **Retrovirus Research Center, Bayamon Puerto Rico:** Robert F Hunter-Mellado and Angel M Mayor. **Southern Alberta Clinic Cohort:** M John Gill. **Studies of the Consequences of the Protease Inhibitor Era:** Steven G Deeks and Jeffrey N Martin. **Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy:** Pragna Patel, John T Brooks. **University of Alabama at Birmingham 1917 Clinic Cohort:** Michael S Saag, Michael J Mugavero, and James Willig. **University of North Carolina at Chapel Hill HIV Clinic Cohort:** Joseph J Eron and Sonia Napravnik. **University of Washington HIV Cohort:** Mari M Kitahata, Heidi M Crane, and Daniel R Drozd. **Vanderbilt Comprehensive Care Clinic HIV Cohort:** Timothy R Sterling, David Haas, Sally Bebawy, and Megan Turner. **Veterans Aging Cohort Study:** Amy C Justice, Robert Dubrow, and David Fiellin. **Women's Interagency HIV Study:** Stephen J Gange and Kathryn Anastos.
NA-ACCORD Study Administration
Executive Committee: Richard D Moore, Michael S Saag, Stephen J Gange, Mari M Kitahata, Keri N Althoff, Rosemary G McKaig, Amy C Justice, and Aimee M Freeman. **Administrative Core:** Richard D Moore, Aimee M Freeman, and Carol Lent.
Data Management Core: Mari M Kitahata, Stephen E Van Rompaey, Heidi M Crane, Daniel R Drozd, Liz Morton, Justin McReynolds, and William B Lober.
Epidemiology and Biostatistics Core: Stephen J Gange, Keri N Althoff, Alison G Abraham, Bryan Lau, Jinbing Zhang, Jerry Jing, Elizabeth Golub, Shari Modur, Cherise Wong, Brenna Hogan, Weiqun Tong, Bin You, and Bin Liu.
Compliance with Ethical Standards
Funding Research reported in this publication was supported by the National Institute of Allergy and Infectious Diseases, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and the National Cancer Institute of the National Institutes of Health under the following award numbers as part of the IeDEA consortium: Caribbean, Central, and South America: U01AI069923; Asia–Pacific: U01AI069907; Central Africa: U01A096299; East Africa: U01AI069911; Southern Africa: U01AI069924; West Africa: U01AI069919; and NA-ACCORD: U01AI069918. NA-ACCORD contribution to this work was also supported by grants F31DA037788, G12MD007583, K01AI093197, K23EY013707, K24DA000432, K24AI065298, KL2TR000421, M01RR000052, N02CP055504, P30AI027757, P30AI027763, P30AI027767, P30AI036219, P30AI050410, P30AI094189, P30AI110527, P30MH62246, R01AA016893, R01CA165937, R01DA004334, R01DA011602, R01DA012568, R24AI067039, U01AA013566, U01AA020790, U01AI031834, U01AI034989, U01AI034993, U01AI034994, U01AI035004, U01AI035039, U01AI035040, U01AI035041, U01AI035042, U01AI037613, U01AI037984, U01AI038855, U01AI038858, U01AI042590, U01AI068634, U01AI068636, U01AI069432, U01AI069434, U01AI103390, U01AI103397, U01AI103401, U01AI103408, U01DA036935, U01HD032632, U10EY008057, U10EY008052, U10EY008067, U24AA020794,U54MD007587, UL1RR024131, UL1TR000004, UL1TR000083, UL1TR000454, UM1AI035043, Z01CP010214 and Z01CP010176; contracts CDC-200-2006-18797 and CDC-200-2015-63931 from the Centers for Disease Control and Prevention, USA; contract 90047713 from the Agency for Healthcare Research and Quality, USA; contract 90051652 from the Health Resources and Services Administration, USA; grants CBR-86906, CBR-94036, HCP-97105, and TGF-96118 from the Canadian Institutes of Health Research, Canada; Ontario Ministry of Health and Long Term Care; and the Government of Alberta, Canada. Additional support was provided by the Intramural Research Program of the National Cancer Institute. IeDEA Asia–Pacific received additional funding from the Dutch Ministry of Foreign Affairs through a partnership with Stichting AIDS Fonds, and from the Australian Government Department of Health and Ageing. REDCap support was provided through Vanderbilt University and UL1 TR000445 from NCATS/NIH. The content is solely the responsibility of the authors and does not necessarily represent the official views of governments or institutions mentioned above. This research has been supported by the President's Emergency Plan for AIDS Relief (PEPFAR) through USAID under the terms of Cooperative Agreement No. AID-623-A-12-0001. It is made possible through joint support of the USAID.
