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

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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.

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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...
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**                                 |
| 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          |
| Laboratory monitoring                         | HIV RNA, HIV DNA, CD4 count, hemoglobin, total |
|                                               | lymphocytes, ALT/AST, creatinine, and lactate: |
|                                               | availability and turnaround time               |
| 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  |
| Human resources                               | Availability of physicians, pharmacists, pharmacy |
|                                               | assistants and data recorders (to record ADRs)  |

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

△ Adis
Table 2  Outcome ascertainment and follow-up 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 ($n=137$) |
|------------------------|-----------------------|--------------------------|----------------------|-------------------------|---------------------|----------------|-------------------------|----------------|
| 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 (75.0%) | 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%) |
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 \((<1–30\text{ days})\) and longest for CD4 count \((1–100\text{ days})\). 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 2 continued |
|-------------------|
| **Category and variables** | **West Africa** \((n = 21)\) | **Southern Africa** \((n = 19)\) | **East Africa** \((n = 43)\) | **Central Africa** \((n = 12a)\) | **South America** \((n = 7)\) | **Asia** \((n = 28b)\) | **North America** \((n = 7c)\) | **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 (72.4) | 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

* Central Africa has 15 facilities but no data were available for three facilities
* Asia–Pacific Region has 29 facilities but no data were available for one facility
* North America has eight facilities but no data were available for one facility
| 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           |
(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

| Category and variables | West Africa (n = 21) | Southern Africa (n = 19) | East Africa (n = 43) | Central Africa (n = 12) | South America (n = 7) | Asia (n = 28) | North America (n = 7) | 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
| Category and variables | West Africa (n = 21) | Southern Africa (n = 19) | East Africa (n = 43) | Central Africa (n = 12) | South America (n = 7) | Asia (n = 28) | North America (n = 7) | 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)            | 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)                  | 0 (0)                | 1 (14.3)    | 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)               | 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)                    | 1 (8.3)                  | 0 (0)                    | 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** |                          |                          |                          |                          |                          |                          |                          |                          |
| 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                   | 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  | 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         | 13 (61.9)                | 0 (0)                    | 18 (41.9)                | 10 (83.3)                | 4 (57.1)                 | 24 (85.7)                | 4 (57.1)                 | 73 (53.3)                |
The 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 4 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 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
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 comorbid 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 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.

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.

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