Conflict of interest Beth Rachlis, Rakhi Karwa, Celia Chema, Sonak Pastakia, Sten Olsson, Beatrice Jakait, Mercy Maina, Nagalingeswaran Kumarsamy, Stephany N Duda, Mary-Ann Davies, and Paula Braitstein have no conflicts of interest that are directly relevant to the content of this study. Kara Wools-Kaloustian, Marcel Yotebieng, Aimee Freeman, and Nathalie de Rekeneire hold NIH grants that directly support content of the work presented (See the Funding section for Grant Numbers).

References

1. Barnighausen T, Bloom DE, Humair S. Human resources for treating HIV/AIDS: needs, capacities and gaps. AIDS Patient Care STDS. 2007;21:799–812.
2. World Health Organization (WHO), International HIV/AIDS Alliance, and PharmAccess International. A public health approach for scaling up antiretroviral therapy (ARV) treatment: a toolkit for programme planners. 2003. http://www.who.int/hiv/pub/prev_care/arvtoolkit_en.pdf. Accessed 14 Oct 2014.
3. Mamlin BW, Biondich PG. AMPATH Medical Record System (AMRS): collaborating toward an EMR for developing countries. AMIA Annu Symp Proc. 2005; 490–4.
4. World Health Organization (WHO). HIV/AIDS Fact Sheet Number 360, 2015. http://www.who.int/mediacentre/factosheets/fs360/en/. Accessed 2 Nov 2015.
5. Bakare N, Edwards IR, Stergachis A, Pal S, Holmes CB, Lindquist M, Duncombe C, Dodoo A, Novendstern J, Nwokike J, Kuchenbecker R, Aberg JA, Miller V, Strobos J. Global pharmacovigilance for antiretroviral drugs: overcoming contrasting priorities. PLoS Med. 2011;8:e1001054.
6. Marcus KA, Sorbello A, Truffa M, Williams J, Raine JM, Powderly WG. Current advances in pharmacovigilance in the USA

and Europe: meeting the challenges of safety monitoring in HIV. Curr Opin HIV AIDS. 2012;7:292–8.
7. Boulle A, Orrel C, Kaplan R, Van Cutsem G, McNally M, Hilderbrand K, Myer L, Egger M, Coetzee D, Maartens G. Wood R; International Epidemiological Databases to Evaluate AIDS in Southern Africa Collaboration. Substitutions due to antiretroviral toxicity or contraindication in the first 3 years of antiretroviral therapy in a large South African cohort. Antivir Ther. 2007;12:753–60.
8. Braitstein P, Ayuo P, Mwangi A, Wools-Kaloustian K, Musick B, Siika A, Kimaiyo S. Sustainability of first-line antiretroviral regimens: findings from a large HIV treatment program in western Kenya. J Acquir Immune Defic Syndr. 2010;53:254–9.
9. Miller V, Nwokike J, Stergachis A. Pharmacovigilance and global HIV/AIDS. Curr Opin HIV AIDS. 2012;7:299–304.
10. Jaquet A, Djima MM, Coffie P, Kacou HD, Eholie SP, Messou E, Minga A, Guehi C, Yavo JC, Bissagnene E, Dabis F. Ekouevi DK; IeDEA West Africa Collaboration. Pharmacovigilance for antiretroviral drugs in Africa: lessons from a study in Abidjan, Cote D'Ivoire. Pharmacoepidemiol Drug Saf. 2011;20:1303–10.
11. World Health Organization. A practical handbook on the pharmacovigilance of antiretroviral medicines. 2009. http://www.who.int/hiv/topics/pharmacovigilance/arv_pharmacovigilance_handbook.pdf. Accessed 11 Nov 2014.
12. Fernandez-Montero JV, Eugenia E, Barreiro P, Labarga P, Sorinano V. Antiretroviral drug-related toxicities- clinical spectrum, prevention, and management. Expert Opin Drug Saf. 2013;12:697–707.
13. Eholie SP. Eba Aoussi F, Songda Ouattara I, Bissagnene E, Anglaret X. HIV treatment and care in resource-constrained environments: challenges for the next decade. J Int AIDS Soc. 2012;15:17734.
14. Mehta S, Vazquez E. Do your meds play well with others? A guide to HIV drug interactions. Posit Aware. 2011;23:52–5.
15. Ssali F, Stohr W, Munderi P, Reid A, Walker AS, Gibb DM, Mugyenyi P, Kityo C, Grosskurth H, Hakim J, Byakwaga H, Katabira E, Darbyshire JH. Gilks CF; DART Trial Team. Prevalence, incidence and predictors of severe anADRmia with zidovudine-containing regimens in African adults with HIV infection within the DART trial. Antivir Ther. 2006;11:741–9.
16. Kigen G, Kimayo S, Nyandiko W, Faragher B, Sang E, Jakait B, Owen A, Back D, Gibbons S, Seden K, Khoo SH. Prevalence of potential drug-drug interactions involving antiretroviral drugs in a large Kenyan cohort. PLoS One. 2011;6:e16800.
17. World Health Organization. The importance of pharmacovigilance safety monitoring of medicinal products. 2002. http://apps.who.int/medicinedocs/pdf/s4893e/s4893e.pdf. Accessed 1 Dec 2014.
18. Agu KA, Oparah AC, Ochie UM. Improving monitoring and reporting of adverse drug reactions (ADRs) in HIV-positive patients on antiretroviral therapy (ART) in Nigeria. J Basic Clin Pharm. 2012;3:299–313.
19. Hazell L, Shaki SA. Under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2006;29:38506.
20. Pal SN, Duncombe C, Falzon D, Olsson S. WHO strategy for collecting safety data in public health programmes: complementary spontaneous reporting systems. Drug Saf. 2013;36:75–81.
21. The Global Fund to Fight AIDS, Tuberculosis, and Malaria, World Health Organization: Minimum requirements for a functional pharmacovigilance system. 2011. http://www.who.int/medicines/areas/quality_safety/safety_efficacy/PV_Minimum_Requirements_2010_2.pdf. Accessed 12 Oct 2014.
22. World Health Organization. Pharmacovigilance indicators: a practical manual for the assessment of pharmacovigilance systems. 2015. https://www.who.int/medicines/areas/quality_safety/safety_efficacy/EMP_PV_Indicators_web_ready_v2.pdf?ua = 1. Accessed 3 Mar 2015.
23. Okezie EO, Olufumilayo F. Adverse drug reactions reporting by physicians in Ibadan, Nigeria. Pharmacoepidemiol Drug Saf. 2008;17:517–22.
24. Koza S, Madungwe I, Nyambayo F, Mthethwa J, Chikuni O. Adverse drug reactions reporting at a referral hospital in Zimbabwe. Cent Afr J Med. 2004;50(11–12):104–7.
25. Sevene E, Mariano A, Mehta U, Machai M, Dodoo A, Vilardell D, Patel S, Barnes K, Carne X. Spontaneous adverse drug reaction reporting in a rural district in Mozambique. Drug Saf. 2008;31:867–76.
26. Olsson S, Pal SN, Stergachis A, Couper M. Pharmacovigilance activities in 55 low- and middle-income countries: a questionnaire-based analysis. Drug Saf. 2010;33:689–703.
27. Zhou J, Jaquet A, Bissagnene E, Musick B, Wools-Kaloustian K, Maxwell N, Boulle A, Wehbe F, Masys D, Iriondo-Perez J, Hemingway-foday J, Law M, for the western Africa, east Africa, southern Africa, Caribbean and central and South America, and Asia Pacific regions of the International epidemiologic Datbases to Evaluate AIDS (IeDEA). Short-term risk of anaemia following initiation of combination antiretroviral treatment in HIV-infected patients in countries in sub-Saharan Africa, Asia-Pacific, and central and South America. J Int AIDS Soc. 2012;15:5.
28. Ndagije H, Nambasa V, Namagala E, Nassali H, Kajungu D, Sematiko G, Olsson S, Pal S. Targeted spontaneous reporting of suspected renal toxicity in patients undergoing highly active antiretroviral therapy in two public health facilities in Uganda. Drug Saf. 2015;38(4):395–408.
29. Egger M, Ekouevi DK, Williams C, Lyamuya RE, Mukumbi H, Braitstein P, Hartwell T, Graber C, Chi BH, Boulle A, Dabis F, Wools-Kaloustian K. Cohort profile: The international epidemiological databases to evaluate AIDS (IeDEA) in sub-Saharan Africa. Int J Epidemiol. 2012;41:1256–64.
30. Duda SN, Farr AM, Lindegren ML, Blevins M, William Wester C, Wools-Kaloustian K, Ekouevi DK, Egger M, Hemingway-Foday J, Cooper DA, Moore RD, McGowan CC, Nash D, and the International Epidemiologic Databases to Evaluate AIDS (IeDEA) Collaboration. Characteristics and comprehensiveness of adult HIV care and treatment programmes in Asia-Pacific, sub-Saharan Africa, and the Americas: results of a site assessment conducted by the International epidemiologic Databases to Evaluate AIDS (IeDEA) Collaboration. J Acquir Immune Defic Syndr. 2014;17:19045.
31. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42:377–81.
32. Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring. Safety monitoring of medicinal products: Guidelines for setting up and running a pharmacovigilance centre. Geneva: UMC, 2000. http://apps.who.int/medicinedocs/en/d/Jh2934e/. Accessed 20 February 2015.
33. World Health Organization. Pharmacovigilance for antiretrovirals in resource-poor countries. Geneva: WHO, 2007. http://www.who.int/medicines/publications/PhV_for_antiretrovirals.pdf. Accessed 2 October 2015.
34. World Health Organization. A practical handbook on the pharmacovigilance of antimalarial medicines. Geneva: WHO, 2008. http://www.who.int/malaria/publications/atoz/malaria-pharmavigil.pdf?ua=1. Accessed 2 March 2016.
35. World Health Organization. A practical handbook on the pharmacovigilance of medicines used in the treatment of tuberculosis: Enhancing the safety of the TB patient. Geneva: WHO, 2012. http://www.who.int/medicines/publications/Pharmaco_TB_web_v3.pdf?ua=1. Accessed 2 Mar 2016.

36. Uppsala Monitoring Centre. The use of the WHO-UMC system for standardized case causality assessment. who-umc.org/Graphics/24734.pdf. Accessed 2 Mar 2016.
37. Brinkhof MW, Pujades-Rodriguez M, Egger M. Mortality of patients lost to follow-up in antiretroviral treatment programmes in resource-limited settings: systematic review and meta-analysis. PLoS One. 2009;4:e5790.
38. Egger M, Spycher BD, Sidle J, Weigel R, Geng EH, Fox MP, MacPhail P, van Custem G, Messou E, Wood R, Nash D, Pascoe M, Dickinson D, Etard JF, McIntyre JA, Brinkhof MWG and the IeDEA East Africa, West Africa and Southern Africa. Correcting mortality for loss to follow-up: a nomogram applied to antiretroviral treatment programmes in sub-Saharan Africa. PLoS Med. 2011;8:e1000390.
39. Geng EH, Emenyonu N, Bwana MB, Glidden DV, Martin JN. A sampling-based approach to determine outcomes of patients lost to follow-up in antiretroviral therapy scale-up programs in Africa. JAMA. 2008;300:506–7.
40. McMahon JH, Elliot JH, Hong SY, Bertagnolio S, Jordan MR. Effects of physical tracing on estimates of loss to follow-up, mortality and retention in low and middle income country antiretroviral therapy programs: a systematic review. PLoS One. 2013;8:e56047.
41. Yiannoustos CT, An MW, Frangakis CE, Musick BS, Braitstein P, Wools-Kaloustian K, Ochieng D, Martin JN, Bacon MC, Ochieng V, Kimaiyo S. Sampling-based approaches to improve estimation of mortality among patient drop-outs: experience from a large PEPFAR-funded program in Western Kenya. PLoS One. 2008;3:e38–43.
42. MacPherson P, MacPherson EE, Mwale D. Bertel Squire S, Makombe SD, Corbett EL, Lalloo DG, Desmond N. Barriers and facilitators to linkage to ART in primary care: a qualitative study of patients and providers in Blantyre, Malawi. J Int AIDS Soc. 2012;15:18020.
43. Musheke M, Bond V, Merten S. Individual and contextual factors influencing patient attrition from antiretroviral therapy care in an urban community of Lusaka, Zambia. J Int AIDS Soc. 2012;15(Suppl 1):17366.
44. Palchaudhuri S, Tweya H, Hossenipour M. Assessment of laboratory test utilization for HIV/AIDS care in urban ART clinics in Lilongwe, Malawi. Malawi Med J. 2014;26:42–4.
45. Kohl KS, Bonhoeffer J, Braun MM, Chen RT, Duclos P, Heijbel H, Heininger U, Loupi E, Marcy SM. The Brighton Collaboration: creating a global standard for case definitions (and guidelines) for adverse events following immunization. In: Henriksen K, Battles JB, Marks ES, Lewin DI, editors. Advances in patient safety: from research to implementation (Volume 2: concepts and methodology). Rockville: Agency for Healthcare Research and Quality; 2005.
46. WHO Uppsala Monitoring Centre. Countries participating in the WHO Programme for International Drug Monitoring, with year of joining. http://www.who-umc.org/DynPage.aspx?id=100653&mn1=7347&mn2=7252&mn3=7322&mn4=7442. Accessed 14 Apr 2016.